Optimising the use of biological medications in inflammatory bowel disease

Aviv Pudipeddi

MBBS (Hons), FRACP

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

Faculty of Medicine and Health

The University of Sydney

September 2023

Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. The thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing the thesis and sources have been acknowledged.

Name: Dr Aviv Pudipeddi

Date: 1st September 2023

Acknowledgements

There are many people I would like to thank for their support and assistance throughout my PhD candidature.

First and foremost, I would like to express my sincere appreciation and gratitude to my primary supervisor, Professor Rupert Leong. After starting my research journey when I first met him 14 years ago as a young, enthusiastic 3rd year medical student, he has guided me along the way by providing continuous encouragement and mentorship. I am immensely grateful for the opportunities that have arisen as a result, and I would not be where I am today without him. Also, I am forever grateful to my co-supervisor, Dr Sudarshan Paramsothy. His research knowledge, rational thinking and sound advice was invaluable and greatly appreciated throughout my PhD journey.

Thank you as well to the Concord Hospital gastroenterology department, including the clinical trials team (in particular Melissa Kermeen and Diane Redmond), for your constant encouragement. The department has had many trainees who have made significant contributions to IBD research, and I am honoured to follow in their footsteps. I would also like to thank Dr Ken Liu who was my first gastroenterology/liver fellow when I was a BPT. He pushed me to achieve my academic potential and his mentorship will never be forgotten.

This PhD would not have been possible without the support of my family. To mum and dad – you sacrificed so much to ensure I succeeded in my academic pursuits, and I will be forever

grateful. To my in-laws Hema Vaidya and the late Sanjay Vaidya – thank you for your help with the kids and supporting me along this journey (and Sanjay, we miss you every day). To my elder brother Anand (my ultimate role model) and his beautiful family – thank you for your constant support and encouragement through this PhD journey.

I owe the biggest thanks to my amazing wife, Ruhie – you are my rock. The countless times you stepped up to look after the kids when I had unexpected phone calls, urgent deadlines to meet or manuscripts to write on weekends will never be forgotten. You encouraged me without hesitation, and this PhD endeavour would not have been possible without you by my side. To my kids Aaryan and Rishaan – you unknowingly provided me the greatest joy throughout this journey. Coming home to you boys after a tough day truly brought me a new perspective on life. I cannot wait to see what the next chapter of our lives holds for us as a family.

Authorship attribution statement

Chapter 1 of this thesis contains material published as **Pudipeddi A**, Kariyawasam V, Haifer C, Baraty B, Paramsothy S, Leong RWL. Safety of drugs used for the treatment of Crohn's disease. *Expert Opin Drug Saf* 2019; 18(5):357-367.

- I performed the literature review. I wrote the first draft of the manuscript and revised the manuscript after review by my co-authors and external reviewers.

Chapter 2 of this thesis is published as **Pudipeddi A**, Liu J, Kariyawasam V, Borody TJ, Cowlishaw JL, McDonald C, Katelaris P, Chapman G, Corte C, Lemberg DA, Lee CH, Keshava A, Napoli J, Clancy R, Chan W, Paramsothy S, Leong R. High prevalence of Crohn disease and ulcerative colitis among older people in Sydney. *Med J Aust* 2021; 214(8):365-370.

- I was involved in collecting data and interpretation of the results. I wrote the first draft of the manuscript and revised the manuscript after review by co-authors and external reviewers.

Chapter 3 of this thesis is published as **Pudipeddi A**, Ko Y, Paramsothy S, Leong R. Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Therap Adv Gastroenterol* 2022; Mar 8;15:17562848221080793.

- I co-designed the study and interpreted the data. I wrote the first draft of the manuscript and revised the manuscript after review by co-authors and external reviewers.

Chapter 4 of this thesis is published as **Pudipeddi A**, Fung C, Christensen B, Bryant RV, Subramaniam K, Chetwood J, Paramsothy S, Leong R. Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologist vs pathologists. *World J Gastroenterol* 2023; 29(2):378-389.

- I co-designed the study, collected and interpreted the data. I wrote the first draft of the manuscript and revised the manuscript after review by co-authors and external reviewers.

Chapter 5 of this thesis has been submitted to a journal as **Pudipeddi A**, Paramsothy S, Kariyawasam V, Paramsothy R, Ghaly S, Haifer C, An Y-K, Begun J, Connor S, Corte C, Ward M, De Cruz P, Fung C, Redmond D, Chan W, Mourad F, Kermeen M, Leong R. Withdrawal versus continuation of thiopurine in vedolizumab-treated patients with ulcerative colitis: a multi-centre randomised controlled trial (VIEWS).

- I co-designed the study, collected and interpreted the data. I wrote the first draft of the manuscript and revised the manuscript after review by co-authors.

Candidate and supervisor authorship statements

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Name: Dr Aviv Pudipeddi

Date: 1st September 2023

As supervisor for the candidate upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Name: Professor Rupert Leong

Date: 1st September 2023

Awards and grants

I am grateful for receiving the following awards and grants for my thesis work:

- National Health and Medical Research Council Postgraduate Scholarship 2020
- Griffith-Hack Concord Innovation Research Awards: Runner-up 2020
- Asian Organisation of Crohn's Colitis (AOCC) Investigator Award, 2020
- Digestive Disease Week Poster of Distinction, 2021
- International Digestive Disease Forum Poster of Distinction, 2022
- Australian Society of Medical Research NSW Annual Scientific Meeting – Finalist 3-minute presentation
- Griffith-Hack Concord Innovation Research Awards: Winner 2022
- Asian Organisation of Crohn's Colitis (AOCC) Travel Grant 2023
- Concord Repatriation General Hospital Research Conference Travel Grant 2023
- AGA-Moti L. & Kamla Rustgi International Abstract Award, Digestive Disease Week 2023
- Poster of Merit x 2, Australian Gastroenterology Week 2023
- Young Investigator Award finalist, Australian Gastroenterology Week 2023

Publications and conference presentations

Review article

- **Pudipeddi A**, Kariyawasam V, Haifer C, Baraty B, Paramsothy S, Leong RW. Safety of drugs used in the treatment of Crohn's disease. *Expert Opin Drug Saf* 2019; 18(5):357-367.
- **Pudipeddi A**. Safety comparisons of therapies used in inflammatory bowel disease. *J Gastroenterol Hepatol* 2021; 36(Suppl 1): 20-21.
- Leong R, **Pudipeddi A**, Chetwood J, Ko Y. The shifting biologic landscape: exploring ustekinumab in Crohn's disease. *Research Review Educational Series*, Oct 2021.

Letter to the editor

- **Pudipeddi A**, Paramsothy S, Leong R. Combination therapy of immunomodulators with non-anti-tumor necrosis factor agents in inflammatory bowel disease: need more evidence? *Clin Gastroenterol Hepatol* 2021 May 25: S1542-3565(21)00575-9. doi: 10.1016/j.cgh.2021.05.037.

Original articles

- **Pudipeddi A**, Liu J, Kariyawasam V, Borody TJ, Cowlishaw JL, McDonald C, Katelaris P, Chapman G, Corte C, Lemberg DA, Lee CH, Keshava A, Napoli J, Clancy R, Chan W, Paramsothy S, Leong R. High prevalence of Crohn's disease and ulcerative colitis among older people in Sydney. *Med J Aust* 2021; 214(8): 365-370.
- **Pudipeddi A**, Ko Y, Paramsothy S, Leong R. Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in

moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Therap Adv Gastroenterol* 2022; 15: 17562848221080793

- **Pudipeddi A**, Fung C, Christensen B, Bryant RV, Subramaniam K, Chetwood J, Paramsothy S, Leong RW. Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologists vs pathologists. *World J Gastroenterol* 2023; 29(2):378-389.

Conference Presentations

- **Pudipeddi A**, Liu J, Kariyawasam V, Borody TJ, Cowlishaw JL, McDonald C, Katelaris P, Chapman G, Corte C, Lemberg DA, Lee CH, Keshava A, Napoli J, Clancy R, Chan W, Paramsothy S, Leong R. High prevalence of Crohn's disease and ulcerative colitis among older people in Sydney
    - Presented as a poster presentation at the Asian Organisation of Crohn's and Colitis 2020, (virtual)
- **Pudipeddi A**, Ko Y, Paramsothy S, Leong R. Vedolizumab is superior to anti-tumour necrosis factor agents as a first-line biological agent but not as a second-line biological agent in moderate to severe ulcerative colitis. *Gastroenterology* 2021;160(6, Suppl 1):S343
    - Presented as an oral presentation (Investigator Award) at the Asian Organisation of Crohn's and Colitis 2020, (virtual)
    - Presented as an oral presentation at the Australian Society of Medical Research NSW Annual Scientific Meeting 2022, Sydney

- Presented as a poster presentation (Poster of Distinction) at Digestive Disease Week 2021, (virtual)
- Presented as a poster presentation at the Australian Gastroenterology Week 2020, (virtual)

- **Pudipeddi A**, Ko Y, Paramsothy S, Leong R. Concomitant immunomodulator use improves medication persistence of anti-tumour necrosis factor agents and vedolizumab in moderate to severe ulcerative colitis. Gastroenterology 2021; 160(6, Suppl 1):S343-344
  - Presented as a poster presentation at Australian Gastroenterology Week 2020, (virtual)
  - Presented as a poster presentation at the Asian Organisation of Crohn's and Colitis 2020, (virtual)
  - Presented as a poster presentation at Digestive Disease Week 2021, (virtual)
- **Pudipeddi A**, Paramsothy S, Leong RW. Utilisation and impact of immunomodulator co-therapy with first-line and second-line anti-tumour necrosis factor agents in Crohn's disease and ulcerative colitis. *Gut* 2022;71:A150-A151.
  - Presented as a digital oral presentation at Australian Gastroenterology Week 2022, Sydney
  - Presented as a poster presentation (Poster of Distinction) at the International Digestive Disease Forum 2022, Hong Kong
  - Presented as a poster presentation at Digestive Disease Week 2022, San Diego
- **Pudipeddi A**, Fung C, Christensen B, Bryant R, Subramaniam K, Chetwood J, Paramsothy S, Leong R. Knowledge and attitudes towards the use of histological

assessments in ulcerative colitis by gastroenterologists versus pathologists. *Gut* 2022;71:A150.

  - Presented as a poster presentation at Australian Gastroenterology Week 2022, Sydney
  - Presented as a poster presentation at the International Digestive Disease Forum 2022, Hong Kong

- **Pudipeddi A**, Fung C, Kariyawasam V, Paramsothy R, Ghaly S, Haifer C, An Y, Begun J, Connor S, Chetwood J, Paramsothy S, Leong RW. Histological remission using a Nancy index of 0 is associated with longer relapse-free survival than histological activity in patients with ulcerative colitis in clinical and endoscopic remission. *Gut* 2022; 71:A149.
  - Presented as an oral presentation at Australian Gastroenterology Week 2022, Sydney
  - Presented as a poster presentation at the International Digestive Disease Forum 2022, Hong Kong
- **Pudipeddi A**, Paramsothy S, Kariyawasam V, Paramsothy R, Ghaly S, Haifer C, An Y-K, Begun J, Connor S, Corte C, Ward M, De Cruz P, Fung C, Chan W, Mourad F, Leong R. Withdrawal versus continuation of thiopurine in vedolizumab-treated patients with ulcerative colitis: a multi-centre randomised controlled trial (VIEWS). *Gastroenterology* 2023; 164(6): S-221.
  - Presented as an oral presentation (Young Investigator Award finalist) at Australian Gastroenterology Week 2023, Brisbane
  - Presented as an oral presentation (Abstract Award) at Digestive Disease Week 2023, Chicago

- Presented as an oral poster presentation at Asian Organisation of Crohn's and Colitis 2023, Busan
- Presented as a poster presentation at European Crohn's and Colitis Organisation 2023, Copenhagen

Table of Contents

List of tables

List of figures

List of abbreviations

CD	Crohn's disease
CDAI	Crohn's disease activity index
CI	Confidence interval
CRP	C-reactive protein
HBI	Harvey Bradshaw index
HR	Hazard ratio
IBD	Inflammatory bowel disease
IFX	Infliximab
IQR	Interquartile range
IUS	Intestinal ultrasound
MES	Mayo endoscopic score
MRE	Magnetic resonance enterography
OR	Odds ratio
PBS	Pharmaceutical benefits scheme
PRO	Patient-reported outcomes
RCT	Randomised controlled trial
SD	Standard deviation
TDM	Therapeutic drug monitoring
TGN	Thioguanine nucleotide
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UCEIS	Ulcerative colitis endoscopic index of severity
VED	Vedolizumab
WCC	White cell count
NRH	Nodular regenerative hyperplasia
TPMT	Thiopurine methyltransferase
MMP	Methylmercaptopurine
NMSC	Non-melanoma skin cancers
HLH	Hemophagocytic lymphohistocytosis

Abstract

Biological agents have revolutionised the management of inflammatory bowel disease (IBD) in the last fifteen years. They target specific pathways of the immune system that are implicated in the pathogenesis of IBD. As treatment choices increase, there is a need to differentiate between these agents to guide medication choice by gastroenterologists. Also, their efficacy may not be long-lasting for all patients. As such, the aim of this thesis was to identify strategies to optimise the effectiveness of biological agents.

Key findings

First, an updated epidemiological study was performed that demonstrated the prevalence of IBD is rising in Australia, particularly in the older population. Two common biological agents, infliximab and vedolizumab, were then compared in the management of ulcerative colitis. It was identified that vedolizumab had a longer treatment persistence when used as a first-line biological agent compared with infliximab, however not as a second-line agent.

To assist in achieving optimal outcomes in IBD, histological remission has emerged as a potential treatment endpoint. However its utility in clinical practice is unknown. In this thesis, a nationwide survey was performed that demonstrated that although histological activity is recognised as a potential treatment goal, there was poor knowledge by gastroenterologists and pathologists of its applicability in ulcerative colitis and associated histological scoring systems.

The VIEWS study was then designed to assess the impact of thiopurine therapy with vedolizumab. This was the first randomised controlled trial comparing the withdrawal or continuation of thiopurine therapy for patients with ulcerative colitis using vedolizumab who were in remission. Histological outcomes were also assessed. This trial demonstrated that although thiopurines do not affect vedolizumab trough levels, thiopurine withdrawal was associated with increased fecal calprotectin, histologic and histo-endoscopic activity. Histological activity and prior anti-tumour necrosis factor exposure predicted disease relapse upon thiopurine withdrawal for patients using vedolizumab for UC.

In conclusion, the findings suggest that as prevalence rates rise particularly in the older population, safer treatment options should be considered for managing our IBD patients. Vedolizumab, which is a safer treatment option than infliximab, was suggested to be the first-line biological agent of choice in ulcerative colitis. Furthermore, thiopurine withdrawal from vedolizumab appears safe in the setting of histological remission and being treatment naïve to anti-TNF agents. However further education is required into the role of histology in clinical practice given its poor knowledge nationwide. The results of these studies will form the foundation of future research into treatment optimisation strategies and guide the development of national histological consensus guidelines.

Chapter 1

Introduction – Literature review and aims

Parts of this chapter are reproduced from the published manuscript "Safety of drugs used for the treatment of Crohn's disease" by Pudipeddi et al.

Journal reference:

- Pudipeddi A, Kariyawasam V, Haifer C, Baraty B, Paramsothy S, Leong RWL. Safety of drugs used for the treatment of Crohn's disease. *Expert Opin Drug Saf* 2019; 18(5):357-367.

1. INTRODUCTION

1.1 INFLAMMATORY BOWEL DISEASE

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic relapsing and remitting inflammatory conditions of the gastrointestinal tract[1]. UC is characterised by mucosal inflammation that typically involves the rectum and extends proximally, involving only the large intestine[2]. CD, on the other hand, involves transmural inflammation that can affect any part of the gastrointestinal tract but most commonly the ileum and large intestine[2]. Both conditions can lead to significant morbidity, with complications of uncontrolled inflammation including strictures, fistulas, abscesses, perforations and colorectal cancer[3]. The aetiology of IBD is unclear, however it is thought to involve a complex interplay between environmental factors and intestinal microflora in a genetically susceptible individual that leads to a dysregulated immune response and resultant chronic intestinal inflammation[4].

1.2 EPIDEMIOLOGY

The burden of IBD is rising worldwide[5]. Although once considered a disease of westernised countries in Norther America, Europe and Oceania, the turn of the 21st century has seen an

accelerated incidence of IBD in the newly industrialised countries of Asia, South America and Africa[5]. Prior Australian epidemiological studies from Victoria and Tasmania demonstrate high prevalence and incidence rates in Australia. Given the chronic, progressive nature of IBD, the burden of IBD in Australia poses a significant socioeconomic impact. In 2012, hospital costs were estimated to be over $100 million per annum, productivity losses attributable to IBD were over $380 million, and total indirect costs associated with the management of IBD were over $2.7 billion[8]. However, more up-to-date epidemiological data is required to guide the planning and distribution of IBD resources and health services within Australia.

1.3 ENDPOINTS

The goal of therapy in IBD is to achieve and maintain disease remission. Previously, clinical remission was the main target of treatment. This is defined as the absence of rectal bleeding, urgency or increased stool frequency in UC, and the absence of abdominal pain or increased stool frequency in CD[9]. Numerous clinical scoring systems are available to assist in quantifying the degree of symptom burden for patients, including the partial Mayo score in UC and the Crohn's disease activity index (CDAI) or Harvey Bradshaw Index (HBI) in CD[10]. More recently, patients' perspectives on disease activity (called 'patient-reported outcomes' or PRO) which incorporate the above symptoms have become an important assessment tool[9]. However, limitations with solely using clinical remission as an endpoint include its subjective nature and lack of correlation with objective measures of disease activity. As such, recent guidelines state that clinical remission should be a short-term target but it is not a sufficient long-term target[9].

Numerous modalities are available to objectively measure disease activity in IBD. Endoscopic disease assessment via a sigmoidoscopy or colonoscopy has occurred in studies since Truelove reported on the efficacy of cortisone in 1955[11]. Endoscopic remission is associated with longer-term clinical remission, decreased corticosteroid use, and a reduced need for hospitalisation or colectomy[12,13]. Commonly used endoscopic scoring systems are the Mayo endoscopic score (MES) and the ulcerative colitis endoscopic index of severity (UCEIS) in UC, and the simple endoscopic score in CD (SES-CD)[14]. Specifically in UC, the definition of remission using MES has evolved from ≤ 1 to a MES of 0 due to recent data demonstrating improved long-term outcomes for patients with an MES of 0[15,16].

Commonly used biomarkers in IBD are faecal calprotectin and C-reactive protein (CRP). These biomarkers play an important role in assessing and monitoring disease activity in IBD. Biochemical remission has been defined for IBD clinical trials as a faecal calprotectin < 150 μg/g (particularly in UC) and CRP < 5mg/L in UC and CD[17]. However, studies have shown that faecal calprotectin measurements are more sensitive than CRP for predicting mucosal healing in UC and can assist in predicting a relapse[18].

Transmural healing has also emerged as an important treatment endpoint, particularly in CD[19]. The use of magnetic resonance enterography (MRE) and intestinal ultrasound (IUS) has increased in recent years, with MRE allowing for an assessment of the entire small intestine and IUS being able to be performed frequently when required. Transmural healing is currently considered an adjunct treatment target, as further studies are required to determine its role in predicting long-term outcomes in CD[9].

More recently, histological remission is being utilised as an endpoint in clinical trials in UC[20]. It is considered the ultimate marker of quiescent disease activity. Its importance has been demonstrated by studies showing worse long-term outcomes for UC patients in clinical and endoscopic remission but with persistent histologic inflammation compared with those in histologic remission[21-25]. Multiple histological scoring systems have been developed, with the three most validated being the Geboes score, Nancy histological index and the Robarts histopathology index[26-29]. However, it is only considered as an adjunct treatment target in UC at present given the lack of data demonstrating clinical utility[9]. Also, despite its increasing use in research studies, it is unknown whether these scoring systems are used in clinical practice and whether pathologists have an understanding of their use. Nonetheless, it has a growing importance in IBD management and an additional endpoint of interest in clinical trials includes combining both endoscopic and histological assessments (histo-endoscopic assessment)[17].

1.4 Safety of immunomodulators and biological agents in inflammatory bowel disease

The last two decades have seen a significant increase in the research and development of new medications to treat patients with IBD. The therapeutic goal in managing these patients is to induce and maintain clinical and endoscopic remission and to avoid relapses, intestinal damage and need for surgical intervention[9]. Inadequate response to conventional therapies including corticosteroids and immunomodulators are commonly the initiating factor for the prescription of biological agents in Australia. They are monoclonal antibodies directed against

specific targets implicated in the pathogenesis of inflammation. Currently approved biological agents in Australia for the treatment of IBD include anti-tumour necrosis factor-α (anti-TNF) agents (infliximab, adalimumab, golimumab), an anti-α4β7-integrin agent (vedolizumab) and an anti-interleukin 12/23 p40 agent (ustekinumab)[30]. Although clinical trials have proven their effectiveness and early safety data, there remain concerns over the safety of these drugs used during their long-term maintenance therapy. Post-marketing data and post-registration data have provided some reassurance of their safety profile. The safety profile of immunomodulators and biological agents in IBD is summarised below.

1.4.1 *Immunomodulators – Thiopurines*

Given their use for over 50 years, there is a large amount of data that demonstrates the efficacy of thiopurine medications especially with azathioprine and mercaptopurine in IBD. In addition to their central role of maintaining remission in patients with IBD[31], they also reduce phenotypic disease progression[32] and improve treatment efficacy when used in combination with anti-TNF agents[33]. Combination therapy with azathioprine and infliximab has been shown to be more effective in achieving corticosteroid-free clinical remission and higher infliximab trough levels than infliximab monotherapy[33,34]. Also, combination therapy with a thiopurines and adalimumab has been shown to increase response and remission rates compared with adalimumab monotherapy, and reduce the risk of developing anti-drug antibodies to adalimumab[35,36]. However, approximately 15% to 40% of patients who use thiopurines develop adverse events that lead to dose reduction or drug withdrawal, and these can be divided into idiosyncratic or dose-dependent adverse events[37].

Idiosyncratic reactions include gastrointestinal disturbance (such as nausea and vomiting), malaise, headache, stomatitis, alopecia and rash in up to 10% to 15% of patients. Thiopurine-induced pancreatitis occurs in up to 4% of patients, particularly during the first weeks of treatment[38] and the HLA-DQA1-HLA-RB1 susceptibility haplotype is associated with 9% risk in heterozygotes and 17% risk in homozygotes[39]. Another rare adverse event is pneumonitis[40].

Myelotoxicity is a dose-dependent adverse event. Gisbert et al. reviewed 66 studies (8,302 patients) and found the incidence rate of thiopurine-induced myelotoxicity was 3 per 100 person-years (95% confidence interval [CI] 3-4%)[41]. Thiopurine-induced myelotoxicity may occur from 12 days to 27 years of treatment, but was more frequent during the first months of treatment. Three deaths occurred due to myelotoxicity (cumulative incidence 0.06%, 95% CI: 0.02-0.17) and the risk of death in patients who developed myelotoxicity was 0.94% (95% CI: 0.32-2.70)[41]. Colombel et al. showed that 27% of patients with CD and azathioprine-induced myelosuppression had mutant alleles of the thiopurine methyltransferase (TPMT) gene[42]. Homozygote and heterozygote TPMT mutations occur in 0.3% and 6-11% of the Caucasian population respectively[38] and thiopurine dose reduction in those identified as variant carriers result in a 10-fold reduction in myelotoxicity[43]. More recently, Yang et al. identified a variant of the Nudix hydrolase 15 (NUDT15) gene that conferred susceptibility to thiopurine-induced leukopenia especially in the South-East Asian population[44]. Thiopurine-associated hepatotoxicity occurs via three broad categories: hypersensitivity reactions, idiosyncratic cholestatic reactions and nodular regenerative hyperplasia (NRH) that may lead to portal hypertension[45]. Dose-dependent toxicity is possible in cases of NRH.

Thiopurine metabolite monitoring of 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) levels reduces adverse reactions, in particular, myelosuppression and hepatotoxicity. 6-TGN is the metabolite responsible for the therapeutic efficacy of thiopurines (therapeutic range: 235–450pmol/8x10^8 erythrocytes), but elevated levels are associated with myelosuppression. Elevated levels of 6-MMP (>5,700pmol/8x10^8 erythrocytes) are associated with hepatotoxicity. In patients who are preferential 6-MMP metabolisers, the addition of the xanthine-oxidase inhibitor allopurinol with a reduced dose of thiopurine can favour the production of 6-TGN over 6-MMP[38].

Thiopurines are associated with an increased risk of malignancies. A meta-analysis showed a four-fold increased risk of lymphoma in IBD patients treated with a thiopurine[46], while in the Cancer and Increased Risk Associated with Inflammatory Bowel Disease in France (CESAME) prospective cohort study by Beaugerie et al., a five-fold increased risk of lymphoproliferative diseases was demonstrated[47]. A recent nationwide cohort study based on French National Health Insurance databases that included 189,289 patients demonstrated thiopurine use was associated with a risk of lymphoma [adjusted hazard ratio (HR): 2.6, 95% CI: 1.96-3.44, P<0.001)[48]. Combination of a thiopurine with an anti-TNFα agent was associated with an even higher risk (adjusted HR: 6.1, 95% CI: 3.5-10.8, P<0.001)[48]. Azathioprine has also been shown to be associated with myeloid neoplasms in autoimmune disorders including IBD [odds ratio (OR): 7.1, 95% CI 2.4-21.1, P<0.001], and there are case reports in patients with IBD[49-51]. The use of thiopurines, either as monotherapy or in combination with anti-TNF agents, has also been shown to be associated with hepatosplenic T-cell lymphoma[52]. This is a rare but aggressive fatal lymphoma that primarily affects men younger than 35 years old and is associated with a poor prognosis.

Non-melanoma skin cancers (NMSC) are increased in thiopurine users. The CESAME study group showed that in 19,486 IBD patients, the risk of NSMC was HR: 5.9, 95% CI: 2.1-16.4, P=0.0006 in those on ongoing thiopurine treatment and HR: 3.9, 95% CI: 1.3-12.1, P=0.02 in previous thiopurine users exposure[53]. This latter finding is contrary to the lymphoma risk, whereby the discontinuation of thiopurines reduces the risk of lymphoma[54]. Urinary tract cancer risk was also increased, with a multivariate-adjusted HR: 2.8, 95% CI: 1.0-7.7, P=0.04 between patients receiving thiopurines and those not receiving thiopurines[55].

Thiopurine use in IBD has also been associated with the rare development of hemophagocytic lymphohistiocytosis (HLH) following viral infections[56]. A systematic review by Fries et al. showed that EBV and cytomegalovirus were the predominant viral infections that caused secondary HLH in IBD patients, with a mortality rate of approximately 30%[57].

1.4.2 *Immunomodulators – Methotrexate*

Methotrexate maintains remission in CD[58] and is most commonly used as second-line therapy in patients intolerant to thiopurines, or at risk of adverse effects from thiopurines. In double-blinded, placebo-controlled, multi-centre studies by Feagan et al., methotrexate effectively improved symptoms[59] and maintained remission[58] in CD. There were no severe adverse events in methotrexate-users up to week 40 of exposure in the maintenance study, with 2.5% of the patients in the methotrexate group withdrawing from the study prematurely due to nausea[58]. A retrospective study of 92 patients showed methotrexate to be well-tolerated[60]. The commonest adverse events were nausea (22%) and elevated liver enzymes (10%), with only 6% of patients needing to cease methotrexate due to persistently abnormal liver enzymes[60].

Methotrexate-induced hepatotoxicity occurs in 3-33% of IBD patients, with underlying cofactors being non-alcoholic fatty liver disease, diabetes or excess alcohol consumption[61]. The addition of folic acid whilst on methotrexate is recommended, as it has been shown to reduce the gastrointestinal and hepatotoxicity risks[62].

Methotrexate-induced lung injury is infrequent but potentially life-threatening, and typically occurs after an extended course of therapy[63]. It is associated with the development of pneumonitis, which has been reported in the IBD population[64]. Other pulmonary complications from methotrexate use include bronchiolitis obliterans with organising pneumonia, acute lung injury with non-cardiogenic pulmonary oedema, pulmonary fibrosis and pleurisy[65-67]. Methotrexate is also associated with myelosuppression and it is important to monitor blood counts regularly[63]. Cancer and lymphoma risk is not increased in methotrexate users and methotrexate may be preferred over thiopurines in those with increased cancer risks or prior cancers[68].

1.4.3 *Anti-TNF*

1.4.3.1 Infliximab – trial data

Infliximab is a mouse-human chimeric IgG1 monoclonal antibody that targets TNFα. The ACCENT 1 study examined the long-term efficacy and safety of infliximab in CD[69]. It showed that repeated treatment with 5mg/kg or 10mg/kg of infliximab was effective in maintaining remission at week 30 and 54 in patients who had an initial response to the drug in comparison to placebo. There was no significant difference between the two dosages. An additional endoscopic ACCENT 1 sub-study showed that 44% of patients with colonic ulcers treated with maintenance doses had complete mucosal healing after 1 year compared with 18% of the

placebo group (P=0.041)[70]. No significant difference in serious adverse events or infections between was found between the placebo and treatment groups[69]. One patient (0.3%) developed tuberculosis 4 weeks after her week 14 infusion and was successfully treated, whilst 6 patients (1.8%) developed malignancy. Cancers included an epithelial-cell skin neoplasm (6.5 months after the first infliximab induction and placebo-maintenance); a natural-killer cell lymphoma (10 months after week 14 infliximab induction and placebo-maintenance); a basal-cell carcinoma (2 weeks after the week 6 infusion); a hypernephroma (9 weeks after the week 6 infusion); a breast cancer (51 days after the week 30 infusion); and a bladder carcinoma (49 days after the week 42 infusion)[69].

1.4.3.1 Adalimumab – trial data

Adalimumab is a humanised monoclonal antibody that targets TNFα. The pivotal CLASSIC-1 trial[71] demonstrated its efficacy in the induction of remission at week 4 in moderate to severe CD. Adverse events occurred at similar frequencies in the adalimumab and placebo groups and no tuberculosis or opportunistic infections were reported during the study[71]. Injection-site reactions occurred in 29% (66/225) of patients in the adalimumab groups, compared with 16% (12/74) in the placebo group[71]. In the CLASSIC-2 trial, longer term data through to week 56 were available[72]. In this study, those randomized to placebo experienced higher overall adverse events, serious adverse events, and adverse events leading to discontinuation than those randomized to adalimumab[72]. No patients withdrew from the study due to injection-site reactions. The commonest reported treated-emergent adverse event was nasopharyngitis in 5%. There were no cases of tuberculosis, demyelinating event, lymphoma, malignancy or death in the adalimumab group[72].

The CHARM trial examined the efficacy and safety of adalimumab in the maintenance of response and remission in patients with moderate to severe CD. Adverse events were reported at similar frequencies between the adalimumab and placebo groups, with a higher discontinuation of treatment rate in the placebo group than in the adalimumab group[73]. Injection-site reactions occurred more frequently in the adalimumab groups (5% [26/517]) compared with the placebo group (0.4% [1/261]), but were generally mild-to-moderate[73]. Tuberculosis was reported in 2 patients (0.4%) treated with adalimumab, both of whom were purified protein derivative-negative and had normal chest radiographs at baseline[73]. One patient had received open-label adalimumab fortnightly for 197 days, and the other had received open-label adalimumab for a total of 260 days (31 days at fortnightly dosing and 229 days at weekly dosing)[73]. The latter patient had also received prednisone and azathioprine as concomitant medications. One patient who was receiving adalimumab died from a pulmonary embolism on day 15, with contributing risk factors including age, a history of pulmonary embolism, hypertension and atrial fibrillation. The event was deemed by the investigators to be unrelated to adalimumab[73].

Papamichael et al. also completed a safety assessment of anti-TNF therapy in literature published up to August 2015 and concluded they were associated with an elevated risk of serious infections, skin cancer and lymphoma[74]. Osterman et al. performed a pooled analysis of data from 1594 patients with CD who participated in clinical trials, and found the combination therapy of adalimumab and an immunomodulator was associated with an increased risk of NMSC and other cancers[75]. However these studies were prior to the era of therapeutic drug monitoring (TDM). The Trough Concentration Adapted Infliximab Treatment (TAXIT) study was a randomised controlled trial (RCT) that aimed to compare the efficacy and

safety of concentration-based dosing of infliximab in a cohort of IBD-responder patients treated with infliximab maintenance therapy[76]. A higher proportion of patients who had dose-escalation based on a sub-therapeutic infliximab trough concentration was in remission than before dose-escalation (88% versus 65%, P=0.020)[76]. One patient in the concentration-based dosing group experienced a serious adverse event (leukocytoclastic vasculitis) leading to discontinuation of infliximab, whilst one patient in the clinically-based dosing group had a psoriaform eczema leading to discontinuation. However, the proportion of patients reporting adverse events that were considered to be linked to infliximab by the treating clinician were similar in both treatment groups[76]. No deaths occurred in the trial. Higher serum trough levels of infliximab have not been linked to greater risk of adverse events[77].

1.4.3.3 Anti-TNF – real-world data

The Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry by Lichenstein et al. evaluated the long-term safety data for infliximab in CD [78]. It recruited 3,420 participants that received infliximab and 2,853 that received conventional therapies, with a mean length of patient follow-up being 5.2 years. Patient mortality was similar between the two groups. However, there was an increased risk of serious infection with infliximab (HR: 1.43, 95% CI: 1.11-1.84; P=0.006)[78]. The commonest infections were pneumonia, cellulitis and abdominal abscesses. However, the severity of CD (HR: 2.2, 95% CI: 1.6-3.2, P<0.001) and the use of prednisone (HR: 1.98, 95% CI: 1.4-2.7, P<0.001) carried a higher risk of serious infection compared with infliximab use[78]. No increased risk of non-Hodgkin's lymphoma (NHL) for CD patients treated with infliximab was found in the TREAT registry[78], however underpowering might have contributed to the lack of that association. Studies examining the combination therapy of anti-TNF agents with immunomodulators showed that there was an increased risk

of opportunistic infection, herpes zoster and non-Hodgkin's lymphoma[79,80]. The ENCORE registry by D'Haens et al. also compared the long-term safety of infliximab compared with conventional therapies[81]. Infliximab was associated with serious infections (HR: 1.66, 95% CI: 1.2-2.3, P=0.005) and benign haematological conditions that included leukopenia, neutropenia and thrombocytopenia (HR: 2.9, 95% CI: 1.5-5.6, P=0.001), but not with lymphoproliferative disorders, malignancy or death[81]. There was no significant difference in the rate of demyelinating neurological disorders between the two groups[81].

The PYRAMID registry examined safety data related to adalimumab[82]. It included 5,025 patients who were evaluated over a six year period. Treatment-emergent adverse events included 4,129 serious adverse events [n=1853 (36.9%); 24.8 events per 100 person-years], 792 serious infections [n=556 (11.1%); 4.7 events per 100 person-years] including 10 cases of active tuberculosis, and 134 malignancies [n=116 (2.3%); 0.8 events per 100 person-years], including ten lymphomas[82]. The observed lymphoma rate (0.060 events per 100 person-years) was lower than the estimated background rate (0.084 events per 100 person-years)[82]. No new safety signals were reported in this registry.

1.4.4 *Vedolizumab*

1.4.4.1 Vedolizumab – trial data

Vedolizumab is a humanised, gut-selective, monoclonal IgG1 antibody to $\alpha_4\beta_7$ integrin, inhibiting migration and leukocyte adhesion from the circulation to the bowel. Gut selectivity with this biological agent means lower risk of potential systemic side effects. Its effectiveness as induction and maintenance therapy in the management of UC and CD was shown in the GEMINI 1 and 2 trials respectively[83,84]. In the latter study at week 52, 39.0 % of patients who

randomized to 8-weekly vedolizumab were in clinical remission compared with 21.6% of patients in the placebo group (P<0.001)[84]. Nasopharyngitis occurred more frequently in the vedolizumab group. Clinically important infusion reactions were infrequent, with only one (0.3%) patient discontinuing the trial due to an infusion reaction[84]. During the trial of maintenance phase, there was one case (0.3%) each of latent tuberculosis, carcinoid tumour in the appendix, squamous-cell carcinoma and basal-cell carcinoma diagnosed in the vedolizumab groups[84]. There were no cases of progressive multifocal leukoencephalopathy (PML).

Feagan et al. examined data from the GEMINI trials and found there was no statistically significant difference in time to first upper or lower respiratory tract infection between vedolizumab and placebo groups[85]. This also included patients who were on 4-weekly vedolizumab maintenance. Colombel et al. examined safety data from six trials of vedolizumab[86]. Adverse events were reported more frequently with placebo (419.4 per 100 person-years) than with vedolizumab (247.8 per 100 person-years). Vedolizumab did not increase the frequency of adverse events. Upper respiratory tract infections accounted for approximately half or more of the total infections reported with incidence rates of 28.6 per 100 person-years with vedolizumab and 34.7 per 100 person-years with placebo[86]. Three patients (0.2%) were diagnosed with pulmonary tuberculosis in patients who tested negative for tuberculosis at baseline and were taking concomitant immunomodulators. There were no cases of PML. They concluded that there were no significant safety concerns associated with vedolizumab treatment[86]. Bye et al. also completed a systematic search that included six registration trials and nine cohort studies[87]. They found the incidence rates of infection and

serious adverse events in the vedolizumab population were comparable to the placebo groups, and post-marketing data did not identify any new concerns[87].

1.4.4.2 Vedolizumab – Real-world data

There have been recent 'real-life' studies evaluating the use of vedolizumab in inflammatory bowel disease. A systematic review by Engel et al. examined real-world studies of vedolizumab in IBD[88]. Nine studies involving 1,565 patients were included. Adverse effects were mostly minor and occurred in 30.6% of patients. Infections were reported in 3.4% of patients[88]. Schreiber et al. incorporated real-world studies to examine the effectiveness and safety of vedolizumab in IBD[89]. Overall adverse event rates were reported in 23 studies (0-67% of patients; n=2,358) and infections in 12 studies (range 5-24%; n=1,176). Post-operative adverse events were reported in 4 studies (n=857). The commonest adverse events were upper respiratory tract infections including nasopharyngitis (range 1-21%), arthralgia (range <1-20%), *Clostridium difficile* infection (range <1-20%) and fatigue (range 1-19%)[89]. The real-world data obtained from this systematic review is consistent with those from the GEMINI trials, with no new or unexpected safety issues.

A systematic review by Dulai et al. included treatment outcomes from the VICTORY consortium and concluded vedolizumab was safe to use in patients with moderate-to-severe CD[90]. A retrospective multi-centre European pooled cohort study by Kopylov et al. showed that in 184 anti-TNF naïve patients on vedolizumab, adverse events were reported in 20 (11%) of the patients, leading to treatment discontinuation in 6 (2 arthralgia, 1 neutropenia, 1 sarcoidosis flare-up, 1 tinnitus, 1 cholestasis)[91]. Lenti et al. reported a multi-centre experience of eight IBD units from Northern England that confirmed the effectiveness and safety of

vedolizumab in both the induction and maintenance of remission in UC and CD in 203 patients[92]. There was a low rate of adverse events, with 5 (2.5%) patients discontinuing the medication (4 [2.0%] due to urticarial rash and 1 [0.5%] supraventricular tachycardia during vedolizumab infusion). The cumulative incidence of non-infective adverse events was 5.1 per 100 person-years, while the cumulative incidence of infectious diseases was 11.9 per 100 person-years (13.7% of the cohort)[92]. Nasopharyngitis and pneumonia were the commonest infections. One patient developed viral meningitis and another patient developed of Epstein-Barr virus infection causing acute hepatitis and both were on concomitant immunomodulators. There was one (0.5%) case of tuberculosis reactivation affecting the central nervous system in a 57-year old female who had type 2 diabetes mellitus. Sub-analysis of the use of vedolizumab in the elderly aged 65 years or above reported that there were no reports of infections[92].

1.4.5 *Ustekinumab*

1.4.5.1 Ustekinumab – trial data

Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23. The pivotal UNITI trials demonstrated its efficacy in patients with moderate to severe CD[93]. The UNITI-1 trial included 741 patients who were primary or secondary non-responders to anti-TNFα agents, whilst the UNITI-2 trials included 628 patients who had failed conventional therapy and had not failed biological agents. The primary end-point was a clinical response at week 6 (defined as a decrease from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥100 points or a CDAI score <150). The rates of response at week 6 were significantly higher in those receiving either 130mg IV ustekinumab, approximately 6mg/kg IV ustekinumab compared to placebo (UNITI-1, 34.3%, 33.7%, and 21.5%, respectively, with P≤0.003 for both

comparisons with placebo; in UNITI-2, 51.7%, 55.5%, and 28.7%, respectively, with P<0.001 for both doses)[93].

From these induction trials, 397 patients who had a response then participated in the IM-UNITI trial. Patients were randomized to receive subcutaneous maintenance injections of 90mg of ustekinumab either every 8 weeks or 12 weeks, or placebo. The primary end point was remission at week 44 (CDAI score < 150). In the groups receiving maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53.1% and 48.8%, respectively, were in remission at week 44, as compared with 35.9% of those receiving placebo (P=0.005 and P=0.04, respectively)[93].

The rates of adverse effects were similar between treatment and placebo groups in both induction trials[93]. At week 44 of the IM-UNITI trials, the percentages of patients in the primary population with at least one adverse event in the groups receiving 90 mg of ustekinumab every 8 weeks, 90 mg of ustekinumab every 12 weeks, and placebo were 81.7%, 80.3%, and 83.5%, respectively[93]. The percentages of patients with a serious adverse event were 9.9%, 12.1%, and 15.0%, respectively[93]. A serious infection developed in 13 patients across all three study groups, occurring in 2.3% in the 8-weekly ustekinumab group, 5.3% in the 12-weekly ustekinumab group, and 2.3% in the placebo group. Three opportunistic infections occurred comprising of one case of listeria meningitis (following induction with 6mg/kg of ustekinumab on concomitant prednisone 30mg per day), and two cases of oesophageal candidiasis (one in a patient taking prednisone 40mg per day and methotrexate and the other in a patient not in the primary IM-UNITI population who was receiving 8-weekly SC ustekinumab)[93]. One case of active pulmonary tuberculosis occurred in a high-tuberculosis endemic area approximately 10

months after the administration of a single 130mg IV ustekinumab and placebo maintenance therapy[93].

Two patients developed a basal cell-carcinoma in the maintenance trial – one in the placebo group and one in the 8-weekly ustekinumab group[93]. One patient in the 12-weekly ustekinumab group developed a metastatic adenocarcinoma in the small bowel and a carcinoid tumour was found incidentally in the resected bowel. After 1 year of therapy, there were no deaths. There was no apparent relationship between dose and safety of ustekinumab in the UNITI trials[93].

Ustekinumab exposure through to 96 weeks of the IM-UNITI maintenance study recruited 718 subjects with 86.5% (621/718) completing Week 96 of follow up[94]. Adverse events per hundred person-years were similar among ustekinumab and placebo groups, including overall adverse events (484.4 versus 447.8), serious adverse events (19.2 versus 18.8) and serious infections (4.1 versus 4.0). Comparable rates of adverse events were noted between the 8-weekly and 12-weekly ustekinumab groups. A 45 year old male from South Africa that was negative for tuberculosis at screening developed tuberculosis. He tested positive to QuantiFERON TB Gold on routine annual screening and bronchial brushings were positive for *Mycobacterium tuberculosis*. This was deemed unrelated to ustekinumab. A serious opportunistic infection of cytomegalovirus colitis occurred in a 32 year old who received ustekinumab induction followed by maintenance (440 days after last exposure to ustekinumab). The number of treatment-emergent malignancies per hundred person-years of follow-up was 2.60 for placebo patients and 0.37 for ustekinumab patients. Three deaths were reported, two due to presumed cardiovascular causes and one suicide. Two of these patients

were receiving 8-weekly ustekinumab and the other patient was receiving 12-weekly ustekinumab. The data from this long-term extension study illustrate that ustekinumab is well tolerated with a favourable safety profile[94].

1.4.5.2 Ustekinumab – Real-world data

A retrospective multi-centre cohort study evaluated the long-term efficacy and safety of ustekinumab in patients with anti-TNF refractory CD[95]. In the study, 122 patients were followed up for a median treatment duration of 26.6 months. At the end of follow-up, 5 patients stopped ustekinumab due to side effects including pulmonary infection (n=1), a flare of hidradenitis suppurativa (n=1), acne (n=1), disabling myalgia (n=1) and anal adenocarcinoma (n=1). The anal adenocarcinoma developed in a 32-year old man with a 26-year history of CD that was treated with ustekinumab for 30 months. There were no opportunistic infections or deaths reported[95].

A notable study that examined the safety profile of ustekinumab in the real-world is the PSOLAR study by Papp et al., albeit in the psoriasis population[96]. A total of 12,093 patients (48,388 person-years) were included and they found that there was no increased risk of malignancy, serious infection, major adverse cardiovascular events or mortality with ustekinumab on multivariate analyses[96]. A sub-analysis of 2.3% of PSOLAR patients with concomitant IBD showed that having IBD increased the risk of infections compared to psoriasis overall. However, patients treated with ustekinumab had numerically lower rates of serious infections compared with patients receiving other biological and non-biological therapies[97].

1.5 WITHDRAWAL OF IMMUNOSUPPRESSIVE THERAPY IN INFLAMMATORY BOWEL DISEASE

Immunosuppressive therapy is fundamental in achieving remission for patients with IBD. However given their safety concerns as described above, particularly when used as combination therapy, clinicians and patients may consider de-escalating or withdrawing immunosuppressive medications once remission has been achieved. This decision involves carefully weighing up the benefits of maintaining remission versus the risks of opportunistic infections, lymphoproliferative disorders and other cancers. However, it is important to consider the risk of disease relapse upon withdrawal of therapy. Prior evidence relates to mesalazine withdrawal, immunomodulator withdrawal or anti-TNF agent withdrawal.

1.5.1 *Topical mesalazine*

Studies assessing topical mesalazine withdrawal date back over 30 years ago. Hanauer et al. performed a multi-centre double-blinded randomised controlled trial for patients with ulcerative proctitis in clinical and endoscopic remission, who were randomised to use a mesalazine suppository once daily versus placebo as sole maintenance therapy[98]. They found that at 12- and 24- months, the proportion of placebo-treated patients who relapsed (86% and 89% respectively) was significantly greater than mesalazine-treated patients (32% and 46% respectively, $P \leq 0.001$)[98]. The mean time to relapse was 158.0 days in the placebo group and 453.4 days in the mesalazine group ($P < 0.001$)[98]. Although this study demonstrated the role of maintenance mesalazine suppository therapy in the setting of remission, Marteau et al. performed a randomised controlled trial on 95 patients with ulcerative proctitis in clinical and endoscopic remission who were randomised to use mesalazine 1g three times per week

versus placebo[99]. The relapse rate was lower in the mesalazine group for the following time periods: 0-90 days (19% versus 38%, *P*=0.035), 0-180 days (29% versus 54%, *P*=0.017) and 0-270 days (38% versus 60%, *P*=0.031). Overall 28% versus 61% of patients who remained in the protocol were in remission at one year (*P*=0.001), concluding that mesalazine suppositories 1g three times per week was effective in preventing relapses[99]. This study confirmed that dose-reducing the suppository therapy schedule was still effective in preventing relapses.

For left-sided colitis, enema therapy is typically used for maximal benefit. Biddle et al. performed a randomised, double-blinded, placebo-controlled trial involving 25 patients in clinical and endoscopic remission who were randomised to either use a mesalazine 1g enema daily for maintenance versus placebo[100]. They found 84.6% (11/13) of patients in the placebo group had a relapse compared to 25% (3/12) of patients in the mesalazine group (*P*<0.005)[100]. Put together, these studies demonstrate that topical mesalazine withdrawal in the setting of remission is associated with a higher rate of disease relapse, with evidence supporting the use of dose-reduced maintenance topical mesalazine therapy.

1.5.2 *Oral mesalazine*

Similar to topical mesalazine, most studies examining the relapse rate following withdrawal of oral mesalazine have shown higher relapse rates in the withdrawal group compared to the continue group. However, studies varied in terms of their compound and frequency of dosing. In a double-blinded randomised controlled trial, Ardizzone et al. compared 12-month relapse rates for patients who withdrew oral mesalazine-based therapy in the setting of clinical, endoscopic and histological remission[101]. Patients were randomised to continue mesalazine or placebo, and were divided into two groups depending on the length of remission before

entering the study – either 1-2 years or greater than 2 years. They found that mesalazine was more effective than placebo in preventing relapse at 12-months for patients who had only been in remission for 1-2 years, however there was no difference in relapse rates for patients who had been in remission for greater than 2 years[101]. It was concluded that mesalazine prophylaxis is required to prevent relapse for patients in remission for less than 2 years, however it may not be required for patients in prolonged remission.

There is limited data on the outcomes of mesalazine-withdrawal for patients on an immunomodulator. Mantzaris et al. performed a randomised controlled trial for patients with UC in clinical, endoscopic and histological remission[102]. Patients were randomised to continue combined azathioprine and olsalazine versus azathioprine monotherapy. They found no significant difference in relapse rates between both groups at 2 years, however compliance was greater in the monotherapy group[102]. Further prospective studies are required to assess whether mesalazine can be safely withdrawn from patients on an immunomodulator, taking into account baseline factors and using other objective markers such as CRP, faecal calprotectin, endoscopic and histological assessments.

1.5.3 *Immunomodulator and anti-TNF agents*

Immunomodulatory therapy forms a cornerstone in managing patients with moderate to severe inflammatory bowel disease. However as described earlier, there are concerns regarding side effects, including opportunistic infections, skin cancers and lymphomas. As such, considerations regarding immunomodulatory withdrawal are not uncommon when patients are in remission. However, understanding relapse rates following immunomodulatory withdrawal is important.

Most studies examining the withdrawal of immunomodulator monotherapy have been in CD. Lémann et al. found that azathioprine withdrawal led to higher relapse rates compared to azathioprine continuation (21% versus 8%) at 18 months for patients who had been in clinical remission for at least 42 months prior[103]. Importantly, they identified that a CRP > 20mg/L and haemoglobin < 120g/L were predictive of relapse on multivariate analysis[103]. Further, a multi-centre retrospective cohort study that included 237 patients from 11 centres in the United Kingdom demonstrated that following thiopurine withdrawal for IBD patients in sustained clinical remission, a moderate-to-severe relapse occurred in 23% of CD and 12% of UC patients at 12 months[104]. This increased to 39% of CD and 26% of UC patients at 24 months[104]. It was found that an elevated CRP at withdrawal was associated with higher relapse rates in the CD group, and an elevated WCC was predictive at 12 months in the UC group[104]. A recent systematic review and meta-analysis that involved seven RCTs, which included a total of 334 patients with CD and 67 patients with UC, found a significantly higher relapse rate after immunomodulator withdrawal compared to continuation (RR: 1.9, 95%CI: 1.4-2.4, P<0.001)[105]. It should be noted there have been limited studies on methotrexate or mercaptopurine withdrawal.

Despite the higher risk of relapse following immunomodulator withdrawal despite remission, multivariable analyses have identified factors, such as elevated inflammatory markers or reduced haemoglobin, that have been associated with relapse. These analyses are important as they identify a sub-group of patients that may benefit from immunomodulator withdrawal without increasing the risk of relapse.

Combination therapy between thiopurines and anti-TNF agents has been shown to be more effective than monotherapy in the treatment of inflammatory bowel disease[4,5]. However, given the higher risks associated with such combination therapy, patients and clinicians may consider withdrawal of one of these agents once in remission. Van Assche et al. examined the impact of withdrawing immunomodulator therapy from infliximab for patients with Crohn's disease in remission for at least 6 months, compared with continuing combination therapy[106]. There was no significant difference in the proportion of patients who required a change in infliximab dosing or stopped infliximab by week 104[106]. However they identified that CRP levels were higher and infliximab levels were lower in the withdrawal group[106].

Conversely, the STORI trial by Louis et al. examined the relapse rate following infliximab withdrawal from combination therapy with an immunomodulator[107]. From a prospective cohort of 115 patients with CD, 43.9% of patients relapsed during a median follow-up period of 28 months. On multivariable analysis, risk factors for relapse included a CRP $\geq$ 5mg/L, faecal calprotectin $\geq$ 300μg/g, haemoglobin < 145g/L, leukocyte counts > 6.0×10^9/L and male sex[107]. These data suggest that despite clinical remission, a consideration into biochemical disease activity is important prior to drug withdrawal. More recently, the SPARE study by Louis et al. compared the relapse rate for patients in steroid-free clinical remission for more than six months who continued combination therapy, or stopped either infliximab or immunosuppressant therapy[108]. They found that infliximab withdrawal was associated with greater risk of relapse at two years compared to the combination group (HR: 3.5, 95%CI: 1.6-7.7, *P*=0.003) and compared to the immunosuppressant withdrawal group (HR: 4.8, 95%CI: 1.9-11.1, *P*=0.0004)[108]. It was concluded that immunosuppressant withdrawal may be

considered as a preferable strategy when considering treatment de-escalation compared with infliximab withdrawal[108].

Despite evidence detailing the relapse rates following treatment de-escalation with immunomodulators and infliximab, there is a lack of data when considering newer biological agents such as vedolizumab. Current evidence suggests that combination therapy between vedolizumab and an immunomodulator is not superior to vedolizumab monotherapy[109], however no study has assessed this as a primary outcome. Also, the effects of immunomodulator withdrawal from vedolizumab therapy in the setting of remission is unknown, despite its importance in clinical practice. As such, randomised controlled studies are required to examine this question.

1.6 PURPOSE OF THIS THESIS:

Given the preceding background provided in this introduction, it is evident that there are a number of gaps in the literature about how best to utilise biological agents whilst taking into account their safety profile. In this context, the overall aims of the current thesis are to:

- Investigate and provide updated epidemiological data to understand the current patient population
- Provide guidance on the sequencing of biological agents in UC given varying efficacy and safety profiles

- Understand the knowledge of the use of histology in UC by gastroenterologists and pathologists given its establishment as a part of current clinical trials and potential role in future clinical management
- Investigate the benefit, or lack thereof, or thiopurine use with vedolizumab

1.6.1 HYPOTHESES AND AIMS

HYPOTHESIS 1:

- The prevalence if IBD is rising in Australia, particularly in the elderly
- **Aims** (Chapter 2):
    - To determine the prevalence of IBD in a metropolitan area of Sydney
    - To determine the prevalence of IBD in older population groups

HYPOTHESIS 2:

- Vedolizumab has a longer persistence of use than infliximab in moderate-to-severe UC as a first-line biological agent
- **Aims** (Chapter 3):
    - To compare the persistence of infliximab and vedolizumab as first- and second-line biological therapies
    - To compare persistence rates of infliximab and vedolizumab at 12-, 24-, 36- and 48- months

- To analyse the persistence of infliximab and vedolizumab stratified by immunomodulator co-therapy

HYPOTHESIS 3:

- Knowledge into the role of histology in UC, including histological scoring systems, by gastroenterologists and pathologists is poor
- **Aim** (Chapter 4):
  - To evaluate the knowledge of histology guidelines and attitudes towards the use of histology in UC by gastroenterologists and pathologists

HYPOTHESIS 4:

- Thiopurines may provide benefit when used together with vedolizumab in UC
- **Aims** (Chapter 5):
  - To determine the impact of withdrawing thiopurine therapy for vedolizumab-treated patients with UC in remission (including vedolizumab levels, clinical remission, endoscopic remission, biochemical remission and histological remission)

1.7 References

1. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. *Nat Rev Immunol.* 2003;3(7):521-533.
2. Satsangi J, Silverberg MS, Vermiere S, Colombel J-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55(6):749-753.
3. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenerol*. 2005;19(Suppl A):5A-36A.
4. de Souza HSP, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol*. 2016;13(1):13-27.
5. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet.* 2018;390:2769-2778.
6. Studd C, Cameron G, Beswick L, et al. Never underestimate inflammatory bowel disease: high prevalence rates and confirmation of high incidence rates in Australia. *J Gastroenterol Hepatol.* 2016;31:81-86.
7. Bhatia R, Yeoh SW, Vaz K, et al. Inflammatory bowel disease incidence, prevalence and 12-month initial disease course in Tasmania, Australia. *Intern Med J.* 2019;49:622-630.
8. PricewaterhouseCoopers Australia; Crohn's and Colitis Australia. Improving inflammatory bowel disease care across Australia. Mar 2013. https://www.crohnsandcolitis.com.au/site/wp-content/uploads/PwC-report-2013.pdf (viewed June 2020).
9. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*. 2021;160(5):1570-1583.
10. Kishi M, Hirai F, Takatsu N, et al. A review on the current status and definitions of activity indices in inflammatory bowel disease: how to use indices for precise definition. *J Gastroenterol*. 2022;57(4):246-266.
11. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. *Br Med J*. 1955;2(4947):1041-1048.
12. Colombel J-F, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology.* 2011;141(4):1194-1201.
13. De Cruz P, Kamm MA, Prideaux L, et al. Mucosal healing in Crohn's disease: a systematic review. *Inflamm Bowel Dis.* 2013;19(2):429-444.
14. Limdi JK, Picco M, Farraye FA. A review of endoscopic scoring systems and their importance in a treat-to-target approach in inflammatory bowel disease (with videos). *Gastrointest Endosc*. 2020;91(4):733-745.
15. Barreiro-de Acosta M, Vallejo N, de la Iglesia D, et al. Evaluation of the risk of relapse in ulcerative colitis according to the degree of mucosal healing (Mayo 0 vs 1): a longitudinal cohort study. *J Crohns Colitis*. 2016;10(1):13-19.

16. Viscido A, Valvano M, Stefanelli G, et al. Systematic review and meta-analysis: the advantage of endoscopic Mayo score 0 over 1 in patients with ulcerative colitis. *BMC Gastroenterol*. 2022;22:92.
17. Ma C, Hanzel J, Panaccione R, et al. CORE-IBD: a multidisciplinary international consensus initiative to develop core outcome set for randomized controlled trials in inflammatory bowel disease. *Gastroenterology*. 2022;163(4):950-964.
18. Mosli MH, Zou G, Garg SK, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am J Gastroenterol*. 2015;110(6):802-819.
19. Geyl S, Guillo L, Laurent V, et al. Transmural healing as a therapeutic goal in Crohn's disease: a systematic review. *Lancet Gastroenterol Hepatol*. 2021;6(8):659-667.
20. Ma C, Sedano R, Almradi A, et al. An international consensus to standardize integration of histopathology in ulcerative colitis clinical trials. *Gastroenterology*. 2021;160(7):2291-2302.
21. Park S, Abdi T, Gentry M, et al. Histological disease activity as a predictor of clinical relapse among patients with ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol.* 2016;111(12):1692-1701.
22. Christensen B, Hanauer S, Erlich J, et al. Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. *Clin Gastroenterol Hepatol.* 2017;15(10):1557-1564.
23. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. *Clin Gastroenterol Hepatol.* 2013;133:1099-1105.
24. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology.* 2007;11:1601-1608.
25. Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut.* 2016;65(3):408-414.
26. Geboes K, Riddell R, Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut.* 2000;47(3):404-409.
27. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. *Gut.* 2017;66:43-49.
28. Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. *Gut.* 2017;66:50-58.
29. Magro F, Doherty G, Peyrin-Biroulet L, et al. ECCO position paper: harmonization of the approach to ulcerative colitis histopathology. *J Crohns Colitis.* 2020;14(11):1503-1511.
30. Wright E, Ding NS, Niewiadomski O. Management of inflammatory bowel disease. *Med J Aust*. 2018;209(7):318-323.
31. Pearson DC, May GR, Fick G, et al. Azathioprine for maintaining remission in Crohn's disease. *Cochrane Database Syst Rev*. 2000;(2):CD000067.
32. Kariyawasam VC, Selinger CP, Katelaris PH, et al. Early use of thiopurine or methotrexate reduces major abdominal and perianal surgery in Crohn's disease. *Inflamm Bowel Dis*. 2014;20(8):1382-1390.
33. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine or combination therapy for Crohn's disease. *N Eng J Med*. 2010;362(15):1383-1395.

34. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology*. 2014;146(2):392-400.
35. Kariyawasam VC, Ward MG, Blaker PA, et al. Thiopurines Dosed to a Therapeutic 6-Thioguanine Level in Combination with Adalimumab Are More Effective Than Subtherapeutic Thiopurine-based Combination Therapy or Adalimumab Monotherapy During Induction and Maintenance in Patients with Long-standing Crohn's Disease. *Inflamm Bowel Dis*. 2017;23(9):1555-1565.
36. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF naïve patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet*. 2019;4(5):341-353.
37. Jharap B, Seinen ML, de Boer NK, et al. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year intercept cohorts. *Inflamm Bowel Dis*. 2010;16(9):1541-1549.
38. Leong RW, Gearry RB, Sparrow MP. Thiopurine hepatotoxicity in inflammatory bowel disease: the role for adding allopurinol. *Expert Opin Drug Saf*. 2008;7(5):607-616.
39. Heap GA, Weedon MN, Bewshea CM, et al._HLA-DQA1-HLA-DRB1 variants confer susceptibility to pancreatitis induced by thiopurines immunosuppressants. *Nat Genet*. 2014;46(10):1131-1134.
40. Ananthakrishnan AN, Attila T, Otterson MF, et al. Severe pulmonary toxicity after azathioprine/6-mercaptopurine initiation for the treatment of inflammatory bowel disease. *J Clin Gastroenterol*. 2007;41(7):682-688.
41. Gisbert JP, Gomollon F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. *Am J Gastroenterol*. 2008;103(7):1783-1800.
42. Colombel JF, Ferrari N, Debuysere H, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology*. 2000;118(6):1025-1030.
43. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease. *Gastroenterology*. 2015;149(4):907-917.
44. Yang SK, Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurines-induced leukopenia. *Nat Genet*. 2014;46(9):1017-1020.
45. Konidari A, Matary WE. Use of thiopurines in inflammatory bowel disease: Safety issues. *World J Gastrointest Pharmacol Ther*. 2014;5(2):63-76.
46. Kandiel A, Fraser AG, Korelitz Bl, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut*. 2005;54(8):1121-1125.
47. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009;374(9701):1617-1625.
48. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA*. 2017;318(17):1679-1686.
49. Ertz-Archambault N, Kosiorek H, Taylor GE, et al. Association of therapy for autoimmune disease with myelodysplastic syndromes and acute myeloid leukemia. *JAMA Onc*. 2017;3(7):936-943.

50. Mullier F, Rahier JF, Maignen F, et al. A case of therapy-related myeloid neoplasm in a patient with Crohn's disease treated with azathioprine. *Acta Haematol*. 2012;128(1):1-6.
51. Ahmad OF, Keane MG, McCartney S, et al. Azathioprine-associated myelodysplastic syndrome in two patients with ulcerative colitis. *Frontline Gastroenterol*. 2013;4(3):205-209.
52. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011;9(1):36-41.
53. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology*. 2011;141(5):1621-1628.
54. Khan N, Abbas AM, Lichtenstein GR, et al. Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study. *Gastroenterology*. 2013;145(5):1007-1015.
55. Bourrier A, Carrat F, Colombel JF, et al. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Aliment Pharmacol Ther*. 2016;43(2):252-261.
56. Li Y, Xia X, Zhang J, et al. Haemophagocytic lymphohistiocytosis in inflammatory bowel disease with virus infection. *Prz Gastroenterol*. 2015;10(2):78-82.
57. Fries W, Cottone M, Cascio A. Systematic review: macrophage activation system in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;37(11):1033-1045.
58. Feagan BG, Richard N, Fedorak MD, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. *N Eng J Med*. 2000;342(22):1627-1632.
59. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. *N Eng J Med*. 1995;332:292-297.
60. Chande N, Abdelgadir I, Gregor J. The safety and tolerability of methotrexate for treating patients with Crohn's disease. *J Clin Gastroenterol*. 2011;45(7):599-601.
61. Herfarth HH, Kappelman MD, Long MD, et al. Use of methotrexate in the treatment of inflammatory bowel diseases (IBD). *Inflamm Bowel Dis*. 2016;22(1):224-233.
62. Shea B, Swinden MV, Tanjong Ghogomu E, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2013;(5):CD000951.
63. McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. *Expert Rev Gastroenterol Hepatol*. 2014;8(3):223-240.
64. D'Andrea N, Triolo L, Margagnoni G, et al. Methotrexate-induced pneumonitis in Crohn's disease. Case report and review of the literature. *Multidiscip Respir Med*. 2010;5(5):312-319.
65. Lateef O, Shakoor N, Balk RA. Methotrexate pulmonary toxicity. *Expert Opin Drug Saf*. 2005;4(4):723-730.
66. Iikuni N, Iwami S, Kasai S, et al. Noncardiogenic pulmonary edema in low-dose oral methotrexate therapy. *Intern Med*. 2004;43(9):846-851.
67. Walden PA, Mitchell-Weggs PF, Coppin C, et al. Pleurisy and methotrexate treatment. *Br Med J*. 1977;2(6091):867.

68. Swoger JM, Regueiro M. Stopping, continuing, or restarting immunomodulators and biologics when an infection or malignancy develops. *Inflamm Bowel Dis*. 2014;20(5):926-935.
69. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549.
70. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of Infliximab in Crohn's disease. *Gastroenterology*. 2004;126:402-413.
71. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130(2):323-333.
72. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007;56(9):1232-1239.
73. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65.
74. Papamichael K, Mantzaris GJ, Peyrin-Biroulet L. A safety assessment of anti-tumor necrosis factor alpha therapy for treatment of Crohn's disease. *Expert Opin Drug Saf*. 2016;15(4);493-501.
75. Osterman MT, Sandborn WJ, Colombel JF, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. *Gastroenterology*. 2014;146(4):941-949.
76. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015;148(7):1320-1329.
77. Mitrev N, Leong RW. Therapeutic drug monitoring of anti-tumour necrosis factor-α agents in inflammatory bowel disease. *Expert Opin Drug Saf*. 2017;16(3):303-317.
78. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol*. 2012;107(9):1409-1422.
79. Osterman MT, Haynes K, Delzell E, et al. Effectiveness and safety of immunomodulators with anti-TNF therapy in Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13(7):1293-1301.
80. Siegel CA, Marden SM, Persing SM, et al. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*. 2009;7(8):874-881.
81. D'Haens G, Reinisch W, Colombel JF, et al. Five-year safety data from ENCORE, a European Observational Safety Registry for Adults With Crohn's Disease Treated with Infliximab [Remicade®] or Conventional Therapy. *J Crohns Colitis*. 2017;11(6):680-689.
82. D'Haens G, Reinisch W, Panaccione R, et al. Lymphoma risk and overall safety profile of adalimumab in patients with Crohn's disease with up to 6 years of follow-up in the PYRAMID registry. *Am J Gastroenterol*. 2018;113(6):872-882.
83. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.
84. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369:711-721.

85. Feagan BG, Bhavat F, Khalid M, et al. Respiratory tract infections in patients with inflammatory bowel disease: safety analyses from vedolizumab clinical trials. *J Crohns Colitis*. 2018;12(8):905-919.
86. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2017;66(5):839-851.
87. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(1):3-15.
88. Engel T, Ungar B, Yung DE, et al. Vedolizumab in IBD-lessons from real-world experience: a systematic review and pooled analysis. *J Crohns Colitis*. 2018;12(2):245-257.
89. Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *J Gastroenterol*. 2018;53(9):1048-1064.
90. Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY consortium. *Am J Gastroenterol*. 2016;111(8):1147-1155.
91. Kopylov U, Verstockt B, Biedermann L, et al. Effectiveness and safety of vedolizumab in anti-TNF-naïve patients with inflammatory bowel disease-A multicenter retrospective European study. *Inflamm Bowel Dis*. 2018;24(11):2442-2451.
92. Lenti MV, Levison S, Eliadou E, et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study. Dig Liver Dis. 2018;50(12):1299-1304.
93. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375(20):1946-1960.
94. Sandborn WJ, Rutgeerts P, Gasink C, et al. Long term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. *Aliment Pharmacol Ther*. 2018;48(1):65-77.
95. Wils P, Bouhnik Y, Michetti P, et al. Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. *Aliment Pharmacol Ther*. 2018;47(5):588-595.
96. Papp K, Gottlieb AB, Naldi L, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and registry (PSOLAR). *J Drugs Dermatol*. 2015;14(7):706-714.
97. Loftus E Jr, Augustin M, Bissonnette R, et al. Prevalence of inflammatory bowel disease amongst patients with psoriasis and incidence of serious infection in the subset: results from the PSOLAR registry. *J Crohns Colitis*. 2016;10(Suppl 1):S418.
98. Hanauer S, Good LI, Goodman MW, et al. Long-term use of mesalamine suppositories in remission maintenance of ulcerative proctitis. *Am J Gastroenterol*. 2000;95(7):1749-1754.
99. Marteau P, Crand J, Foucault M, Rambaud J. Use of mesalazine slow release suppositories 1g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled maintenance study. *Gut*. 1998;42(2):195-199.
100. Biddle W, Greenberger NJ, Swan JT, McPhee MS, Miner Jr PB. 5-aminosalicylic acid enemas: effective agent in maintaining remission in left-sided ulcerative colitis. *Gastroenterology*. 1988;94(4):1075-1079.

101. Ardizzone S, Petrillo M, Imbesi V, et al. Is maintenance therapy always necessary for patients with ulcerative colitis in remission? *Aliment Pharmacol Ther*. 1999;13(3):373-379.
102. Mantzaris GJ, Sfakianakis M, Archavlis E, et al. A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis. *Am J Gastroenterol*. 2004;99(6):1122-1128.
103. Lémann M, Mary J-Y, Colombel J-F, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology*. 2005;128(7):1812-1818.
104. Kennedy NA, Kalla R, Warner B, et al. Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: relapse and recapture rates, with predictive factors in 237 patients. *Aliment Pharmacol Ther*. 2014;40(11-12):1313-1323.
105. Dohos D, Hanak L, Szakacs Z, et al. Systematic review with meta-analysis: the effects of immunomodulator or biological withdrawal from mono- or combination therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2021;53(2):220-233.
106. Van Assche G, Magdaleine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology*. 2008;134(7):1861-1868.
107. Louis E, Mary J-Y, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology*. 2012;142(1):63-70.
108. Louis E, Resche-Rigon M, Laharie D, et al. Withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease on combination therapy (SPARE): a multicentre, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2023;8(3):215-227.
109. Yzet C, Diouf M, Singh S, et al. No benefit of concomitant immunomodulator therapy on efficacy of biologics that are non tumor necrosis factor antagonists in patients with inflammatory bowel diseases: a meta-analysis. *Clin Gastroenterol Hepatol* 2021: 19(4): 668-679.

Chapter 2

High prevalence of Crohn's disease and ulcerative colitis among older people in Sydney

This chapter is a reproduction of the published manuscript "High prevalence of Crohn disease and ulcerative colitis among older people in Sydney" by Pudipeddi et al.

Journal reference:

- Pudipeddi A, Liu J, Kariyawasam V, Borody TJ, Cowlishaw JL, McDonald C, Katelaris P, Chapman G, Corte C, Lemberg DA, Lee CH, Keshava A, Napoli J, Clancy R, Chan W, Paramsothy S, Leong R. High prevalence of Crohn disease and ulcerative colitis among older people in Sydney. *Med J Aust* 2021; 214(8):365-370.

High prevalence of Crohn's disease and ulcerative colitis among older people in Sydney

Authors

Aviv Pudipeddi[1] MBBS (Hons), FRACP

Jeffrey Sung Ming Liu[1] BMed, MD, BSc(Med) Hons

Viraj Kariyawasam[1] MBBS, MRCP, FRACP, PhD

Thomas J Borody[2] MD, PhD, DSc, FRACP, FACP, FACG, AGAF

James Cowlishaw[1] MBBS, FRACP

Charles McDonald[1] MBBS, FRACP

Peter Katelaris[3] MBBS, FRACP, FRCP, MD, AGAF

Grace Chapman[1] MBBS, FRACP

Crispin Corte[4] MBBS (Hons), BSc(Med), FRACP, PhD

Daniel Lemberg[5] MBBS, BSc(Med), DipPaed, FRACP

Cheng Hiang Lee[6] MB BCh BAO, DipPaed, FRACP

Anil Keshava[1] MBBS, MS, FRACS

John Napoli[7] MBBS, FRACP, PhD

Robert Clancy[2] MBBS(Hons), BSc(Med), PhD, AM, FRACP, FRCPA

Webber Chan[1] MBBS, MRCP

Sudarshan Paramsothy[1] BSc(Med), MBBS (Hons 1), MRCP (UK), FRACP, PhD

Rupert WL Leong[1] MBBS, FRACP, MD, AGAF

Affiliations

[1]Concord Repatriation General Hospital, Sydney, NSW

[2]Centre for Digestive Diseases, Sydney, NSW

[3]University of Sydney, Sydney, NSW

[4]AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney, NSW

[5]Sydney Children's Hospital, Sydney, NSW

[6]The Children's Hospital at Westmead, Sydney, NSW

[7]Ryde Hospital, Sydney, NSW

Corresponding Author

Rupert WL Leong

Department of Gastroenterology and Liver Services

Level 1 West, Gastroenterology Unit, Concord Hospital

Hospital Road

Concord NSW 2139

Phone: +61 2 97676111

Email: rupertleong@hotmail.com

Guarantor of the article:

Rupert WL Leong

Author contributions:

AP – acquisition, analysis and interpretation of data, drafting the work, final approval

JL – acquisition, analysis and interpretation of data, drafting the work, final approval

VK, SP – design and critical revision of the work, final approval

TB, JC, CM, PK, GC, CC, DL, CL, AK, JN, RC, WC – acquisition of data, critical revision, final approval

RL – conception and design of the work, acquisition of data, critical revision, final approval

All authors had full access to all of the data and approved the final version of this article.

Statement of interests:

VK does consultancy work for Janssen-Cilag Pty Limited and has received grants from Takeda, Ferring, Abbvie and Shire.

TJB has a pecuniary interest in the Centre for Digestive Diseases and is in advisory boards of Redhill, Crestovo and Finch Therapeutics.

CC has received unrestricted research grants from Shire and Ferring, and has received speakers' honoraria from Abbvie, Ferring, Janssen, Takeda and Shire.

RWL has served on the advisory boards of AbbVie, Aspen, Celgene, Ferring, Janssen, Takeda and has received unrestricted research support from Shire, Janssen, NHMRC of Australia and speakers Honoria from Emerge Health.

There are no conflicts of interests for AP, JL, JC, CM, PK, GC, DL, CHL, AK, JN, RC, WC and SP.

Financial support: Nil

ABSTRACT

Objectives: To determine the age-standardised prevalence of inflammatory bowel disease (IBD) in a metropolitan area of Sydney, with a focus on its prevalence among older people.

Design, setting: This population-based epidemiological study was conducted within the metropolitan area of inner-west Sydney. Age-standardisation was performed according to the World Health Organisation Standard Population.

Participants: Patients diagnosed with IBD using the Copenhagen or revised Porto criteria and confirmed through medical records. Elderly was defined as age $\geq$ 65 years.

Main outcome measures: Crude prevalence of IBD, including Crohn's disease and ulcerative colitis; age-standardised prevalence of IBD based on the World Health Organisation standard population; prevalence rates in the population aged 65 years or more.

Results: The median age of 364 people with IBD was 47 years (IQR, 34–62 years); 185 were women (50.8%). The crude IBD prevalence rate was 414 cases (95% CI, 371–456 cases) per 100 000 population; the age-standardised rate was 348 cases (95% CI, 312–385 cases) per 100 000 population. The age-standardised rate for Crohn disease was 166 cases (95% CI, 141–192 cases) per 100 000 population; for ulcerative colitis, 148 cases (95% CI, 124–171 cases) per 100 000 population. The IBD prevalence rate in people aged 65 years or more was 612 cases (95% CI, 564–660 cases) per 100 000, and for those aged 85 years or more, 891 cases (95% CI, 833–949 cases) per 100 000; for people under 65, the rate was 380 cases (95% CI, 342–418 cases) per 100 000.

Conclusions: We found that the prevalence of confirmed IBD in a metropolitan sample was highest among older people. Challenges for managing older patients with IBD include higher rates of comorbid conditions, polypharmacy, and cognitive decline, and the immunosuppressive nature of standard therapies for IBD.

2.1 INTRODUCTION

The worldwide burden of inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, has increased markedly over the past sixty years,[1] partly because IBD is incurable but rarely fatal.[2] Its prevalence is greatest (but stable) in western Europe and North America,[1] but its incidence has risen over the past two decades in more recently industrialised countries in Asia, South America, and Africa.[3,4]

The burden associated with IBD in Australia is high; it was estimated to have incurred more than $2.7 billion in costs in 2012.[5] Earlier epidemiological studies in Victoria (2010–11)[6] and Tasmania (2013–14)[7] included mixed urban and rural populations; in a multi-nation Asia–Pacific study, epidemiological variations were associated with population density and proximity to metropolitan areas.[8] Young people with IBD may move to cities for education and employment, reducing the apparent prevalence of IBD in rural areas.

It was recently reported that IBD prevalence rates in Lothian (Scotland) were very high among people aged 60–79 years (1178 per 100 000) or 80 years or more (1042 per 100 000), and they are projected to rise further by 2028.[9] The use of immunosuppressive therapies to treat IBD in these age groups is problematic, as opportunistic infections, sepsis, comorbid conditions, and malignancy are more frequent in older patients.

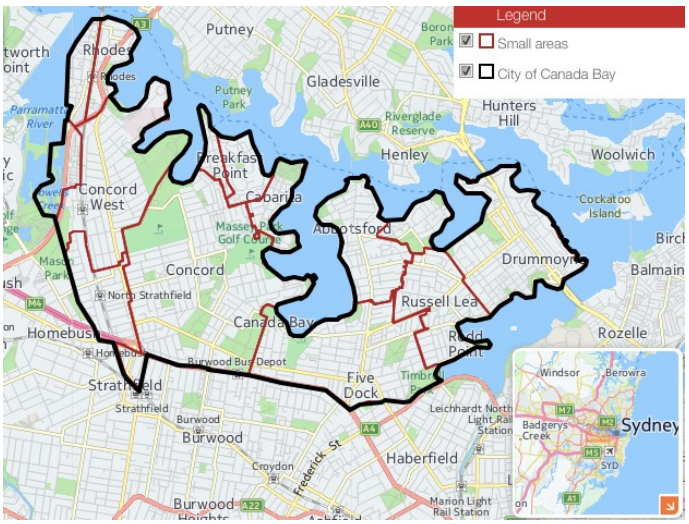
We therefore examined age-specific prevalence rates of IBD in a defined metropolitan area of Australia, focusing on its prevalence in older people.

2.2 METHODS

2.2.1 Population characteristics

We assessed the prevalence of IBD in the City of Canada Bay, a local government area in the inner west of Sydney, with a population of 88 015 at the time of data collection (Figure 2.1).[10] Concord Hospital, a centrally located public hospital with an established IBD clinic, provides free health care for patients with IBD.

Figure 2.1. The City of Canada Bay local government area



2.2.2 Data collection

We analysed clinical data for people with IBD living in the City of Canada Bay (postcodes 2046, 2047, 2137, 2138) during 1 March 2016 – 10 November 2016, including those reviewed by gastroenterologists outside the study area. We identified people treated at Concord Hospital according to International Classification of Diseases, 10th revision (ICD-10) coding. We also obtained information on patients from gastroenterologists and colorectal surgeons at

Concord Hospital, private gastroenterology and colorectal surgery practices, the Sydney IBD database (ambulatory IBD patients identified in medical records from Concord Hospital and City of Canada Bay community gastroenterologists), and the paediatric IBD database of the Westmead Children's Hospital.

Two authors (AP, JL) collected patient data in standardised forms. Given the heterogeneity of the data sources, various search methods were employed to identify patients, including searches for keywords (e.g., Crohn's, colitis, IBD), pharmaceutical prescriptions, and ICD-10 codes. Demographic data (patient's initials, sex, age, postcode) were collected to check for duplication and for analyses of point prevalence. "Older person" was defined as someone aged 65 years or more. Clinical data (IBD subtype, age at diagnosis) were obtained from patient medical records. The most recently updated IBD phenotype details (according to the Montreal classification[11]) were also collected.

2.2.3 Inflammatory bowel disease diagnostic criteria

We included only patients with confirmed IBD according to the internationally recognised Copenhagen[12,13] (Table 2.1) and revised Porto criteria[14] for clinical, endoscopic, radiological and histological findings. Each included IBD case was independently verified by two of the authors (AP, JL).

Table 2.1. Copenhagen Diagnostic Criteria for inflammatory bowel disease

Crohn's disease (two or more of the criteria present)	1. History of abdominal pain, weight loss, and/ diarrhea for more than three months 2. Characteristics endoscopic findings of ulceration (aphthous lesions, snail track ulceration) or cobble-stoning or radiological features of stricture or cobble-stoning 3. Histopathology consistent with Crohn's disease (epithelioid granuloma of Langerhans type or transmural discontinuous focal or patchy inflammation) 4. Fistula and/or abscess in relation to affected bowel segments
Ulcerative colitis (all 3 criteria present)	1. History of diarrhea and/or rectal bleeding and pus for more than a week or repeated episodes 2. Characteristic endoscopic findings of continuous ulceration, vulnerability or granulated mucosa 3. Histopathology consistent with ulcerative colitis (neutrophils within epithelial structures, cryptitis, crypt distortion, crypt abscesses)
Inflammatory bowel disease, unspecified	Where intestinal inflammation with acute and chronic colitis is seen but with no pathognomonic histological signs of Crohn's disease or consistent signs of ulcerative colitis, and where treatment is necessary

2.2.4 Data analysis

Crude IBD prevalence rates were calculated by dividing the number of confirmed cases by the City of Canada Bay resident population; rates were separately calculated for Crohn's disease, ulcerative colitis, and IBD unclassified (IBDU). Rates, with 95% confidence intervals (CIs), were expressed per 100 000 population. Direct age standardisation was based on the World Health Organization standard population,[15] permitting comparisons with overseas data; 95% CIs were calculated with the Keyfitz formula.[16] Statistical analysis was performed in the Statistical Package for the Social Sciences (SPSS) Statistics 23.

2.2.5 Ethical considerations

Our study was approved by the Sydney Local Health District Human Research Ethics Committee (reference, HREC/16/CGH/21).

2.3 RESULTS

2.3.1 Demographics characteristics and phenotypes

We identified 364 prevalent cases of IBD; the median age of patients was 47 years (interquartile range [IQR], 34–62 years; range, 7–100 years), and 185 patients were women (50.8%). The median duration of IBD was 8 years for Crohn's disease (IQR, 4–17 years), 10 years for ulcerative colitis (IQR, 4–18 years) and 11 years for IBDU (IQR, 4–14.5 years) (Table 2.2).

Table 2.2. Demographic characteristics of residents of the City of Canada Bay with inflammatory bowel disease

	All	Crohn's disease	Ulcerative colitis	IBD-unspecified
	364	164	160	40
Male sex, n (%)	179 (49)	82 (50)	83 (52)	14 (35)
Age (years), median (IQR)	47.0 (34.0-62.0)	45.5 (31.0-56.3)	46.5 (36.0-63.0)	56.5 (43.3-76.0)
Disease duration (years), median (IQR)	9.0 (4.0-17.0)	8.0 (4.0-17.0)	10.0 (4.0-18.0)	11.0 (4.0-13.5)

IBD = inflammatory bowel disease; IQR = interquartile range

Complete phenotypic details were available for 163 of 164 cases of Crohn's disease (99.4%) and 159 of 160 cases of ulcerative colitis (99.4%). Most patients with Crohn's disease were diagnosed when aged 17–40 years and had disease affecting both the ileum and colon (68 of 164 patients, 41%). Disease was usually inflammatory but non-stricturing and non-penetrating (98 patients, 60%); 37 patients (23%) were classified as having peri-anal disease. The most frequent disease extent for ulcerative colitis was left-sided colitis (63 of 160 patients, 39%) (Table 2.3).

Table 2.3. Inflammatory bowel disease phenotypes of patients in the City of Canada Bay, according to the Montreal classification[11]

Phenotypic characteristics	Number of cases (%)
Crohn's disease	164
Age at diagnosis (years)	
< 16	17 (10%)
17 – 40	95 (58%)
> 40	51 (31%)
Disease extent	
L1 (Ileal)	43 (26%)
L2 (Colonic)	53 (32%)
L3 (Ileo-colonic)	68 (41%)
L4 (isolated upper GI involvement)	0 (0.0)
Disease behaviour	
B1 (Non-stricturing and non-penetrating)	98 (60%)
B2 (Stricturing)	34 (21%)
B3 (Penetrating)	31 (19%)
P (Perianal involvement)	37 (23%)
Ulcerative colitis	
Disease extent	
E1 (Proctitis)	56 (35%)
E2 (Left-sided colitis)	63 (39%)
E3 (Pancolitis)	40 (25%)

2.3.2 Prevalence rates

The crude IBD prevalence rate was 414 cases (95% CI, 371–456 cases) per 100 000 population; the age-standardised rate was 348 cases (95% CI, 312–385 cases) per 100 000 population. The age-standardised prevalence of Crohn's disease was slightly higher than that of ulcerative colitis (Table 2.4).

Table 2.4. Prevalence of inflammatory bowel disease and its subtypes in the City of Canada Bay

Subtype	Number of cases	Crude point prevalence rate, per 100,000 (95% CI)	Age-standardised prevalence rate, per 100,000 (95% CI)
All types	364	414 (371-456)	348 (312-385)
Crohn's disease	164 (45%)	186 (158-215)	166 (141-192)
Ulcerative colitis (n=160)	160 (44%)	182 (154-210)	148 (124-171)
IBD-U (n=40)	40 (11%)	45 (31-60)	34 (23-46)

CI = confidence interval

2.3.3 Age-specific Prevalence Rates

IBD prevalence increased with age (Table 5). The prevalence of Crohn's disease peaked in the 50–54-year age group, that of ulcerative colitis in the 35–39-year and the 85 years or more age groups (Figure 2.2). The age distribution was similar for both sexes (Figure 2.3).

Table 2.5. Age-specific prevalence of inflammatory bowel disease in the City of Canada Bay

Age group (years)	Number of cases	Prevalence rate, per 100 000 (95% CI)
0 – 64	285	380 (342-418)
0 – 4	0	0
5 – 9	1	21 (12-30)
10 – 14	7	174 (146-202)
15 – 19	7	175 (149-204)
20 – 24	18	287 (253-320)
25 – 29	29	354 (318-391)
30 – 34	31	365 (327-402)
35 – 39	42	606 (558-654)
40 – 44	31	484 (441-527)
45 – 49	34	586 (539-633)
50 – 54	36	663 (612-713)
55 – 59	26	522 (477-566)
60 – 64	23	538 (492-583)
≥ 65	79	612 (564-660)
65 – 69	20	507 (463-551)
70 – 74	15	512 (468-556)
75 – 79	13	572 (526-619)
80 – 84	13	743 (689-796)
≥ 85	18	891 (833-949)

CI = confidence interval

Figure 2.2. Age-specific prevalence of inflammatory bowel disease in the City of Canada Bay, by type and age

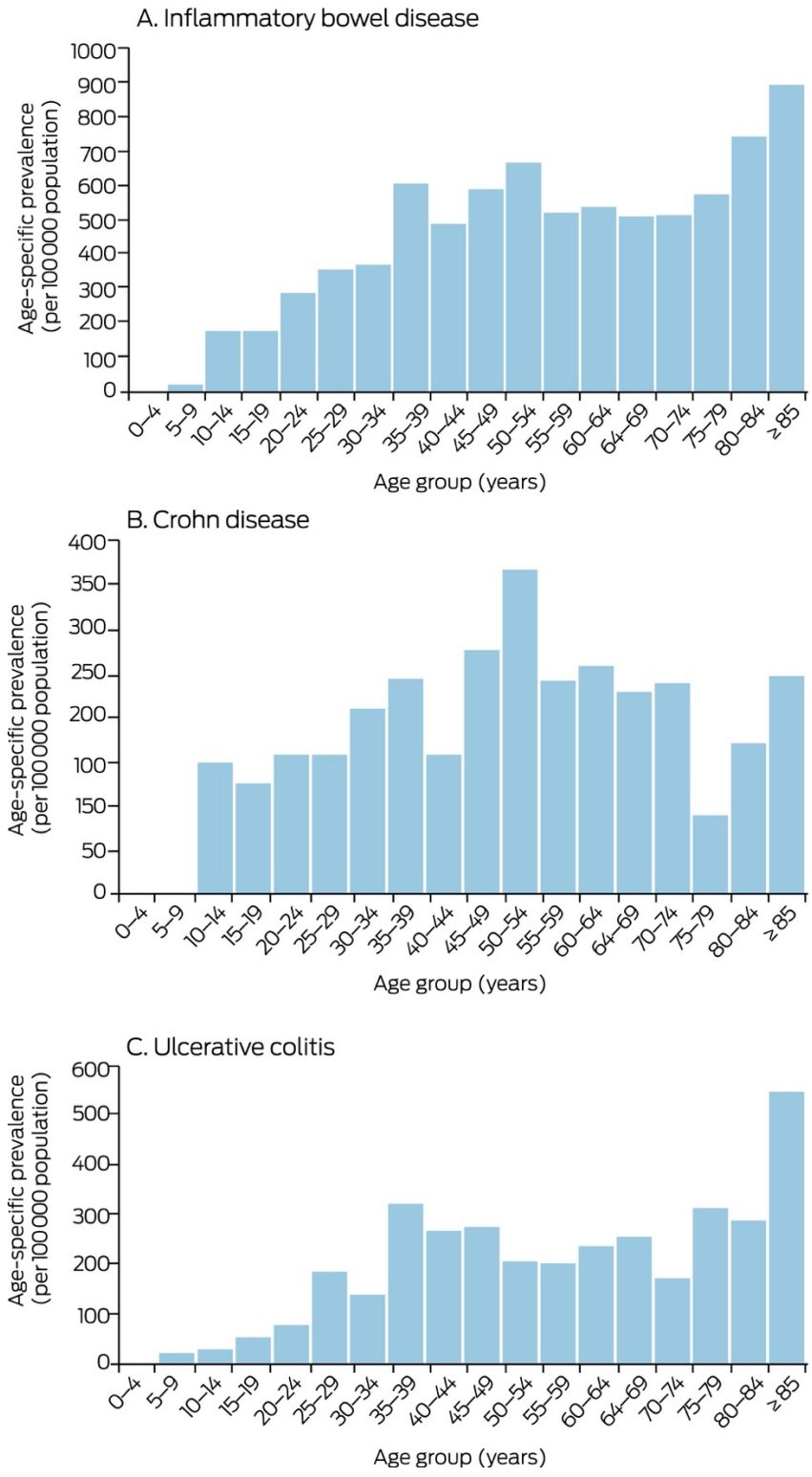
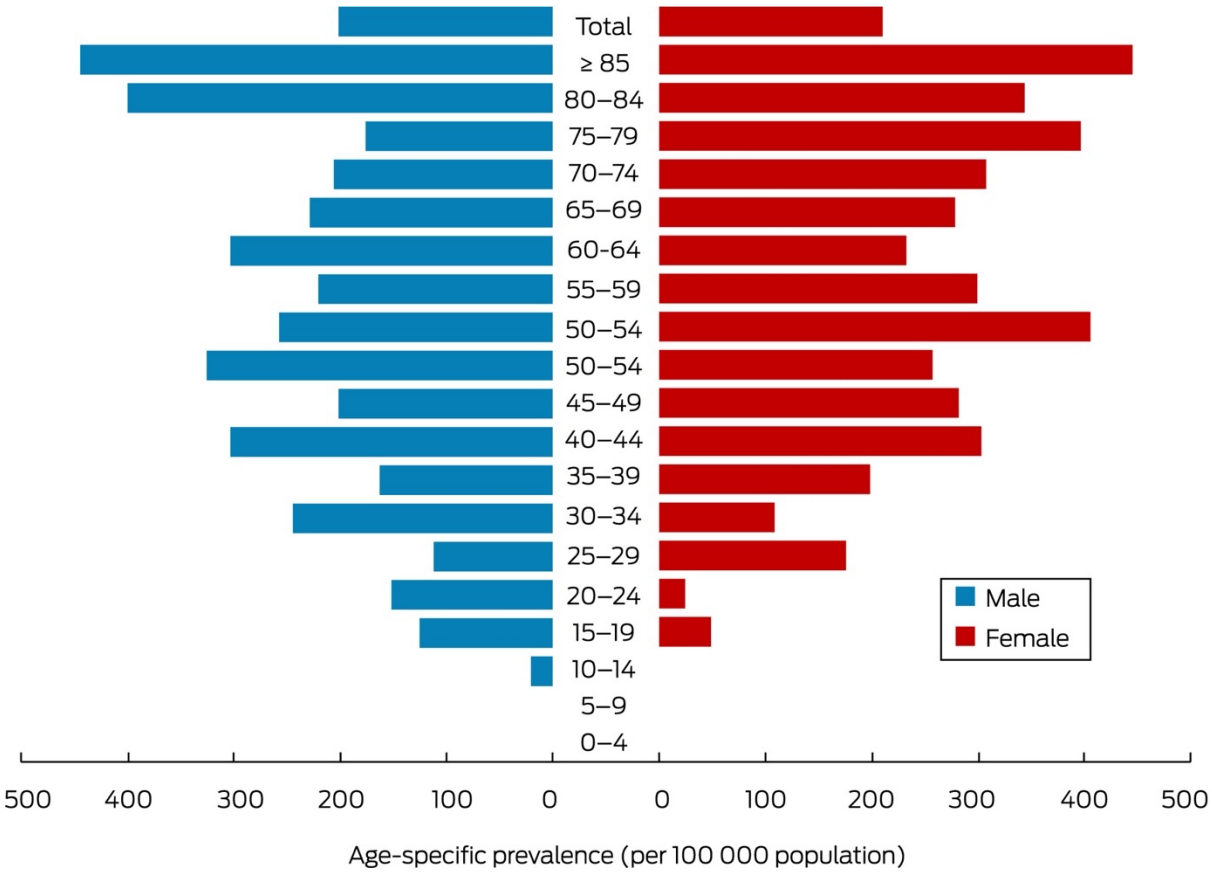


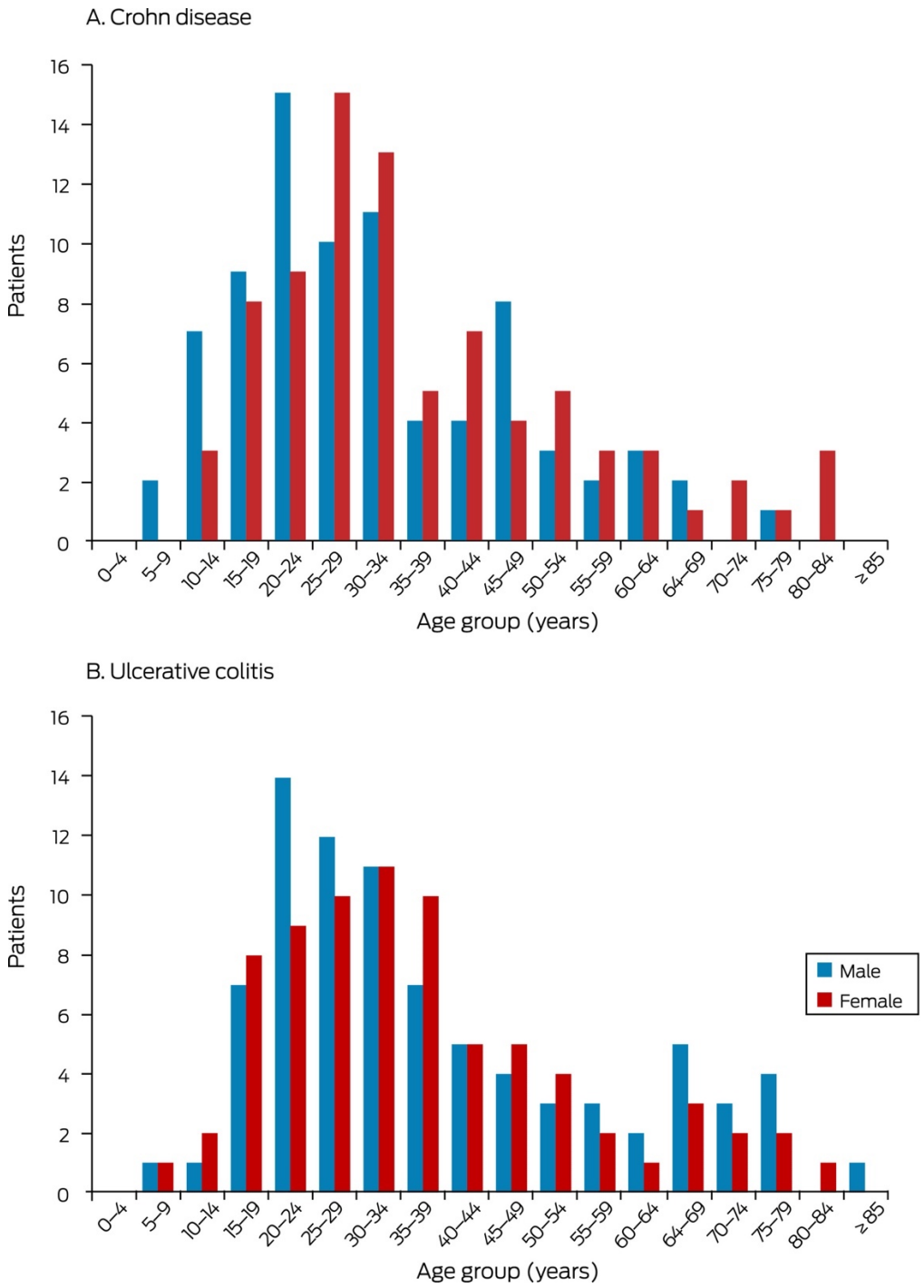
Figure 2.3. Age-specific prevalence of inflammatory bowel disease in the City of Canada Bay, by sex



2.3.4 Age at diagnosis

Age at diagnosis was available for 362 of 364 patients (99.5%). Median age at diagnosis was 32 years (IQR, 23–48 years). For Crohn's disease, the median age of diagnosis was 27 years (IQR, 20–41.5 years) for men, 31.5 years (IQR, 25–47 years) for women. For ulcerative colitis, the median age at diagnosis was 31 years (IQR, 24–53 years) for men, 32 years (IQR, 23–46 years) for women (Figure 2.4).

Figure 2.4. Age at diagnosis for people in the City of Canada Bay with Crohn's disease or ulcerative colitis, by sex



2.3.5 Data Sources

Of the 364 cases, 175 (48%) were identified in a single data source, including 139 patients of a private gastroenterologist (Table 2.6).

Table 2.6. Number of data sources including data on prevalent inflammatory bowel disease cases

Number of data sources	Number of cases
1	175 (48%)
2	125 (34%)
3	48 (13%)
4	15 (4%)
5	1 (0.3%)
Total	364

2.4 Discussion

We have reported the first population-based IBD prevalence study in New South Wales, and the first IBD prevalence study in Australia restricted to a metropolitan area. Our population-based methodology allows direct comparison with other national and international studies (Table 2.7). We found the highest age-standardised rates of IBD (348 cases per 100 000 population), Crohn's disease (166 per 100 000 population) and ulcerative colitis (148 per 100 000 population) reported by any study in Australia or New Zealand.[5,7,17] The prevalence rate of Crohn's disease was higher than that of ulcerative colitis, as also found by earlier

Australian, New Zealand and Canadian studies,[5,7,17-19] but not by older studies from Scandinavia and North America.[20-22] These differences are consistent with observations over the past fifty years that the incidence of ulcerative colitis had increased but then plateaued, while that of Crohn's disease has continued to increase.[23]

Table 2.7. Comparison of historical population based data on inflammatory bowel disease prevalence rates (per 100 000 population)

First author	Region	Year published	Date of study	All inflammatory bowel disease	Crohn's disease	Ulcerative colitis
Studd[6]	Barwon, Victoria	2016	2010–2011	315	191	115
Gearry[17]	Canterbury, NZ	2006	2004	274	145	122
Bernstein[18]	Canada	2006	1998–2000	473	279	194
Bitton[19]	Canada	2014	2001–2008	441	277	164
Jacobsen[20]	Denmark	2006	2002	445	151	294
Loftus[21]	Olmsted, USA	2007	2001	388	174	214
Kappelman[22]	USA	2007	2003–2004	444	201	238
Bhatia[7]	Tasmania	2019	2013–2014	304	166	131
Jones[9]	Lothian, Scotland	2019	2018	784	284	432

Our prevalence rates are slightly higher than reported by earlier Australian studies for mixed urban and rural populations.[6,7] The difference is probably attributable to a time-cohort effect (cumulative increase in number of IBD cases over time), but our higher rate may be related to the urban nature of our sample. A systematic review and meta-analysis found that the risks

of Crohn's disease (incidence rate ratio [IRR], 1.42; 95% CI, 1.26–1.60) and ulcerative colitis (IRR, 1.17; 95% CI, 1.03–1.32) were higher for urban than rural residents.[22] Factors that may contribute to greater risk include higher rates of smoking (for Crohn's disease), better hygiene and sanitation, antibiotic use, and air pollution in urban areas, as well as migration of young people from rural to metropolitan regions for education and employment. Further exploration of risk factors associated with urban living that may contribute to the pathogenesis of IBD is required.[24]

Our major finding was that the age-specific prevalence of IBD increased with age. The prevalence rate among people aged 65 years or more was 612 (95% CI, 564–660 cases) per 100 000 population, and 380 (95% CI, 342–418 cases) per 100 000 people under 65 years of age; 79 patients with IBD (22%) were 65 years or more old, compared with 12 916 of 88 015 people (14.7%) in the City of Canada Bay population. We also found that the prevalence of IBD among people aged 85 years or more was 891 per 100 000 people. Both rates are higher than the 483 cases per 100 000 people for age 65 years or more reported by an earlier Australian study, which found that IBD prevalence increased from the age of 15–24 years, and was highest among those aged 25–54 years and people aged 65 years or more.[6] Our differing finding is probably attributable to a cumulative increase in the number of IBD cases over time. A Canadian study found that the prevalence of ulcerative colitis was highest among people aged 40–49 years, but was similar for older age groups.[19] Findings from other studies have been heterogeneous; some North American studies reported, like us, a steady increase in IBD prevalence with age, particularly of ulcerative colitis.[18,22] As ulcerative colitis is more common among non-smokers, these patients may have lower mortality, as they are healthier than the age-matched general population, as previously reported.[25]

The rising prevalence of IBD with age is important for management strategies, including the use of immunosuppressive medications that exacerbate the risks of infections and malignancies in older people.[26] Accurate prevalence rates allow health care administrators to efficiently plan for investigating IBD and managing patients. Our findings highlight the importance of safer therapies, appropriate cancer screening, and taking comorbid conditions into account when managing older people with IBD.[27] Systemic immunosuppressive therapies should be de-escalated when possible, and newer biological agents less likely to lead to sepsis, such as ustekinumab and vedolizumab, should be considered.[26]

The demographic features of the City of Canada Bay are similar to those of Greater Sydney, NSW, and Australia (Table 2.8), except for higher proportions than the Australian population of people with Chinese (17% *v* 5.2%) or Italian ancestry (15% *v* 4.3%). Extrapolating the IBD prevalence rate in Canada Bay would suggest that 16 797 people in Greater Sydney, 26 046 in NSW, and 81 485 in Australia live with IBD. By way of comparison, it was estimated in 2013 that the number of people in Australia living with IBD in 2016 would lie in the range 72 805–89 502.[6]

Table 2.8. Comparison of population demographic features and estimated numbers of cases of inflammatory bowel disease, based on City of Canada Bay data[28]

	City of Canada Bay	Greater Sydney	New South Wales	Australia
Estimated number of patients with inflammatory bowel disease	364	16,797	26,046	81,485
Population	88,015	4,823,991	7,480,228	23,401,892
Males	48.1%	49.3%	49.3%	49.3%
Median age	36.0	36.2	38.0	38.0
Born overseas	40.5%	42.9%	34.5%	33.3%
Indigenous Australians	0.5%	1.3%	2.9%	2.8%
Occupation: professionals	33.1%	26.3%	23.6%	22.2%
Unemployment	5.0%	6.0%	6.3%	6.9%

Strengths and limitations

We fully characterised all included patients to confirm diagnoses according to the Copenhagen and revised Porto criteria. Duplication of cases was avoided by uniquely identifying each case. Phenotypic details were available for all but two patients, perhaps explaining the larger proportion of IBD-U patients than in other studies. In contrast, detailed information on disease location in another Australian study was available for only 350 of 579 patients with prevalent Crohn's disease (60%).[5]

Limitations include the fact that we undertook a retrospective review of medical records, and we may have missed patients who sought gastroenterology care outside the City of Canada Bay. Mild cases of IBD may be managed by family physicians, but they do not usually manage IBD without involving a specialist gastroenterologist.[29] We used different search methods to

reduce selection bias, including searches of paper medical records and for keywords in electronic medical records. Further, we selected an area with a small population compared with some other studies. However, the smaller population facilitated full case ascertainment in a metropolitan area, an approach not previously undertaken in Australia. The ethnic background, socio-economic status, and urban nature of our population may affect the generalisability of our findings to Australia as a whole. Finally, undiagnosed IBD is possible, as the median time from symptom onset to diagnosis is 4 months for ulcerative colitis and 9 months for Crohn's disease.[30]

2.5 CONCLUSION

In the first IBD prevalence study in New South Wales, the most populous state in Australia, we found that its prevalence was high in the City of Canada Bay, particularly among people aged 65 years or more. The high age-specific IBD prevalence in the middle-aged and older people has important implications for treatment decisions.

2.6 REFERENCES

1. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2018; 390: 2769-2778.
2. Coward S, Clement F, Benchimol EI, et al. Past and future burden of inflammatory bowel disease based on modeling of population-based data. Gastroenterology 2019; 156: 1345-1353.
3. Ng SC, Tang W, Ching JY, et al; Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS) Study Group. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiological study. Gastroenterology 2013; 145: 158-165.
4. Ray K. IBD: the changing epidemiology of IBD. Nat Rev Gastroenterol Hepatol 2017; 14: 690.
5. PricewaterhouseCoopers Australia; Crohn's and Colitis Australia. Improving inflammatory bowel disease care across Australia. Mar 2013. https://www.crohnsandcolitis.com.au/site/wp-content/uploads/PwC-report-2013.pdf (viewed June 2020).
6. Studd C, Cameron G, Beswick L, et al. Never underestimate inflammatory bowel disease: high prevalence rates and confirmation of high incidence rates in Australia. J Gastroenterol Hepatol 2016; 31: 81-86.
7. Bhatia R, Yeoh SW, Vaz K, et al. Inflammatory bowel disease incidence, prevalence and 12-month initial disease course in Tasmania, Australia. Intern Med J 2019; 49: 622-630.
8. Ng SC, Kaplan GG, Tang W, et al. Population density and risk of inflammatory bowel disease: a prospective population-based study in 13 countries or regions in Asia–Pacific. Am J Gastroenterol 2019; 114: 107-115.
9. Jones GR, Lyons M, Plevris N, et al. IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. Gut 2019; 68: 1953-1960.
10. City of Canada Bay Council. Welcome to the City of Canada Bay: community profile. Updated Oct 2016. http://profile.id.com.au/canada-bay/about (viewed Nov 2016).
11. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005; 19 (Suppl A): 5A-36A.
12. Munkholm P. Crohn's disease: occurrence, course and prognosis. An epidemiologic cohort-study. Dan Med Bull 1997; 44: 287-302.
13. Langholz E. Ulcerative colitis. An epidemiological study based on a regional inception cohort, with special reference to disease course and prognosis. Dan Med Bull 1999; 46: 400-415.
14. Levine A, Koletzko S, Turner D, et al; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr 2014 ; 58: 795-806.
15. Ahmad OB, Boschi-Pinot C, Lopez AD, et al. Age standardization of rates: a new WHO standard (GPE Discussion paper series: No. 31). Geneva: World Health Organization, 2001. http://who.int/healthinfo/paper31.pdf (viewed Sept 2019).
16. Keyfitz N. Sampling variance of standardized mortality rates. Hum Biol 1966; 38: 309-317.

17. Gearry RB, Richardson A, Frampton C, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. Inflamm Bowel Dis 2006; 12: 936-943.
18. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol 2006; 101: 1559-1568.
19. Bitton A, Vutcovici M, Patenaude V, et al. Epidemiology of inflammatory bowel disease in Quebec: recent trends. Inflamm Bowel Dis 2014; 20: 1770-1776.
20. Jacobsen BA, Fallingborg J, Rasmussen HH, et al. Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978–2002. Eur J Gastroenterol Hepatol 2006; 18: 601-606.
21. Loftus CG, Loftus EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. Inflamm Bowel Dis 2007; 13: 254-261.
22. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol 2007; 5(12): 1424-1429.
23. Ng SC, Bernstein CN, Vatn MH, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. Gut 2013; 62: 630-649.
24. Soon IS, Molodecky NA, Rabi DM, et al. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. BMC Gastroenterol 2012; 12: 51.
25. Selinger CP, Andrews J, Dent OF, et al. Cause-specific mortality and 30-year relative survival of Crohn's disease and ulcerative colitis. Inflamm Bowel Dis 2013; 19: 1880-1888.
26. Pudipeddi A, Kariyawasam V, Haifer C, et al. Safety of drugs used for the treatment of Crohn's disease. Expert Opin Drug Saf 2019; 18: 357-367.
27. Kariyawasam VC, Kim S, Mourad FH, et al. Comorbidities rather than age are associated with the use of immunomodulators in elderly-onset inflammatory bowel disease. Inflamm Bowel Dis 2018; 25: 1390-1398.
28. City of Canada Bay Council. Welcome to the City of Canada Bay: community profile. Updated Oct 2016. http://profile.id.com.au/canada-bay/about
29. Tan M, Holloway RH, Lange K, et al. General practitioners' knowledge of and attitudes to inflammatory bowel disease. Intern Med J 2012; 42: 801-807.
30. Vavricka SR, Spigaglia SM, Rogler G, et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. Inflamm Bowel Dis 2012; 18: 496-505.

Chapter 3

Sequencing of infliximab and vedolizumab in moderate-to-severe ulcerative colitis

This chapter is a reproduction of the published manuscript "Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study" by Pudipeddi et al.

Journal reference:

- Pudipeddi A, Ko Y, Paramsothy S, Leong R. Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Therap Adv Gastroenterol* 2022; Mar 8;15:17562848221080793

Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study

Authors

Aviv Pudipeddi[1,2] MBBS (Hons 1), FRACP

Yanna Ko[1,2] MBBS

Sudarshan Paramsothy[1,2] BSc(Med), MBBS (Hons 1), MRCP (UK), FRACP, PhD

Rupert W Leong[1,2] MBBS, FRACP, MD, AGAF

for the PANIC Study Group – Persistence in Australian National IBD Cohort

Affiliations

[1]Gastroenterology and Liver Services, Concord Repatriation General Hospital, Sydney, Australia

[2]Faculty of Medicine and Health, Concord Clinical School, The University of Sydney, Sydney, Australia

Corresponding Author

Prof Rupert Leong

Concord Repatriation General Hospital, Hospital Road, Concord NSW 2139, Australia

Tel: 612 97676111 Fax: 612 97676767 rupertleong@outlook.com

Word Count: 3197

ABSTRACT

Background: The choice between infliximab (IFX) and vedolizumab (VED) as a first-line biological agent in moderate-to-severe ulcerative colitis (UC) can be difficult. Second-line vedolizumab (VED) efficacy may decline following prior infliximab (IFX) treatment failure in UC patients. However, it is not known whether second-line IFX efficacy declines after failure of first-line VED.

Aims: We aimed to compare first-line and second-line persistence of IFX and VED, in particular whether second-line IFX persistence declines after failure of first-line VED.

Methods: Persistence of IFX and VED was analysed from the Australian Pharmaceutical Benefits Scheme registry data as either first- or second-line treatment in UC. Propensity score matching (1:1) was conducted in the comparison of first-line treatments. Cox proportional hazard regression analysis was used to identify significant predictors and expressed as a hazard ratio (HR and 95%CI).

Results: There were 420 subjects with moderate-severe UC who received either first-line IFX (n=251) or VED (n=169), with 774 patient-years of follow up. First-line VED had significantly longer persistence than first-line IFX (>50.2 versus 22.2 months, *P*=0.001). 53 subjects failed first-line IFX and swapped to second-line VED (IFX→VED group). 22 subjects failed first-line VED group and swapped to second-line IFX (VED→IFX group). First-line VED persistence was significantly longer than second-line VED (>50.2 versus 32.0 months, *P*=0.03), but first-line IFX persistence was not statistically significantly different to second-line IFX (27.6 months versus >38.6 months, *P*=0.30). Immunomodulator co-therapy was significantly associated with a lower risk of non-persistence of first-line VED (HR: 0.55,95%CI: 0.33-0.89, *P*=0.02) and IFX (HR: 0.63,95%CI: 0.33-0.92, *P*=0.02).

Conclusions: VED had a significantly longer persistence than IFX as first-line biological agent but does not disadvantage second-line IFX use in moderate-to-severe UC. VED after IFX is associated with significantly poorer persistence. VED, therefore, should be considered as the first-line biological agent of choice in UC.

KEYWORDS

Infliximab, vedolizumab, ulcerative colitis, sequencing

3.1 INTRODUCTION

Ulcerative colitis (UC) is an increasingly prevalent chronic inflammatory bowel disease (IBD) with 15% of patients having an aggressive disease course.[1,2] The cumulative risk of relapse is 70%-80% at 10-years[2] and as such, many patients require maintenance treatment with an advanced therapy.[3] Recent guidelines recommend the use of infliximab (IFX) or vedolizumab (VED) as a first-line biological agent for patients with moderate-to-severe UC who are naïve to biological therapy.[4] However, 10-40% of patients have a primary non-response to IFX, whilst 23-46% of patients have a secondary loss of response to IFX at 12-months after induction.[5] Furthermore, 35% of patients lose response to VED at 12-months.[6] Therefore, many patients will switch to a second-line biological agent. VED may be less effective in those who have failed prior anti-tumour necrosis factor-alpha (anti-TNFα) therapy including IFX.[7,8] The effectiveness of second-line IFX after failure of VED, however, is less well-known. The optimal sequencing of these agents as first- and second-line agents is a key knowledge gap that requires addressing to reduce disease burden.[9]

Treatment persistence measures continuing medication prescription based on ongoing therapeutic efficacy in the absence of significant adverse effects.[10] Persistence reflects willingness by patient and their physician to continue a medication in the absence of therapeutic failure or a better treatment alternative.[11] Importantly, it reflects real-world practice that allows for treatment optimisation including dose-adjustment, addition of temporary induction treatments and other strategies. The rate of failure and duration of persistence for various drugs are different, and provides important comparative efficacy data given the paucity of head-to-head trials of advanced therapies in UC.[10,12]

Persistence data, in some respects, may be even more informative than head-to-head trials. Population-based persistence data are cost-efficient and might include sufficient statistical power to identify clear clinical differences through long-term follow-up. Persistence data may be similar to clinical drug trials in that both have strict inclusion and exclusion eligibility criteria, collect data prospectively, include data on prior- or ongoing use of conventional and biological agents, and are multi-centre and generalizable. The Persistence in Australian National IBD Cohort (PANIC) is a large real-world national population-based registry with 8219 patient-years of follow-up, in which biological agents were fully funded without stipulated hierarchical prescribing order.[13] Hence this database allows for an objective comparison of persistence between biological agents.

The primary aim of this population-based prospective study was to compare the persistence of IFX and VED as first- and second-line therapies, including second-line IFX following VED failure versus first-line IFX use. Factors affecting the persistence of these biological agents were examined.

3.2 METHODS

3.2.1 Study population

Consecutive adult subjects (aged ≥18 years) prescribed IFX or VED for the treatment of moderate-severe UC were included. The diagnosis of moderate-severe UC had to be definite using the Copenhagen diagnostic criteria[14] and we excluded biological agents prescribed to treat acute severe UC, Crohn's disease or rheumatological/dermatological indications.

3.2.2 Study design and data source

The Persistence Australian National IBD Cohort (PANIC) study used prospective script data collected from the Australian Pharmaceutical Benefits Scheme (PBS) database from December 2014 to September 2019. This included immunomodulator (azathioprine, mercaptopurine or methotrexate) and biological agent use and dates of prescription. Immunomodulator co-therapy was defined as the use of an immunomodulator during the same time period of a biological agent prescription. The PBS subsidises treatment with biological agents under the National Health Act 1953. Patients with UC and a partial Mayo score of ≥6 are provided biological agents at no cost if they fail to achieve adequate treatment response following a 3-month course of mesalazine and either 3-months of thiopurine (or shorter due to toxicity) or at least a 6-week course of a corticosteroid.[15] Following induction therapy, demonstration of response to PBS subsidised treatment must be conducted 6-monthly in order to continuing maintenance treatment. The PBS does not enforce hierarchical prescribing order so there is no need to prescribe anti-TNFα agents or biosimilars prior to VED. Script data was linked to the patients' unique Medicare number. Data was analysed using a 10% random sample, which is a standardised accepted strategy[13]. PBS data were acquired and collated by an independent provider (Model Solutions, Australia) and validated through a second provider to ensure robustness of data. All analyses, however, were performed by the researchers.

3.2.3 Study definitions

Persistence was defined as the duration of time from initiation to discontinuation of biological therapy for moderate-to-severe UC.[11] Non-persistence was defined as discontinuation of that agent, and represented objectively as a switch in- or out-of biological class or complete cessation. Persistence rate was the proportion of patients who continued on a biological agent

at a particular time point. Immunomodulator co-therapy was defined as the concurrent use of a thiopurine or methotrexate during the period of biological agent use.

3.2.4 Sample size calculation

Sample size calculation was based on results from a retrospective real-world study that found a persistence rate of 78% for VED patients and 64% for IFX patients with IBD at 24-months.[16] Assuming a two-sided alpha of 0.05 and a power of 80%, a total of 249 IFX and 166 VED patients would be required at a ratio of 3 IFX patients to every 2 VED patients. The 3:2 ratio of IFX:VED was based on PBS biological agent prescription use for UC in Australia.[17]

3.2.5 Study outcomes, propensity score matching and statistical analysis

Baseline characteristics of continuous variables were described as medians with interquartile ranges (IQR). Categorical variables were described as percentages. Outcomes comparing the persistence of first-line and second-line IFX and VED were analysed using unadjusted Kaplan-Meier survival curves and statistically significant differences in persistence were identified using the log-rank test. Cox proportional hazard regression was used to identify factors affecting persistence, adjusting for covariates and described as hazard ratios (HR) and 95% confidence intervals (CI). Secondary outcomes included comparing the persistence rates between each biological agent at 12-, 24-, 36- and 48 months using Chi-square testing. We also analysed the persistence of first-line IFX and VED stratified by immunomodulator co-therapy using unadjusted Kaplan-Meier survival curves and log-rank testing. Propensity score matching was also performed in first-line therapy comparisons to control for age and gender as possible confounders of medication persistence. Using the propensity scores, first-line VED patients were matched with first-line IFX patients using a 1:1 matching algorithm, with a

proximity caliper of 0.1. A *P* value of <0.05 was considered statistically significant. Bonferroni correction was applied in the setting of multiple comparisons during analysis of persistence rates. Statistical analysis was performed using IBM SPSS software version 27.0 (SPSS Inc., Chicago, III., USA).

3.2.6 Ethics approval

The study was approved by the Services Australia External Request Evaluation Ethics Committee with approval number RMS1531. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

3.3 RESULTS

3.3.1 Study population and baseline characteristics

In total, 420 patients were prescribed either IFX (251 patients) or VED (169 patients) as a first-line biological agent for moderate-severe UC, equating to 774 person-years of follow-up. Males comprised 54.2% (136/251) of the IFX group and 49.7% (84/169) of the VED group (*P*=0.38). The median age of the VED group (44.0 years, IQR: 33.0-56.0) was older than the IFX group (37.0 years, IQR: 28.0-54.0, *P*=0.003). The baseline characteristics of the study population are shown in Table 3.1.

Table 3.1. Baseline characteristics of moderate-severe UC patients using first-line and second line infliximab or vedolizumab

Biological agent	Infliximab n=251	Vedolizumab n=169	*P*-value
Male, n (%)	136 (54.2%)	84 (49.7%)	0.38
Median age, years (IQR)	37.0 (28.0 – 54.0)	44.0 (33.0 – 56.0)	0.003
Immunomodulator co-therapy, n (%)	160 (63.7%)	80 (47.3%)	0.001
Thiopurine, n (%)	145 (57.8%)	75 (44.4%)	0.01
Methotrexate, n (%)	21 (8.4%)	7 (4.1%)	0.09
Time on combination therapy between biological agent and immunomodulator, months (IQR)	17.3 (5.1 – 27.6)	13.3 (3.6 – 17.5)	0.03

n, number; IQR, interquartile range.

Figure 3.1 illustrates the PBS prescription of IFX and VED as first-line and second-line biological agents. From the 251 patients who used IFX as a first-line biological agent, 53 used VED as a second-line biological agent (IFX→VED group). From the 169 patients who used VED as a first-line biological agent, 22 used IFX as a second-line biological agent (VED→IFX group). The baseline characteristics of the IFX→VED and VED→IFX groups are shown in Table 3.2. The median ages of the IFX→VED and VED→IFX groups were 38.0 years (IQR: 28.5-55.0) and 41.5

years (IQR: 29.5-58.8) respectively (*P*=0.30). 67.9% (36/53) of the IFX→VED group were treated with immunomodulator co-therapy during first-line biological agent use, compared with 36.4% (8/22) of the VED→IFX group (*P*=0.01). 52.8% (28/53) of the IFX→VED group were treated with immunomodulator co-therapy during second-line biological agent use, compared with 50.0% (11/22) of the VED→IFX group (*P*=0.82).

Figure 3.1. Flow diagram of infliximab and vedolizumab choice in moderate-severe UC from PBS

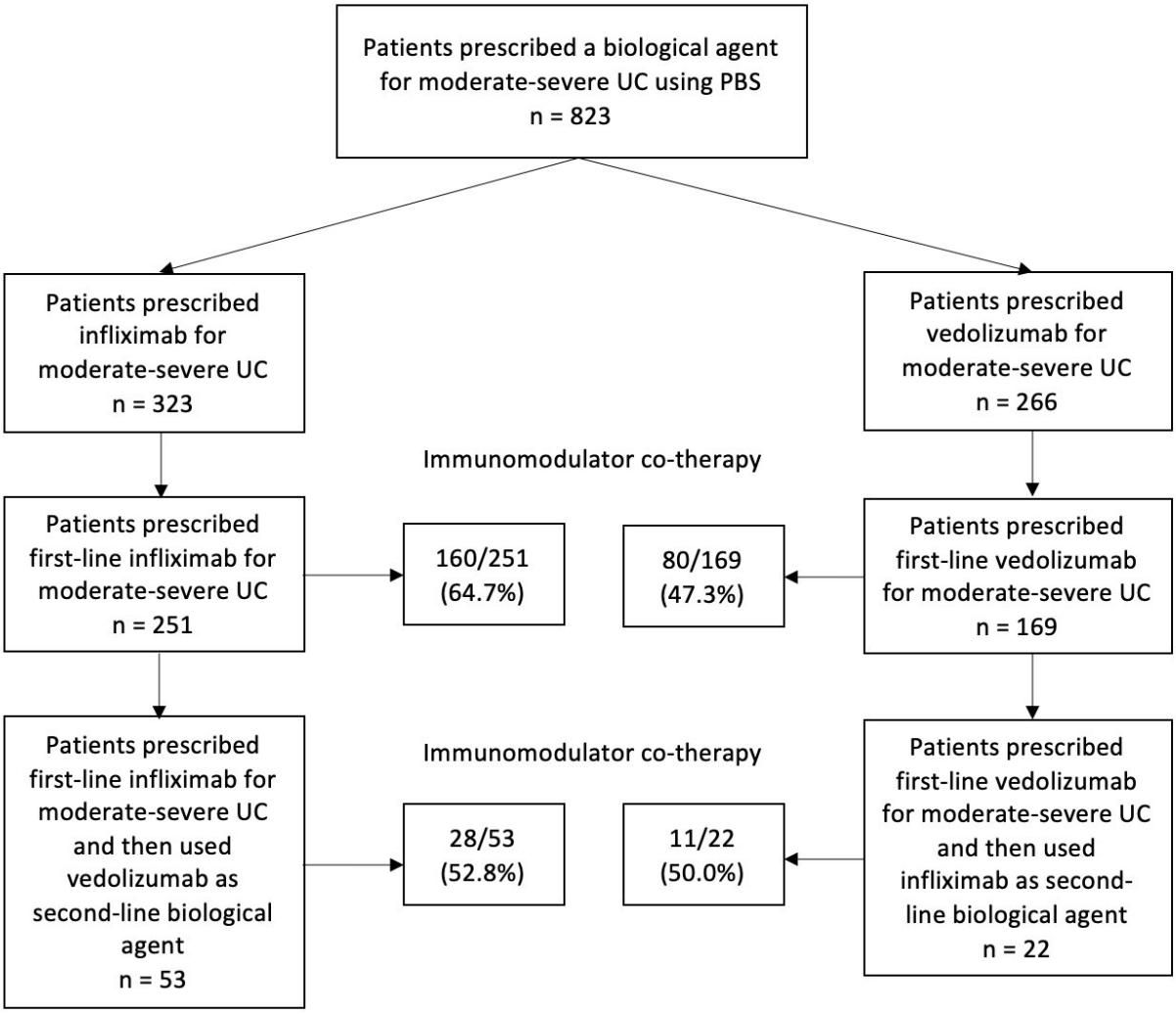


Table 3.2. Baseline characteristics of moderate-severe UC patients using second-line vedolizumab or infliximab (IFX→VED and VED→IFX groups respectively)

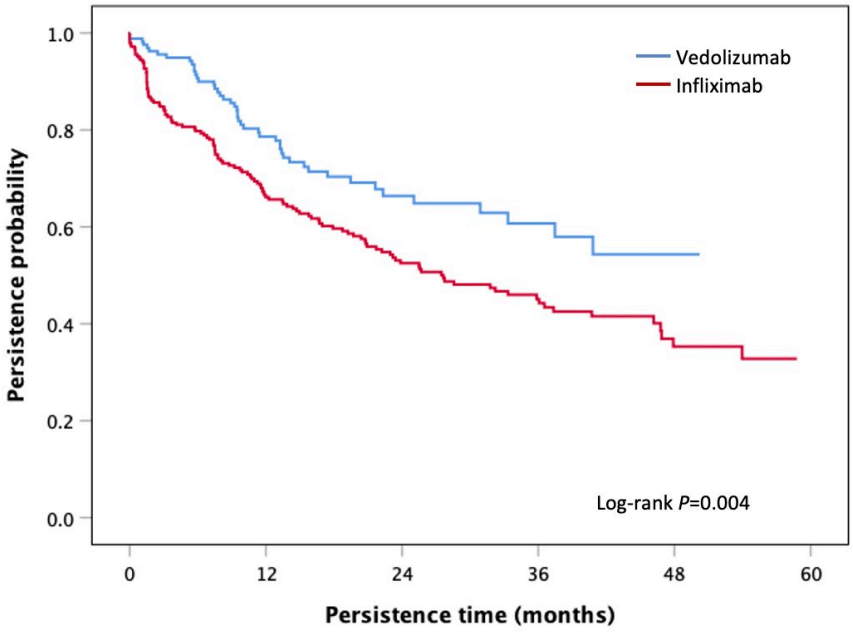
Biological agent	IFX→VED n = 53	VED→IFX n = 22	*P*-value
Male, n (%)	32 (60.4%)	14 (63.6%)	0.79
Median age, years (IQR)	38.0 (28.5 – 55.0)	41.5 (29.5 – 58.8)	0.30
First-line immunomodulator co-therapy	36 (67.9%)	8 (36.4%)	0.01
Second-line immunomodulator co-therapy	28 (52.8%)	11 (50.0%)	0.82

IFX, infliximab; VED, vedolizumab; n, number; IQR, interquartile range.

3.3.2 Persistence of infliximab and vedolizumab as first-line biological agents in moderate-severe ulcerative colitis

VED had a significantly longer persistence than IFX when used as a first-line biological agent in moderate-severe UC (>50.2 months versus 27.6 months [95%CI: 18.7-36.6], *P*=0.004) (Figure 2). VED use was associated with a 43% lower risk of non-persistence than IFX (HR: 0.57, 95%CI: 0.41-0.80, *P*=0.001) (Table 3.3). Persistence rates and their 95% CIs at 12-, 24-, 36- and 48-months are reported in Figure 3.2. Immunomodulator co-therapy use was higher in the IFX group (63.7%, 160/251) than the VED group (47.3%, 80/169; *P*=0.001), and was associated with a 44% lower risk of non-persistence of first-line biological therapy (HR: 0.56, 95%CI: 0.42-0.77, *P*<0.001).

Figure 3.2. Kaplan-Meier curve for persistence of first-line infliximab and vedolizumab in moderate-severe UC



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
Infliximab	66.1 (60.0-72.1)	52.5 (46.3-58.7)	45.1 (38.9-51.3)	35.3 (29.4-41.2)	27.6 (18.7–36.6)
Vedolizumab	78.6 (72.3-84.8)	66.4 (59.3-73.5)	60.7 (53.3-68.1)	54.3 (46.8-61.8)	> 50.2*
P-value†	0.01‡	0.01‡	0.001‡	<0.001‡	

CI, confidence interval

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

†Based on Bonferroni correction, statistical significance defined as $P<0.0125$

‡Statistically significant values

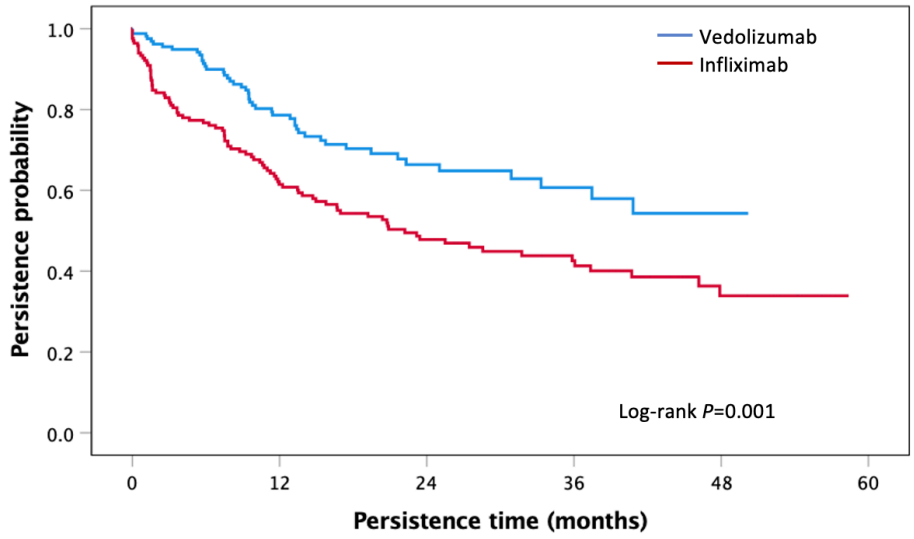
Table 3.3. Predictors of medication non-persistence

First-line biological therapy of vedolizumab and infliximab		
	HR (95% CI)	***P*-value**
Female versus male gender	1.03 (0.76 – 1.39)	0.84
Age	1.00 (0.99 – 1.01)	0.67
VED versus IFX	0.57 (0.41 – 0.80)	0.001
Immunomodulator co-therapy	0.56 (0.42 – 0.77)	<0.001
Second-line biological therapy of infliximab (VED→IFX group) and vedolizumab (IFX→VED) group		
Female versus male gender	0.61 (0.25 – 1.49)	0.28
Age	0.98 (0.96 – 1.01)	0.34
VED versus IFX	1.66 (0.63 – 4.40)	0.31
Immunomodulator co-therapy	0.66 (0.30 – 1.47)	0.31
Vedolizumab use as a first-line or second-line biological therapy		
Female versus male gender	0.85 (0.52 – 1.39)	0.51
Age	1.00 (0.98 – 1.01)	0.59
First-line VED vs second-line VED	0.56 (0.34 – 0.92)	0.02
Immunomodulator co-therapy	0.55 (0.33 – 0.89)	0.02
Infliximab use as a first-line or second-line biological therapy		
Female versus male gender	0.86 (0.59 – 1.25)	0.43
Age	1.00 (0.99 – 1.01)	0.90
First-line IFX vs second-line IFX	1.49 (0.61 – 3.67)	0.39
Immunomodulator co-therapy	0.63 (0.44 – 0.92)	0.02

IFX, infliximab; VED, vedolizumab; HR, hazard ratio; CI, confidence interval

Using propensity score matching, 169 IFX patients were matched with 169 VED patients using age and gender as covariates. VED had a significant longer persistence than IFX as a first-line biological agent (>50.2 months versus 22.2 months, *P*=0.001) (Figure 3.3).

Figure 3.3. Kaplan-Meier curve for persistence of first-line infliximab and vedolizumab in moderate-severe UC using propensity score matching



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
Infliximab	61.5 (52.0-71.0)	47.9 (38.1-57.7)	43.8 (34.1-53.5)	33.9 (24.6-43.2)	22.2 (12.7–31.7)
Vedolizumab	78.6 (72.3-84.8)	66.4 (59.3-73.5)	60.7 (53.3-68.1)	54.3 (46.8-61.8)	> 50.2*
P-value†	<0.001‡	<0.001‡	<0.001‡	<0.001‡	

CI, confidence interval

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

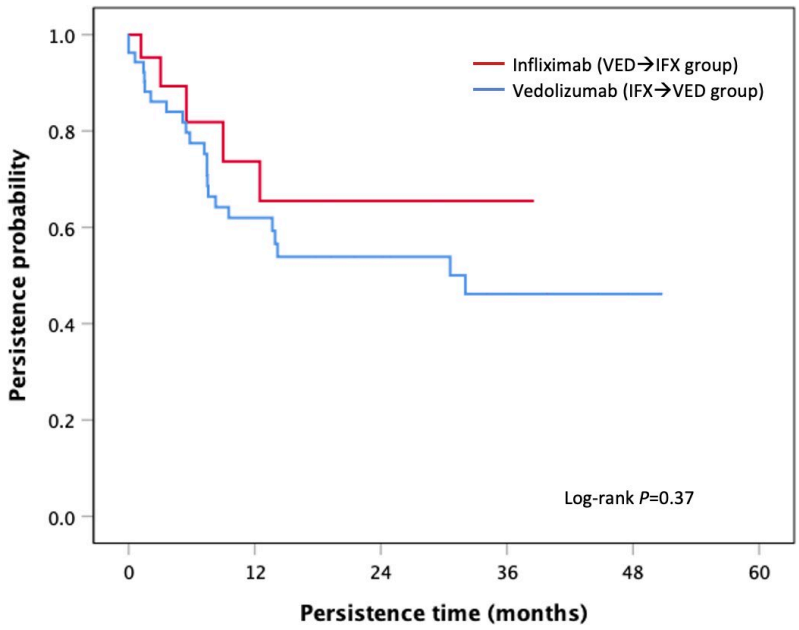
†Based on Bonferroni correction, statistical significance defined as *P*<0.0125

‡Statistically significant values

3.3.3 Persistence of infliximab and vedolizumab as second-line biological agents in moderate-severe ulcerative colitis

There was no difference between the persistence of second-line IFX in the VED→IFX group versus second-line VED use in the IFX→VED group (>38.6 months versus 32.0 months, *P*=0.37, Figure 3.4). However there were numerically higher persistence rates with second-line IFX in the VED→IFX group compared with second-line VED in the IFX→VED group at 12- and 24-months (Figure 3.4). No significant predictors of non-persistence were identified (Table 3.3).

Figure 3.4. Kaplan-Meier curve for persistence of second-line infliximab and vedolizumab in VED → IFX and IFX → VED groups respectively



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
Infliximab	73.7 (68.3-79.1)	65.5 (59.6-71.4)	65.5 (59.6-71.4)	-	> 38.6*
Vedolizumab	62.0 (54.7-69.3)	53.9 (46.4-61.4)	46.2 (38.7-53.7)	46.2 (38.7-53.7)	32.0^
P-value†	0.39	0.48	0.15	n/a	

IFX, infliximab; VED, vedolizumab; CI, confidence interval; n/a, not applicable

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

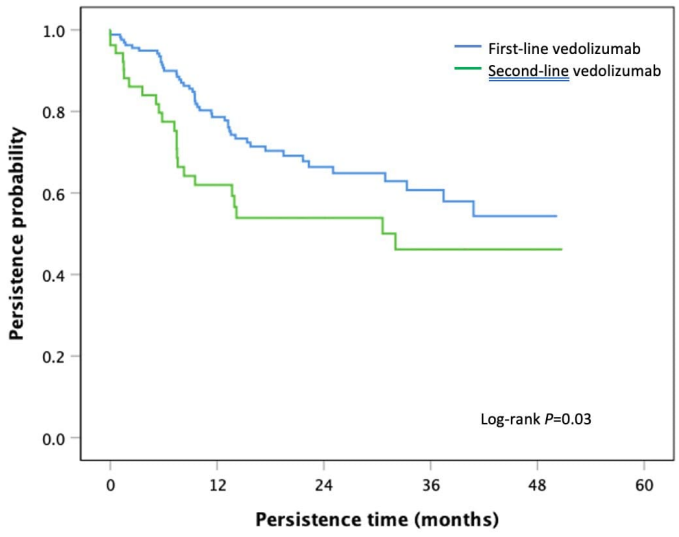
^Unable to compute confidence interval when event rate is higher than 45%

†Based on Bonferroni correction, statistical significance defined as *P*<0.017

3.3.4 Persistence comparison between first-line vedolizumab and second-line vedolizumab

First-line VED use had a significantly longer persistence than when used as a second-line biological agent (>50.2 months versus 32.0 months, *P*=0.03, Figure 3.5). First-line VED use was associated with a 44% lower risk of non-persistence compared with second-line VED use (HR: 0.56, 95%CI: 0.34-0.92, *P*=0.02). Persistence rates at 12-, 24-, and 36-months between first-line VED and second-line VED are shown in Figure 3.5. Immunomodulator co-therapy occurred in 47.3% (80/169) of the first-line VED group versus 52.8% (28/53, *P*=0.49) of the second-line VED group, and was associated with a 45% lower risk of non-persistence of VED therapy (HR: 0.55, 95%CI: 0.33-0.89, *P*=0.02).

Figure 3.5. Kaplan-Meier curve for persistence of first-line vedolizumab compared with second-line vedolizumab in moderate-severe UC



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	Time in months (95% CI)
First-line VED	78.6 (72.4-84.8)	66.4 (59.3-73.5)	60.7 (53.3-68.1)	54.3 (46.8-61.8)	> 50.2*
Second-line VED	62.0 (48.9-75.1)	53.9 (40.5-67.3)	46.2 (32.8-59.6)	-	32.0^
P-value†	0.02	0.13	0.04	n/a	

CI, confidence interval; VED, vedolizumab; n/a, not applicable

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

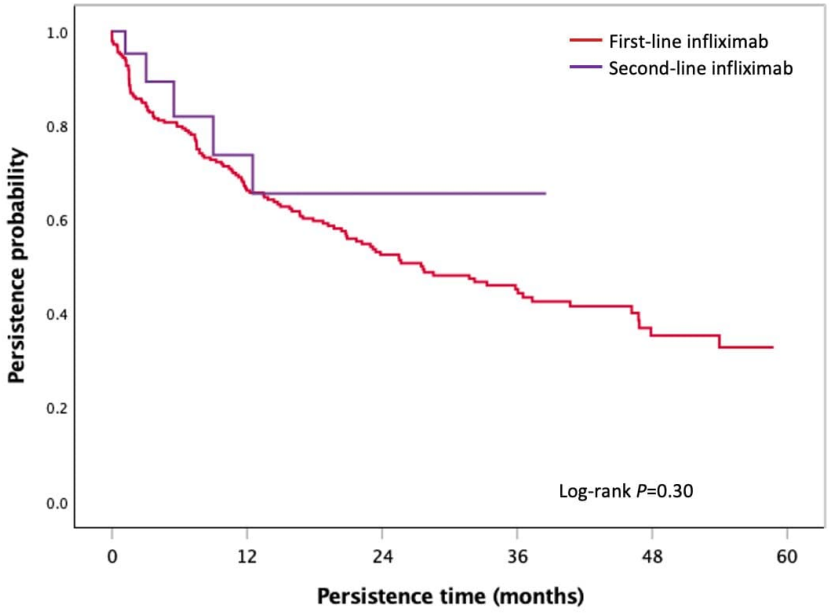
^Unable to compute confidence interval when event rate is higher than 45%

†Based on Bonferroni correction, statistical significance defined as *P*<0.017

3.3.5 Persistence comparison between first-line infliximab and second-line infliximab

There was no significant difference between first-line IFX and second-line IFX persistence (27.6 months [95%CI: 18.7-36.6] versus >38.6 months, *P*=0.30, Figure 3.6). The use of IFX as a first- versus second-line agent did not significantly predict for non-persistence (HR: 1.49, 95%CI 0.61-3.67, *P*=0.39). Immunomodulator co-therapy occurred in 64.7% (160/251) of the first-line IFX group versus 50.0% (11/22, *P*=0.20) of the second-line IFX group, and was associated with a 37% lower risk of non-persistence of IFX therapy (HR: 0.63, 95%CI: 0.44-0.92, *P*=0.02).

Figure 3.6. Kaplan-Meier curve for persistence of first-line infliximab compared with second-line infliximab in moderate-severe UC



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
First-line IFX	66.1 (60.2-71.9)	52.5 (46.3-58.7)	45.1 (38.9-51.3)	35.3 (29.4-41.2)	27.6 (18.7–36.6)
Second-line IFX	73.7 (55.3-92.1)	65.5 (45.6-85.4)	65.5 (45.6-85.4)	-	> 38.6*
P-value†	0.53	0.32	0.09	n/a	

CI, confidence interval; IFX, infliximab; n/a, not applicable

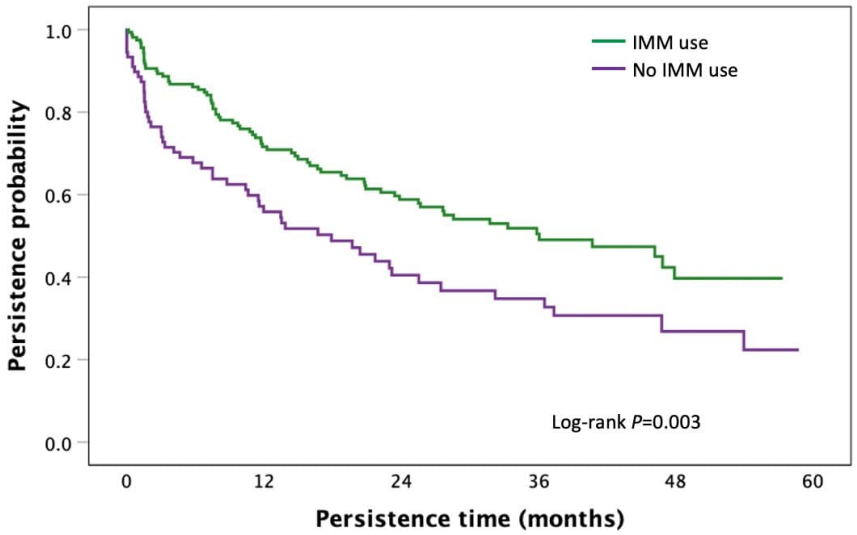
*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

†Based on Bonferroni correction, statistical significance defined as *P*<0.017

3.3.6 Persistence of infliximab and vedolizumab stratified by immunomodulator use

First-line IFX and first-line VED had a significantly longer persistence when used in combination with an immunomodulator compared with monotherapy (36.0 months [95%CI: 22.4-49.8] versus 17.9 months [95%CI: 8.8-26.9], *P*=0.003 for IFX group; > 50.2 months versus 40.8 months [95%CI: 10.3-71.3], *P*=0.02 for VED group, Figure 3.7 and Figure 3.8). There was no significant difference in persistence between second-line IFX (*P*=0.95) and VED (*P*=0.30) when stratified by immunomodulator co-therapy (Figure 3.9 and Figure 3.10).

Figure 3.7. Kaplan-Meier curve for persistence of first-line infliximab stratified by immunomodulator co-therapy in moderate-severe UC

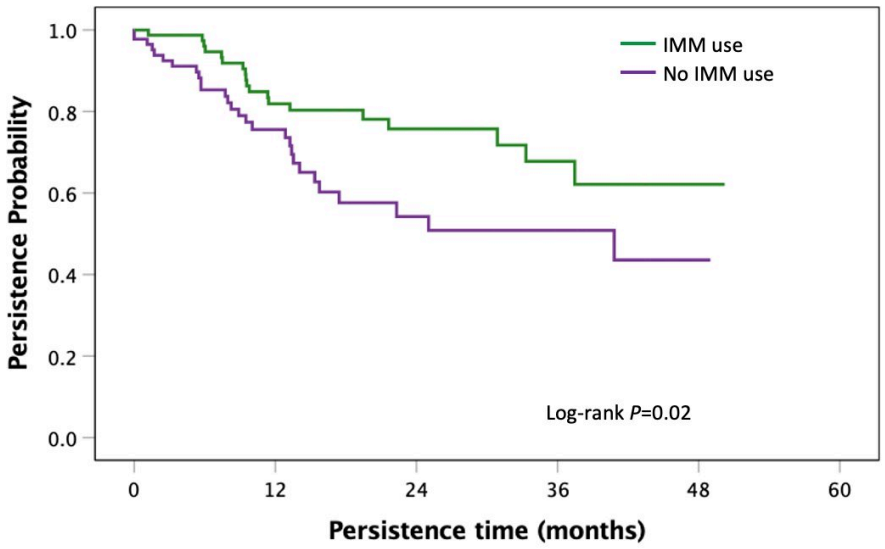


	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
IMM use	71.6 (62.8-80.4)	58.8 (49.2-68.4)	50.5 (40.7-60.3)	39.7 (30.1-49.3)	36.0 (22.4-49.8)
No IMM use	55.8 (46.4-65.2)	40.5 (30.9-50.1)	34.8 (25.5-44.1)	26.9 (18.2-35.6)	17.9 (8.8-30.0)
P-value†	0.04	0.03	0.07	0.06	

CI, confidence interval; IMM, immunomodulator;

†Based on Bonferroni correction, statistical significance defined as *P*<0.0125

Figure 3.8. Kaplan-Meier curve for persistence of first-line vedolizumab stratified by immunomodulator co-therapy in moderate-severe UC



	Persistence Percentage (95%CI) (%)				Median survival time in months
	12 months	24 months	36 months	48 months	
IMM use	81.9 (74.7-89.4)	75.7 (67.3-84.1)	67.8 (58.7-77.0)	62.1 (52.6-71.6)	> 50.2*
No IMM use	75.6 (67.2-84.0)	54.2 (44.4-64.0)	50.8 (41.0-60.6)	43.6 (33.9-53.3)	40.8 (10.3-71.3)
P-value†	0.62	0.17	0.25	0.26	

CI, confidence interval; IMM, immunomodulator;

*The median survival or its confidence interval cannot be calculated when event rate is higher than 50%.

†Based on Bonferroni correction, statistical significance defined as $P<0.0125$

Figure 3.9. Kaplan-Meier curve for persistence of second-line infliximab stratified by immunomodulator co-therapy in moderate-severe UC

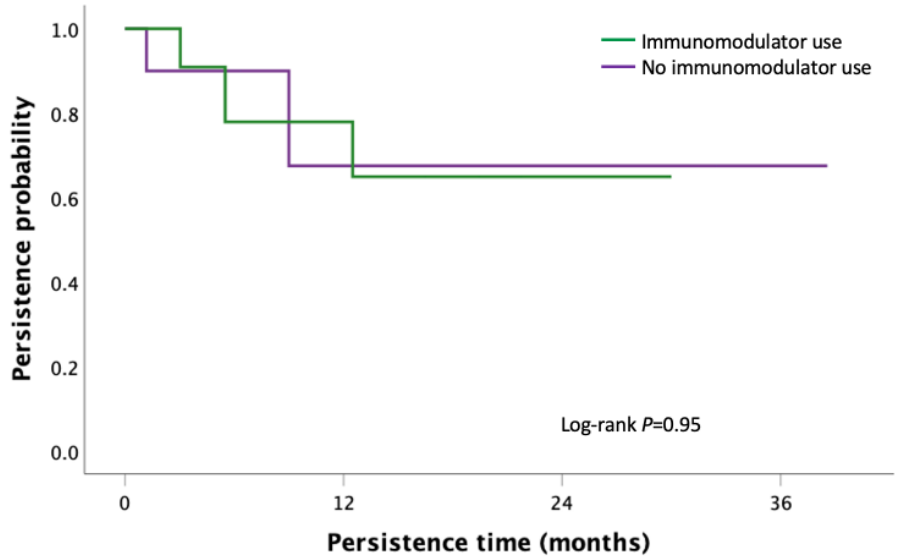
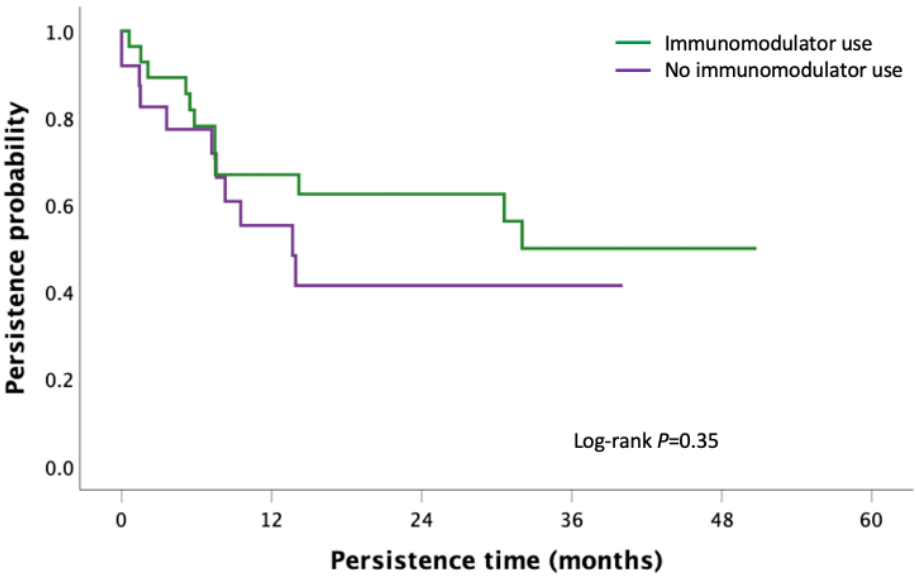


Figure 3.10. Kaplan-Meier curve for persistence of second-line vedolizumab stratified by immunomodulator co-therapy in moderate-severe UC



3.4 DISCUSSION

In this large population-based prospective registry providing 774 patient-years of real-world follow-up, the persistence of VED was significantly longer than IFX as a first-line biological agent in moderate-to-severe UC. Persistence of second-line IFX after VED-exposure was not significantly impaired when compared against second-line VED after IFX-exposure. First-line VED persistence had significantly longer persistence than second-line VED. There was no significant difference in persistence between first-line IFX and second-line IFX. These data support the use of VED as first-line biological treatment in moderate-to-severe UC given the longer persistence when used first-line and the decline in persistence when used second-line. Conversely IFX persistence when used as a second-line agent after switch from VED was not impaired.

There is a lack of data on the long-term effectiveness of biological agents in UC, and persistence data provides an indirect approach for assessing the long-term therapeutic benefit and safety of therapies.[19] The VARSITY study recently demonstrated that VED was superior to adalimumab in achieving clinical remission and endoscopic improvement, however, there are no direct comparisons between IFX and VED.[12] In the absence of head-to-head comparisons between IFX and VED, real-world persistence data acts as a surrogate marker for treatment efficacy, safety and acceptability by patients and physicians.[19] Our results demonstrate significantly greater persistence of first-line VED over first-line IFX in both short term (12-months) and the longer term (24-, 36- and 48-months) (Figure 3.2). The results from this PANIC study are supported by a retrospective study which also demonstrated that VED had higher persistence rates than IFX in biological-naïve IBD patients.[16] The addition of propensity score matching was relevant due to the significant increased age of VED subjects compared to IFX

in the PANIC registry. We previously demonstrated the increasing age of IBD subjects in developed countries[1] and for age to be a significant determinant in the deciding a biological agent in IBD.[20] Therefore, propensity score matching was performed to reduce the selection bias associated with older age and the risk of adverse effects.[21]

Consistent with other studies[7,8], we found VED had significantly longer persistence when used as a first-line agent versus second-line use following IFX failure. To our knowledge, however, there are no data comparing second-line biological agents in IFX→VED with VED→IFX sequences. There is a need to explore the correct positioning of biological agents, as less than half of all UC patients continue their first-line biological agent after 1 year.[19] The persistence of second-line IFX (after VED-exposure) of 65.5% (95%CI: 59.6-71.4%) compared against second-line VED of 46.2% (95%CI: 38.7-53.7%) at 36 months (*P*=0.15, Figure 3.3) suggests a trend of IFX being a better second-line agent than VED. There have been no studies that evaluated persistence up to 3-years previously with others limited to only 6-months of follow-up.[22,23] The persistence of IFX was not dissimilar when used first-line or second-line following VED.

Second-line IFX use was not reduced following first-line VED, as supported by the EVOLVE study which also found that anti-TNF effectiveness may not be compromised by prior VED exposure.[24] However, our study found that VED persistence reduced following IFX therapy.[7,8] A possible explanation is a pharmacokinetic impact of prior IFX exposure on VED trough levels, with one study noting lower VED trough levels at week 6 compared with biological-naïve patients (22.5 vs. 36.0 μg/ml, *P*=0.03).[25] Previous research has also demonstrated that MAdCAM-1 is downregulated by TNFα blockade, so prior IFX-exposed patients may need

higher doses of vedolizumab to bind a higher target burden.[26] These detectable biological changes, therefore, support VED to be considered as a first-line biological agent in moderate-severe UC, followed by IFX as a second-line agent. However further comparative studies are required.

Immunomodulator use improved the persistence of first-line IFX and first-line VED. Immunomodulator co-therapy is known to reduce immunogenicity and improve the persistence and effectiveness of IFX.[13] However, the benefit of combination immunotherapy with VED is less clear. This is the first study to demonstrate the increased persistence of first-line VED when combined with immunomodulators through the use of prospectively collected data for immunomodulators in our PANIC registry. We found larger differences in persistence rates between combination VED and immunomodulator co-therapy versus VED monotherapy after 12-months of VED use, suggesting a greater benefit with long-term follow-up. Other studies suggest a lack of advantage of combination therapy versus monotherapy but were limited to 6-12-months of data and may not have verified ongoing immunomodulator use.[27] The smaller sample size of the EVOLVE study (22 patients in the combination group) identified numerically higher persistence in the combination group at 18- and 24-months but might be underpowered to demonstrate statistical significance.[28] It is possible that newer monoclonal antibodies, although less immunogenic than older anti-TNFα agents, are still complex glycoproteins that may result in the eventual development of antibodies. Additive anti-inflammatory effects of immunomodulators with VED are also possible. A prospective study primarily focusing on the benefits of combination therapy with VED is recommended.

This study has limitations. Firstly, this study was not a randomised controlled trial controlling for patient characteristics and disease severity. However, there is no proposed randomised controlled trial of IFX versus VED currently planned, and it would not be possible to include a sufficient sample size and follow-up duration to be able to follow-up those that require switching to a second-line treatment. Real-world evidence with sufficient patient-years of follow-up may address these data gaps. Secondly, the clinical, biochemical and endoscopic outcomes are not known. Although patients with acute severe UC were excluded, it is possible that patients were prescribed IFX as they had a more severe phenotype, hence biasing the results. However, as only experienced gastroenterologists prescribe these agents in Australia, it is expected that relevant clinical information would be incorporated into any decision to continue or discontinue treatment. The population-based database also means data are not limited to specialised centres so that data can be generalized. Thirdly, data on therapeutic drug monitoring and corticosteroid use are unknown. However, current conventional practice allows for treatment escalation of IFX and VED to be provided under compassionate access at no cost to the hospitals or subjects so it is likely that dose optimisation is performed prior to treatment switching. Whereas clinical trials might deem such dose escalations as treatment failure on intention-to-treat, persistence data allow these subjects to be included and provides a more realistic comparison of treatment efficacy. Ideally, correcting for clinical characteristics beyond age in propensity score matching might further reduce bias in comparing subjects on VED versus IFX. However, age was the most important factor identified previously[18] and subjected to propensity score matching. Also, there was a relatively small number of patients in the second-line groups which may impact on the results. However there is limited available data on second-line use (particularly IFX) so our results will be beneficial. Finally, only a randomly selected ten percent of the population database could be used for analysis due to

national ethical criteria for data accessibility. However, this was a random sampling without selection bias and similar publications were deemed robust given the large patient-years of follow-up.[29]

Strengths include the use of a large, national, population-based study where biological agents are prescribed without a hierarchical prescribing order and are fully reimbursed indefinitely. All subjects had verified Mayo scores of ≥6 which indicates consistency of disease severity. All data were collected prospectively with clinical remission being an absolute requirement for ongoing treatment. Whether treatment escalation was performed or concurrent immunomodulator was used was decided between the clinician and patients consistent with real-world practice. Further, individual switches to other biological agents and immunomodulator co-therapy are prospectively recorded and long-term follow-up data beyond 4-years is an advantage over clinical trials that have relatively short durations of follow-up. The population-based data also means the results are more generalizable. In the absence of large head-to-head studies with long-term follow-up, population-based persistence data can effectively compare the efficacy of IFX versus VED.

3.5 CONCLUSION

In summary, the PANIC cohort with real-world dataset of non-hierarchical prescribing of biological agents supports the use of VED over IFX as a first-line biological agent in moderate-severe UC. Following failure of VED, there is no impact on IFX persistence when used second-line. Immunomodulator treatment significantly increases the persistence of VED, but further

prospective data are required to confirm this observation. Our findings will assist in the positioning of biological therapies in moderate-severe UC.

Declaration of conflicting interests

Aviv Pudipeddi has received speaker fees from Takeda. Yanna Ko reports no conflicts. Sudarshan Paramsothy is a consultant for Finch Therapeutics and received speaker fees from Ferring, Janssen and Takeda. Rupert Leong reports advisory board fees from AbbVie, Aspen, Celgene, Ferring, Gilead, Hospira, Janssen, MSD, Pfizer, and Takeda; research fees from Gastrointestinal Society of Australia (GESA), Endochoice, Janssen, National Health and Medical Research Council of Australia, Shire, and Takeda; and speaker fees from Emerge Health, Ferring, Janssen, Shire, and Takeda.

3.6 REFERENCES

1. Pudipeddi A, Liu J, Kariyawasam V, et al. High prevalence of Crohn disease and ulcerative colitis among older people in Sydney. Med J Aust 2021;214(8):365-370.
2. Fumery M, Singh S, Dulai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol 2018;16(3):343-356.
3. Jeong DY, Kim S, Son MJ, et al. Induction and maintenance treatment of inflammatory bowel disease: a comprehensive review. Autoimmun Rev 2019;18(5):439-454.
4. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology 2020;158(5):1450-1461.
5. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmun Rev 2014;13(1):24-30.
6. Schmidt E, Kochhar G, Hartke J, et al. Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. Inflamm Bowel Dis 2018;24(11):2461-2467.
7. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clin Gastroenterol Hepatol 2017;15(2):229-239.
8. Narula N, Peerani F, Meserve J, et al. Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY consortium. Am J Gastroenterol 2018;113(9):1345.
9. Danese S, Fiorino G, Peyrin-Biroulet L. Positioning therapies in ulcerative colitis. Clin Gastroenterol Hepatol 2020;18(6):1280-1290.
10. Patel H, Lissoos T, Rubin DT. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn's disease in the United States. PLoS ONE 2017;12(4):e0175099
11. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11: 44–47.
12. Sands BE, Peyrin-Biroulet L, Loftus Jr EV, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med 2019;381:1215-1226.
13. Ko Y, Paramsothy S, Yau Y, Leong R. Superior treatment persistence with ustekinumab in Crohn's disease and vedolizumab in ulcerative colitis compared with anti-TNF biological agents: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. Aliment Pharmacol Ther 2021;54(3):292-301.
14. Langholz E. Ulcerative colitis. An epidemiological study based on a regional inception cohort, with special reference to disease course and prognosis. Dan Med Bull 1999; 46: 400-415.
15. Australian Government Services Australia. Ulcerative colitis Adult patient, https://www.servicesaustralia.gov.au/organisations/health-professionals/forms/pb127. (2020, accessed 20 March 2020).
16. Patel H, Latremouille-Viau D, Burne R, et al. Comparison of real-world treatment outcomes with vedolizumab versus infliximab in biologic-naïve patients with inflammatory bowel disease. Crohns Colitis 360 2019;1(2): otz022.
17. Pharmaceutical Benefits Scheme. Analysis of medicines used to treat ulcerative colitis: drug utilisation sub-committee (DUSC),

https://www.pbs.gov.au/industry/listing/participants/public-release-docs/2017-06/ulcerative-colitis-dusc-prd-2017-06.pdf (2017, accessed 5 November 2020).
18. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335(7624):806-808.
19. Chen C, Hartzema AG, Xiao H, et al. Real-world pattern of biologic use in patients with inflammatory bowel disease: treatment persistence, switching, and importance of concurrent immunosuppressive therapy. Inflamm Bowel Dis 2019;25(8):1417-1427.
20. Chan W, Kariyawasam V, Kim S, et al. Gastroenterologists' preference and risk perception on the use of immunomodulators and biological therapies in elderly patients with ulcerative colitis: an international survey. Eur J Gastroenterol Hepatol 2020;32(8):976-983.
21. Pudipeddi A, Kariyawasam V, Haifer C, et al. Safety of drugs used for the treatment of Crohn's disease. Expert Opin Drug Saf 2019;18(5):357-367.
22. Ritter T, Fourment C, Kuten SA, et al. Second-line biologic therapy after vedolizumab. Am J Gastroenterol 2019;114(Suppl):S429-S430.
23. Bressler B, Yarur A, Kopylov U, et al. Clinical effectiveness of first-line anti-TNF therapies and second-line anti-TNF therapy post-vedolizumab discontinuation in patients with ulcerative colitis and Crohn's disease. Am J Gastroenterol 2019;114(Suppl): S373.
24. Bressler B, Yarur A, Silverberg M, et al. Vedolizumab and anti-TNFα real-world outcomes in biologic-naïve inflammatory bowel disease patients: results from the EVOLVE study. J Crohns Colitis. Epub ahead of print 31 March 2021. DOI: 10.1093/ecco-jcc/jjab058.
25. Liefferinckx C, Minsart C, Cremer A, et al. Early vedolizumab trough levels at induction in inflammatory bowel disease patients with treatment failure during maintenance. Eur J Gastroenterol Hepatol 2019;31(4):478-485.
26. Biancheri P, Di Sabatino A, Rovedatti L, et al. Effect of tumor necrosis factor-α blockade on mucosal addressin cell-adhesion molecule-1 in Crohn's disease. Inflamm Bowel Dis 2013;19(2):259-264.
27. Yzet C, Diouf M, Singh S, et al. No benefit of concomitant immunomodulator therapy on efficacy of biologics that are not tumor necrosis factor antagonists in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2020;19(4):668-679.
28. Bressler B, Yarur A, Kopylov U, et al. Clinical effectiveness and safety of first-line biologic vedolizumab as a monotherapy or combination therapy in ulcerative colitis and Crohn's disease patients: results from the EVOLVE study. J Crohns Colitis 2020;14(Suppl 1):S381-S382.
29. Simons LA, Ortiz M, Calcino G. Persistence with a single pill versus two pills of amlodipine and atorvastatin: the Australian experience, 2006-2010. Med J Aust 2011;195(3):134-137.

Chapter 4

Knowledge of histological assessments in ulcerative colitis

This chapter is a reproduction of the published manuscript “Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologist vs pathologists” by Pudipeddi et al.

Journal reference:

- Pudipeddi A, Fung C, Christensen B, Bryant RV, Subramaniam K, Chetwood J, Paramsothy S, Leong R. Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologist vs pathologists. *World J Gastroenterol* 2023; 29(2):378-389.

Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologists versus pathologists

Authors

Aviv Pudipeddi[1,2] MBBS (Hons 1), FRACP

Caroline Fung[3] MBBS (Hons), FRCPA

Britt Christensen[4,5] BSc, MBBS, MPH, PhD

Robert V Bryant[6] MBBS, FRACP, MScR, PhD

Kavitha Subramaniam[7,8] MBBS, MPH, FRACP

John Chetwood[1] BSc (Hons), MBBS, DTM&H

Sudarshan Paramsothy[1,2,9] MBBS (Hons 1), MRCP (UK), FRACP, PhD

Rupert W Leong[1,2,9] MBBS, FRACP, MD, AGAF

Affiliations

Aviv Pudipeddi, John Chetwood, Sudarshan Paramsothy, Rupert W Leong, Gastroenterology and Liver Services, Concord Repatriation General Hospital, Sydney 2139, Australia

Aviv Pudipeddi, Sudarshan Paramsothy, Rupert W Leong, Faculty of Medicine and Health, Concord Clinical School, University of Sydney, Sydney 2138, Australia

Caroline Fung, Department of Anatomical Pathology, Concord Repatriation General Hospital, Sydney 2139, Australia

Britt Christensen, Department of Gastroenterology, Royal Melbourne Hospital, Melbourne 3050, Australia

Britt Christensen, Department of Medicine, University of Melbourne, Melbourne 3052,

Australia

Robert V Bryant, Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital, Adelaide 5011, Australia

Kavitha Subramaniam, Gastroenterology and Hepatology Unit, Canberra Hospital, Canberra 2605, Australia

Kavitha Subramaniam, Australian National University Medical School, Australian National University, Canberra 2601, Australia

Sudarshan Paramsothy, Rupert W Leong, Faculty of Medicine and Health Sciences, Macquarie University Hospital, Sydney 2109, Australia

Corresponding author

Aviv Pudipeddi, FRACP, MBBS, Doctor, Gastroenterology and Liver Services, Concord Repatriation General Hospital, Level 1West ACE Unit, Concord Repatriation General Hospital, Hospital Road, Concord, Sydney 2139, Australia. avivpudipeddi@gmail.com

Financial disclosures or conflicts of interest:

Nil

Ethics approval statement

The study was approved by the Sydney Local Health District Human Research Ethics Committee (HREC CH62/6/2021-055). The STROBE guidelines have been adopted.

Word Count: 2279

ABSTRACT

Background: Histological remission is increasingly accepted as a treatment endpoint in the management of ulcerative colitis (UC). However, the knowledge of histology guidelines and the attitudes towards their use in clinical practice by gastroenterologists and pathologists is unknown.

Aim: To evaluate the knowledge of histology guidelines and attitudes towards the use of histology in UC by gastroenterologists and pathologists.

Methods: A prospective, cross-sectional nationwide survey of gastroenterologists and pathologists who analyse UC specimens was conducted. The survey consisted of 34 questions to assess gastroenterologists' and pathologists' knowledge (score out of 19) and attitudes towards histological assessment in UC. Survey questions were formulated using the European Crohn's and Colitis position paper on histopathology and the British Society of Gastroenterology biopsy reporting guidelines. It included knowledge of histological assessment of disease activity and dysplasia, knowledge of histological scoring systems for ulcerative colitis, uptake of histology scoring systems in routine practice, attitudes towards the role of histological activity, and the use of histological activity in clinical scenarios.

Results: Of 89 responders (77 gastroenterologists, 12 pathologists), there was almost universal acceptance that histological assessment should form part of UC evaluation [95% gastroenterologists, 92% pathologists]. However, gastroenterologists reported that 92% of their pathologists do not use a histological scoring system. Utilisation of a formal histological scoring system was preferred by 77% of gastroenterologists and 58% of pathologists. Both groups lacked awareness of the Geboes Score, Nancy Index and Robarts Histopathological Index scoring systems with 91%, 87%, and 92% of gastroenterologists respectively; and 83%, 83%, and 92% pathologists respectively, being uncertain of scoring systems' remission

definitions. Histology knowledge score was not significantly different between gastroenterologists and pathologists [9/19 (IQR:8-11) versus 8/19 (IQR:7-10), *P*=0.54]. Higher knowledge scores were predicted by hospital attending gastroenterologists (*P*=0.004), participation in inflammatory bowel disease (IBD) multidisciplinary teams (*P*=0.009), and self-declared IBD sub-specialist (*P*=0.03).

Conclusions: Histological remission is a recognised target for both gastroenterologists and pathologists. Despite this, knowledge of histological scoring systems and their utilisation is poor.

Keywords:

Histology, ulcerative colitis, survey

Core Tip

This manuscript describes, for the first time, the knowledge and attitudes of gastroenterologists and pathologists towards the use of histology in clinical practice. Given then increasing literature and use of histology in trials, there is a need to understand the current perceptions of using histology in the real-world. Using a novel IBD Knowledge score, we demonstrate that although histology is an accepted endpoint, knowledge is poor, particularly relating to histological scoring systems. As such, these results illustrate a pressing need and opportunity to improve knowledge around histology scores amongst gastroenterologists and pathologists and develop consensus agreements on a reporting approach.

4.1 INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease characterised by a relapsing and remitting course.[1] Disease activity is typically evaluated using clinical, biochemical and endoscopic assessments. Treatment goals have evolved over time, and current consensus guidelines from the Selecting Therapeutic Targets in Inflammatory Bowel Disease initiative (STRIDE-II) recommend achieving clinical and endoscopic remission.[2] However, up to 40% of patients who achieve these therapeutic endpoints may have persistent histological inflammatory activity.[3,4]

Despite endoscopic normalization, ongoing active histological activity may be associated with poorer clinical outcomes including higher clinical relapse rates, corticosteroid requirement, hospitalization, colectomy and development of colorectal neoplasia.[3-7] Although histological remission is currently not a formal treatment target by consensus expert-opinion, STRIDE-II guidelines do recommend that formal histological assessment take place to determine the depth of remission and help prognosticate patient outcomes. Further, it is increasingly incorporated into clinical drug trials, with central reading to reduce bias, to provide objective scoring of inflammatory activity.[2] Standardized histological scoring systems with varying levels of validity have been developed to quantify the degree of microscopic inflammatory activity and provide a more accurate assessment of mucosal inflammation.[8-12] The three most commonly used are the Geboes score, Nancy index and Robarts histopathology index due to evidence of their content validity and reliability in evaluating histological features.[13]

Although accepted in modern clinical drug trials and research settings, histological disease activity and scoring systems have not been incorporated in routine clinical practice. It is not

known whether gastroenterologists understand these scoring systems or if they welcome their incorporation into routine clinical care. Achieving consensus in a formal reporting scoring system will require agreement by pathologists, but their knowledge of these scoring systems and willingness to use them is also unknown. Many pathologists use written descriptions of UC activity in their reports. Whether this translates to a numerical value, if they favour a particular scoring system, or their attitude towards synaptic reporting of histological activity, is not known. This cross-sectional survey study evaluated gastroenterologist and pathologist knowledge of histological findings and scoring systems, together with their attitudes towards the role of histology in UC management. We hypothesised that based on their dedicated training, knowledge of histological scoring systems would be significantly higher in pathologists than gastroenterologists.

4.2 METHODS

4.2.1 Study cohort

This was a prospective cross-sectional survey of Australian gastroenterologists and pathologists from July 2021 to January 2022. Gastroenterologists were contacted by proxy through the Gastroenterological Society of Australia, and pathologists who review UC specimens were contacted by their associated gastroenterologists to participate in the survey.

4.2.2 Survey questionnaire and Inflammatory Bowel Disease histology knowledge score

A survey was developed to explore the knowledge and attitudes towards the use of histology in IBD for both gastroenterologists and pathologists. The European Crohn's and Colitis Organisation (ECCO) position paper on histopathology and the British Society of

Gastroenterology (BSG) biopsy reporting guidelines were utilised to formulate questions and quantify knowledge.[14,15] The structured survey was designed by a focus group of three gastroenterologists and comprised of 34 questions. It included knowledge of histological assessment of disease activity and dysplasia, knowledge of histological scoring systems for ulcerative colitis, uptake of histology scoring systems in routine practice, attitudes towards the role of histological activity, and the use of histological activity in clinical scenarios (Supplementary data). Questionnaire language and ambiguity were evaluated by the focus group. A novel IBD Histology Knowledge Score was created that was derived from the survey as a tool to measure overall performance and tested for construct validity and discriminant ability (Supplementary data). The IBD Histology Knowledge Score was calculated as the sum of correct responses to survey questions that aligned with the ECCO position paper on histopathology and the BSG reporting guidelines on IBD biopsies.[14,15] The maximum possible score was nineteen. For construct validity, a high-performance score had to represent a good understanding of histological findings. During the development phase, the survey was administered to senior gastroenterologists and pathologists not directly involved in designing the study, and they were deemed as criterion standards. The survey was then administered to gastroenterology fellows, junior resident medical officers and non-medical staff. Senior staff scored significantly higher (P=0.001) than junior doctors, establishing content validity. Discriminant validity compared the knowledge scores of those who followed published guidelines versus those who did not.

4.2.3 Statistical analysis

The IBD Histology Knowledge Score was analysed as a non-parametric continuous variable, described as medians with interquartile ranges and compared using Mann-Whitney U-test

and Kruskal-Wallis test. Parametric continuous variables were described as means and compared using the *t*-test and ANOVA test. Predictors of the IBD histology knowledge score were determined using linear regression with backward elimination regression modelling. A *P*-value of <0.05 was deemed statistically significant. Statistical analyses were performed with SPSS version 27 (SPSS Inc, Chicago, Ill).

4.2.4 Ethics approval

The study was approved by the Sydney Local Health District Human Research Ethics Committee (HREC CH62/6/2021-055).

4.3 RESULTS

4.3.1 Study cohort

A total of 89 responses were obtained, comprising 77 gastroenterologists and 12 pathologists. The response rate for gastroenterologists was 25% (n=77/310). Subspecialty breakdown of gastroenterologists is shown in Figure 4.1. Gastroenterologists listed their predominant work as 31% public hospital staff specialists, 30% private practice, 21% trainee gastroenterologists, 17% visiting medical officers and 1% research-based gastroenterologist. Ninety-four percent of respondents saw >2 IBD patients each week and 30% saw >10 patients each week. Forty-five percent of gastroenterologists were involved in a regular IBD multidisciplinary team. Full study cohort characteristics are shown in Table 4.1.

Figure 4.1. Subspeciality characteristics of gastroenterologists

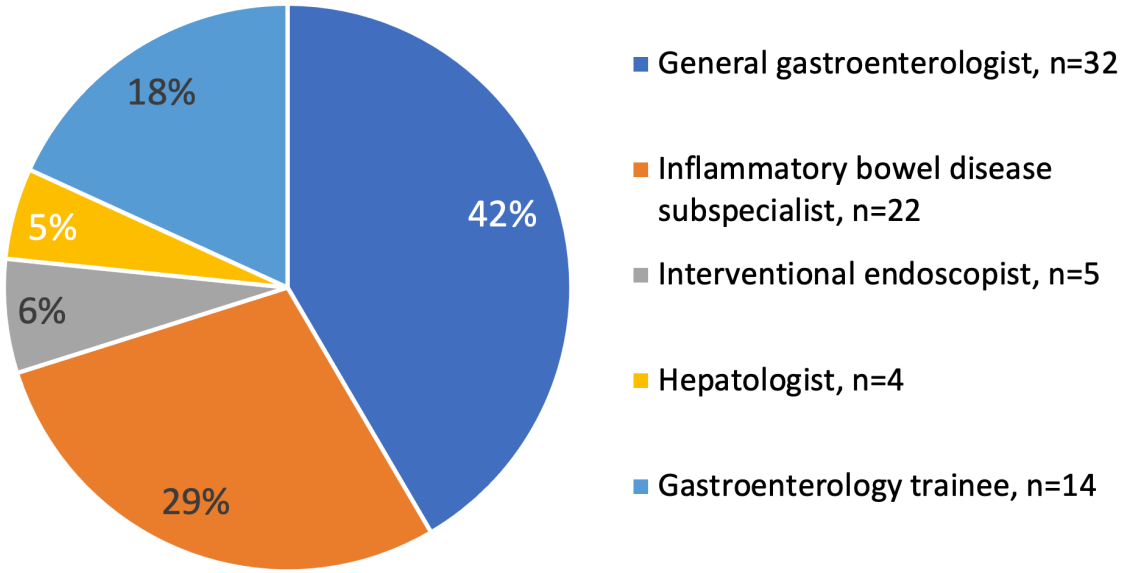


Table 4.1. Demographics and study cohort characteristics

	Gastroenterologists [n = 77]	Pathologists [n = 12]
Age [n (%)]		
< 30 years	4 (5.2%)	0 (0.0%)
30 – 40 years	30 (39.0%)	1 (8.3%)
41 – 50 years	15 (19.5%)	4 (33.3%)
51 – 60 years	19 (24.7%)	4 (33.3%)
> 60 years	9 (11.7%)	3 (25.0%)
Location [n (%)]		
New South Wales	46 (59.7%)	8 (66.7%)
Victoria	11 (14.3%)	2 (16.7%)
Queensland	11 (14.3%)	2 (16.7%)

Western Australia	8 (10.4%)	0 (0.0%)
Australian Capital Territory	1 (1.3%)	0 (0.0%)
Highest level of education [n (%)]		
Bachelor of medicine/Bachelor of surgery	51 (66.2%)	11 (91.7%)
Masters	10 (13.0%)	0 (0.0%)
PhD	16 (20.8%)	1 (8.3%)
What is your predominant practice? [n (%)]		
Staff specialist	24 (31.2%)	10 (83.3%)
University academic work	1 (1.3%)	0 (0.0%)
Visiting medical officer	13 (16.9%)	0 (0.0%)
Private practice	23 (29.9%)	2 (16.7%)
In training program	16 (20.8%)	0 (0.0%)
How many IBD patients do you see each week? [n (%)]		
0 – 1	5 (6.5%)	N/A
2 – 5	31 (40.3%)	N/A
6 – 10	18 (23.4%)	N/A
> 10	23 (29.9%)	N/A
Involved in regular IBD multidisciplinary meeting? [n (%)]		
Yes	35 (45.5%)	6 (50.0%)
No	42 (54.5%)	6 (50.0%)

n, number; PhD, Doctor of Philosophy; IBD, inflammatory bowel disease; N/A, not applicable

Of the 12 surveyed pathologists, 83% worked in tertiary teaching hospitals and 17% were solely in private practice. Half of all pathologists were involved in regular IBD multidisciplinary meetings. Full study cohort characteristics are shown in Table 4.1.

4.3.2 Attitudes towards histology and scoring systems in ulcerative colitis

Histological activity was considered to have an 'emerging' or 'established' role in UC by 40% and 55% of gastroenterologists respectively. Proportions for pathologists were 33% and 58% respectively. Histological remission was considered more important to achieve than endoscopic remission by 65% of gastroenterologists ('somewhat agree' and 'agree') (Table 4.2).

Table 4.2. Attitudes towards histology and histological scoring systems

	Gastroenterologists [n = 77]	Pathologists [n = 12]
The role of histological activity in IBD is:		
Not established	3 (3.9%)	1 (8.3%)
Preliminary	1 (1.3%)	0 (0.0%)
Emerging	31 (40.3%)	4 (33.3%)
Established	42 (54.5%)	7 (58.3%)
Histological remission is more important to achieve than endoscopic remission		
Disagree	4 (5.2%)	N/A
Somewhat disagree	13 (16.9%)	N/A
Neither agree nor disagree	10 (13.0%)	N/A

Somewhat agree	36 (46.8%)	N/A
Agree	14 (18.2%)	N/A
What histological scoring system does your pathologist routinely or frequently use in their reports?		
Geboes	2 (2.6%)	0 (0.0%)
Nancy index	3 (3.9%)	1 (8.3%)
RHI	1 (1.3%)	0 (0.0%)
They do not routinely use a scoring system	71 (92.2%)	10 (83.3%)
Other		IBD-DCA score (n=1)
I would like to use a histological scoring system for my IBD patients		
Never	8 (10.4%)	4 (33.3%)
Rarely	10 (13.0%)	1 (8.3%)
Occasionally	14 (18.2%)	1 (8.3%)
Sometimes	23 (29.9%)	3 (25.0%)
Always	22 (28.6%)	3 (25.0%)
Which scoring systems have undergone the most validation?		
Modified Riley score	1 (1.3%)	1 (8.3%)
Geboes score	13 (16.9%)	3 (25.0%)
Nancy index	20 (26.0%)	5 (41.7%)
RHI	9 (11.7%)	3 (25.0%)
Truelove and Richards score	5 (6.5%)	0 (0.0%)
Not sure	49 (63.6%)	7 (58.3%)

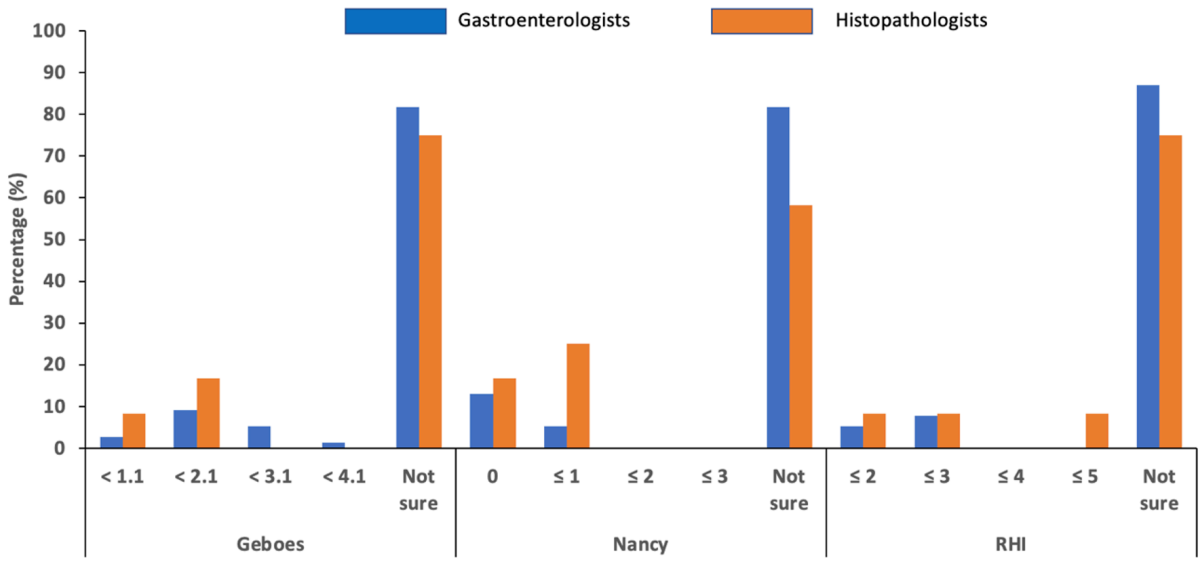
What Geboes score is considered histological remission?		
< 1.1	2 (2.6%)	1 (8.3%)
< 2.1	7 (9.1%)	2 (16.7%)
< 3.1	4 (5.2%)	0 (0.0%)
< 4.1	1 (1.3%)	0 (0.0%)
Not sure	63 (81.8%)	9 (75.0%)
What Nancy index is considered histological remission?		
0	10 (13.0%)	2 (16.7%)
≤ 1	4 (5.2%)	3 (25.0%)
≤ 2	0 (0.0%)	0 (0.0%)
≤ 3	0 (0.0%)	0 (0.0%)
Not sure	63 (81.8%)	7 (58.3%)
What Robarts histopathology index is considered histological remission?		
≤ 2	4 (5.2%)	1 (8.3%)
≤ 3	6 (7.8%)	1 (8.3%)
≤ 4	0 (0.0%)	0 (0.0%)
≤ 5	0 (0.0%)	1 (8.3%)
Not sure	67 (87.0%)	9 (75.0%)

n, number; RHI, Robarts histopathology index; IBD, inflammatory bowel disease; N/A, not applicable

The proportion of gastroenterologists who want to use a histological scoring system at least 'sometimes' or 'always' was 59%, and 50% for pathologists. Gastroenterologists reported that 92% of their pathologists do not routinely use a histological scoring system, whilst 83% pathologists report not routinely using a scoring system. More than half of gastroenterologists (64%) and pathologists (58%) did not know which scoring systems had undergone the most validation (Table 4.2).

For the Geboes score, 91% of gastroenterologists and 83% of pathologists did not know the defined histological remission score of '< 2.1'.[13] For the Nancy index, 87% of gastroenterologists and 83% of pathologists did not know the defined histological remission score of '0'.[15] For the Robarts histopathology index (RHI), 92% of gastroenterologists and pathologists did not know the defined histological remission score of '≤ 3' (Table 4.2 and Figure 4.2).[17]

Figure 4.2. Knowledge of histological remission definitions for scoring systems by gastroenterologists and pathologists



Percentage of Gastroenterologists	2.6	9.1	5.2	1.3	81.8	13	5.2	0	0	81.8	5.2	7.8	0	0	87
Percentage of Histopathologists	8.3	16.7	0	0	75	16.7	25	0	0	58.3	8.3	8.3	0	8.3	75

4.3.3 Impact of histological activity on treatment decisions in clinical scenarios

The impact of histological disease activity on gastroenterologists' decisions to escalate treatment or de-escalate in particular scenarios is summarised in Table 4.3. In the setting of clinical and endoscopic remission, but histological activity alone, 10% of gastroenterologists would escalate therapy ('often' or 'always'). When combined with an elevated faecal calprotectin, 30% of gastroenterologists would escalate treatment. A greater proportion of gastroenterologists would de-escalate treatment if two consecutive colonoscopies showed endoscopic and histological remission, compared with a single episode of endoscopic and histological remission (53% versus 19% respectively). A greater proportion of gastroenterologists would aim for histological remission if a patient with UC had other risk factors for colon cancer (71%).

Table 4.3. Impact of histological disease activity on treatment management in clinical scenarios

Scenario	Never [n (%)]	Not often [n (%)]	Sometimes [n (%)]	Often [n (%)]	Always [n (%)]
1. If a patient is in clinical and endoscopic remission, but has histological activity, then I will escalate medical therapy	14 (18.2%)	35 (45.5%)	20 (26.0%)	5 (6.5%)	3 (3.9%)
2. If a patient is in clinical and endoscopic remission, but has an elevated faecal calprotectin (>100ug/g) and histological activity, then I will escalate medical therapy	4 (5.2%)	18 (23.4%)	31 (40.3%)	19 (24.7%)	5 (6.5%)
3. If a patient is in clinical, endoscopic and histological remission, (but prior colonoscopy showed Mayo 1 endoscopic disease), then I will de-escalate medical therapy	7 (9.1%)	19 (24.7%)	36 (46.8%)	15 (19.5%)	0 (0.0%)
4. If a patient is in clinical remission, with their last 2 colonoscopies showing endoscopic and histological remission, then I will de-escalate medical therapy	2 (2.6%)	2 (2.6%)	31 (40.3%)	38 (49.4%)	4 (5.2%)
5. If a patient with ulcerative colitis has other risk factors for colon cancer, then I will aim to achieve histological remission	0 (0.0%)	7 (9.1%)	14 (18.2%)	27 (35.1%)	29 (37.7%)

n, number; ug/g, micrograms/gram

4.3.4 IBD histology knowledge score

Gastroenterologists and pathologists had similar IBD histology knowledge scores [8.0 (IQR: 6.5-10.0) versus 9.0 (IQR: 7.8-11.0), *P*=0.54] (Table 4.4). Within gastroenterologists, IBD sub-specialists had higher knowledge scores compared with other gastroenterologists [10.5 (IQR: 7.3-14) versus 9.0 (IQR: 7.8-10.0), *P*=0.02] (Figure 4.3a). Public hospital staff specialists had higher knowledge scores than visiting medical officers [11.0 (IQR: 9.0-13.0) versus 8.0 (IQR: 8.0-9.0), *P*=0.003] and those in private practice [11.0 (IQR: 9.0-13.0) versus 8.0 (IQR: 6.3-9.8), *P*=0.002] (Figure 4.3b). Gastroenterologists with a PhD had higher knowledge scores than those whose highest level of education was a bachelor degree [11.0 (IQR: 7.0-14.0) versus 9.0 (IQR: 8.0-10.0), *P*=0.01] (Figure 4.3c). Involvement in an IBD multidisciplinary team was associated with a higher knowledge score [9.5 (IQR: 8.0-11.0) versus 8.0 (IQR: 6.0-10.0), *P*=0.002] (Figure 4.3d).

Figure 4.3. Comparisons of IBD histology knowledge score for gastroenterologists based on a) subspecialty type, b) predominant practice, c) highest education level, and d) involvement in IBD multidisciplinary team

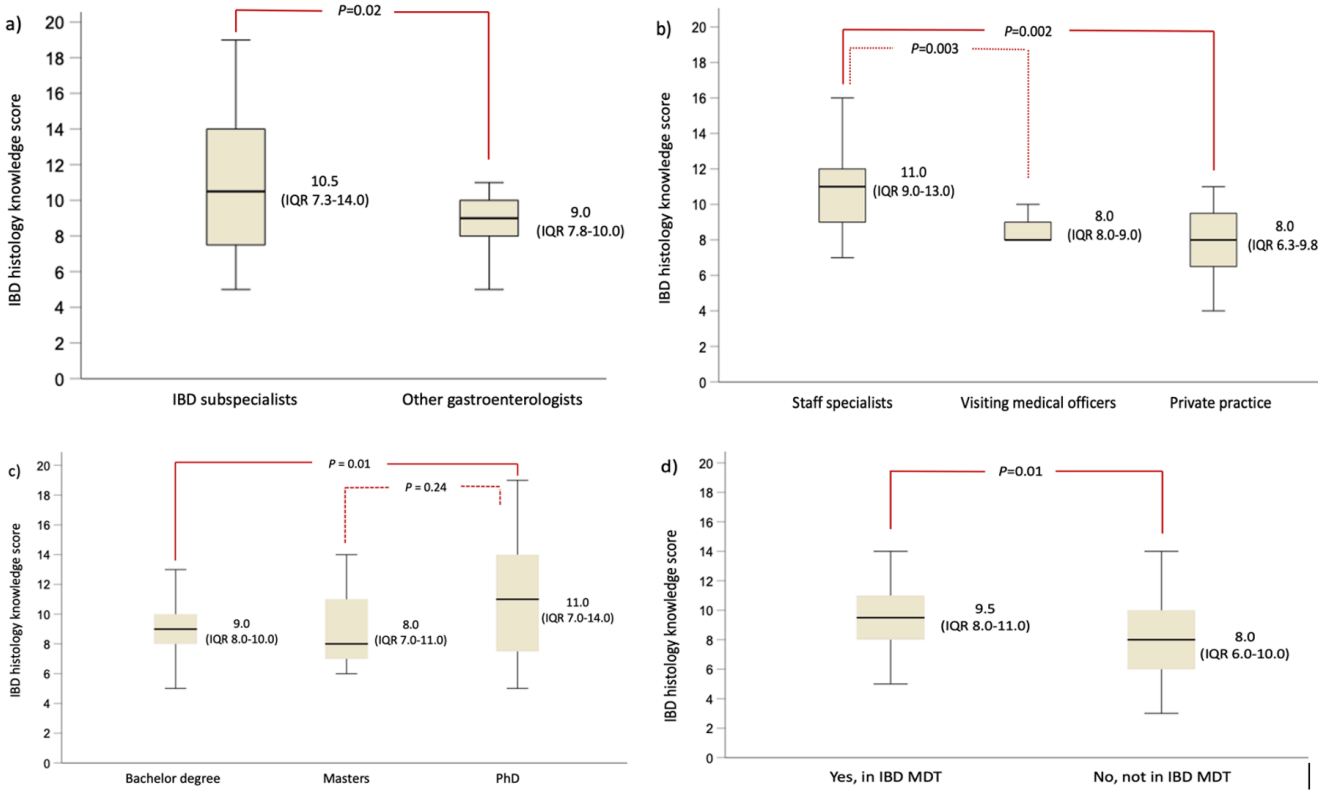


Table 4.4. IBD histology knowledge scores

	Gastroenterologists [n = 77]	Pathologists [n = 12]
IBD Histology Knowledge Score [median (IQR)]	9.0 (7.8-11.0)	8.0 (6.5-10.0)
Type of subspecialist		
General gastroenterologist	8.0 (7.0 – 9.0)	N/A
IBD subspecialist	10.5 (7.3 – 14)	N/A

Interventional endoscopist	9.0 (4.5 – 9.8)	N/A
Hepatologist	10.5 (8.5 – 11)	N/A
Gastroenterology trainee	8.5 (6.0 – 10.0)	N/A
Predominant practice		
Staff specialist	11.0 (9.0 – 13.0)	N/A
Visiting medical officer	8.0 (8.0 – 9.0)	N/A
Private practice	8.0 (6.3 – 9.8)	N/A
In training program	8.5 (6.0 – 10.0)	N/A
Highest level of education		
Bachelor degree	9.0 (8.0 – 10.0)	N/A
Masters	8.0 (7.0 – 11.0)	N/A
PhD	11.0 (7.0 – 14.0)	N/A
Involved in regular IBD multidisciplinary meeting?	35 (45.5%)	6 (50.0%)
Yes	9.5 (8.0 – 11.0)	N/A
No	8.0 (6.0 – 10.0)	N/A

n, number; IQR, interquartile range; N/A, not applicable; IBD, inflammatory bowel disease; PhD, Doctor of Philosophy

On univariate analysis, subspecialty type (p=0.005), predominant practice (p=0.004), involvement in an IBD multidisciplinary team (p=0.002) and a higher level of education (p=0.02) were all significantly associated with higher IBD histology knowledge scores (Table 5). On multivariate analysis, subspecialty type (p=0.03), predominant practice (p=0.005) and

involvement in an IBD multidisciplinary team (p=0.009) remained significant predictors for higher IBD histology knowledge scores (Table 4.5).

Table 4.5. Significant predictors of IBD histology knowledge score for gastroenterologists on univariate and multivariate analyses

	Univariate analysis *P-value*	Multivariate analysis *P-value*
Type of subspecialty	0.005	0.03
Predominant practice	0.004	0.005
Involvement in IBD MDT	0.002	0.009
Highest level of education	0.02	

IBD, inflammatory bowel disease; MDT, multidisciplinary team

4.4 Discussion

Therapeutic goals in UC have evolved from achieving clinical response to attaining objective targets of resolution of inflammation beyond symptoms such as biochemical and endoscopic remission. However, histological remission outside of the research setting has yet to be adopted by gastroenterologists and pathologists. Our study revealed firstly that histological activity is a recognised treatment goal for gastroenterologists who wish to use histology results in combination with other endpoints to guide management decisions. Secondly and conversely, despite this awareness and use of histology, there is a poor knowledge of histological scoring systems in UC not only by gastroenterologists, but by pathologists as well. As such there is an opportunity to develop consensus guidelines incorporating

gastroenterologists and pathologists that are adopted by the respective societies to further this evolving field.

Our study showed 95% of gastroenterologists believe histological activity plays a role in the management of UC, with 76% wanting to use a histological scoring system in clinical practice. Further evidence on the role of UC histological activity scores are required as only a small proportion of gastroenterologists currently make treatment decisions based solely on histological activity. In UC patients with clinical and endoscopic remission but ongoing histological disease activity, 10% of gastroenterologists would escalate medical therapy. However, when histological activity coincides with elevated faecal calprotectin, 30% were prepared to escalate treatment. These decisions match the current STRIDE-II guidelines given that histological activity is not currently an accepted target, but shows that gastroenterologists are prepared to include this endpoint as a treatment target.[2] Histological remission becomes even more important if a patient with UC had other risk factors for colon cancer, with 72% prepared to escalate treatment, given that histological activity increases the risk of colorectal neoplasia (odds ratio 3.0, 95% CI: 1.4-6.3).[5] Therefore, when UC subjects have greater colonic disease extent, more prolonged duration of UC, presence of primary sclerosing cholangitis, or presence of a family history of colorectal cancer, gastroenterologists might escalate treatment in the presence of histological disease activity irrespective of symptoms.

Despite the awareness of the importance of histology in UC, our survey demonstrated a lack of knowledge of histological scoring systems by gastroenterologists. Clinical trials have used Nancy index, RHI and the Geboes score but recent European Crohn's and Colitis Organisation (ECCO) guidelines recommended the use of the Nancy index and RHI for randomised clinical

trials, and the Nancy index for clinical practice given its ease of use.[14] Gastroenterologists did not know which scoring systems had undergone the most validation, or were unaware of the histological remission scores for the Geboes score (91%), Nancy index (87%) and RHI (92%). Despite the increasing interest and evolving role of histological scoring systems in UC, there is an opportunity to educate gastroenterologists about these scoring systems and how to apply them in clinical practice. Predictors for higher knowledge included employment as a public hospital staff specialist and involvement in an IBD multidisciplinary team. As such, it is likely working in public hospitals within an IBD team would lead to increased exposure to the understanding of common histological scoring systems in UC. Conversely, gastroenterologists working in private practice would have less exposure to these scoring systems and their utility in UC management, contributing to lower knowledge scores.

Few studies have evaluated pathologists' views on histological activity, but most believe that they have a role in evaluating UC. However, pathologists' knowledge of UC histology was comparable to gastroenterologists (median knowledge score 8.0 [IQR: 6.5-10.0] versus 9.0 [IQR: 7.8-11.0] *P*=0.54). Similar to gastroenterologists, they also lacked knowledge of histological scoring systems and their remission definitions. There is an opportunity, therefore, to improve the utilisation of histological activity scoring for both pathologists and gastroenterologists. A harmonised approach to histological assessment in UC is lacking.[16] Future directions should include the development of histology consensus guidelines in consultation with pathologists to ensure homogeneity in reporting across hospitals to permit comparability of mucosal biopsies across different sites.

This study has several limitations. First, responder bias may have played a role, whereby responders having greater knowledge were more likely to take part on the survey. However, this would indicate a greater unawareness of histological activity scoring in the assessment of UC and a greater need for education and a harmonized approach towards the adoption of a scoring system. Secondly, a smaller respondent number for pathologists was surveyed. However, we demonstrated statistically that pathologists did not differ in their knowledge of histological scoring systems in UC despite expertise in reading biopsy histology. Thirdly, the results may lack worldwide generalisability given the survey was sent to Australian health professionals.

Strengths of this study included: (1) being the first to report gastroenterologists' knowledge and attitudes towards the use of histology in UC; (2) recruitment of pathologists to compare their awareness against gastroenterologists, and (3) to target respondents nationwide to demonstrate generalisability.

4.5 CONCLUSION

The study highlights that while there is an acknowledgment of the importance of histological assessment in UC, there is a lack of knowledge of histological scoring systems. It indicates areas of educational need in the field of UC histology, and the importance of including pathologists in developing future consensus guidelines on the use of histology in clinical practice.

4.6 REFERENCES

1. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *Lancet* 2017;389(10080):1756-1770
2. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021;160(5):1570-1583
3. Park S, Abdi T, Gentry M, et al. Histological disease activity as a predictor of clinical relapse among patients with ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2016;111(12):1692-1701
4. Christensen B, Hanauer S, Erlich J, et al. Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. *Clin Gastroenterol Hepatol* 2017;15(10):1557-1564
5. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007;11:1601-1608
6. Hefti MM, Chessin DB, Harpaz NH, et al. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. *Dis Colon Rectum* 2009;52:193-197
7. Wang H, Fewings I, Bornman L, et al. Histologic remission (NANCY Index) is superior to endoscopic mucosal healing in predicting relapse free survival in patients with ulcerative colitis in clinical and endoscopic remission. *J Clin Gastroenterol* 2022 Feb 28; doi: 10.1097/MCG.0000000000001681
8. Geboes K, Riddell R, Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000;47(3):404-409
9. Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991;32:174-178
10. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. *Gut* 2017;66:43-49
11. Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. *Gut* 2017;66:50-58
12. Chateau T, Feakins R, Marchal-Bressenot A, et al. Histological remission in ulcerative colitis: under the microscopic is the cure. *Am J Gastroenterol* 2020;115(2):179-189
13. Mosli MH, Parker CE, Nelson SA et al. Histological scoring indices for evaluation of disease activity in ulcerative colitis. *Cochrane Database Syst Rev* 2017;5(5):CD011256
14. Magro F, Doherty G, Peyrin-Biroulet L, et al. ECCO position paper: harmonization of the approach to ulcerative colitis histopathology. *J Crohns Colitis* 2020;14(11):1503-1511
15. Feakins RM. Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. *J Clin Pathol* 2013;66(12):1005-1026
16. Vespa E, D'Amico F, Sollai M, et al. Histological scores in patients with inflammatory bowel diseases: the state of the art. *J Clin Med* 2022;11(4):939

4.7 SUPPLEMENTARY DATA

4.7.1 Survey questions

Participant demographics

1. Age (years):
    a. < 30
    b. 30-40
    c. 41-50
    d. 51-60
    e. > 60

2. In which state/territory is your primary practice?

    - New South Wales
    - Victoria
    - Queensland
    - South Australia
    - Western Australia
    - Tasmania
    - Northern Territory
    - Australian Capital Territory

3. For gastroenterologists, how would you best describe yourself? (may select more than one option)

    - General gastroenterologist
    - Interventional endoscopist
    - Hepatologist
    - Inflammatory bowel disease sub-specialist
    - Gastroenterology trainee or fellow
    - Other: _____

4. What is your predominant practice?

    - Staff specialist
    - University academic work
    - Visiting Medical Officer
    - Private Practice
    - Non-clinical
    - Training
    - Other, please describe in the space below

      _____

5. What is the highest level of education that you have completed?

   - ○ MBBS / MD
   - ○ Masters
   - ○ PhD or equivalent

6. How many IBD patients do you see weekly?

   - ○ 0-1
   - ○ 2-5
   - ○ 6-10
   - ○ >10

7. Are you involved in a regular multidisciplinary IBD meeting?

   - ○ Yes
   - ○ No

Knowledge and attitudes of histological scoring systems in UC

8. The role of histological activity in IBD is:

Not established	Preliminary	Emerging	Established
○	○	○	○

9. Histologic remission is more important to achieve than endoscopic remission:

Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree
○	○	○	○	○

10. Which of the following histological scores have undergone the most validation? (you may pick more than one)

    - ☐ Modified Riley score
    - ☐ Geboes score
    - ☐ Nancy index
    - ☐ Robarts histopathology index
    - ☐ Truelove and Richards index
    - ☐ Not sure

11. Which score does your pathologist routinely or frequently use in their official reports?

- ☐ Modified Riley score
- ☐ Geboes score
- ☐ Nancy index
- ☐ Robarts histopathology index
- ☐ Truelove and Richards Index
- ☐ They do not routinely use a scoring system

12. What Geboes score is considered histological remission?

- ☐ ≤ 1.0
- ☐ ≤ 2.0
- ☐ ≤ 3.0
- ☐ ≤ 4.0
- ☐ Not sure

13. What Nancy index score is considered histological remission?

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ Not sure

14. What Robarts histopathology index score is considered remission?

- ☐ ≤ 2
- ☐ ≤ 3
- ☐ ≤ 4
- ☐ ≤ 5
- ☐ Not sure

15. I would like to use a histological scoring system for my UC patients:

Never	Rarely	Occasionally	Sometimes	Always
○	○	○	○	○

Please answer each of the following statements about treatment decision making based on histological disease activity status.

	Never	Not often	Sometimes	Often	Always
If a patient is in clinical and endoscopic remission, but has histological activity, then I will escalate medical therapy	o	o	o	o	o
If a patient is in clinical and endoscopic remission, but has an elevated faecal calprotectin (> 100 ug/g) and histological activity, then I will escalate therapy	o	o	o	o	o
If a patient is in clinical, endoscopic and histological remission (but prior colonoscopy showed Mayo 1 endoscopic disease), then I will de-escalate therapy	o	o	o	o	o
If a patient is in clinical remission, with their last two colonoscopies showing endoscopic and histological remission, then I will de-escalate therapy	o	o	o	o	o
If a patient with ulcerative colitis has other risk factors for colon cancer, then I will aim to achieve histological remission	o	o	o	o	o

Please answer each of the following statements about histological disease activity.

	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Unsure
Neutrophils are normally not present within the lamina propria or epithelium	☐	☐	☐	☐	☐	☐
Eosinophils alone can be used as a marker of histological activity in ulcerative colitis	☐	☐	☐	☐	☐	☐
Paneth cell metaplasia may not be abnormal in the proximal colon but is a sign of disease activity in the distal colon	☐	☐	☐	☐	☐	☐
Chronic inflammatory cells are most dense in the upper third of the mucosa compared with the lower third, resulting in a ‘plasma cell gradient’	☐	☐	☐	☐	☐	☐
Crypt architectural changes are associated with histological activity	☐	☐	☐	☐	☐	☐
C-reactive protein levels have been found to correlate with histological activity	☐	☐	☐	☐	☐	☐
Lower levels of faecal calprotectin have been found to correlate with histological remission	☐	☐	☐	☐	☐	☐

Histological remission predicts a lower risk of colectomy	☐	☐	☐	☐	☐	☐
A higher score for histological activity predicts a higher likelihood of neoplasia	☐	☐	☐	☐	☐	☐
Endoscopic inflammation is a better predictor of neoplasia risk than histological activity	☐	☐	☐	☐	☐	☐
Histological chronic inflammation is not a significant risk factor for neoplasia	☐	☐	☐	☐	☐	☐
Serrated epithelial changes may be associated with a higher risk of developing dysplasia in IBD patients	☐	☐	☐	☐	☐	☐
Older age at diagnosis of low-grade dysplasia (age > 55 years) is a risk factor for progression to high-grade dysplasia in IBD	☐	☐	☐	☐	☐	☐
High-grade dysplastic features include more prominent nucleoli and ‘ovoid-shaped’ nuclei	☐	☐	☐	☐	☐	☐

4.7.2 Calculating the IBD histology knowledge score

Questions relevant to calculating the knowledge score	**Appropriate responses**	**Score**
Which of the following histological scoring systems have undergone the most validation?	Nancy index, Robarts histopathology index	2 (1 for each)
What Geboes score is considered histological remission?	< 2.1	1
What Nancy index score is considered histological remission?	0	1
What Robarts histopathology index score is considered histological remission?	≤ 3	1
Neutrophils are normally not present within the lamina propria or epithelium	Agree, strongly agree	1 for either option
Eosinophils alone can be used as a marker of histological activity in ulcerative colitis	Disagree, strongly disagree	1 for either option
Paneth cell metaplasia may not be abnormal in the proximal colon but is a sign of disease activity in the distal colon	Agree, strongly agree	1 for either option
Chronic inflammatory cells are most dense in the upper third of the mucosa compared with the lower third, resulting in a 'plasma cell gradient'	Agree, strongly agree	1 for either option
Crypt architectural changes are associated with histological activity	Agree, strongly agree	1 for either option
C-reactive protein levels have been found to correlate with histological activity	Disagree, strongly disagree	1 for either option
Lower levels of faecal calprotectin have been found to correlate with histological remission	Agree, strongly agree	1 for either option
Histological remission predicts a lower risk of colectomy	Agree, strongly agree	1 for either option
A higher score for histological activity predicts a higher likelihood of neoplasia	Agree, strongly agree	1 for either option
Endoscopic inflammation is a better predictor of neoplasia risk than histological activity	Disagree, strongly disagree	1 for either option
Histological chronic inflammation is not a significant risk factor for neoplasia	Disagree, strongly disagree	1 for either option
Serrated epithelial changes may be associated with a higher risk of developing dysplasia in IBD patients	Agree, strongly agree	1 for either option
Older age at diagnosis of low-grade dysplasia (age > 55 years) is a risk factor for progression to high-grade dysplasia in IBD	Agree, strongly agree	1 for either option
High-grade dysplastic features include more prominent nucleoli and 'ovoid-shaped' nuclei	Agree, strongly agree	1 for either option

Chapter 5

De-escalation of thiopurine therapy in vedolizumab-treated patients with ulcerative colitis

This chapter is a reproduction of the manuscript “Withdrawal versus continuation of thiopurine in vedolizumab-treated patients with ulcerative colitis (VIEWS): a multi-centre randomised controlled trial” by Pudipeddi et al, submitted for publication.

Withdrawal versus continuation of thiopurine in vedolizumab-treated patients with ulcerative colitis (VIEWS): a multi-centre randomised controlled trial

Authors

Aviv Pudipeddi[1,2] FRACP

Sudarshan Paramsothy[1,2] PhD

Viraj Kariyawasam[3,4] PhD

Ramesh Paramsothy[3] FRACP

Simon Ghaly[5,6] PhD

Craig Haifer[5,6] PhD

Yoon-Kyo An[7,8] FRACP

Jakob Begun[7.8] PhD

Susan J Connor[9,10] PhD

Crispin Corte[11] PhD

Mark G Ward[12] MD

Peter De Cruz[13,14] PhD

Caroline Lan-San Fung[15] FRCPA

Diane Redmond[1] BSc (Hons)

Webber Chan[1] MRCP(UK)

Fadi Mourad[1] FRACP

Melissa Kermeen[1] BN

Rupert W Leong[1,2] MBBS, FRACP, MD, AGAF

Affiliations

[1]Department of Gastroenterology and Hepatology, Concord Repatriation General Hospital, Sydney, Australia

[2]Faculty of Medicine and Health, University of Sydney, Sydney, Australia

[3]Department of Gastroenterology, Blacktown Hospital, Sydney, Australia

[4]Blacktown Clinical School, Faculty of Medicine, Western Sydney University, Sydney, Australia

[5]Department of Gastroenterology and Hepatology, St Vincent's Hospital, Sydney, Australia

[6]School of Clinical Medicine, St Vincent's Healthcare Campus, UNSW, Sydney, Australia

[7]Department of Gastroenterology, Mater Hospital, Brisbane, Australia

[8]Mater Research Institute, The University of Queensland, Brisbane, Australia

[9]Department of Gastroenterology, Liverpool Hospital, Sydney, Australia

[10]South West Sydney Clinical Campuses, UNSW Medicine & Health, UNSW, Sydney, Australia

[11]AW Morrow Gastroenterology Centre, Royal Prince Alfred Hospital, Sydney, Australia

[12]Department of Gastroenterology, The Alfred Hospital, Melbourne, Australia

[13]Department of Gastroenterology, Austin Hospital, Melbourne, Australia

[14]Department of Medicine, Austin Academic Centre, The University of Melbourne, Melbourne, Australia

[15]Department of Anatomical Pathology, Concord Repatriation General Hospital, Sydney, Australia

Grant support

Takeda Australia, Crohn's Colitis Australia

The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Abbreviations

UC (ulcerative colitis), TNFα (tumor necrosis factor alpha), 6-TGN (6-thioguanine nucleotide), CRP (C-reactive protein), CTCAE (common terminology criteria for adverse events), SD (standard deviation), IQR (interquartile range), OR (odds ratio), HR (hazard ratio)

Correspondence

Dr Aviv Pudipeddi

Level 1 West, Department of Gastroenterology and Hepatology, Concord Repatriation General Hospital, Hospital Road, Concord NSW 2139, Australia

Tel: 612 97676111 Fax: 612 97676767

Disclosures

Aviv Pudipeddi has received speaking and consulting fees from AbbVie and Takeda.

Sudarshan Paramsothy has received speaking and consulting fees from AbbVie, Janssen and Takeda.

Craig Haifer has received speaking and consulting fees from Takeda.

Jakob Begun has received speaking and consulting fees from Takeda.

Crispin Corte has received speaking and consulting fees from AbbVie, Takeda, Janssen, Pfizer, Ferring and Celltrion.

Mark Ward has received speaking and consulting fees from AbbVie, Takeda, Janssen and Pfizer.

Peter De Cruz has received speaking and consulting fees from AbbVie, Janssen and Celltrion.

Rupert Leong has received unrestricted funding from Takeda.

Viraj Kariyawasam, Ramesh Paramsothy, Simon Ghaly, Yoon-Kyo An, Susan Connor, Caroline Lan-San Fung, Diane Redmond, Webber Chan, Fadi Mourad and Melissa Kermeen disclose no conflicts.

Transcript profiling: nil

Writing assistance: nil

Author contributions

1. Aviv Pudipeddi: Literature search, study design, data collection and curation, data analysis, data interpretation, writing - original draft
2. Sudarshan Paramsothy: Supervision, data interpretation, writing - review and editing
3. Viraj Kariyawasam: Data collection, writing - review and editing
4. Ramesh Paramsothy: Data collection, writing - review and editing
5. Simon Ghaly: Data collection, writing - review and editing
6. Craig Haifer: Data collection, writing - review and editing
7. Yoon-Kyo An: Data collection, writing - review and editing
8. Jakob Begun: Data collection, writing - review and editing
9. Susan J Connor: Data collection, writing - review and editing
10. Crispin Corte: Data collection, writing - review and editing
11. Mark Ward: Data collection, writing - review and editing
12. Peter De Cruz: Data collection, writing - review and editing
13. Caroline Fung: Data analysis, writing - review and editing
14. Diane Redmond: Project administration, resources, supervision
15. Webber Chan: Conceptualisation, study design, writing - review and editing

16. Fadi Mourad: Conceptualisation, study design, writing - review and editing
17. Melissa Kermeen: Project administration, IRB communication, supervision
18. Rupert Leong: Conceptualisation, study design, supervision, data analysis, data interpretation, writing - review and editing

ABSTRACT

Background and aims: The benefit of continuing thiopurine with vedolizumab versus vedolizumab monotherapy for patients with ulcerative colitis (UC) is unclear. We aimed to determine the effect of thiopurine withdrawal for patients with UC in remission on vedolizumab.

Methods: This multi-centre randomized controlled trial recruited UC patients on vedolizumab 300mg IV every 8 weeks and a thiopurine. Patients in steroid-free clinical remission for ≥6 months and endoscopic remission/improvement (Mayo endoscopic subscore[MES]≤1) were randomized 2:1 to withdraw or continue thiopurine. Primary outcome was comparing week 48 vedolizumab trough concentrations. Secondary outcomes were clinical relapse (partial Mayo score≥3 and fecal calprotectin>150μg/g or increase in MES≥1 from baseline), fecal calprotectin remission (<150μg/g), C-reactive protein remission (<5mg/L), centrally-read endoscopic remission (MES=0), histologic remission (Nancy index=0), histo-endoscopic remission and adverse events.

Results: In total, 62 patients were randomized to withdraw (n=42) or continue (n=20) thiopurine. At week 48, vedolizumab trough concentrations were not significantly different between continue and withdrawal groups (14.7μg/mL [IQR:12.3-18.5μg/mL] versus 15.9μg/mL [IQR:10.1-22.7μg/mL] respectively, *P*=0.36). The continue group had significantly higher fecal calprotectin remission (95.0% [19/20] versus 71.4% [30/42], Δ23.6% [95%CI:2.4%-38.5%],*P*=0.03), histologic remission (80.0% [16/20] versus 48.6% [18/37], Δ31.4% [95%CI:5.0%-52.1%],*P*=0.02) and histo-endoscopic remission (75.0% [15/20] versus 32.4% [12/37], Δ42.6% [95%CI:15.6%-63.2%],*P*=0.002) than the withdrawal group. Histological activity at baseline (HR:15.5 [95%CI:1.6-146.5],*P*=0.02) and prior anti-TNF exposure (HR:6.5 [95%CI:1.3-33.8],*P*=0.03) predicted clinical relapse after thiopurine withdrawal.

Conclusion: Thiopurine withdrawal did not affect vedolizumab trough concentrations. However, it was associated with increased fecal calprotectin, histologic and histo-endoscopic activity. Histological activity and prior anti-TNF exposure predicted disease relapse upon thiopurine withdrawal for patients using vedolizumab for UC.

This trial was registered with the Australian and New Zealand Trial Registry, number ACTRN 12618000812291.

Keywords: vedolizumab**;** thiopurine; combination; withdrawal

5.1 INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon characterized by immunologically-driven progressive intestinal damage.[1] A therapeutic ceiling is recognized with current advanced therapies, so therefore, newer treatment strategies are needed to maximize treatment effectiveness.[2] Tumour necrosis factor alpha (TNFα) inhibitor monoclonal antibodies are prone towards immunogenicity, which might result in loss of response.[3] To optimize their effectiveness, combining anti-TNFα agents with thiopurine immunomodulators has been shown to increase drug concentrations, reduce immunogenicity, and improve clinical and endoscopic remission rates in inflammatory bowel diseases.[4,5,6] However, the benefit of thiopurine therapy with vedolizumab is less clear. Vedolizumab is manufactured using the phage display technique of humanized IgG1 antibody structure which is less prone towards anti-vedolizumab antibody development.[7] Despite this, however, neutralising anti-vedolizumab antibodies have been identified in clinical trials at a rate of up to 6%.[8] Although overall treatment persistence is high in UC, up to 39% of patients lose response to vedolizumab after 1 year indicating a need to further optimize this drug.[9,10]

Most studies to date have not identified an incremental benefit of thiopurine co-therapy with vedolizumab.[11] Limitations of these studies, however, include retrospective study designs which have been unclear as to whether thiopurines were discontinued during treatment maintenance[12,13,14], short durations of follow-up of less than six months[15,16], and heterogeneity in definitions of clinical benefit in systematic analyses.[11,17] Real-world data demonstrated thiopurine co-therapy with vedolizumab may lower the risk of treatment failure compared with vedolizumab monotherapy.[18] However, selection bias is possible over use- and non-use of thiopurines, and other real-world cohort data did not identify such benefit.[9]

Furthermore, there is a lack of prospective controlled data examining the impact of thiopurines on serum vedolizumab trough concentrations, and the safety signal of thiopurine when combined with vedolizumab in UC. It is also relevant to compare study arms using the more stringent endpoints of histological remission and histo-endoscopic remission which are increasingly important in UC.[19] The Vedolizumab Immunomodulator Enforced Withdrawal Study (VIEWS) aimed to assess the impact of withdrawing thiopurine therapy in vedolizumab-treated patients with UC in remission on combination therapy.

5.2 Materials and Methods

5.2.1 Study design and participants

This multi-centre, randomized, single-blind trial of withdrawing or continuing thiopurine therapy in vedolizumab-treated patients with UC was conducted at nine hospitals in Australia. Patients aged ≥ 18 years with a diagnosis of UC on vedolizumab 300mg intravenously every 8 weeks and a thiopurine (azathioprine, mercaptopurine or tioguanine) for more than 6 months were assessed for eligibility. Dosing for azathioprine and mercaptopurine was 2-2.5mg/kg/day and 1-1.5mg/kg/day respectively, or a 6-thioguanine nucleotide (6-TGN) metabolite level >235 pmol/8 × 10^8 erythrocytes, or the maximally tolerated dose. Tioguanine dosing was 20mg daily or the maximally tolerated dose. In Australia, UC patients are required to have failed at least 3 months of an immunomodulator prior to initiation of vedolizumab. Resultantly, most patients are on combination therapy with a thiopurine at the time of vedolizumab initiation.

Eligible patients were in corticosteroid-free clinical remission (partial Mayo score ≤2 with no sub-score >1) for at least 6 months and endoscopic remission/improvement (Mayo endoscopic score of 0 or 1). Concomitant use of oral mesalazine was permitted and patients were required to continue a stable dose during the trial period (see Table 5.1 for full inclusion criteria). Patients were excluded if they had indeterminate colitis or Crohn's disease, had used oral or rectal steroids in the six months prior to screening, had a prior ostomy or ileoanal pouch, or had used another biological agent or oral small molecule agent in the six months prior to screening (see Table 5.2 for full exclusion criteria).

Table 5.1. Inclusion criteria

Patients must meet all the following inclusion criteria at enrolment to be eligible to participate
1. Age ≥ 18 years
2. Ulcerative colitis
3. Steroid-free clinical remission for at least 6 months
4. Treated with a combination of vedolizumab and a thiopurine for at least the preceding 6 months
5. Scheduled administration of vedolizumab 300mg every 8 weeks during the preceding 6 months
6. Appropriate and stable dose of thiopurine for the preceding 3 months
7. Appropriate dose of thiopurine is defined as: a) Azathioprine: maintenance dose of 2-2.5mg/kg/day OR 6TGN level > 235 pmol/8 × 10^8 erythrocytes OR the maximally tolerated dose b) Mercaptopurine: maintenance dose of 1-1.5mg/kg/day OR 6TGN level > 235 pmol/8 × 10^8 erythrocytes OR the maximally tolerated dose
8. Mayo endoscopic score 0 or 1 at baseline in the 12 weeks preceding randomisation
9. Contraceptive use during the whole study for childbearing female patients
10. Provide written informed consent to participate as shown by a signature on the consent form

Table 5.3. Exclusion criteria

Patients must not meet any of the following exclusion criteria at enrolment to be eligible to participate
1. Consent not obtained or unable to give informed consent
2. Unable to communicate with the investigators and comply with the study requirements
3. Females who are pregnant or actively trying to fall pregnant
4. Patients unwilling to practice an effective method of contraception throughout the study period
5. Patients with an ostomy or ileoanal pouch
6. Patients who had used steroid therapy in the last 6 months prior to screening
7. A diagnosis of Crohn's disease or indeterminate colitis
8. Other biologic use (not vedolizumab), Janus kinase (JAK) inhibitor use or other trial therapies in the last 6 months prior to screening

This investigator-initiated study was approved by the Concord Repatriation General Hospital Human Research Ethics Committee (HREC/17/CRGH/22). Written informed consent was obtained from all patients before screening. This trial is registered with the Australian and New Zealand Trial Registry, number ACTRN 12618000812291.

5.2.2 Randomisation

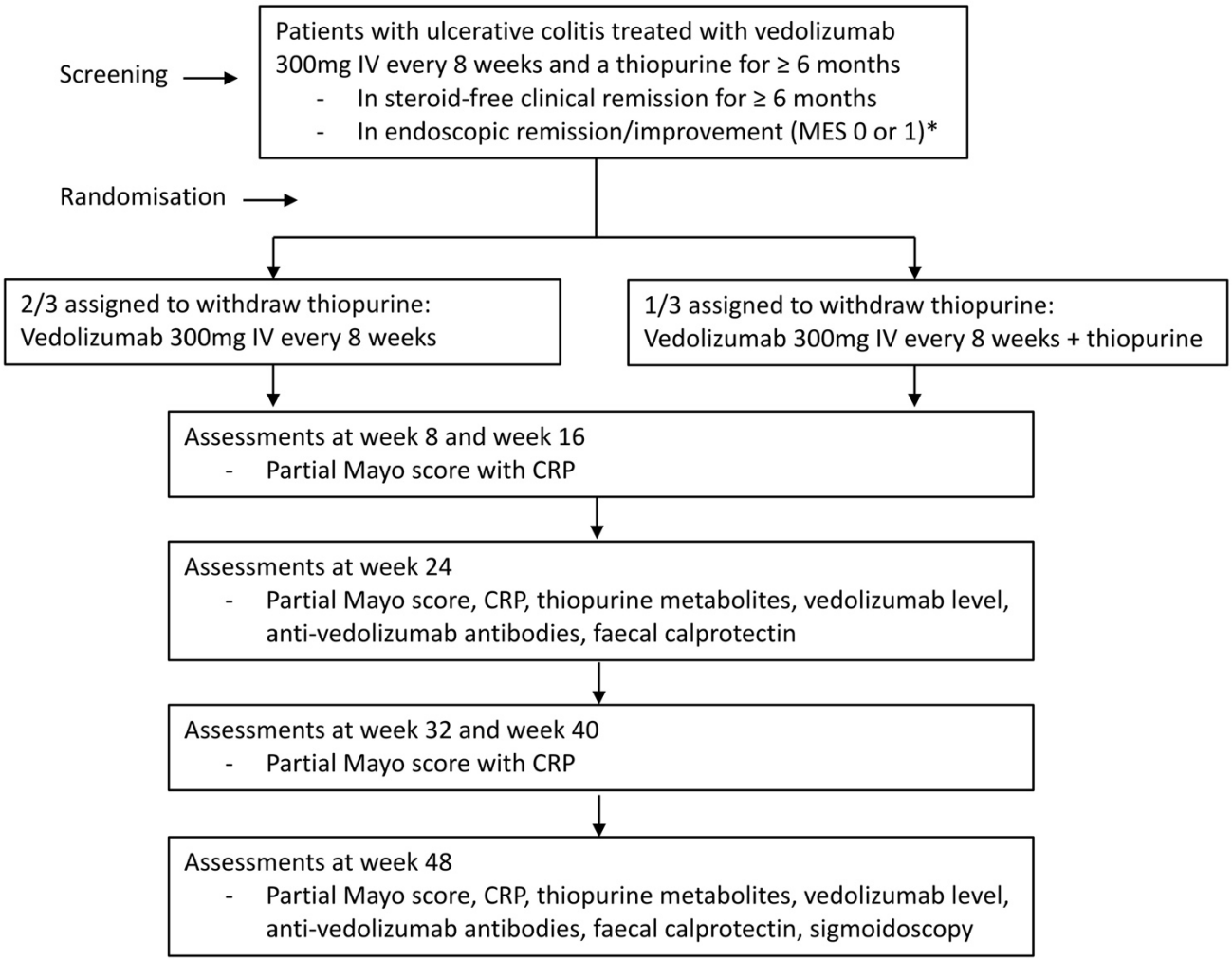
Patients were randomised centrally in a 1:2 ratio to either continue thiopurine use ('continue' group) or withdraw thiopurine ('withdrawal' group), using a computer-generated randomization list. Study investigators who were involved in patients' clinical assessments were blinded to the arm to which patients were randomized. Endoscopic images and histology slides were both read centrally by two expert gastroenterologists (SP, CH) and a histopathologist (CF) respectively, who were blinded to the treatment allocation.

5.2.3 Procedures

Blood tests and a flexible sigmoidoscopy with standardized biopsies were performed at screening. For sites unable to perform a sigmoidoscopy due to the COVID-19 pandemic, a fecal calprotectin of less than 100 μg/g was used as a surrogate marker for endoscopic remission.[20]

Scheduled study visits occurred at weeks 0, 8, 16, 24, 32, 40 and 48 to assess for symptoms, adherence and adverse events (Figure 5.1). A partial Mayo score was calculated for stool frequency, rectal bleeding and physician's global assessment. Blood tests, including C-reactive protein (CRP), were performed at each study visit. Vedolizumab trough concentrations, anti-vedolizumab antibody concentrations and fecal calprotectin were performed at week 0, 24 and 48. Thiopurine metabolite levels were performed at weeks 0, 24 and 48 to objectively assess for adherence to patients' randomisation group. A study-completion sigmoidoscopy with biopsies was performed at week 48 (depending on site endoscopy protocol during the COVID-19 pandemic). If a clinical relapse was suspected, patients underwent a partial Mayo score assessment, blood tests including CRP and vedolizumab trough and antibody concentrations, stool testing including a fecal calprotectin, and a sigmoidoscopy with biopsies (depending on site endoscopy protocol during the COVID-19 pandemic). Adverse events were classified in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. An independent Data Safety Monitoring Board reviewed masked safety data and approved study continuation in the absence of safety concerns of ongoing use of thiopurines.

Figure 5.1. Trial design



*if unable to perform sigmoidoscopy due to COVID-19, then faecal calprotectin <100μg/g was accepted
IV=intravenous. CRP=C-reactive protein.

Endoscopic disease activity was assessed at each sigmoidoscopy using the Mayo endoscopic subscore. Protocolized 2-4 biopsies using standard forceps were taken at every colonoscopy / sigmoidoscopy 20-30cm proximal to the anal verge and also at the most inflamed site, with the most severely active area used to define histological activity and described using the Nancy score.[21]

Vedolizumab trough concentrations were analyzed at QPS Holdings LLC (Newark, DE, USA) core laboratory using an enzyme-linked immunosorbent assay and qualitative anti-vedolizumab antibodies, including neutralizing antibodies, were analyzed using electrochemiluminescence independent to drug concentrations. Fecal calprotectin levels were analyzed at QML Pathology (Murarrie, Queensland, Australia) using the DiaSorin Liaison® Calprotectin assay (DiaSorin, Saluggia, Italy).

5.2.4 Outcomes

The primary outcome was comparing the week 48 vedolizumab trough concentrations between the continue and withdrawal groups. Secondary outcomes were: proportion of patients who remained in clinical remission; proportion of patients who had a clinical relapse up to week 48 (defined as a partial Mayo score ≥3 and fecal calprotectin >150 μg/g or ≥1-point increase in the Mayo endoscopic subscore from baseline sigmoidoscopy); fecal calprotectin remission (defined as less than 150 μg/g) and change in fecal calprotectin level; CRP remission (defined as less than 5 mg/L) and change in CRP; endoscopic remission (defined as Mayo endoscopic subscore of 0); histologic remission (defined as Nancy score of 0); combined histo-endoscopic remission (defined as Mayo endoscopic subscore of 0 and Nancy score of 0); and rates of adverse events. Histologic outcomes were added after the trial commenced due to its recent increasing importance in UC clinical trials.[19]

5.2.5 Sample Size Calculation and Statistical Analysis

Based on available data on longer term vedolizumab trough concentrations at the time the study was designed, our sample size calculation assumed a vedolizumab trough concentration of 8.8 μg/mL in the continue group and 5.2 μg/mL in the withdrawal group.[22] A total of 60

subjects recruited at a ratio of 1:2 into the continue- versus withdrawal- arms are required to demonstrate the difference in vedolizumab trough levels between groups with 80% power on a two-sided alpha of 0.05 on an intention-to-treat analysis. A total of 66 subjects were recruited to permit 10% subject drop-out rate. The modified intention-to-treat analysis included all patients who reached week 24 of the study (first vedolizumab trough concentration after baseline) or had a clinical relapse. Missing values were imputed with the use of the last observation carried forward method for measurements made after baseline.

Parametric continuous variables were described as mean ± standard deviation (SD) and compared with the unpaired *t*-test. Non-parametric continuous variables were described as median (interquartile range, IQR) and compared with the Mann-Whitney *U* test. Categorical data was analyzed using the chi-square test (or Fisher's exact test, where indicated). Kaplan-Meier survival curves with log rank testing was used to compare disease relapse-free survival. Univariable and multivariable survival analysis using Cox proportional-hazards regression was performed to identify variables associated with disease relapse. All variables with *P*-values <0.1 on univariate analysis were retained and integrated into the multivariable analysis. *P*-values <0.05 were deemed to be statistically significant. Statistical analyses were completed using IBM SPSS version 29.0 (SPSS Inc., Chicago, Ill., USA).

5.3 Results

Between Sept 2018, and Dec 2021, 74 patients were screened (Figure 5.2). Of these, 10 patients were excluded due to active disease (Mayo endoscopic subscore > 1) on sigmoidoscopy (n=5), undetectable TGN level due to cessation of thiopurine (n=4) and a clinical relapse prior to randomization (n=1). Hence, 64 patients were randomly assigned to withdraw thiopurine therapy (n=43) or continue (n=21). Two patients withdrew from the study. One patient in the withdrawal group moved overseas after week 8, and one patient in the continue group had a change in their vedolizumab dosing schedule to every 10 weeks after their week 0 visit. As such, 62 patients (withdrawal, n=42 and continue, n=20) were included in the modified intention-to-treat analysis. Patient and disease characteristics were similar between the two groups (Table 5.3).

Figure 5.2. Trial profile

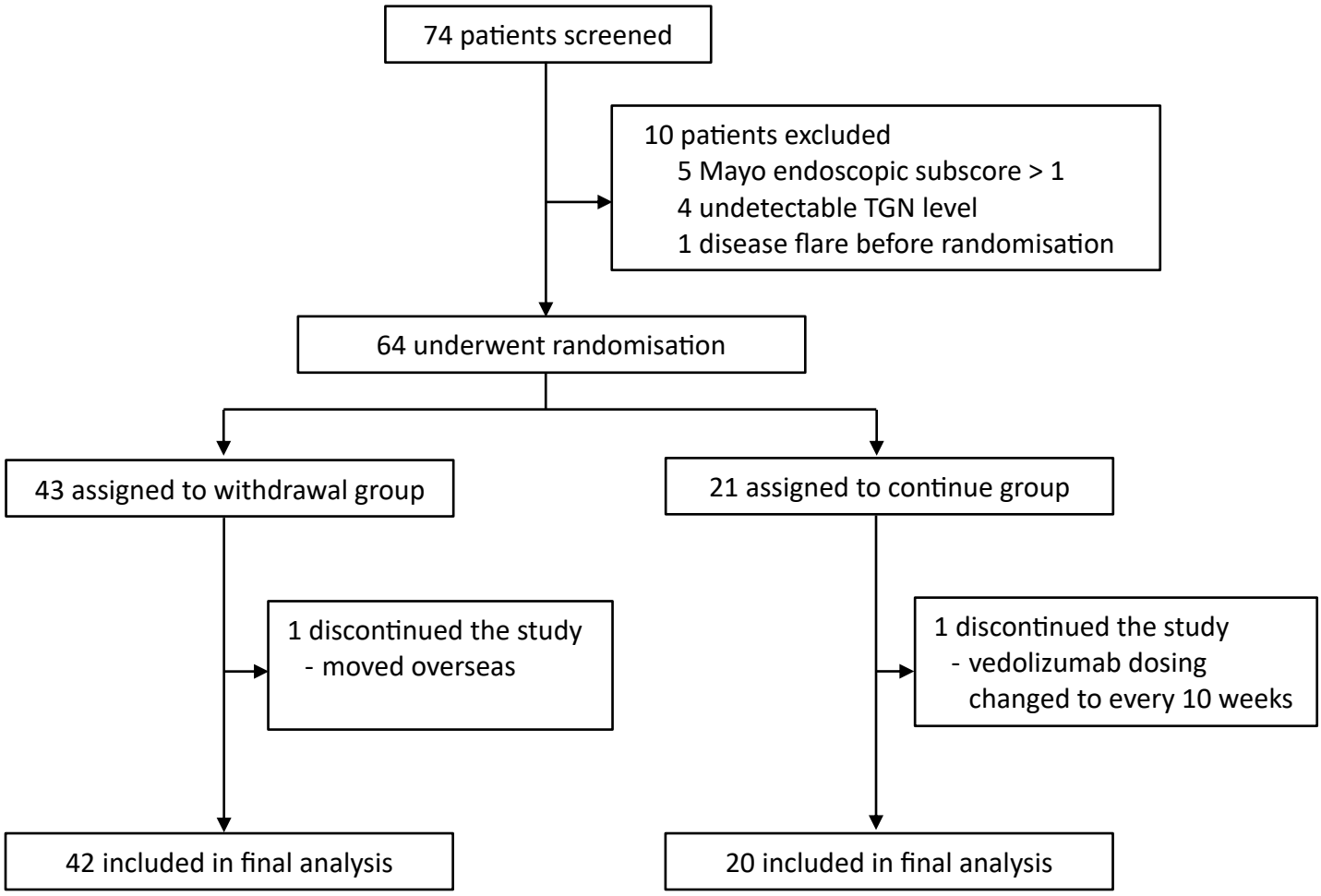


Table 5.3. Patient and disease characteristics at baseline.

	Withdrawal group (N=42)	Continue group (N=20)
Patient characteristics		
Male sex – no. (%)	21 (50.0%)	15 (75.0%)
Age – year	41.5 (26.8-60.3)	46.0 (27.3-53.0)
Smoking status – no. (%)		
Current	2 (4.7%)	2 (10.0%)
Ex-smoker	9 (21.4%)	4 (20.0%)
Never smoked	31 (73.8%)	14 (70.0%)
Disease characteristics		
Disease duration – yr	8.0 (3.0-13.0)	6.5 (4.0-11.8)
Disease extent – no. (%)		
Proctitis	3 (7.1%)	0 (0.0%)
Left-sided colitis	24 (57.1%)	14 (70.0%)
Pancolitis	15 (35.7%)	6 (30.0%)
Concomitant mesalazine – no. (%)	33 (78.5%)	16 (80.0%)
Prior anti-TNF exposure – no. (%)	12 (28.5%)	4 (20.0%)
C-reactive protein – mg/litre	1.2 (0.0-2.8)	0.8 (0.4-3.5)
Faecal calprotectin – µg/g	18.6 (7.3-54.7)	36.3 (7.8-97.2)
TGN level – pmol/8x10^8	298.8 (187.1)	314.0 (178.0)
Endoscopic activity – no. (%)†‡		
MES 0	28 (77.8%)	15 (83.3%)
MES 1	8 (22.2%)	3 (16.7%)

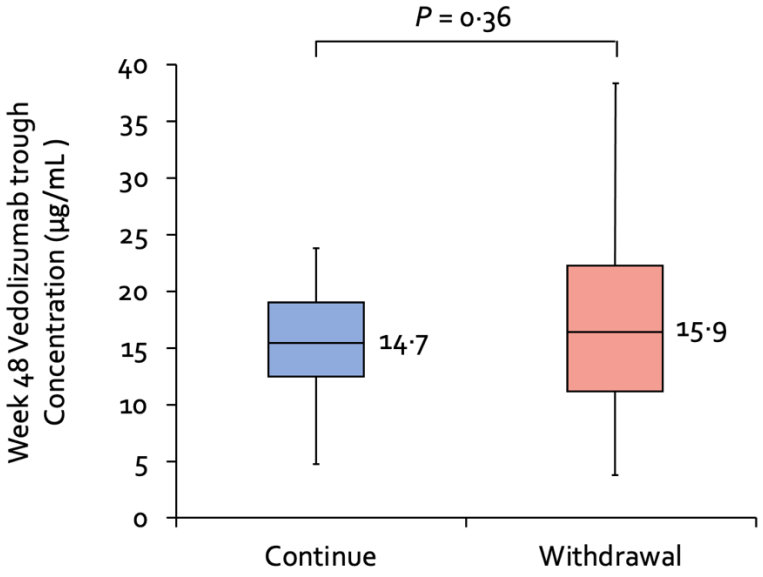
Data are n (%), median (IQR) or mean (SD). TNF=tumour necrosis factor. TGN=thioguanine nucleotide. MES=Mayo endoscopic subscore.
†Mayo endoscopic subscore (MES) ranges from 0 to 3 and is based on endoscopic findings. The percentages described are based on the total number of patients who had a screening sigmoidoscopy.
‡ Endoscopic images were read by two central readers, with blinded adjudication by a third central reader when necessary

5.3.1 Primary outcome

At week 48, vedolizumab trough concentrations were 14.7µg/mL (IQR: 12.3-18.5µg/mL) in the continue group versus 15.9µg/mL (IQR: 10.1-22.7µg/mL) in the withdrawal group (*P*=0.36; Figure 5.3). No anti-vedolizumab antibodies were detected in either group. Change in vedolizumab trough concentration from week 0 to week 48 was -0.2µg/mL (IQR: -1.7-

2.5μg/mL) in the continue group versus -0.1μg/mL (IQR: -3.4-2.3μg/mL) in the withdrawal group (*P*=0.44).

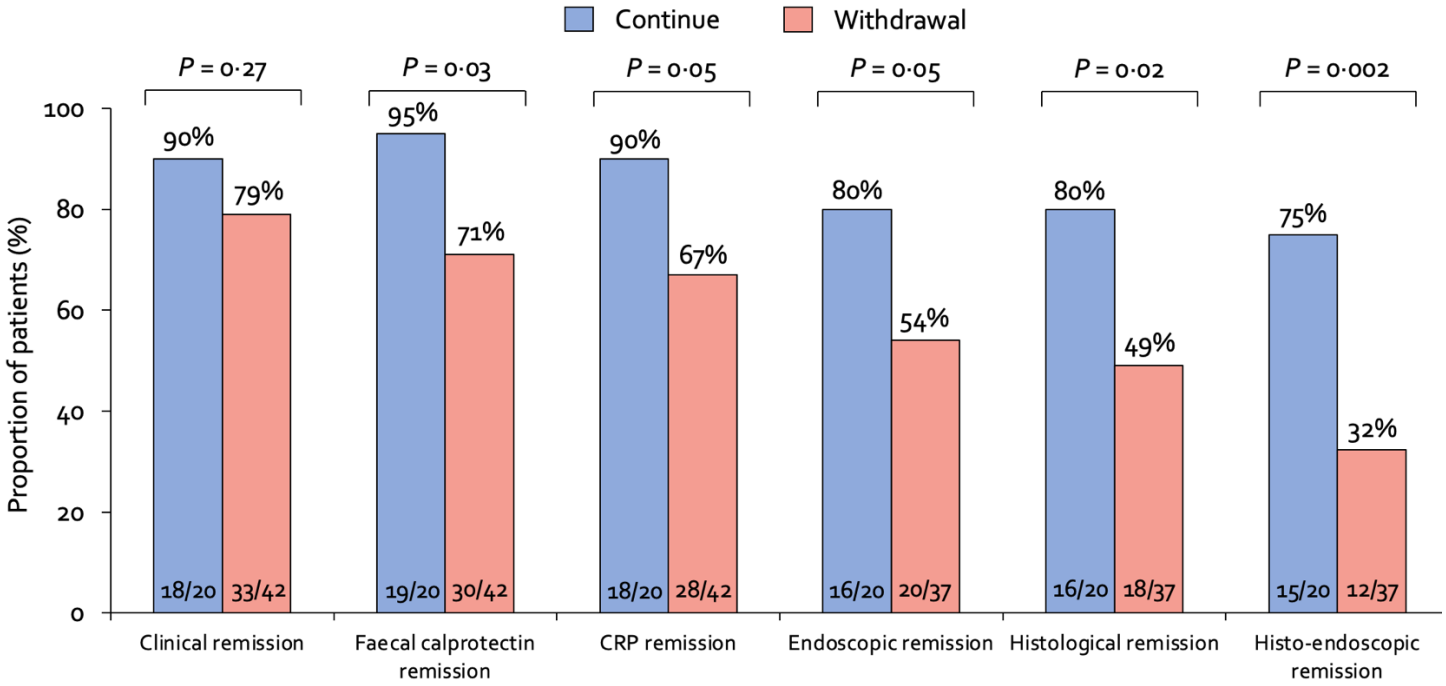
Figure 5.3. Vedolizumab trough concentration at week 48 in continue and withdrawal groups



5.3.2 Secondary outcomes

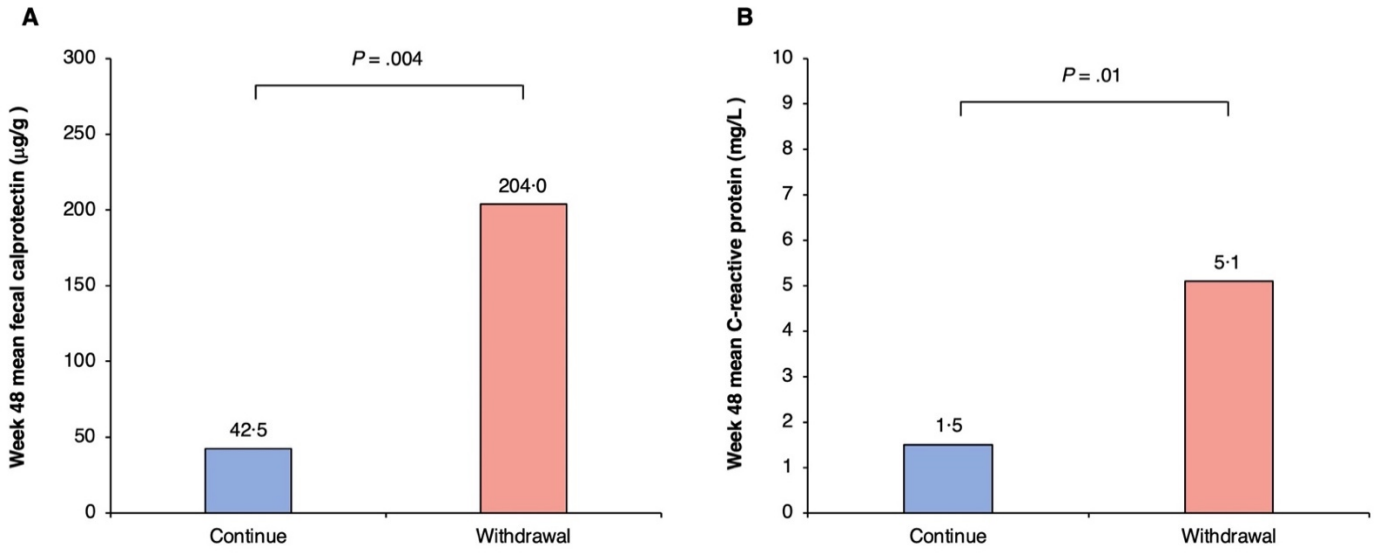
By week 48, 90.0% (18/20) of patients in the continue group and 78.6% (33/42) of patients in the withdrawal group were in clinical remission (difference 11.4%, 95%CI: -9.9% - 28.0%, *P*=0.27; odds ratio [OR] 2.5, 95%CI: 0.5-12.7; Figure 5.4). Faecal calprotectin remission occurred in 95.0% (19/20) of patients in the continue group and 71.4% (30/42) of patients in the withdrawal group (difference 23.6%, 95%CI: 2.4%-38.5%, *P*=0.03; OR: 7.6, 95%CI: 1.0-62.5; Figure 5.4). Week 48 mean faecal calprotectin level was 43.3μg/g (SD 52.7μg/g) in the continue group and 204.0μg/g (SD 336.8μg/g) in the withdrawal group (difference 160.6 μg/g, 95% CI 53.3 – 267.9μg/g, *P*=0.004; Figure 5.5). Mean change in faecal calprotectin was -47.4μg/g (SD 111.6 μg/g) in the continue group and 137.1μg/g (SD 281.5 μg/g) in the withdrawal group (difference 184.6μg/g, 95% CI 83.6 – 285.5μg/g, *P*<0.001).

Figure 5.4. Secondary outcomes



Clinical relapse was defined as a partial Mayo score ≥3 and faecal calprotectin >150 µg/g or ≥1-point increase in the Mayo endoscopic subscore from baseline sigmoidoscopy. Faecal calprotectin remission was defined as < 150 µg/g. CRP remission was defined as < 5mg/L. Endoscopic remission was defined as Mayo endoscopic subscore of 0. Histological remission was defined as a Nancy index of 0. Histo-endoscopic remission was defined as a combination of endoscopic and histological remission.
Nominal *P*-values described.

Figure 5.5. Mean faecal calprotectin (A) and C-reactive protein (B) at week 48 in continue and withdrawal groups



CRP remission occurred in 90.0% (18/20) patients in the continue group and 66.7% (28/42) of patients in the withdrawal group (difference 23.3%, 95%CI: 0.4%-40.5%, *P*=0.05; OR: 4.5, 95%CI: 0.9-22.2; Figure 5.4). Week 48 mean CRP level was 1.9mg/L (SD 2.5mg/L) in the continue group and 5.1mg/L (SD 8.5mg/L) in the withdrawal group (difference 3.2mg/L, 95%CI: 0.3–6.0mg/L, *P*=0.03; Figure 5.5). Mean change in CRP level was 0.3mg/L (SD 1.1mg/L) in the continue group and 2.5mg/L (SD 7.5mg/L) in the withdrawal group (difference 2.2mg/L, 95%CI: -0.1 - 4.6mg/L, *P*=0.07).

Endoscopic remission was noted in 80.0% (16/20) patients in the continue group and 54.1% (20/37) of patients in the withdrawal group (difference 25.9%, 95%CI: -0.1% - 46.9%, *P*=0.05; OR: 3.4, 95%CI: 0.95-12.2; Figure 5.4). Histologic remission was noted in 80.0% (16/20) of patients in the continue group and 48.6% (18/37) of patients in the withdrawal group (difference 31.4%, 95%CI: 5.0% - 52.1%, *P*=0.02; OR: 4.2, 95%CI: 1.2-15.2; Figure 5.4). Histo-endoscopic remission was noted in 75.% (15/20) of patients in the continue group and 32.4% (12/37) of patients in the withdrawal group (difference 42.6%, 95%CI: 15.6%-63.2%, *P*=0.002; OR: 6.3, 95%CI: 1.8-21.3; Figure 5.4).

Clinical relapses occurred in 10.0% (2/20) of patients in the continue group and 21.4% (9/42) of patients in the withdrawal group by week 48 (difference 11.4%, 95%CI: -9.9% - 28.0%; OR: 2.5, 95%CI: 0.5-12.6, *P*=0.27; Figure 5.6). On multivariable analysis, histological activity at baseline was associated with clinical relapse by week 48 (adjusted hazard ratio [aHR]: 7.6, 95%CI: 1.4-42.5, *P*=0.02; Table 5.4). When examining the withdrawal group alone, clinical relapse was associated with baseline histological activity (aHR: 15.5, 95%CI: 1.6-146.5, *P*=0.02;

Table 5.5 and Figure 5.7A) and prior anti-TNF exposure (aHR: 6.5, 95%CI: 1.3-33.8, *P*=0.03; Table 5.5 and Figure 5.7B).

Table 5.4. Univariable and multivariable Cox regression analysis for clinical relapse-free survival in total population at week 48

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Mean age, years	1.01 (0.98-1.04)	0.55		
Sex				
Male vs female	7.69 (0.98-60.14)	0.05	2.41 (0.26-22.85)	0.44
Smoking				
Ex- vs never-smoker	1.63 (0.43-6.16)	0.47		
Current- vs never-smoker	0.04 (0.00-2480.27)	0.58		
Current- vs ex-smoker	0.03 (0.00-1559.83)	0.53		
Extent of UC				
Pancolitis vs left-sided colitis	0.66 (0.18-2.49)	0.54		
Disease duration				
>5 years vs <5 years	5.33 (0.68-41.69)	0.11		
Oral mesalazine use	0.68 (0.18-2.57)	0.57		
Prior anti-TNF exposure	4.77 (1.45-15.65)	0.01	2.21 (0.49-9.91)	0.30
Albumin level at week 0	1.04 (0.92-1.18)	0.50		
TGN level at week 0	1.00 (0.99-1.00)	0.38		
Vedolizumab trough concentration week 0	0.95 (0.86-1.05)	0.29		
Screening MES				
MES 1 vs MES 0	1.30 (0.26-6.46)	0.75		
Histological activity at baseline	12.22 (2.45-60.90)	0.002	7.58 (1.35-42.50)	0.02
Randomisation				
Withdrawal vs continue	2.27 (0.49-10.53)	0.29		

The variables with univariate analysis *P*-value <0.1 were included in the multivariate analysis. HR=hazard ratio. CI=confidence interval. UC=ulcerative colitis. TNF=tumour necrosis factor. TGN=thioguanine nucleotide. MES=Mayo endoscopic subscore.

Table 5.5. Univariate and multivariate Cox regression analysis for clinical relapse-free survival in the withdrawal group at week 48

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Mean age, years	1.02 (0.99-1.06)	0.23		
Sex				
Male vs female	8.93 (1.12-71.59)	0.04	1.95 (0.20-19.27)	0.57
Smoking				
Ex- vs non-smoker	2.51 (0.63-10.03)	0.20		
Current- vs non-smoker	0.06 (0.00-92449.96)	0.68		
Current- vs ex-smoker	0.03 (0.00-3716.47)	0.57		
Extent of UC				
Pancolitis vs left-sided colitis	0.78 (0.19-3.10)	0.72		
Disease duration				
>5 years vs <5 years	4.18 (0.52-33.43)	0.18		
Oral mesalazine use	0.50 (0.13-2.02)	0.33		
Prior anti-TNF exposure	8.23 (2.05-33.16)	0.003	6.52 (1.26-33.78)	0.03
Albumin level at week 0	1.04 (0.92-1.17)	0.55		
TGN level at week 0	1.00 (0.99-1.00)	0.32		
Vedolizumab trough concentration week 0	0.94 (0.85-1.04)	0.23		
Screening MES				
MES 1 vs MES 0	1.41 (0.28-7.42)	0.67		
Histological activity at baseline	19.55 (2.33-164.03)	0.006	15.51 (1.64-146.46)	0.02

The variables with univariate analysis *P*-value < 0.1 were included in the multivariate analysis. HR=hazard ratio. CI=confidence interval. UC=ulcerative colitis. TNF=tumour necrosis factor. TGN=thioguanine nucleotide. MES=Mayo endoscopic subscore.

Figure 5.6. Kaplan-Meier graph demonstrating clinical relapse-free survival in continue and withdrawal groups at week 48

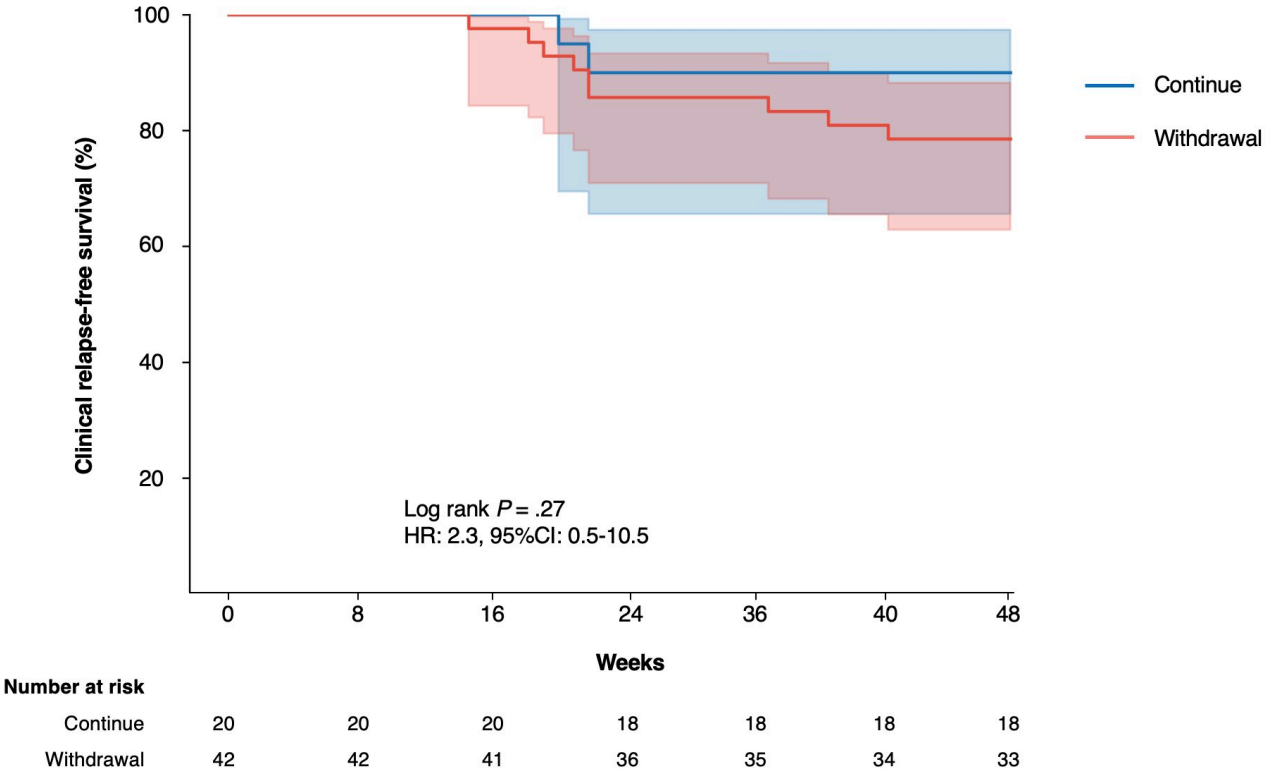
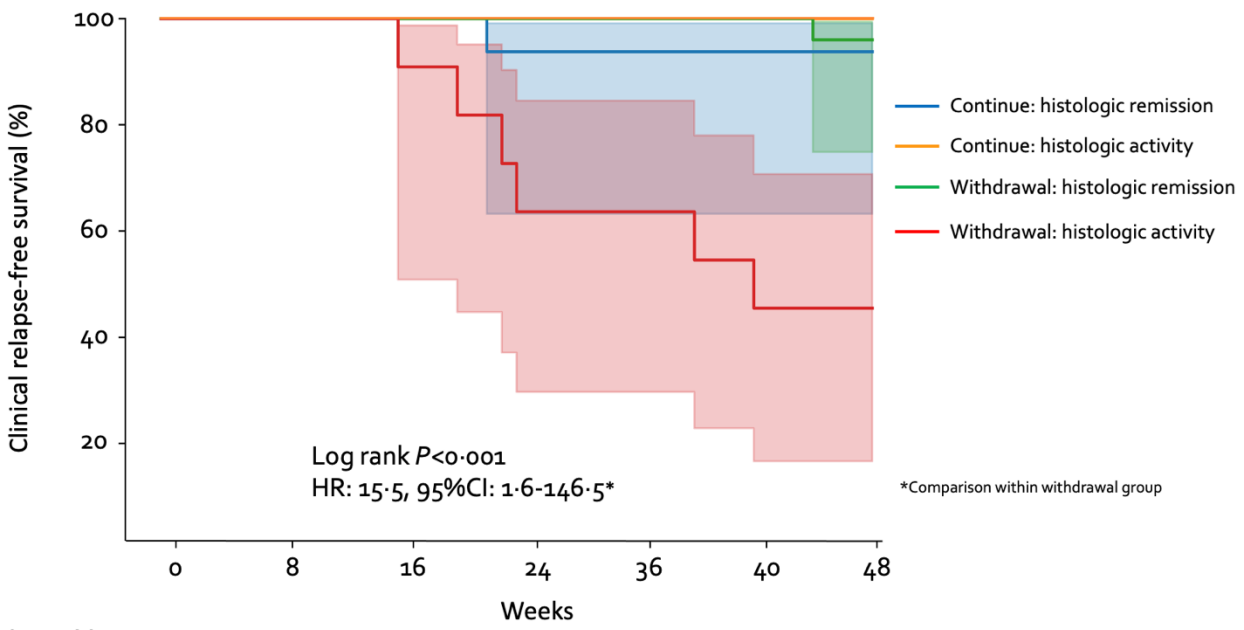


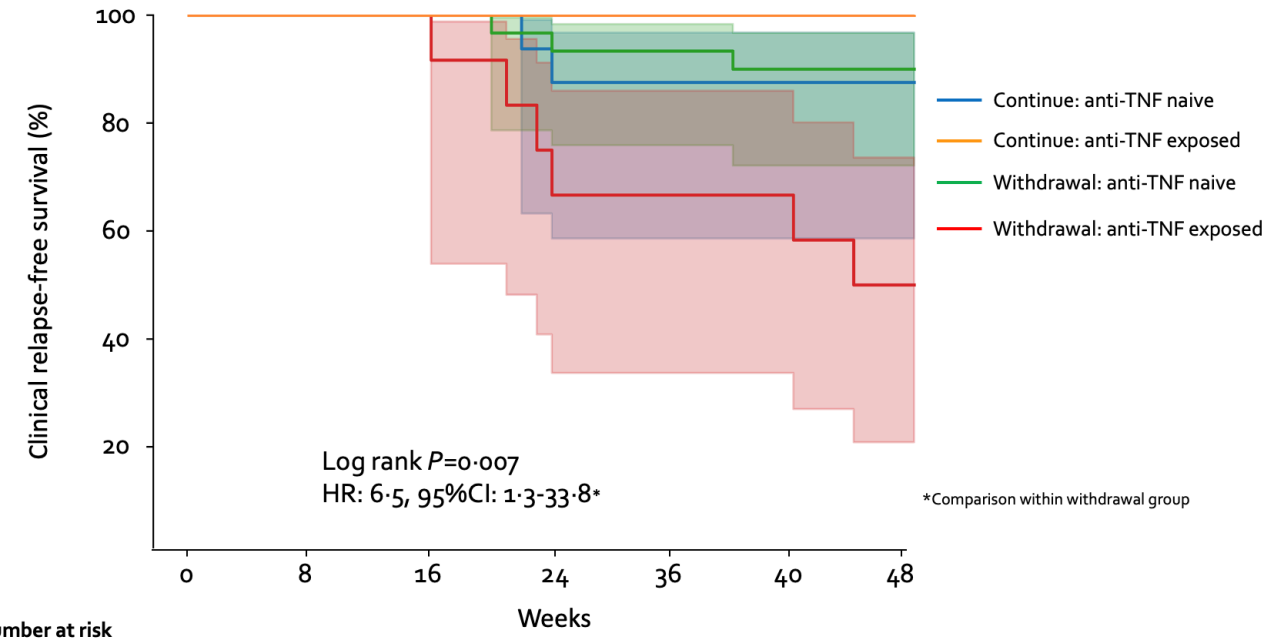
Figure 5.7. Kaplan-Meier graph demonstrating clinical relapse-free survival between continue and withdrawal groups stratified by (A) baseline histological activity, and (B) prior anti-TNF exposure

A



Number at risk							
Continue: histologic remission	15	15	15	14	14	14	14
Continue: histologic activity	1	1	1	1	1	1	1
Withdrawal: histologic remission	25	25	25	25	25	25	24
Withdrawal: histologic activity	11	11	10	7	7	5	5

B



Number at risk							
Continue: anti-TNF naive	16	16	16	14	14	14	14
Continue: anti-TNF exposed	3	3	3	3	3	3	3
Withdrawal: anti-TNF naive	30	30	30	28	27	27	27
Withdrawal: anti-TNF exposed	12	12	11	8	8	7	6

5.3.3 Adverse events

At least one adverse event occurred in 7 (35%) of 20 patients in the continue group and 5 (12%) of 42 patients in the withdrawal group (Table 5.6). Three (15%) patients in the continue group had an upper respiratory tract infection, one (5%) patient had gastroenteritis, and one (5%) patient had folliculitis. These were mild and did not require hospitalisation or discontinuation of thiopurine. Two (5%) patients in the withdrawal group had nasopharyngitis and blepharitis. There were no serious adverse events in either group. There were no cancers or deaths in either group during the study.

Table 5.6. Adverse events

	Withdrawal (n=42)	Continue (n=20)
Total adverse events	5	12
Total patients with a severe adverse event	0 (0%)	0 (0%)
Total patients with adverse events: n, (%)	5 (12%)	7 (35%)
Upper respiratory tract infection	1 (2%)	3 (15%)
Abdominal pain	1 (2%)	1 (5%)
Anaemia	0 (0%)	1 (5%)
Hypothyroidism	0 (0%)	1 (5%)
Acute kidney injury	0 (0%)	1 (5%)
Enterocolitis infectious	0 (0%)	1 (5%)
Arthritis	0 (0%)	2 (10%)
Folliculitis	0 (0%)	1 (5%)
Hypertension	0 (0%)	1 (5%)
Blepharitis	1 (2%)	0 (0%)
Osteoporosis	1 (2%)	0 (0%)
Peripheral sensory neuropathy	1 (2%)	0 (0%)

Data are number of events or number of patients (%)

5.4 Discussion

This randomised controlled study found that withdrawing thiopurine therapy does not affect vedolizumab trough concentrations for patients with UC. However, thiopurine withdrawal was associated with higher faecal calprotectin levels, and higher degree of endoscopic and histological activity, albeit in a smaller cohort. Overall, this study suggested that thiopurines might provide an incremental benefit to patients with UC using vedolizumab, which was independent of vedolizumab pharmacokinetics. Subjects with histological activity at baseline and prior anti-TNF exposure were more likely to relapse following thiopurine withdrawal.

There are limited prospective data on the pharmacokinetic effects of thiopurine therapy on vedolizumab trough concentrations. This is despite knowledge that loss of response to infliximab may occur due to the development of immunogenicity, particularly in the setting of infliximab monotherapy.[5,6] Prior studies of thiopurine co-therapy with vedolizumab have been limited by defining combination therapy as baseline thiopurine use at the initiation of vedolizumab, as opposed to continued thiopurine use.[7] This has led to widespread use of vedolizumab as monotherapy, which might have contributed to some eventual loss of response demonstrated in real world cohorts.[9,23] In this randomised trial, we have shown that vedolizumab trough concentrations are similar when thiopurines are continued or withdrawn. Furthermore, no anti-vedolizumab antibodies were detected in either group, demonstrating that unlike with infliximab, thiopurines are less likely to impact on immunogenicity rates. In Australia, requirements are for UC patients to have failed at least 3 months of an immunomodulator prior to vedolizumab initiation. Resultantly, UC patients are typically on combination therapy initially and hence this study was designed as a withdrawal trial.

Despite no pharmacokinetic effect on vedolizumab, we found that withdrawing thiopurine therapy led to increased inflammatory biomarker levels, with higher faecal calprotectin levels, as well as lower rates of endoscopic and histological remission. It should be noted that these were secondary outcomes and can be considered exploratory in nature given the primary outcome was not met. The benefit of thiopurines for patients with UC on vedolizumab has been questioned in recent years. Previous studies have shown that combination therapy with vedolizumab and thiopurines was not associated with superior clinical outcomes.[11] However, methodological flaws, heterogenous outcomes and shorter durations of treatment limit these findings. When considering our pharmacokinetic and clinical findings, thiopurines may provide an added immunosuppressive effect which is independent of vedolizumab pharmacokinetics. This is supported by recent data demonstrating greater rates of clinical remission and mucosal healing with combination therapy compared with monotherapy after sixty weeks, despite similar vedolizumab trough concentrations in both groups.[24] Also, in a recent large multicentre retrospective study, immunomodulator use was associated with clinical remission independent of vedolizumab concentration (OR: 2.8, 95%CI: 1.3-5.7, *P*=0.006).[25] These findings contrast to anti-TNF agents, whereby the predominant benefit of thiopurine co-therapy has been reduced immunogenicity and resultant improved clinical outcomes.[6] Our study found a more than doubling of clinical relapse rates in the withdrawal group (21.4% versus 10.0%), and although this was not significantly different, this study was likely underpowered and the findings hypothesis generating. Also, longer term follow-up past one year may be required to identify a significant clinical difference, as supported by recent evidence.[23]

Histological activity is an emerging endpoint in clinical trials.[19] Despite endoscopic remission, ongoing histological activity is associated with higher clinical relapse rates, hospitalisation and colectomy.[26,27] These data, however, have been mostly from retrospective cohorts without a standardized biopsy protocol, defined clinical and histological assessment definitions and time points, and other biases that might have accounted for their findings. We showed histological activity at baseline was associated with clinical relapse in the total population (HR: 7.6, 95%CI: 1.4-42.5, *P*=0.02), with the risk of relapse greatest in those withdrawing thiopurines based on a prospectively conducted endoscopic biopsy protocol.

Prior anti-TNF exposure was identified as being associated with clinical relapse for patients who withdrew thiopurine therapy on vedolizumab. Vedolizumab is more effective when used as a first-line biological agent compared with second-line use following anti-TNF agents.[9,28] These data may translate into caution against withdrawal of thiopurine immunomodulator in UC subjects refractory to prior anti-TNF and with histologic activity despite being in clinical and endoscopic remission. Our secondary findings suggest that patients with prior anti-TNF exposure should continue thiopurines whilst on vedolizumab to prevent a clinical relapse. Importantly, our study did show higher infections in the continue group. However these were all mild and did not require hospitalisation or discontinuation of the thiopurine. Nonetheless, safety considerations should be taken into account if continuing thiopurine therapy.

Our study has several strengths. This is the first prospective randomised controlled trial that has specifically examined the impacts of thiopurine co-therapy with vedolizumab in UC, which might reduce selection bias observed in use versus non-use of thiopurines in retrospective observational studies. Thiopurine use was verified by 6-TGN levels to ensure subjects

remained true to their randomization. Vedolizumab trough concentrations were performed centrally using a drug-tolerant assay. To our knowledge, there have been no published controlled data on thiopurine withdrawal in vedolizumab, and the long-term effectiveness of combination therapy on clinical, endoscopic and histological outcomes. Endoscopic and histological assessments were centralized and investigators performing clinical assessments were blinded to the study arm.

Study limitations include an inability to gather complete endoscopic and histological data due to the COVID-19 pandemic impacting on sigmoidoscopy procedures in some centres. However, we performed an urgent safety strategy to use a faecal calprotectin less than 100μg/g as a surrogate marker for endoscopic remission, which allowed recruitment to continue. As such, the COVID-19 pandemic did not impact on our ability to gather vedolizumab levels which was our primary outcome. Secondly, as this study had a negative primary outcome, secondary outcomes are considered exploratory and likely underpowered due to the smaller sample size. This may impact on odds ratio and hazard ratio values. Nonetheless, we still identified significant biochemical, endoscopic and histological differences between both groups. Thirdly, this was a single-blinded study, and subjects were aware of their thiopurine allocation. However, most endpoints were assessed independent to subjective symptoms by blinded staff, such as serum vedolizumab trough levels, biochemical activity, endoscopic activity, and histologic activity. Symptomatic activity had to be verified with objective endoscopic and biochemical evidence of inflammation to be defined as clinical relapse. Fourthly, the subjects' attending physicians may be aware of the thiopurine allocation. However, we encouraged sites to use an unblinded physician to prescribe the

thiopurines and some sites utilised a central unblinded physician to prescribe thiopurine directly to subjects randomized to the continue arm to maintain blinding at study sites.

5.5 CONCLUSION

In summary, the VIEWS study has demonstrated that thiopurine withdrawal does not impact on serum vedolizumab trough concentrations, nor the development of anti-vedolizumab antibodies, out to 1 year. However, it is associated with worse biochemical, endoscopic and histologic outcomes at one year. Histological activity at baseline and prior anti-TNF exposure were identified as factors associated with a clinical relapse in the withdrawal group. Although these secondary results should be interpreted with caution due to the smaller sample size, our novel exploratory findings will assist clinicians in decision-making prior to thiopurine de-escalation for patients with UC in clinical and endoscopic remission on vedolizumab.

5.6 REFERENCES

1. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. Lancet 2017;389(10080):1756-1770.
2. Alsoud D, Verstockt B, Fiocchi C, Vermeire S. Breaking the therapeutic ceiling in drug development in ulcerative colitis. Lancet Gastroenterol Hepatol 2021; 6(7):589-595.
3. Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol 2018; 11:1756283X17750355
4. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014; 146(2): 392-400.
5. Colombel JF, Sandborn W, Reinisch W, et al. Infliximab, azathioprine or combination therapy for Crohn's disease. N Engl J Med 2010; 362:1383-1395.
6. Colombel JF, Adedokun OJ, Gasink C, et al. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: a post hoc analysis. *Clin Gastroenterol Hepatol* 2019; 17(8): 1525-1532.
7. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; 369(8): 699-710.
8. Sandborn WJ, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020; 158(3): 562-572.
9. Ko Y, Paramsothy S, Yau Y, Leong R. Superior treatment persistence with ustekinumab in Crohn's disease and vedolizumab in ulcerative colitis compared with anti-TNF biological agents: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. Aliment Pharmacol Ther 2021; 54(3):292-301.
10. Shmidt E, Kochhar G, Hartke J, et al. Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. *Inflamm Bowel Dis* 2018; 24(11): 2461-2467.
11. Yzet C, Diouf M, Singh S, et al. No benefit of concomitant immunomodulator therapy on efficacy of biologics that are non tumor necrosis factor antagonists in patients with inflammatory bowel diseases: a meta-analysis. *Clin Gastroenterol Hepatol* 2021: 19(4): 668-679.
12. Shelton E, Allegretti J, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. Inflamm Bowel Dis 2015; 21(12):2879-2885.
13. Lenti MV, Levison S, Eliadou E, et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study. Dig Liver Dis 2018; 50(12):1299-1304.
14. Shmidt E, Kochhar G, Hartke J, et al. Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. Inflamm Bowel Dis 2018; 24(11):2461-2467.
15. Kopylov U, Verstockt B, BiedermannL, et al. Effectiveness and safety of vedolizumab in anti-TNF naïve patients with inflammatory bowel disease-a multicenter retrospective European study. Inflamm Bowel Dis 2018; 24(11):2442-2451.
16. Macaluso FS, Orlando R, Fries W, et al. The real-world effectiveness of vedolizumab on intestinal and articular outcomes in inflammatory bowel disease. Dig Liver Dis 2018; 50(7):675-681.

17. Pudipeddi A, Paramsothy S, Leong RW. Combination therapy of immunomodulators with non anti-tumor necrosis factor agents in inflammatory bowel disease: need more evidence? *Clin Gastroenterol Hepatol* 2022; 20(3): e640-e641.
18. Kirchgesner J, Desai RJ, Schneeweiss MC, et al. Decreased risk of treatment failure with vedolizumab and thiopurines combined compared with vedolizumab monotherapy in Crohn's disease. *Gut* 2022; 71(9): 1781-1789.
19. Ma C, Hanzel J, Panaccione R, et al. CORE-IBD: a multidisciplinary international consensus initiative to develop a core outcome set for randomized controlled trials in inflammatory bowel disease. Gastroenterology 2022; 163(4):950-964.
20. Zittan E, Kelly OB, Gralnek IM, Silverberg M, Steinhart AH. Fecal calprotectin correlates with active colonic inflammatory bowel disease but not with small intestinal Crohn's disease activity. JGH Open 2018; 2(5):201-206.
21. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histologic index for UC. *Gut* 2017; 66(1): 43-49.
22. Yarur AJ, Bruss A, Naik S, et al. Vedolizumab concentrations are associated with long-term endoscopic remission in patients with inflammatory bowel diseases. *Dig Dis Sci* 2019; 64(6): 1651-1659.
23. Pudipeddi A, Ko Y, Paramsothy S, Leong R. Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Therap Adv Gastroenterol* 2022; Mar 8: 15:17562848221080793
24. Naganuma M, Watanabe K, Motoya S, et al. Potential benefits of immunomodulator use with vedolizumab for maintenance of remission in ulcerative colitis. *J Gastroenterol Hepatol* 2022; 37(1): 81-88.
25. Vaughn BP, Yarur AJ, Graziano E, et al. Vedolizumab serum trough concentrations and response to dose escalation in inflammatory bowel disease. *J Clin Med* 2020; 9(10): 3142.
26. Christensen B, Hanauer S, Erlich J, et al. Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. *Clin Gastroenterol Hepatol* 2017; 15(10): 1557-1564
27. Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut* 2016; 65(3): 408-414.
28. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol* 2017; 15(2): 229-239.

Chapter 6

Summary and Conclusions

6.1 SUMMARY OF THE ISSUES

Inflammatory bowel disease is associated with a significant clinical and economic burden worldwide. Despite advances in treatments over the last two decades, remission rates in clinical trials are less than 40% at one year, demonstrating a therapeutic ceiling with our current therapeutic options. Real-world studies have also shown at least one-third of patients will switch to another advanced therapy after their first-line biological agent, with limited options available. Therefore, strategies are required to optimise our current therapies, with an aim to prolong their use for patients. A holistic approach needs to be undertaken, and this thesis resultantly attempted to address some unanswered questions in the current epidemiology of IBD, sequencing of biological agents, applicability of histological remission in clinical practice, and the impact of immunomodulator de-escalation for patients using vedolizumab.

6.2 KEY FINDINGS, THEIR SIGNIFICANCE AND FUTURE DIRECTIONS

6.2.1 Epidemiology

The last two decades has seen increasing research and development of biological agents to treat moderate-to-severe IBD. However over this time, it is important to recognise that our population demographics may have changed. There have been limited epidemiological studies in Australia, and it is known that epidemiological variations are associated with population density and proximity to metropolitan areas. As such, studies within metropolitan areas of Australia are required to better understand IBD prevalence rates. In Chapter 2 of this thesis, the age-specific prevalence rate of IBD was assessed within a defined metropolitan area of

Australia. This defined region allowed for more complete characterisation of phenotypic details whilst avoiding duplication of cases, ensuring the most accurate representation of IBD prevalence. The age-standardised prevalence rate of IBD was 348 per 100 000, which was the highest rate reported by any study in Australia or New Zealand to that date. This likely represented compounding prevalence over time, and these updated prevalence rates allow administrators to efficiently plan ongoing health care utilisation for this population. However, we also found that IBD prevalence increased with age (612 per 100 000 for people aged 65 years and over). This better understanding of our IBD population will have implications for therapeutic options. It highlights the importance of using safer therapies and de-escalating immunosuppressive medications when appropriate given the risks of infections and malignancies particularly in the older population.

6.2.2 Sequencing of infliximab and vedolizumab in ulcerative colitis

The findings from Chapter 2 led to the importance of comparing safer treatment options such as vedolizumab against systemic immunosuppressives such as infliximab. Prior guidelines recommend using vedolizumab or infliximab as a first-line biological agent in moderate to severe ulcerative colitis. However, no head-to-head trial comparing these two agents has occurred. As such, real-world studies are required to assist with sequencing. Measurements to compare drug efficacy include rates of clinical remission, biochemical remission and endoscopic remission. However treatment persistence can be used as a surrogate marker for drug efficacy and safety, as it reflects willingness by the patient and physician to continue using a particular medication. In Chapter 3, treatment persistence was utilised as a relatively novel surrogate marker for treatment efficacy and safety. Despite limitations with the PBS data, vedolizumab's longer persistence as a first-line biological agent compared with infliximab

suggests that it should be considered as the more optimal first-line biological agent of use. Also, given the persistence of infliximab was similar when used first-line or second-line, together with vedolizumab's lower persistence when used second line, it was suggested that the optimal sequencing would be vedolizumab followed by infliximab.

In the setting of a higher prevalence of IBD particularly in the elderly, as identified in Chapter 2, the results from Chapter 3 provide further reassurance in using vedolizumab as a first-line biological agent in UC, particularly given its better safety profile compared to infliximab. Interestingly, it was noted that both infliximab and vedolizumab had a longer persistence when used in combination with an immunomodulator compared with monotherapy. Although high-quality studies have been performed assessing combination therapy between infliximab and an immunomodulator compared with infliximab monotherapy, a prospective study primarily focusing on the benefits of combination therapy with vedolizumab was also recommended from Chapter 3.

6.2.3 Knowledge of histological assessments in ulcerative colitis

The role of histology in ulcerative colitis has evolved over the last five to ten years. There has been increasing literature into the importance of histological assessments and its ability to prognosticate patient outcomes. However despite its increasing use as an endpoint in clinical trials in recent years, it was not known whether it had been incorporated into daily clinical practice or if gastroenterologists and pathologists had an understanding into the scoring systems. In Chapter 4, a nationwide survey was performed to assess gastroenterologist and pathologists knowledge of histological findings and scoring systems, together with their attitudes towards the role of histology in UC management. It was identified that despite the

awareness of the importance of histology in UC, there was poor knowledge about histological scoring systems by both groups in Australia. There is an opportunity, therefore, to improve knowledge through potential consensus guidelines and to develop a harmonised approach to histological assessment in UC in Australia. This will then allow for homogeneity across the nation for an increasing important treatment endpoint for IBD patients.

6.2.4 Thiopurine use with vedolizumab in ulcerative colitis

Combination therapy between biological agents and immunomodulators is a proposed strategy to increase treatment efficacy in inflammatory bowel disease. Prior research has shown combining infliximab with thiopurines increases infliximab trough concentrations and improves clinical and endoscopic remission rates. However, the benefit of using thiopurines with vedolizumab is less clear. Most studies have not demonstrated a significant benefit of thiopurine therapy with vedolizumab. Limitations of these studies, however, include retrospective study designs which have been unclear as to whether thiopurines were discontinued during treatment maintenance, short durations of follow-up of less than six months, and a heterogeneity in definitions of clinical benefit in a systematic review and meta-analysis that included sixteen vedolizumab-related studies. No studies have prospectively examined the impact of thiopurines on serum vedolizumab trough concentrations or objective markers of disease activity.

In Chapter 5, we performed the VIEWS study, which is the first randomised controlled trial comparing withdrawal versus continuation of thiopurine therapy for patients with ulcerative colitis on vedolizumab. Given the survey results from Chapter 4, we incorporated histologic outcomes due to its increasing importance. Our findings showed that thiopurines do not affect

vedolizumab trough concentrations. However, we identified increased faecal calprotectin, histologic and histo-endoscopic activity in the thiopurine withdrawal group. VIEWS is also the first study to prospectively assess risk factors of relapse upon thiopurine withdrawal whilst on vedolizumab. Prior anti-TNF therapy and histological activity were associated with a higher risk of clinical relapse upon thiopurine withdrawal. These findings will assist clinicians worldwide as it provides novel information about outcomes after withdrawal of thiopurines whilst on vedolizumab. In particular, it has identified a subset of vedolizumab-treated patients at a higher risk of relapse following thiopurine withdrawal. This is an important consideration, particularly in the elderly when vedolizumab is typically used as monotherapy to avoid the potential side effects of thiopurines. Given the rising prevalence of IBD in the elderly identified in Chapter 2, thiopurine use may be de-escalated when on vedolizumab. However the VIEWS study suggests that patients should be closely monitored for a flare if they have histological activity at the time of thiopurine de-escalation or had prior anti-TNF therapy. This thesis highlights the significance of balancing efficacy with safety of our biological agents.

Furthermore, the identification of the importance of histological assessments prior to thiopurine withdrawal contrasts against the overall lack of knowledge of histological scoring systems in daily clinical practice identified in Chapter 4. Histological remission is typically seen as a ‘deeper’ endpoint and the VIEWS study highlights its importance in making nuanced comparisons between treatment groups. These findings add to the importance of providing education and improving gastroenterologists’ and pathologists’ knowledge of histological scoring systems that may then be utilised more frequently in regular clinical practice.

6.3 CONCLUDING REMARKS

IBD remains an incurable disease and efforts are required to optimise care for our patients living with this chronic health problem. Epidemiological studies have shown that its prevalence is rising and this will resultantly increase the burden on the health system. As our therapeutic armamentarium increases, it is important we acknowledge the safety factors of our current medications whilst identifying ways to enhance their efficacy. At present, there is a 'therapeutic ceiling' for most medical therapies, and using combination therapy in a safe manner whilst achieving deeper treatment endpoints such as histological remission may reduce relapse rates even further whilst improving treatment persistence. Most of the novel findings from this thesis have direct clinical application and can help the current IBD community in optimising care for patients. By incrementally filling these knowledge gaps, it is hoped that we can eventually break the 'therapeutic ceiling' and lead to meaningful improvements in treatment efficacy, with an ultimate aim to avoid relapses, prevent complications and improve patients' wellbeing long-term.

APPENDICES – MANUSCRIPTS RELATING TO THIS THESIS PUBLISHED IN PEER-REVIEWED JOURNALS

APPENDIX 1. **Pudipeddi A**, Kariyawasam V, Haifer C, Baraty B, Paramsothy S, Leong RWL. Safety of drugs used for the treatment of Crohn's disease. *Expert Opin Drug Saf* 2019; 18(5):357-367.

EXPERT OPINION ON DRUG SAFETY
2019, VOL. 18, NO. 5, 357–367
https://doi.org/10.1080/14740338.2019.1612874

Taylor & Francis
Taylor & Francis Group

REVIEW

Safety of drugs used for the treatment of Crohn's disease

Aviv Pudipeddi[a,b], Viraj Kariyawasam [a,b], Craig Haifer[a,b], Brandon Baraty[a,b], Sudarshan Paramsothy[a,b,c] and Rupert WL Leong [a,b,c,d]

[a]Department of Gastroenterology and Liver Services, Concord Hospital, Sydney, Australia; [b]Faculty of Medicine and Health, University of Sydney, Sydney, Australia; [c]Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia; [d]Faculty of Medicine, UNSW, Sydney, Australia

ABSTRACT

Introduction: Medications in treating Crohn's disease (CD) have evolved over the last two decades, particularly with the use of biologic agents. There are, however, concerns about the safety and adverse events associated with these medications. The authors review the safety profile of immunosuppressive medications used in Crohn's disease in adult patients.

Areas covered: The authors performed a literature search until October 2018 to examine safety data on thiopurines, methotrexate, anti-TNFα agents, vedolizumab and ustekinumab. The authors focused on 'trial' and 'real-world' data for the biologic agents. Safety in pregnancy and the elderly are also presented.

Expert opinion: Available data in CD suggest that immunosuppressive medications are relatively safe, although there are concerns about an elevated risk of serious infections, skin cancer and lymphoma particularly with thiopurines and anti-TNFα agents. Data on vedolizumab and ustekinumab suggest these newer biologic agents are well tolerated; however, longer term data in CD are required to identify risks with extended use. Apart from methotrexate, there appear to be no adverse congenital outcomes with exposure of drugs during pregnancy.

ARTICLE HISTORY
Received 13 January 2019
Accepted 25 April 2019

KEYWORDS
Adalimumab; anti-TNFα; Crohn's disease; inflammatory bowel disease; infliximab; methotrexate; safety; thiopurine; ustekinumab; vedolizumab

1. Introduction

The last two decades have seen a significant increase in the research and development of new medications to treat patients with moderate to severe Crohn's disease (CD). The therapeutic goal in managing these patients is to induce and maintain clinical and endoscopic remission and to avoid relapses, intestinal damage and need for surgical intervention. Inadequate response to conventional therapies including corticosteroids and immunomodulators are commonly the initiating factor for the prescription of biological agents. The biological agents are monoclonal antibodies directed against specific targets implicated in the pathogenesis of CD inflammation [1]. Although clinical trials have proven their effectiveness and early safety data, there remain concerns over the safety of these drugs used during their long-term maintenance therapy. Post-marketing data and post-registration data have provided some reassurance of their safety profile.

This review article aims to evaluate the safety of treating adult patients with CD using immunomodulating medications, particularly with the use of biological therapies. A search through the PubMed and EMBASE databases was performed to obtain data from large-scale cohort and case-control studies, post-marketing registries and meta-analyses of randomized controlled trials (RCTs) published until October 2018. Search terms included 'thiopurines', 'azathioprine', 'mercaptopurine', 'methotrexate', 'antitumor necrosis factorα', 'infliximab', 'adalimumab', 'vedolizumab', 'ustekinumab' in combination with 'safety', 'adverse events', 'pregnancy' and 'elderly'. The search was limited to studies published in English. Reference lists of published articles were manually searched to identify additional relevant studies. Articles that focused on the adult population were reviewed.

2. Safety of medications

2.1. Immunomodulators

2.1.1. Thiopurines

Given their use for over 50 years, there is a large amount of data that demonstrates the efficacy of thiopurine medications especially with azathioprine and mercaptopurine in CD. In addition to their central role of maintaining remission in patients with CD [2], they also reduce phenotypic disease progression [3] and improve treatment efficacy when used in combination with antitumor necrosis factor-α (TNFα) agents [4]. Combination therapy with azathioprine and infliximab has been shown to be more effective in achieving corticosteroid-free clinical remission and higher infliximab trough levels than infliximab monotherapy [4,5]. Also, combination therapy with a thiopurines and adalimumab has been shown to increase response and remission rates compared with adalimumab monotherapy, and reduce the risk of developing anti-drug antibodies to adalimumab [6,7]. However, approximately 15% to 40% of patients who use thiopurines develop adverse events that lead to dose reduction or drug withdrawal, and

CONTACT Aviv Pudipeddi avivpudipeddi@hotmail.com Department of Gastroenterology and Liver Services, Concord Hospital, Hospital Road, Concord, NSW 2137, Australia

Article highlights

- Immunomodulators are important in the maintenance of remission in CD, however, there are concerns about lymphoma and NMSC adverse events
- Anti-TNFα agents are effective agents in CD, however, there are small but significant risks of infections, skin cancer and lymphoma in some studies
- Vedolizumab and ustekinumab are relatively safe medications in CD with the limited data available
- We suggest HIV serological testing prior to starting vedolizumab use, as the risk of PML will be higher if patients are HIV-positive

This box summarizes key points contained in the article.

these can be divided into idiosyncratic or dose-dependent adverse events [8].

Idiosyncratic reactions include gastrointestinal disturbance (such as nausea and vomiting), malaise, headache, stomatitis, alopecia, and rash in up to 10% to 15% of patients. Thiopurine-induced pancreatitis occurs in up to 4% of patients, particularly during the first weeks of treatment [9] and the HLA-DQA1-HLA-DRB1 susceptibility haplotype is associated with 9% risk in heterozygotes and 17% risk in homozygotes [10]. Another rare adverse event is pneumonitis [11].

Myelotoxicity is a dose-dependent adverse event. Gisbert et al. reviewed 66 studies (8,302 patients) and found the incidence rate of thiopurine-induced myelotoxicity was 3 per 100 person-years (95% confidence interval [CI] 3–4%) [12]. Thiopurine-induced myelotoxicity may occur from 12 days to 27 years of treatment but was more frequent during the first months of treatment. Three deaths occurred due to myelotoxicity (cumulative incidence 0.06%, 95% CI: 0.02–0.17) and the risk of death in patients who developed myelotoxicity was 0.94% (95% CI: 0.32–2.70) [12]. Colombel et al. showed that 27% of patients with CD and azathioprine-induced myelosuppression had mutant alleles of the thiopurine methyltransferase (TPMT) gene [13]. Homozygote and heterozygote TPMT mutations occur in 0.3% and 6–11% of the Caucasian population, respectively [9] and thiopurine dose reduction in those identified as variant carriers result in a 10-fold reduction in myelotoxicity [14]. More recently, Yang et al. identified a variant of the Nudix hydrolase 15 (NUDT15) gene that conferred susceptibility to thiopurine-induced leukopenia especially in the South East Asian population [15]. Thiopurines-associated hepatotoxicity occurs via three broad categories: hypersensitivity reactions, idiosyncratic cholestatic reactions and nodular regenerative hyperplasia (NRH) that may lead to portal hypertension [16]. Dose-dependent toxicity is possible in cases of NRH.

Thiopurine metabolite monitoring of 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) levels reduces adverse reactions, in particular, myelosuppression and hepatotoxicity. 6-TGN is the metabolite responsible for the therapeutic efficacy of thiopurines (therapeutic range: 235–450 pmol/8x10^8 erythrocytes), but elevated levels are associated with myelosuppression. Elevated levels of 6-MMP (>5700 pmol/8x10^8 erythrocytes) are associated with hepatotoxicity. In patients who are preferential 6-MMP metabolizers, the addition of the xanthine-oxidase inhibitor allopurinol with a reduced dose of thiopurine can favor the production of 6-TGN over 6-MMP [9].

Thiopurines are associated with an increased risk of malignancies. A meta-analysis showed a four-fold increased risk of lymphoma in IBD patients treated with a thiopurine [17], while in the Cancer and Increased Risk Associated with Inflammatory Bowel Disease in France (CESAME) prospective cohort study by Beaugerie et al., a five-fold increased risk of lymphoproliferative diseases was demonstrated [18]. A recent nationwide cohort study based on French National Health Insurance databases that included 189,289 patients demonstrated thiopurine use was associated with a risk of lymphoma (adjusted hazard ratio (HR): 2.6, 95% CI: 1.96–3.44, $P < 0.001$). Combination of a thiopurine with an anti-TNFα agent was associated with an even higher risk (adjusted HR: 6.11, 95% CI: 3.46–10.8, $P < 0.001$) [19]. Azathioprine has also been shown to be associated with myeloid neoplasms in autoimmune disorders including IBD [odds ratio (OR): 7.05, 95% CI 2.35–21.13, $P < 0.001$], and there are case reports in patients with IBD [20–22]. The use of thiopurines, either as monotherapy or in combination with anti-TNFα agents, has also been shown to be associated with hepatosplenic T-cell lymphoma [23]. This is a rare but aggressive fatal lymphoma that primarily affects men younger than 35 years old and is associated with a poor prognosis.

Non-melanoma skin cancers (NMSC) are increased in thiopurine users. The CESAME study group showed that in 19,486 IBD patients, the risk of NSMC was HR: 5.9, 95% CI: 2.1–16.4, $P = 0.0006$ in those on ongoing thiopurine treatment and HR: 3.9, 95% CI: 1.3–12.1, $P = 0.02$ in previous thiopurine users exposure [24]. This latter finding is contrary to the lymphoma risk, whereby the discontinuation of thiopurines reduces the risk of lymphoma [25]. Urinary tract cancer risk was also increased, with a multivariate-adjusted HR of 2.82, 95% CI: 1.04–7.68, $P = 0.04$ between patients receiving thiopurines and those not receiving thiopurines [26].

Thiopurine use in IBD has also been associated with the rare development of hemophagocytic lymphohistiocytosis (HLH) following viral infections [27]. A systematic review by Fries et al. showed that EBV and cytomegalovirus were the predominant viral infections that caused secondary HLH in IBD patients, with a mortality rate of approximately 30% [28].

2.1.1.1. Pregnancy and the elderly. The use of thiopurines is not contraindicated during pregnancy. A retrospective multicenter study that included 571 pregnant women on thiopurines found no increase in adverse outcomes for mothers and newborns [29]. Exposure to thiopurines at the time of conception was not associated with an increased risk of congenital malformations [30]. It is important to maintain patients in clinical remission during pregnancy to prevent adverse pregnancy outcomes in the setting of a relapse. Also, breastfeeding by IBD patients using thiopurines does not affect child long-term development or immune function [31,32]. Exposure to thiopurines in male patients is not associated with reduced fertility or congenital abnormalities [30,33]. In the elderly population, there is an increased risk of infections and malignancies, and hence the benefit of long-term thiopurine use may not outweigh the risks [16].

2.1.2. Methotrexate

Methotrexate maintains remission in CD [34] and is most commonly used as second-line therapy in those intolerant to or had failed thiopurine treatment. In double-blinded, placebo-controlled, multicenter studies by Feagan et al., methotrexate effectively induced remission [35] and maintained remission [34] in CD. There were no severe adverse events in methotrexate-users up to week 40 of exposure in the maintenance study, with 2.5% of the patients in the methotrexate group withdrawing from the study prematurely due to nausea [34]. A retrospective study of 92 patients with CD showed methotrexate to be well tolerated [36]. The commonest adverse events were nausea (22%) and elevated liver enzymes (10%), with only 6% of patients needing to cease methotrexate due to persistently abnormal liver enzymes [36]. Methotrexate-induced hepatotoxicity occurs in 3–33% of IBD patients, with underlying cofactors being non-alcoholic fatty liver disease, diabetes or excess alcohol consumption [37]. The addition of folic acid while on methotrexate is recommended, as it has been shown to reduce the gastrointestinal and hepatotoxicity risks [38].

Methotrexate-induced lung injury is infrequent but potentially life-threatening, and typically occurs after an extended course of therapy [39]. It is associated with the development of pneumonitis, which has been reported in the IBD population [40]. Other pulmonary complications from methotrexate use include bronchiolitis obliterans with organizing pneumonia, acute lung injury with non-cardiogenic pulmonary edema, pulmonary fibrosis and pleurisy [41–43]. Methotrexate is also associated with myelosuppression, and it is important to monitor blood counts regularly [39]. Cancer and lymphoma risk is not increased in methotrexate users and methotrexate may be preferred over thiopurines in those with increased cancer risks or prior cancers [44].

2.1.2.1. Pregnancy and the elderly. Methotrexate is teratogenic, and pregnancy is therefore absolutely contraindicated. Methotrexate may be toxic to sperm too, and men should cease methotrexate for at least 3 months before trying to conceive [45]. There is no safety data on the use of methotrexate in elderly CD patients; however, caution should be exercised given the increased rate of gastrointestinal and myelotoxicity adverse events in elderly patients receiving methotrexate for rheumatoid arthritis [46].

2.2. Anti-TNFα

2.2.1. Trial data

2.2.1.1. Infliximab. Infliximab is a mouse-human chimeric IgG1 monoclonal antibody that targets TNF-α. The ACCENT 1 study examined the long-term efficacy and safety of infliximab in CD [47]. It showed that repeated treatment with 5mg/kg or 10mg/kg of infliximab was effective in maintaining remission at week 30 and 54 in patients who had an initial response to the drug in comparison to placebo. There was no significant difference between the two dosages. An additional endoscopic ACCENT 1 sub-study showed that 44% of patients with colonic ulcers treated with maintenance doses had complete mucosal healing after 1 year compared with 18% of the placebo group (P = 0.041) [48]. No significant difference in serious adverse events or infections between was found between the placebo and treatment groups [47]. One patient (0.3%) developed tuberculosis 4 weeks after her week 14 infusion and was successfully treated, while six patients (1.8%) developed malignancy. Cancers included an epithelial-cell skin neoplasm (6.5 months after the first infliximab induction and placebo-maintenance); a natural-killer cell lymphoma (10 months after week 14 infliximab induction and placebo-maintenance); a basal-cell carcinoma (2 weeks after the week 6 infusion); a hypernephroma (9 weeks after the week 6 infusion); a breast cancer (51 days after the week 30 infusion); and a bladder carcinoma (49 days after the week 42 infusion) [47].

2.2.1.2. Adalimumab. Adalimumab is a humanized monoclonal antibody that targets TNFα. The pivotal CLASSIC-1 trial [49] demonstrated its efficacy in the induction of remission at week 4 in moderate to severe CD. Adverse events occurred at similar frequencies in the adalimumab and placebo groups, and no tuberculosis or opportunistic infections were reported during the study [49]. Injection-site reactions occurred in 29% (66/225) of patients in the adalimumab groups, compared with 16% (12/74) in the placebo group [49]. In the CLASSIC-2 trial, longer term data through to week 56 were available [50]. In this study, those randomized to placebo experienced higher overall adverse events, serious adverse events, and adverse events leading to discontinuation than those randomized to adalimumab [50]. No patients withdrew from the study due to injection-site reactions. The commonest reported treated-emergent adverse event was nasopharyngitis in 5%. There were no cases of tuberculosis, demyelinating event, lymphoma, malignancy or death in the adalimumab group [50].

The CHARM trial examined the efficacy and safety of adalimumab in the maintenance of response and remission in patients with moderate to severe CD. Adverse events were reported at similar frequencies between the adalimumab and placebo groups, with a higher discontinuation of treatment rate in the placebo group than in the adalimumab group [51]. Injection-site reactions occurred more frequently in the adalimumab groups (5% [26/517]) compared with the placebo group (0.4% [1/261]), but were generally mild-to-moderate [51]. Tuberculosis was reported in twopatients (0.4%) treated with adalimumab, both of whom were purified protein derivative-negative and had normal chest radiographs at baseline [51]. One patient had received open-label adalimumab fortnightly for 197 days, and the other had received open-label adalimumab for a total of 260 days (31 days at fortnightly dosing and 229 days at weekly dosing) [51]. The latter patient had also received prednisone and azathioprine as concomitant medications. One patient who was receiving adalimumab died from a pulmonary embolism on day 15, with contributing risk factors including age, a history of pulmonary embolism, hypertension and atrial fibrillation. The event was deemed by the investigators to be unrelated to adalimumab [51].

Peyrin-Biroulet et al. performed a meta-analysis of placebo-controlled trials to evaluate the safety and efficacy of anti-TNFα agents for CD [52]. In 21 studies enrolling 5,356

patients, anti-TNFα therapy did not increase the risks of serious infection, malignancy or death [52]. Papamichael et al. also completed a safety assessment of anti-TNFα therapy in CD in literature published up to August 2015 and concluded they were associated with an elevated risk of serious infections, skin cancer and lymphoma [53]. Osterman et al. performed a pooled analysis of data from 1594 patients with CD who participated in clinical trials, and found the combination therapy of adalimumab and an immunomodulator was associated with an increased risk of NMSC and other cancers [54]. However, these studies were prior to the era of therapeutic drug monitoring (TDM). The Trough Concentration Adapted Infliximab Treatment (TAXIT) study was a RCT that aimed to compare the efficacy and safety of concentration-based dosing of infliximab in a cohort of CD- and ulcerative colitis (UC)-responder patients treated with infliximab maintenance therapy [55]. A higher proportion of CD patients who had dose-escalation based on a sub-therapeutic infliximab trough concentration was in remission than before dose-escalation (88% versus 65%, P = 0.020) [55]. One patient in the concentration-based dosing group experienced a serious adverse event (leukocytoclastic vasculitis) leading to discontinuation of infliximab, while one patient in the clinically based dosing group had a psoriaform eczema leading to discontinuation. However, the proportion of patients reporting adverse events that were considered to be linked to infliximab by the treating clinician were similar in both treatment groups [55]. No deaths occurred in the trial. Higher serum trough levels of infliximab have not been linked to greater risk of adverse events [56].

2.2.2. Real-world data

The Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry by Lichenstein et al. evaluated the long-term safety data for infliximab in CD [57]. It recruited 3420 participants that received infliximab and 2853 that received conventional therapies, with a mean length of patient follow-up being 5.2 years. Patient mortality was similar between the two groups. However, there was an increased risk of serious infection with infliximab (HR: 1.43, 95% CI: 1.11–1.84; P = 0.006) [57]. The commonest infections were pneumonia, cellulitis and abdominal abscesses. However, the severity of CD (HR: 2.24, 95% CI: 1.57–3.19, P < 0.001) and the use of prednisone (HR: 1.98, 95% CI: 1.44–2.73, P < 0.001) carried a higher risk of serious infection compared with infliximab use [57]. No increased risk of non-Hodgkin's lymphoma (NHL) for CD patients treated with infliximab was found in the TREAT registry [57], however underpowering might have contributed to the lack of that association. Studies examining the combination therapy of anti-TNFα agents with immunomodulators showed that there was an increased risk of opportunistic infection, herpes zoster and non-Hodgkin's lymphoma [58,59]. The ENCORE registry by D'Haens et al. also compared the long-term safety of infliximab in CD compared with conventional therapies [60]. Infliximab was associated with serious infections (HR: 1.64, 95% CI: 1.17–2.31, P = 0.005) and benign hematological conditions that included leukopenia, neutropenia, and thrombocytopenia (HR: 2.91, 95% CI: 1.51–5.59, P = 0.001), but not with lymphoproliferative disorders, malignancy or death [60]. There was no significant difference in the rate of demyelinating neurological disorders between the two groups [60]. In a large, single-center, cohort study that included 734 patients treated with infliximab (median time 58 months) and 666 controls (median time 144 months) not treated with infliximab, the frequency of serious infections in the infliximab-group of 1.6 per 100 person-years was not significantly different from the control group of 1.1 per 100 person-years [61]. There was also no difference in malignancies or mortality rate between the two groups. Concomitant corticosteroid use was an independent risk factor for infections [61].

The PYRAMID registry examined safety data related to adalimumab in CD [62]. It included 5025 patients who were evaluated over a 6-year period. Treatment-emergent adverse events included 4129 serious adverse events [n = 1853 (36.9%); 24.8 events per 100 person-years], 792 serious infections [n = 556 (11.1%); 4.7 events per 100 person-years] including 10 cases of active tuberculosis, and 134 malignancies [n = 116 (2.3%); 0.8 events per 100 person-years], including 10 lymphomas [62]. The observed lymphoma rate (0.060 events per 100 person-years) was lower than the estimated background rate (0.084 events per 100 person-years) [62]. No new safety signals were reported in this registry.

2.2.3. Pregnancy

The Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry by Mahadevan et al. found that children born to mothers who were treated with anti-TNFα agents did not have an increased risk of congenital anomalies, delayed infant growth or developmental problems [63]. However, the risk of infection for the children at 9–12 months of age was higher if the mother was using combination therapy with a thiopurine [Relative risk (RR) 1.50, 95% CI 1.08–2.09]. It was also found that breastfeeding did not increase or decrease the infection risk among drug exposures [63]. Similar findings relating to the safety of breastfeeding in IBD patients using anti-TNFα drugs were found by Matro et al. [64]. Gisbert et al. examined studies that included 462 women with IBD who were exposed to anti-TNFα agents during pregnancy [65]. Anti-TNFα agents were likely to be safe during pregnancy despite these drugs being able to cross the placenta after the second trimester. A further retrospective, multi-center study by Casanova et al. examined the safety of anti-TNFα and thiopurine use in pregnancy. It was concluded that combination therapy did not increase the risk of complications during pregnancy and does seem to be safe for the newborn [29]. However, a single case of disseminated BCG sepsis following live vaccination in a newborn exposed to infliximab *in utero* highlighted the need to avoid live vaccinations in the first year of life [66]. This was also confirmed by Julsgaard et al. who showed that anti-TNFα drugs were not detected in infants after 12 months [67]. A recent study examining the safety of anti-TNFα use during pregnancy on the long-term outcome of exposed children

showed no significant negative impact on postnatal development with regards to infections, allergy, growth or psychomotor development when compared with unexposed children of non-IBD women [68].

Few studies have examined the effects of anti-TNFα therapy on male fertility. Mahadeven et al. showed a trend towards decrease sperm motility; however, data is conflicting with Villiger et al. showing no statistically significant difference in sperm quality between healthy controls and anti-TNFα treated patients with spondyloarthropathies [69,70]. More recent data from Valer et al. showed anti-TNFα use in male IBD patients is not associated with poor sperm quality, while Puchner et al. found anti-TNFα use shortly before conception did not increase the risk of adverse pregnancy outcomes [71,72].

2.2.4. Elderly

Elderly IBD patients treated with anti-TNFα agents may have a lower rate of short-term clinical response and a higher rate of severe adverse events than in the younger IBD population. Cottone et al. recruited 3079 IBD patients on infliximab and adalimumab with 95 patients (3%) older than 65 years of age [73] and found a higher rate of severe infections and mortality in the elderly group compared with younger patients or patients of the same age who did not receive anti-TNFα agents [73].

2.3. Vedolizumab

2.3.1. Trial data

Vedolizumab is a humanized, gut-selective, monoclonal IgG1 antibody to $\alpha_4\ \beta_7$ integrin, inhibiting migration and leukocyte adhesion from the circulation to the bowel. Gut selectivity with this biological agent means a lower risk of potential systemic side effects. Its effectiveness as induction and maintenance therapy in the management of CD was shown in the GEMINI 2 trial [74]. In this study at week 52, 39.0% of patients who randomized to 8-weekly vedolizumab were in clinical remission compared with 21.6% of patients in the placebo group ($P < 0.001$) [74]. Nasopharyngitis occurred more frequently in the vedolizumab group. Clinically important infusion reactions were infrequent, with only one (0.3%) patient discontinuing the trial due to an infusion reaction [74]. During the trial of maintenance phase, there was one case (0.3%) each of latent tuberculosis, carcinoid tumor in the appendix, squamous-cell carcinoma and basal-cell carcinoma diagnosed in the vedolizumab groups [74]. There were no cases of progressive multifocal leukoencephalopathy (PML).

Feagan et al. examined data from the GEMINI trials and found there was no statistically significant difference in time to first upper or lower respiratory tract infection between vedolizumab and placebo groups [75]. This also included patients who were on 4-weekly vedolizumab maintenance. Colombel et al. examined safety data from six trials of vedolizumab [76]. Adverse events were reported more frequently with placebo (419.4 per 100 person-years) than with vedolizumab (247.8 per 100 person-years) [76]. Vedolizumab did not increase the frequency of adverse events. Upper respiratory tract infections accounted for approximately half or more of the total infections reported with incidence rates of 28.6 per 100 person-years with vedolizumab and 34.7 per 100 person-years with placebo [76]. Three patients (0.2%) were diagnosed with pulmonary tuberculosis in patients who tested negative for tuberculosis at baseline and were taking concomitant immunomodulators. There were no cases of PML. They concluded that there were no significant safety concerns associated with vedolizumab treatment [76]. Bye et al. also completed a systematic search that included six registration trials and nine cohort studies [77]. They found the incidence rates of infection and serious adverse events in the vedolizumab population were comparable to the placebo groups, and post-marketing data did not identify any new concerns [77].

The concern about PML is derived from prior confirmed cases of PML in patients treated with natalizumab. Natalizumab is a humanized monoclonal antibody that inhibits the α_4 subunit of the $\alpha_4\ \beta_1$ integrin, preventing it from binding to vascular cell adhesion molecule 1 (VCAM-1). Bloomgren et al. found that as of 29 February 2012, there were 212 confirmed cases of PML among 99,571 patients treated with natalizumab (2.1 cases per 1000), with the risk increasing in patients with positive anti-John Cunningham (JC) virus antibodies, using immunomodulators before natalizumab, and having received 25 to 48 months of natalizumab [78]. Its mechanism of action is similar to vedolizumab; however, vedolizumab does not inhibit binding at VCAM-1. Selective targeting of the $\alpha_4\ \beta_7$ integrin expressed on gut-homing lymphocytes allows non-gut-homing T-lymphocytes to remain unaffected. Card et al. examined the current and future expected occurrence of PML with vedolizumab use, and found that approximately 30.2 cases of PML would have occurred by May 2016 assuming an equivalent risk to that of patients treated with natalizumab [79]. They concluded that the risk of PML with vedolizumab use is smaller compared with natalizumab use. Despite there being no published cases of PML based on vedolizumab-use alone, an investigator safety letter (June 2018 letter from JD Bornstein, Entyvio Global Clinical Lead, unreferenced) indicated that a case of PML was diagnosed in a CD patient being treated with vedolizumab and methotrexate with concomitant HIV infection. He had previously been treated with corticosteroids, azathioprine, infliximab, and adalimumab, before starting vedolizumab in 2016 and undergoing 20 intravenous infusions. He developed neurological symptoms in early 2018, with investigations including a magnetic resonance imaging (MRI) brain that showed white matter changes and a lumbar puncture confirming positivity of the JC virus. He underwent a HIV test thereafter which was positive, with a CD4 count of 300. It was considered that the PML risk was more related to the HIV infection, low CD4 count and prior exposure to immunomodulators, rather than from vedolizumab use. HIV infection accounts for approximately 80% of PML cases [80].

2.3.2. Real-world data

There have been recent 'real-life' studies evaluating the use of vedolizumab in inflammatory bowel disease. A systematic review by Engel et al. examined real-world studies of vedolizumab in IBD [81]. Nine studies involving 1565 patients were included. Adverse effects were mostly minor and occurred in 30.6% of patients. Infections were reported in 3.4% of patients [81]. Schreiber et al. incorporated real-world studies to

examine the effectiveness and safety of vedolizumab in IBD [82]. Overall adverse event rates were reported in 23 studies (0–67% of patients; n = 2358) and infections in 12 studies (range 5–24%; n = 1176). Post-operative adverse events were reported in four studies (n = 857). The commonest adverse events were upper respiratory tract infections including nasopharyngitis (range 1–21%), arthralgia (range <1–20%), *Clostridium difficile* infection (range <1–20%) and fatigue (range 1–19%) [82]. The real-world data obtained from this systematic review is consistent with those from the GEMINI trials, with no new or unexpected safety issues.

A systematic review by Dulai et al. included treatment outcomes from the VICTORY consortium and concluded vedolizumab was safe to use in patients with moderate-to-severe CD [83]. A retrospective multi-centre European pooled cohort study by Kopylov et al. showed that in 184 anti-TNFα-naïve patients on vedolizumab, adverse events were reported in 20 (11%) of the patients, leading to treatment discontinuation in 6 (2 arthralgia, 1 neutropenia, 1 sarcoidosis flare-up, 1 tinnitus, 1 cholestasis) [84]. Lenti et al. reported a multi-center experience of eight IBD units from Northern England that confirmed the effectiveness and safety of vedolizumab in both the induction and maintenance of remission in UC and CD in 203 patients [84]. There was a low rate of adverse events, with 5 (2.5%) patients discontinuing the medication (4 (2.0%) due to urticarial rash and 1 (0.5%) supraventricular tachycardia during vedolizumab infusion). The cumulative incidence of non-infective adverse events was 5.1 per 100 person-years, while the cumulative incidence of infectious diseases was 11.9 per 100 person-years (13.7% of the cohort) [85]. Nasopharyngitis and pneumonia were the commonest infections. One patient developed viral meningitis and another patient developed of Epstein-Barr virus (EBV) infection causing acute hepatitis and both were on concomitant immunomodulators. There was one (0.5%) case of tuberculosis reactivation affecting the central nervous system in a 57-year-old female who had type 2 diabetes mellitus. Sub-analysis of the use of vedolizumab in the elderly aged 65 years or above reported that there were no reports of infections [85].

2.3.3. Pregnancy

Mahadevan et al. examined the safety of vedolizumab in pregnancy [86] after reviewing data of 27 pregnancies in female participants and 19 pregnancies in partners of male participants. Among 24 vedolizumab-treated females, 11 had live births, 5 had elective terminations, 4 had spontaneous abortions and there were 4 undocumented outcomes. Of the 19 pregnancies in partners of male participants, there were 11 live births, 3 elective terminations, 2 spontaneous abortions, and 3 undocumented outcomes. Post-marketing reports included 81 pregnancies, with 66 pregnancies ongoing or reported undocumented outcomes. Overall, the study concluded that there were no new safety concerns for pregnancy outcomes in females directly or indirectly exposed to vedolizumab [86]. Lahat et al. showed that vedolizumab can be detected in the breast milk of nursing mothers; however, the concentrations are small and unlikely to result in systemic or gastrointestinal immune suppression of the infant [87]. More recently, Moens et al. showed that pregnancies for women with IBD using vedolizumab were associated with more miscarriages compared with anti-TNFα exposed pregnant women or immunomodulator/biologic-naïve pregnant women [88]. However, after the exclusion of patients with active disease, there was no statistically significant difference noted between the groups. As such, it was postulated that active disease rather than vedolizumab was the main cause for adverse pregnancy outcomes, however larger prospective studies are needed for confirmation [88].

2.3.4. Elderly

Yajnik et al. performed a *post-hoc* analysis from the GEMINI trials that examined the safety profile of vedolizumab in various age groups [89]. The safety profile was similar between patients aged <35, 35 to <55, and ≥55 years [89]. Another single-center, retrospective study showed that vedolizumab was safe in 29 patients (19 of whom had CD) who were more than 60 years old [90]. Chan et al. have shown that vedolizumab is the preferred choice of immunosuppression in elderly patients with comorbidities [91].

2.4. Ustekinumab

2.4.1. Trial data

Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23. The pivotal UNITI trials demonstrated its efficacy in patients with moderate to severe CD [92]. The UNITI-1 trial included 741 patients who were primary or secondary non-responders to anti-TNFα agents, while the UNITI-2 trials included 628 patients who had failed conventional therapy and had not failed biological agents. The primary end-point was a clinical response at week 6 (defined as a decrease from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥100 points or a CDAI score <150). The rates of response at week 6 were significantly higher in those receiving either 130 mg IV ustekinumab, approximately 6mg/kg IV ustekinumab compared to placebo (UNITI-1, 34.3%, 33.7%, and 21.5%, respectively, with $P \leq 0.003$ for both comparisons with placebo; in UNITI-2, 51.7%, 55.5%, and 28.7%, respectively, with $P < 0.001$ for both doses) [92].

From these induction trials, 397 patients who had a response then participated in the IM-UNITI trial. Patients were randomized to receive subcutaneous maintenance injections of 90 mg of ustekinumab either every 8 weeks or 12 weeks, or placebo. The primary end point was remission at week 44 (CDAI score < 150). In the groups receiving maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53.1% and 48.8%, respectively, were in remission at week 44, as compared with 35.9% of those receiving placebo ($P = 0.005$ and $P = 0.04$, respectively) [92].

The rates of adverse effects were similar between treatment and placebo groups in both induction trials [92]. At week 44 of the IM-UNITI trials, the percentages of patients in the primary population with at least one adverse event in the groups receiving 90 mg of ustekinumab every 8 weeks, 90 mg of ustekinumab every 12 weeks, and placebo were 81.7%, 80.3%, and 83.5%, respectively [92]. The percentages of patients with a serious adverse event were 9.9%, 12.1%, and 15.0%, respectively [92]. A serious infection developed in 13 patients across

all three study groups, occurring in 2.3% in the 8-weekly ustekinumab group, 5.3% in the 12-weekly ustekinumab group, and 2.3% in the placebo group. Three opportunistic infections occurred comprising of one case of listeria meningitis (following induction with 6mg/kg of ustekinumab on concomitant prednisone 30 mg per day), and two cases of esophageal candidiasis (one in a patient taking prednisone 40 mg per day and methotrexate and the other in a patient not in the primary IM-UNITI population who was receiving 8-weekly SC ustekinumab) [92]. One case of active pulmonary tuberculosis occurred in a high-tuberculosis endemic area approximately 10 months after the administration of a single 130 mg IV ustekinumab and placebo maintenance therapy [92].

Two patients developed a basal cell carcinoma in the maintenance trial – one in the placebo group and one in the 8-weekly ustekinumab group [92]. One patient in the 12-weekly ustekinumab group developed a metastatic adenocarcinoma in the small bowel and a carcinoid tumor was found incidentally in the resected bowel. After 1 year of therapy, there were no deaths. There was no apparent relationship between dose and safety of ustekinumab in the UNITI trials [92]. The phase 2 ustekinumab CERTIFI study recruited 526 subjects in the induction study and followed 145 responders in the maintenance study. Serious infections occurred in 7 patients (6 received ustekinumab) during induction and 11 patients (4 receiving ustekinumab) during maintenance. Basal-cell carcinoma developed in onepatient receiving ustekinumab [93].

Ustekinumab exposure through to 96 weeks of the IM-UNITI maintenance study recruited 718 subjects with 86.5% (621/718) completing Week 96 of follow up [94]. Adverse events per hundred person-years were similar among ustekinumab and placebo groups, including overall adverse events (484.4 versus 447.8), serious adverse events (19.2 versus 18.8) and serious infections (4.1 versus 4.0). Comparable rates of adverse events were noted between the 8-weekly and 12-weekly ustekinumab groups. A 45-year-old male from South Africa that was negative for tuberculosis at screening developed tuberculosis. He tested positive to QuantiFERON TB Gold on routine annual screening, and bronchial brushings were positive for *Mycobacterium tuberculosis*. This was deemed unrelated to ustekinumab. A serious opportunistic infection of cytomegalovirus colitis occurred in a 32-year-old who received ustekinumab induction followed by maintenance (440 days after last exposure to ustekinumab). The number of treatment-emergent malignancies per hundred person-years of follow-up was 2.60 for placebo patients and 0.37 for ustekinumab patients. Three deaths were reported, two due to presumed cardiovascular causes and one suicide. Two of these patients were receiving 8-weekly ustekinumab and the other patient was receiving 12-weekly ustekinumab. The data from this long-term extension study illustrate that ustekinumab is well tolerated with a favorable safety profile [94].

2.4.2. Real-world data

A retrospective multicenter cohort study evaluated the long-term efficacy and safety of ustekinumab in patients with anti-TNFα refractory CD [95]. In the study, 122 patients were followed up for a median treatment duration of 26.6 months. At the end of follow-up, five patients stopped ustekinumab due to side effects including pulmonary infection (n = 1), a flare of hidradenitis suppurativa (n = 1), acne (n = 1), disabling myalgia (n = 1) and anal adenocarcinoma (n = 1). The anal adenocarcinoma developed in a 32-year-old man with a 26-year history of CD that was treated with ustekinumab for 30 months. There were no opportunistic infections or deaths reported [95].

A notable study that examined the safety profile of ustekinumab in the real-world is the PSOLAR study by Papp et al., albeit in the psoriasis population [96]. A total of 12,093 patients (48,388 person-years) were included and they found that there was no increased risk of malignancy, serious infection, major adverse cardiovascular events or mortality with ustekinumab on multivariate analyses [96]. A subanalysis of 2.3% of PSOLAR patients with concomitant IBD showed that having IBD increased the risk of infections compared to psoriasis overall. However, patients treated with ustekinumab had numerically lower rates of serious infections compared with patients receiving other biological and non-biological therapies [97].

2.4.3. Pregnancy

There has been one case report of a pregnant patient with CD who was successfully treated with ustekinumab maintenance therapy throughout the pregnancy and delivered a baby boy without any congenital malformation, neurological abnormalities or birth defects [98]. Also, Matro et al. recently showed similar rates of infection and developmental milestones at 12 months in breastfed and non-breastfed infants of patients on biologic agents, including ustekinumab [64].

2.4.4. Elderly

To date, there has been no published data on the safety of ustekinumab specifically in the elderly CD population.

3. Conclusion

Immunosuppressive medications in moderate to severe CD are relatively safe. However, physicians should be aware of the potential short- and long-term adverse events, particularly with the use of thiopurines and anti-TNFα agents (Table 1). Long-term observational studies and post-marketing safety data for vedolizumab and ustekinumab are required to establish their long-term safety profiles; however, they are currently safe and well tolerated by patients with CD. HIV serology testing should be considered prior to start vedolizumab given the increased risk of PML in this population.

4. Expert opinion

Given the long period of time since initial trials confirmed the efficacy of thiopurines and anti-TNFα agents in CD, there is substantial short- and longer-term safety data available from cohort studies, meta-analyses of RCTs and 'real-world' experiences. As a result, there is a greater awareness of the potential serious adverse events that can occur with these medications, particularly in combination use. Nonetheless, the benefits of these medications in controlling moderate-to-severe CD typically outweigh the risks, and physicians should ensure close monitoring occurs during the treatment phase.

Table 1. Summary of the safety of drugs used in Crohn's disease.

Medication class	General safety concerns	Safety in Pregnancy
Thiopurine	• Nausea, vomiting, malaise, headache • Alopecia, rash, pancreatitis, pneumonitis • Myelotoxicity Check TPMT, 6-TGN, and 6-MMP Consider checking NUDT15 gene • Elderly ∘ risk of infections and malignancies • Malignancies ∘ Lymphoproliferative diseases, myeloid neoplasms, hepatosplenic T-cell lymphoma (male, <35 years) ∘ NMSC ∘ Urinary tract cancer • Secondary HLH following viral infections	• Not contraindicated • Able to breastfeed • Males ∘ Not associated with reduced fertility or congenital abnormalities
Methotrexate	• Nausea • Elevated liver function tests • Pulmonary toxicity • Myelosuppression • Not associated with increased risk of cancer or lymphoma	• Contraindicated ∘ Teratogenic
Anti-TNFα	• Increased risk of serious infection ∘ Note tuberculosis risk • Combination therapy with thiopurine: ∘ risk of opportunistic infections ∘ risk of NMSC and lymphoma • Elderly ∘ rate of serious infections and mortality than younger patients	• No increased risk of congenital anomalies, delayed infant growth or developmental problems • Combination therapy: increased risk of infection at age 9–12 months • Safe to breastfeed • Males: ∘ Does not reduce sperm quality ∘Not associated with adverse pregnancy outcomes
Vedolizumab	• Upper respiratory tract infections including nasopharyngitis • No major concerns with serious infections or malignancies • Potential concern with PML if HIV positive • Elderly: ∘ Safe, no new safety concerns	• Limited data, but no new safety concerns for pregnancy outcomes
Ustekinumab	• No increased risk of adverse events in long-term trial data • Limited data on risk in the elderly	• Limited data

With an increasing choice of biological agents in the treatment of IBD, the newer biological agents vedolizumab and ustekinumab appear to be safer options in comparison to anti-TNF drugs. The main adverse event from vedolizumab is an upper respiratory tract infection/nasopharyngitis, however, there appears to be no serious risk of opportunistic infections or malignancy from this medication. It also appears to be well tolerated in the elderly population. PML continues to be monitored closely in those prescribed vedolizumab but without a logical reason, and real-world data have not shown vedolizumab use to be a risk factor for the development of PML. Given that HIV infection increases the risk of PML, however, we suggest performing baseline HIV serological testing prior to starting vedolizumab in the rare event of PML being diagnosed later.

Reassuringly, ustekinumab has been used for a longer period of time in the psoriasis and psoriatic arthritis population and has been shown to be safe, albeit mostly at a lower maintenance dose. Its safety profile in CD patients requires further evaluation in longer-term post-marketing and real-world studies.

In summary, there has been an increasing amount of research into immunosuppressive medications in CD over the last two decades, particularly with the advent of newer biologic therapies. The benefits of these medications typically outweigh the risks, taking into account the high disease burden of CD. However, safety data are generally derived from studies whose primary aim is to assess efficacy, while meta-analyses of RCTs include patients who may not be representative of real-life clinical practice and are usually underpowered to assess safety [53]. Hence, there is a need for larger, statistically powered, prospective studies specifically designed to assess the safety of immunosuppressive medications in CD [53]. An important prospective observational cohort study is the I-CARE (Ibd CAncer and serious infections in Europe) that will aim to assess the long-term safety profile of these medications in more than 10,000 adult patients with IBD. In the meantime, careful pre-treatment evaluation (including HIV serological testing pre-vedolizumab use) and close monitoring while on current immunosuppressive medications is essential in patients with CD.

Funding

This paper was not funded.

Declaration of interest

V Kariyawasam does consultancy work for Janssen-Cilag Pty Limited and has grants from Takeda, Ferring, Abbvie and Shire. S Paramsothy does consultancy work for Janssen-Cilag Pty Limited and is a consultant to Finch Therapeutics, Inc. RW Leong has served on the advisory boards of AbbVie, Aspen, Celgene, Ferring, Hospira, Janssen, MSD, Pfizer and Takeda, and has received unrestricted research support from Shire, Janssen and NHMRC of Australia, and speakers honoraria from Emerge Health. The authors have no other relevant affiliations or financial involvement with any organization or

entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed that they are an advisory board member of AbbVie and Janssen Canada. All other peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

ORCID

Viraj Kariyawasam http://orcid.org/0000-0003-2623-1336
Rupert WL Leong http://orcid.org/0000-0001-5944-3488

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Moss AC. Optimizing the use of biological therapy in patients with inflammatory bowel disease. Gastroenterol Rep. 2015;3(1):63–68.
2. Pearson DC, May GR, Fick G, et al. Azathioprine for maintaining remission in Crohn's disease. Cochrane Database Syst Rev. 2000;(2):CD000067
3. Kariyawasam VC, Selinger CP, Katelaris PH, et al. Early use of thiopurine or methotrexate reduces major abdominal and perianal surgery in Crohn's disease. Inflamm Bowel Dis. 2014;20(8):1382–1390.
4. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine or combination therapy for Crohn's disease. N Eng J Med. 2010;362(15):1383–1395.
5. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146(2):392–400.
6. Kariyawasam VC, Ward MG, Blaker PA, et al. Thiopurines dosed to a therapeutic 6-thioguanine level in combination with adalimumab are more effective than subtherapeutic thiopurine-based combination therapy or adalimumab monotherapy during induction and maintenance in patients with long-standing Crohn's disease. Inflamm Bowel Dis. 2017;23(9):1555–1565.
7. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF naïve patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet. 2019;4(5):341–353.
8. Jharap B, Seinen ML, de Boer NK, et al. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year intercept cohorts. Inflamm Bowel Dis. 2010;16(9):1541–1549.
9. Leong RW, Gearry RB, Sparrow MP. Thiopurine hepatotoxicity in inflammatory bowel disease: the role for adding allopurinol. Expert Opin Drug Saf. 2008;7(5):607–616.
10. Heap GA, Weedon MN, Bewshea CM, et al. HLA-DQA1-HLA-DRB1 variants confer susceptibility to pancreatitis induced by thiopurines immunosuppressants. Nat Genet. 2014;46(10):1131–1134.
11. Ananthakrishnan AN, Attila T, Otterson MF, et al. Severe pulmonary toxicity after azathioprine/6-mercaptopurine initiation for the treatment of inflammatory bowel disease. J Clin Gastroenterol. 2007;41(7):682–688.
12. Gisbert JP, Gomollon F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. Am J Gastroenterol. 2008;103(7):1783–1800.
13. Colombel JF, Ferrari N, Debuysere H, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology. 2000;118(6):1025–1030.
14. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of patients with variants in TPMT and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. Gastroenterology. 2015;149(4):907–917.
15. Yang SK, Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurines-induced leukopenia. Nat Genet. 2014;46(9):1017–1020.
16. Konidari A, Matary WE. Use of thiopurines in inflammatory bowel disease: safety issues. World J Gastrointest Pharmacol Ther. 2014;5(2):63–76.
17. Kandiel A, Fraser AG, Korelitz B, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54(8):1121–1125.
18. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617–1625.
19. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA. 2017;318(17):1679–1686.
20. Ertz-Archambault N, Kosiorek H, Taylor GE, et al. Association of therapy for autoimmune disease with myelodysplastic syndromes and acute myeloid leukemia. JAMA Onc. 2017;3(7):936–943.
21. Mullier F, Rahier JF, Maignen F, et al. A case of therapy-related myeloid neoplasm in a patient with Crohn's disease treated with azathioprine. Acta Haematol. 2012;128(1):1–6.
22. Ahmad OF, Keane MG, McCartney S, et al. Azathioprine-associated myelodysplastic syndrome in two patients with ulcerative colitis. Frontline Gastroenterol. 2013;4(3):205–209.
23. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):36–41.
24. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141(5):1621–1628.
25. Khan N, Abbas AM, Lichtenstein GR, et al. Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study. Gastroenterology. 2013;145(5):1007–1015.
26. Bourrier A, Carrat F, Colombel JF, et al. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Aliment Pharmacol Ther. 2016;43(2):252–261.
27. Li Y, Xia X, Zhang J, et al. Haemophagocytic lymphohistiocytosis in inflammatory bowel disease with virus infection. Prz Gastroenterol. 2015;10(2):78–82.
28. Fries W, Cottone M, Cascio A. Systematic review: macrophage activation system in inflammatory bowel disease. Aliment Pharmacol Ther. 2013;37(11):1033–1045.
29. Casanova MJ, Chaparro M, Domenech E, et al. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol. 2013;108(3):433–440.
30. Akbari M, Shah S, Velayos FS, et al. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(1):15–22.
31. Angelberger S, Reinisch W, Messerschmidt A, et al. Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. J Crohns Colitis. 2011;5(2):95–100.
32. Christensen LA, Dahlerup JF, Nielsen MJ, et al. Azathioprine treatment during lactation. Aliment Pharmacol Ther. 2008;28(10):1209–1213.
33. Dejaco C, Mittermaier C, Reinisch W, et al. Azathioprine treatment and male fertility in inflammatory bowel disease. Gastroenterology. 2001;121(5):1048–1053.
34. Feagan BG, Richard N, Fedorak MD, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. N Eng J Med. 2000;342(22):1627–1632.
35. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. N Eng J Med. 1995;332:292–297.
36. Chande N, Abdelgadir I, Gregor J. The safety and tolerability of methotrexate for treating patients with Crohn's disease. J Clin Gastroenterol. 2011;45(7):599–601.

37. Herfarth HH, Kappelman MD, Long MD, et al. Use of methotrexate in the treatment of inflammatory bowel diseases (IBD). Inflamm Bowel Dis. 2016;22(1):224–233.
38. Shea B, Swinden MV, Tanjong Ghogomu E, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev. 2013;(5):CD000951.
39. McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. Expert Rev Gastroenterol Hepatol. 2014;8(3):223–240.
40. D'Andrea N, Triolo L, Margagnoni G, et al. Methotrexate-induced pneumonitis in Crohn's disease. Case report and review of the literature. Multidiscip Respir Med. 2010;5(5):312–319.
41. Lateef O, Shakoor N, Balk RA. Methotrexate pulmonary toxicity. Expert Opin Drug Saf. 2005;4(4):723–730.
42. Iikuni N, Iwami S, Kasai S, et al. Noncardiogenic pulmonary edema in low-dose oral methotrexate therapy. Intern Med. 2004;43(9):846–851.
43. Walden PA, Mitchell-Weggs PF, Coppin C, et al. Pleurisy and methotrexate treatment. Br Med J. 1977;2(6091):867.
44. Swoger JM, Regueiro M. Stopping, continuing, or restarting immunomodulators and biologics when an infection or malignancy develops. Inflamm Bowel Dis. 2014;20(5):926–935.
45. Siegel CA, Sands BE. Review article: practical management of inflammatory bowel disease patients taking immunomodulators. Aliment Pharmacol Ther. 2005;22(1):1–16.
46. Sturm A, Maaser C, Mendall M, et al. European Crohn's and colitis organisation topical review on IBD in the elderly. J Crohns Colitis. 2017;11(3):263–273.
47. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541–1549.
48. Ruutgers P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of Infliximab in Crohn's disease. Gastroenterology. 2004;126:402–413.
49. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130(2):323–333.
50. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232–1239.
51. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52–65.
52. Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2008;6(6):644–653.
53. Papamichael K, Mantzaris GJ, Peyrin-Biroulet L. A safety assessment of anti-tumor necrosis factor alpha therapy for treatment of Crohn's disease. Expert Opin Drug Saf. 2016;15(4):493–501.
54. Osterman MT, Sandborn WJ, Colombel JF, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology. 2014;146(4):941–949.
55. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148(7):1320–1329.
56. Mitrev N, Leong RW. Therapeutic drug monitoring of anti-tumour necrosis factor-α agents in inflammatory bowel disease. Expert Opin Drug Saf. 2017;16(3):303–317.
57. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol. 2012;107(9):1409–1422.
- **Large sample size with long-term safety data provided**
58. Osterman MT, Haynes K, Delzell E, et al. Effectiveness and safety of immunomodulators with anti-TNF therapy in Crohn's disease. Clin Gastroenterol Hepatol. 2015;13(7):1293–1301.
59. Siegel CA, Marden SM, Persing SM, et al. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol. 2009;7(8):874–881.
60. D'Haens G, Reinisch W, Colombel JF, et al. Five-year safety data from ENCORE, a European observational safety registry for adults with Crohn's disease treated with infliximab [Remicade®] or conventional therapy. J Crohns Colitis. 2017;11(6):680–689.
61. Fidder H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. Gut. 2009;58(4):501–508.
62. D'Haens G, Reinisch W, Panaccione R, et al. Lymphoma risk and overall safety profile of adalimumab in patients with Crohn's disease with up to 6 years of follow-up in the PYRAMID registry. Am J Gastroenterol. 2018;113(6):872–882.
- **Large sample size with long-term safety data provided**
63. Mahadevan U, Martin CF, Sandler RS, et al. PIANO: A 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology. 2012;142(5,Suppl 1):140.
64. Matro R, Martin CF, Wolf D, et al. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. Gastroenterology. 2018;155(3):696–704.
65. Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol. 2013;108(9):1426–1438.
66. Cheent K, Nolan J, Shariq S, et al. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis. 2010;4(5):603–605.
67. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. Gastroenterology. 2016;151(1):110–119.
68. Duricova D, Dvorakova E, Hradsky O, et al. Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: A controlled, multicentre observation. Inflamm Bowel Dis. 2018 Sep 20; doi:10.1093/ibd/izy294
- **Safety data for pregnant women and exposed children**
69. Mahadevan U, Terdiman JP, Aron J, et al. Infliximab and semen quality in men with inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(4):395–399.
70. Villiger PM, Caliezi G, Cottin V, et al. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Ann Rheum Dis. 2010;69(10):1842–1844.
71. Valer P, Algaba A, Santos D, et al. Evaluation of the quality of semen and sexual function in men with inflammatory bowel disease. Inflamm Bowel Dis. 2017;23(7):1144–1153.
72. Puchner R, Danninger K, Puchner A, et al. Impact of TNF-blocking agents on male sperm characteristics and pregnancy outcomes in fathers exposed to TNF-blocking agents at time of conception. Clin Exp Rheumatol. 2012;30(5):765–767.
73. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):30–35.
74. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. Nejm. 2013;369:711–721.
75. Feagan BG, Bhavat F, Khalid M, et al. Respiratory tract infections in patients with inflammatory bowel disease: safety analyses from vedolizumab clinical trials. J Crohns Colitis. 2018;12(8):905–919.
76. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017;66(5):839–851.
77. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46(1):3–15.
78. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366(20):1870–1880.

79. Card T, Xu J, Liang H, et al. What is the risk of progressive multifocal leukoencephalopathy in patients with ulcerative colitis and Crohn's disease treated with vedolizumab? Inflamm Bowel Dis. 2018;24 (5):953–959.
80. Pavlovic D, Patera A, Nyberg F, et al. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. Ther Adv Neurol Disord. 2015;8(6):255–273.
81. Engel T, Ungar B, Yung DE, et al. Vedolizumab in IBD-lessons from real-world experience: a systematic review and pooled analysis. J Crohns Colitis. 2018;12(2):245–257.
82. Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. J Gastroenterol. 2018;53(9):1048–1064.
83. Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY consortium. Am J Gastroenterol. 2016;111 (8):1147–1155.
84. Kopylov U, Verstockt B, Biedermann L, et al. Effectiveness and safety of vedolizumab in anti-TNF-naïve patients with inflammatory bowel disease-A multicenter retrospective European study. Inflamm Bowel Dis. 2018;24(11):2442–2451.
85. Lenti MV, Levison S, Eliadou E, et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: the cross pennine study. Dig Liver Dis. 2018 Jul 18. doi:10.1016/j.dld.2018.07.007
86. Mahadevan U, Vermeire S, Lasch K, et al. Vedolizumab exposure in pregnancy: outcomes from clinical studies in inflammatory bowel disease. Aliment Pharmacol Ther. 2017;45 (7):941–950.
87. Lahat A, Shitrit AB, Naftali T, et al. Vedolizumab levels in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis. 2018;12(1):120–123.
88. Moens A, van Hoeve K, Humblet E, et al. Outcome of pregnancies in female IBD patients treated with vedolizumab. Paper presented at: European Crohn's and Colitis Organisation. 14th Congress of ECCO; 2019 March 7–9;Copenhagen, DK.
89. Yajnik V, Khan N, Dubinski M, et al. Efficacy and safety of vedolizumab in ulcerative colitis and Crohn's disease patients stratified by age. Adv Ther. 2017;34(2):542–559.
90. Navaneethan U, Edminister T, Zhu X, et al. Vedolizumab is safe and effective in elderly patients with inflammatory bowel disease. Inflamm Bowel Dis. 2017;23(4):E17.
91. Chan WPW, Kim S, Ding JN, et al. P140 Physician attitudes about the use of immunosuppressive therapy for inflammatory bowel disease in the elderly. J Crohns Colitis. 2018;12(Suppl 1):S165–S167.
92. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. Nejm. 2016;375 (20):1946–1960.
93. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012 Oct 18;367(16):1519–1528.
94. Sandborn WJ, Rutgeerts P, Gasink C, et al. Long term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. Aliment Pharmacol Ther. 2018;48(1):65–77.
95. Wils P, Bouhnik Y, Michetti P, et al. Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. Aliment Pharmacol Ther. 2018;47(5):588–595.
96. Papp K, Gottlieb AB, Naldi L, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and registry (PSOLAR). J Drugs Dermatol. 2015;14(7):706–714.
97. Loftus E Jr, Augustin M, Bissonnette R, et al. Prevalence of inflammatory bowel disease amongst patients with psoriasis and incidence of serious infection in the subset: results from the PSOLAR registry. Poster session presented at: Clinical – Therapy & Observation. 11th Congress of European Crohn's and Colitis Organization. 2016 Mar 16–19;Amsterdam.
98. Cortes X, Borrás-Blasco J, Antequera B, et al. Ustekinumab therapy for Crohn's disease during pregnancy: a case report and review of the literature. J Clin Pharm Ther. 2017;42(2):234–236.

APPENDIX 2. **Pudipeddi A**, Liu J, Kariyawasam V, Borody TJ, Cowlishaw JL, McDonald C, Katelaris P, Chapman G, Corte C, Lemberg DA, Lee CH, Keshava A, Napoli J, Clancy R, Chan W, Paramsothy S, Leong R. High prevalence of Crohn disease and ulcerative colitis among older people in Sydney. *Med J Aust* 2021; 214(8):365-370.

High prevalence of Crohn disease and ulcerative colitis among older people in Sydney

Aviv Pudipeddi[1], Jeffrey Liu[1], Viraj Kariyawasam[1], Thomas J Borody[2], James L Cowlishaw[1], Charles McDonald[1], Peter Katelaris[3], Grace Chapman[1], Crispin Corte[4], Daniel A Lemberg[5], Cheng H Lee[6], Anil Keshava[1], John Napoli[7], Robert Clancy[2], Webber Chan[1], Sudarshan Paramsothy[1], Rupert Leong[1]

The known: The prevalence of inflammatory bowel disease (IBD) is increasing worldwide. However, recent age-standardised prevalence data for Australia are not available.

The new: The age-standardised IBD prevalence rate of 348 cases per 100 000 population we found is the highest ever reported in Australia. Its prevalence was higher in older people: 612 per 100 000 people aged 65 years or more and 891 per 100 000 people aged 85 years or more.

The implications: Given the higher prevalence of IBD among older people in metropolitan Sydney, and their higher risk of infections, doctors should consider replacing systemic immunosuppressive therapies with alternatives when possible.

Abstract

Objectives: To determine the age-standardised prevalence of inflammatory bowel disease (IBD) in a metropolitan area of Sydney, with a focus on its prevalence among older people.

Design, setting: Population-based epidemiological study of people with IBD in the City of Canada Bay, a local government area in the inner west of Sydney, during 1 March 2016 – 10 November 2016.

Participants: Patients diagnosed with confirmed IBD according to the Copenhagen or revised Porto criteria.

Main outcome measures: Crude prevalence of IBD, including Crohn disease and ulcerative colitis; age-standardised prevalence of IBD, based on the World Health Organization standard population; prevalence rates among people aged 65 years or more.

Results: The median age of 364 people with IBD was 47 years (IQR, 34–62 years); 185 were women (50.8%). The crude IBD prevalence rate was 414 cases (95% CI, 371–456 cases) per 100 000 population; the age-standardised rate was 348 cases (95% CI, 312–385 cases) per 100 000 population. The age-standardised rate for Crohn disease was 166 cases (95% CI, 141–192 cases) per 100 000 population; for ulcerative colitis, 148 cases (95% CI, 124–171 cases) per 100 000 population. The IBD prevalence rate in people aged 65 years or more was 612 cases (95% CI, 564–660 cases) per 100 000, and for those aged 85 years or more, 891 cases (95% CI, 833–949 cases) per 100 000; for people under 65, the rate was 380 cases (95% CI, 342–418 cases) per 100 000.

Conclusions: We found that the prevalence of confirmed IBD in a metropolitan sample was highest among older people. Challenges for managing older patients with IBD include higher rates of comorbid conditions, polypharmacy, and cognitive decline, and the immunosuppressive nature of standard therapies for IBD.

The worldwide burden of inflammatory bowel disease (IBD), which includes Crohn disease and ulcerative colitis, has increased markedly over the past sixty years,[1] partly because IBD is incurable but rarely fatal.[2] Its prevalence is greatest (but stable) in western Europe and North America,[1] but its incidence has risen over the past two decades in more recently industrialised countries in Asia, South America, and Africa.[3,4]

The burden associated with IBD in Australia is high; it was estimated to have incurred more than $2.7 billion in costs in 2012.[5,6] Earlier epidemiological studies in Victoria (2010–11)[5] and Tasmania (2013–14)[7] included mixed urban and rural populations; in a multi-nation Asia–Pacific study, epidemiological variations were associated with population density and proximity to metropolitan areas.[8] Young people with IBD may move to cities for education and employment, reducing the apparent prevalence of IBD in rural areas.

It was recently reported that IBD prevalence rates in Lothian (Scotland) were very high among people aged 60–79 years (1178 per 100 000) or 80 years or more (1042 per 100 000), and they are projected to rise further by 2028.[9] The use of immunosuppressive therapies to treat IBD in these age groups is problematic, as opportunistic infections, sepsis, comorbid conditions, and malignancy are more frequent in older patients.

We therefore examined age-specific prevalence rates of IBD in a defined metropolitan area of Australia, focusing on its prevalence in older people.

Methods

Population characteristics

We assessed the prevalence of IBD in the City of Canada Bay, a local government area in the inner west of Sydney, with a population of 88 015 at the time of data collection (Box 1).[10] Concord Hospital, a centrally located public hospital with an established IBD clinic, provides free health care for patients with IBD.

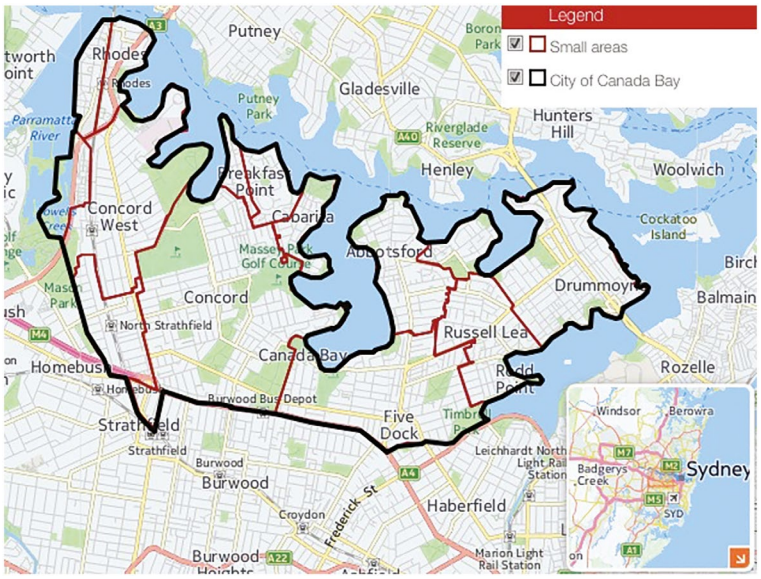
Data collection

We analysed clinical data for people with IBD living in the City of Canada Bay (postcodes 2046, 2047, 2137, 2138) during 1 March 2016 – 10 November 2016, including those reviewed by gastroenterologists outside the study area. We identified people treated at Concord Hospital according to International Classification of Diseases, 10th revision (ICD-10) coding. We also obtained information on patients from gastroenterologists and colorectal surgeons at Concord Hospital, private gastroenterology and colorectal surgery practices, the Sydney IBD database (ambulatory IBD patients identified in medical records from Concord Hospital and City of Canada Bay community gastroenterologists), and the paediatric IBD database of the Westmead Children's Hospital.

Two authors (AP, JL) collected patient data in standardised forms. Given the heterogeneity of the data sources, various search methods were employed to identify patients, including searches for keywords (eg, Crohn, colitis, IBD), pharmaceutical prescriptions, and ICD-10 codes. Demographic data

[1] Concord Repatriation General Hospital, Sydney, NSW. [2] Centre for Digestive Diseases, Sydney, NSW. [3] University of Sydney, Sydney, NSW. [4] AW Morrow Gastroenterology and Liver Centre, Royal Prince Albert Hospital, Sydney, NSW. [5] Sydney Children's Hospital, Sydney, NSW. [6] Children's Hospital at Westmead, Sydney, NSW. [7] Ryde Hospital, Sydney, NSW.
avivpudipeddi@gmail.com • doi: 10.5694/mja2.50910 • See Editorial (Loftus).

1 The City of Canada Bay local government area



Source: City of Canada Bay Council.[10] Reproduced with kind permission of the copyright holder, .id (https://home.id.com.au).

(patient's initials, sex, age, postcode) were collected to check for duplication and for analyses of point prevalence. "Older person" was defined as someone aged 65 years or more. Clinical data (IBD subtype, age at diagnosis) were obtained from patient medical records. The most recently updated IBD phenotype details (according to the Montreal classification[11]) were also collected.

Inflammatory bowel disease: diagnostic criteria

We included only patients with confirmed IBD according to the internationally recognised Copenhagen[12,13] (Supporting Information, table 1) and revised Porto criteria[14] for clinical, endoscopic, radiological and histological findings. Each included IBD case was independently verified by two of the authors (AP, JL).

Data analysis

Crude IBD prevalence rates were calculated by dividing the number of confirmed cases by the City of Canada Bay resident population; rates were separately calculated for Crohn disease, ulcerative colitis, and IBD unclassified (IBDU). Rates, with 95% confidence intervals (CIs), were expressed per 100 000 population. Direct age standardisation was based on the World Health Organization standard population,[15] permitting comparisons with overseas data; 95% CIs were calculated with the Keyfitz formula.[16] Statistical analysis was performed in the Statistical Package for the Social Sciences (SPSS) Statistics 23.

Ethics approval

Our study was approved by the Sydney Local Health District Human Research Ethics Committee (reference, HREC/16/CRGH/21).

Results

Demographic characteristics and phenotypes

We identified 364 prevalent cases of IBD; the median age of patients was 47 years (interquartile range [IQR], 34–62 years; range, 7–100 years), and 185 patients were women (50.8%). The median duration of IBD was 8 years for Crohn disease (IQR, 4–17 years), 10 years for ulcerative colitis (IQR, 4–18 years) and 11 years for IBDU (IQR, 4–14.5 years) (Box 2).

Complete phenotypic details were available for 163 of 164 cases of Crohn disease (99.4%) and 159 of 160 cases of ulcerative colitis (99.4%). Most patients with Crohn disease were diagnosed when aged 17–40 years and had disease affecting both the ileum and colon (68 of 164 patients, 41%). Disease was usually inflammatory but non-stricturing and non-penetrating (98 patients, 60%); 37 patients (23%) were classified as having perianal disease. The most frequent disease extent for ulcerative colitis was left-sided colitis (63 of 160 patients, 39%) (Box 3).

Prevalence rates

The crude IBD prevalence rate was 414 cases (95% CI, 371–456 cases) per 100 000 population; the age-standardised rate was 348 cases (95% CI, 312–385 cases) per 100 000 population. The age-standardised prevalence of Crohn disease was slightly higher than that of ulcerative colitis (Box 4).

Age-specific prevalence rates

IBD prevalence increased with age (Box 5). The prevalence of Crohn disease peaked in the 50–54-year age group, that of ulcerative colitis in the 35–39-year and the 85 years or more age groups (Box 6). The age distribution was similar for both sexes (Box 7).

Age at diagnosis

Age at diagnosis was available for 362 of 364 patients (99.5%). Median age at diagnosis was 32 years (IQR, 23–48 years). For Crohn disease, the median age of diagnosis was 27 years (IQR,

2 Demographic characteristics of residents of the City of Canada Bay with inflammatory bowel disease

		Inflammatory bowel disease type		
	All	Crohn disease	Ulcerative colitis	Unspecified
	364	164	160	40
Sex (male)	179 (49%)	82 (50%)	83 (52%)	14 (35%)
Age (years), median (IQR)	47.0 (34.0–62.0)	45.5 (31.0–56.3)	46.5 (36.0–63.0)	56.5 (43.3–76.0)
Disease duration (years), median (IQR)	9.0 (4.0–17.0)	8.0 (4.0–17.0)	10.0 (4.0–18.0)	11.0 (4.0–13.5)

IQR = interquartile range.

3 Inflammatory bowel disease phenotypes of patients in the City of Canada Bay, according to the Montreal classification[11]

Phenotype characteristics	
Crohn disease	164
Age at diagnosis (years)	
< 16	17 (10%)
17–40	95 (58%)
> 40	51 (31%)
Missing data	1
Disease extent	
L1 (ileal)	43 (26%)
L2 (colonic)	53 (32%)
L3 (ileo-colonic)	68 (41%)
L4 (isolated upper gastrointestinal involvement)	0
Disease behaviour	
B1 (non-stricturing and non-penetrating)	98 (60%)
B2 (stricturing)	34 (21%)
B3 (penetrating)	31 (19%)
P (perianal involvement)	37 (23%)
Missing data	1
Ulcerative colitis	
Disease extent	160
E1 (proctitis)	56 (35%)
E2 (left-sided colitis)	63 (39%)
E3 (pancolitis)	40 (25%)
Missing data	1

4 Prevalence of inflammatory bowel disease and its subtypes in the City of Canada Bay

Subtype	Number of cases	Crude point prevalence rate, per 100 000 (95% CI)	Age-standardised prevalence rate, per 100 000 (95% CI)
All types	364	414 (371–456)	348 (312–385)
Crohn disease	164 (45%)	186 (158–215)	166 (141–192)
Ulcerative colitis	160 (44%)	182 (154–210)	148 (124–171)
Unspecified	40 (11%)	45 (31–60)	34 (23–46)

CI = confidence interval.

5 Age-specific prevalence of inflammatory bowel disease in the City of Canada Bay

Age group (years)	Number of cases	Prevalence rate, per 100 000 (95% CI)
0–64	285	380 (342–418)
0–4	0	0
5–9	1	21 (12–30)
10–14	7	174 (146–202)
15–19	7	175 (149–204)
20–24	18	287 (253–320)
25–29	29	354 (318–391)
30–34	31	365 (327–402)
35–39	42	606 (558–654)
40–44	31	484 (441–527)
45–49	34	586 (539–633)
50–54	36	663 (612–713)
55–59	26	522 (477–566)
60–64	23	538 (492–583)
≥ 65	79	612 (564–660)
65–69	20	507 (463–551)
70–74	15	512 (468–556)
75–79	13	572 (526–619)
80–84	13	743 (689–796)
≥ 85	18	891 (833–949)

CI = confidence interval.

20–41.5 years) for men, 31.5 years (IQR, 25–47 years) for women. For ulcerative colitis, the median age at diagnosis was 31 years (IQR, 24–53 years) for men, 32 years (IQR, 23–46 years) for women (Box 8).

Data sources

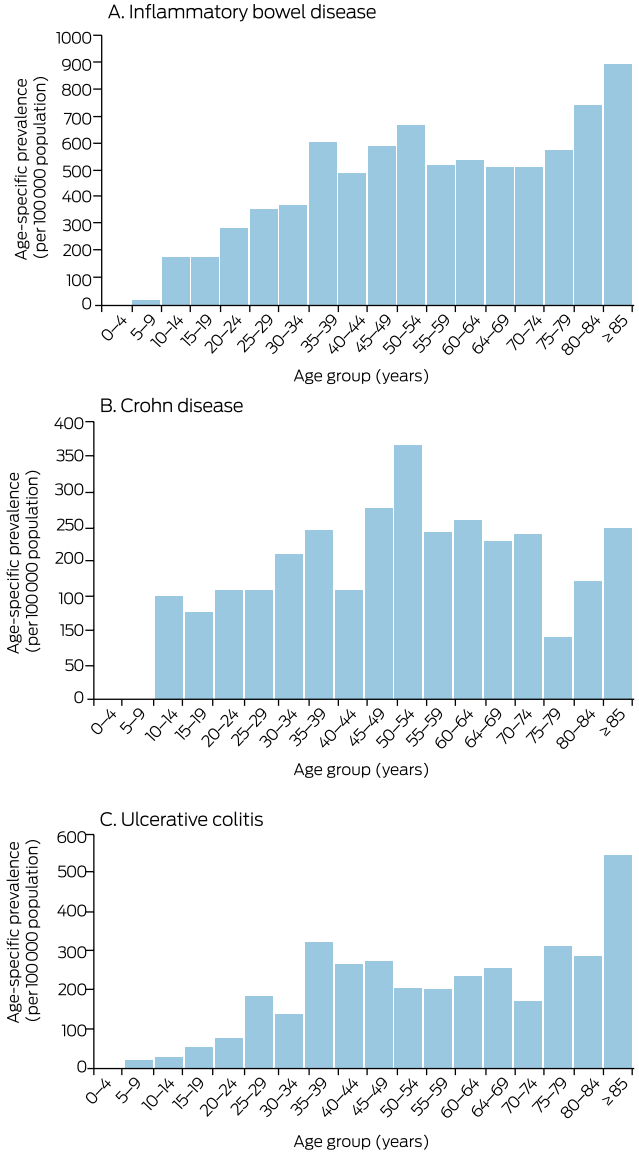
Of the 364 cases, 175 (48%) were identified in a single data source, including 139 patients of a private gastroenterologist (Supporting Information, table 2).

Discussion

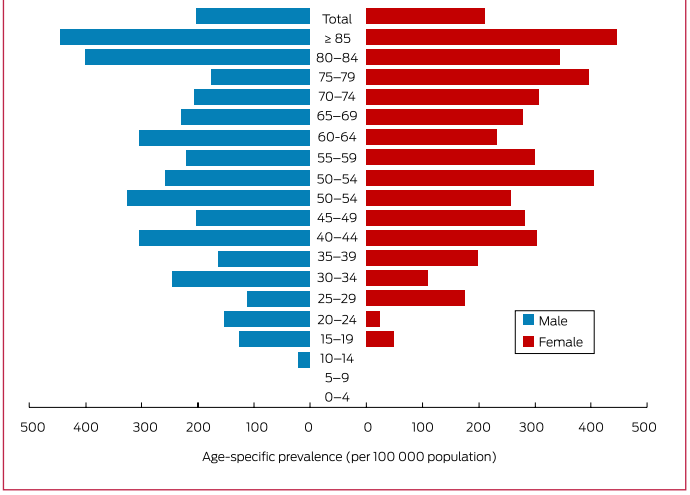
We have reported the first population-based IBD prevalence study in New South Wales, and the first IBD prevalence study in Australia restricted to a metropolitan area. Our population-based methodology allows direct comparison with other national and international studies (Supporting Information, table 3). We found the highest age-standardised rates of IBD (348 cases per 100 000 population), Crohn disease (166 per 100 000 population) and ulcerative colitis (148 per 100 000 population) reported by any study in Australia or New Zealand.[5,7,17] The prevalence rate of Crohn disease was higher than that of ulcerative colitis, as also found by earlier Australian, New Zealand and Canadian studies,[5,7,17-19] but not by older studies from Scandinavia and North America.[20-22] These differences are consistent with observations over the past fifty years that the incidence of ulcerative colitis had increased but then plateaued, while that of Crohn disease has continued to increase.[23]

Our prevalence rates are slightly higher than reported by earlier Australian studies for mixed urban and rural populations.[5,7] The difference is probably attributable to a time-cohort effect (cumulative increase in number of IBD cases over time), but our higher rate may be related to the urban nature of our sample. A systematic review and meta-analysis found that the risks of Crohn disease (incidence rate ratio [IRR], 1.42; 95% CI, 1.26–1.60) and ulcerative colitis (IRR, 1.17; 95% CI, 1.03–1.32) were higher for urban than rural residents.[22] Factors that may contribute to greater risk include higher rates of smoking (for Crohn disease),

6 Age-specific prevalence of inflammatory bowel disease in the City of Canada Bay, by type and age



7 Age-specific prevalence of inflammatory bowel disease in the City of Canada Bay, by sex



better hygiene and sanitation, antibiotic use, and air pollution in urban areas, as well as migration of young people from rural to metropolitan regions for education and employment. Further exploration of risk factors associated with urban living that may contribute to the pathogenesis of IBD is required.[24]

Our major finding was that the age-specific prevalence of IBD increased with age. The prevalence rate among people aged 65 years or more was 612 (95% CI, 564–660 cases) per 100 000 population, and 380 (95% CI, 342–418 cases) per 100 000 people under 65 years of age; 79 patients with IBD (22%) were 65 years or more old, compared with 12 916 of 88 015 people (14.7%) in the City of Canada Bay population. We also found that the prevalence of IBD among people aged 85 years or more was 891 per 100 000 people. Both rates are higher than the 483 cases per 100 000 people age 65 years or more reported by an earlier Australian study, which found that IBD prevalence increased from the age of 15–24 years, and was highest among those aged 25–54 years and people aged 65 years or more.[5] Our differing finding is probably attributable to a cumulative increase in the number of IBD cases over time.

A Canadian study found that the prevalence of ulcerative colitis was highest among people aged 40–49 years, but was similar for older age groups.[19] Findings from other studies have been heterogeneous; some North American studies reported, like us, a steady increase in IBD prevalence with age, particularly of ulcerative colitis.[18,22] As ulcerative colitis is more common among non-smokers, these patients may have lower mortality, as they are healthier than the age-matched general population, as previously reported.[25]

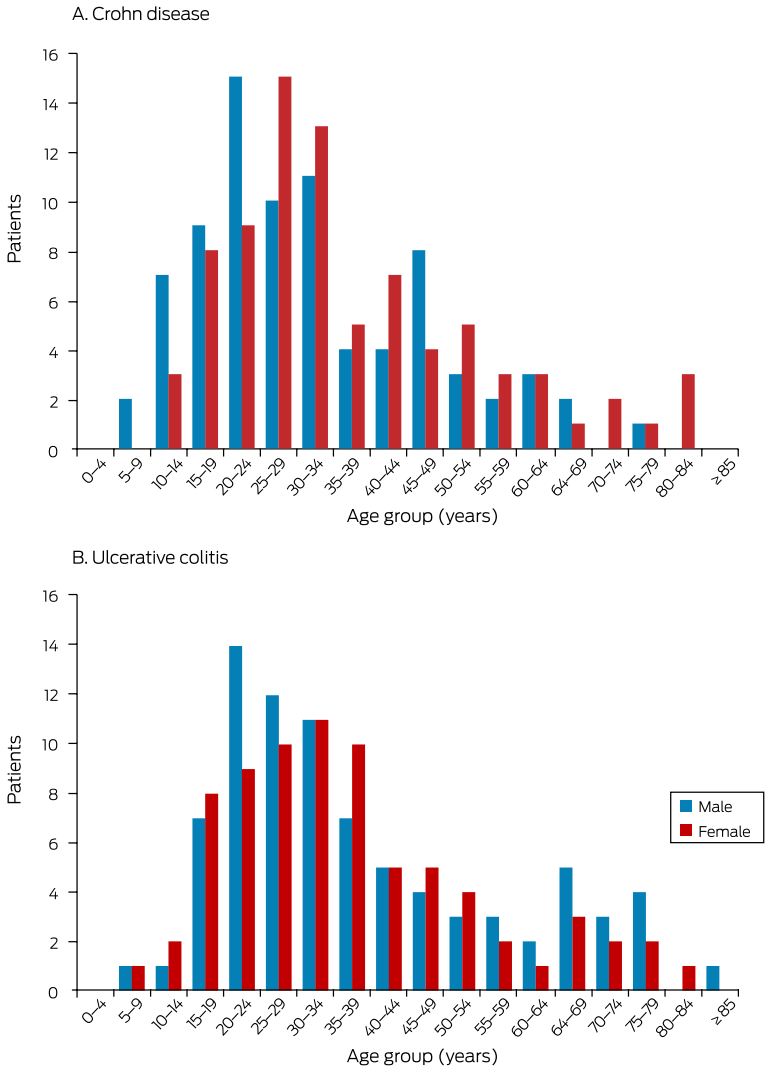
The rising prevalence of IBD with age is important for management strategies, including the use of immunosuppressive medications that exacerbate the risks of infections and malignancies in older people.[26] Accurate prevalence rates allow health care administrators to efficiently plan for investigating IBD and managing patients. Our findings highlight the importance of safer therapies, appropriate cancer screening, and taking comorbid conditions into account when managing older people with IBD.[27] Systemic immunosuppressive therapies should be de-escalated when possible, and newer biological agents less likely to lead to sepsis, such as ustekinumab and vedolizumab, should be considered.[26]

The demographic features of the City of Canada Bay are similar to those of Greater Sydney, NSW, and Australia (Supporting Information, table 4), except for higher proportions than the Australian population of people with Chinese (17% *v* 5.2%) or Italian ancestry (15% *v* 4.3%). Extrapolating the IBD prevalence rate in Canada Bay would suggest that 16 797 people in Greater Sydney, 26 046 in NSW, and 81 485 in Australia live with IBD. By way of comparison, it was estimated in 2013 that the number of people in Australia living with IBD in 2016 would lie in the range 72 805–89 502.[6]

Strengths and limitations

We fully characterised all included patients to confirm diagnoses according to the Copenhagen and revised Porto criteria. Duplication of cases was avoided by uniquely identifying each case. Phenotypic details were available for all but two patients, perhaps explaining the larger proportion of IBDU patients than in other studies. In contrast, detailed information on disease location in another Australian study was available for only 350 of 579 patients with prevalent Crohn disease (60%).[5]

8 Age at diagnosis for people in the City of Canada Bay with Crohn disease or ulcerative colitis, by sex



Limitations include the fact that we undertook a retrospective review of medical records, and we may have missed patients who sought gastroenterology care outside the City of Canada Bay. Mild cases of IBD may be managed by family physicians, but they do not usually manage IBD without involving a specialist gastroenterologist.[28] We used different search methods to reduce selection bias, including searches of paper medical records and for keywords in electronic medical records. Further, we selected an area with a small population compared with some other studies. However, the smaller population facilitated full case ascertainment in a metropolitan area, an approach not previously undertaken in Australia. The ethnic background, socio-economic status, and urban nature of our population may affect the generalisability of our findings to Australia as a whole. Finally, undiagnosed IBD is possible, as the median time from symptom onset to diagnosis is 4 months for ulcerative colitis and 9 months for Crohn disease.[29]

Conclusion

In the first IBD prevalence study in New South Wales, the most populous state in Australia, we found that its prevalence was high in the City of Canada Bay, particularly among people aged 65 years or more. The high age-specific IBD prevalence in the middle-aged and older people has important implications for treatment decisions.

Competing interests: Viraj Kariyawasam undertakes consultancy work for Janssen-Cilag and has received grants from Takeda, Ferring, Abbvie, and Shire. Thomas Borody has a pecuniary interest in the Centre for Digestive Diseases and sits on advisory boards for Redhill, Crestovo, and Finch Therapeutics. Crispin Corte has received unrestricted research grants from Shire and Ferring, and has received speakers' honoraria from Abbvie, Ferring, Janssen, Takeda, and Shire. Rupert Leong has served on advisory boards for AbbVie, Aspen, Celgene, Ferring, Janssen, and Takeda, and has received unrestricted research support from the National Health and Medical Research Council, Shire, and Janssen, and speakers' honoraria from Emerge Health.

Received 11 May 2020, accepted 11 August 2020

1 Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; 390: 2769–2778.

2 Coward S, Clement F, Benchimol EI, et al. Past and future burden of inflammatory bowel disease based on modeling of population-based data. *Gastroenterology* 2019; 156: 1345–1353.

3 Ng SC, Tang W, Ching JY, et al. Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS) Study Group. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiological study. *Gastroenterology* 2013; 145: 158–165.

4 Ray K. IBD: the changing epidemiology of IBD. *Nat Rev Gastroenterol Hepatol* 2017; 14: 690.

5 Studd C, Cameron G, Beswick L, et al. Never underestimate inflammatory bowel disease: high prevalence rates and confirmation of high incidence rates in Australia. *J Gastroenterol Hepatol* 2016; 31: 81–86.

6 PricewaterhouseCoopers Australia; Crohn's and Colitis Australia. Improving inflammatory bowel disease care across Australia. Mar 2013. https://www.crohnsandcolitis.com.au/site/wp-content/uploads/PwC-report-2013.pdf (viewed June 2019).

7 Bhatia R, Yeoh SW, Vaz K, et al. Inflammatory bowel disease incidence, prevalence and 12-month initial disease course in Tasmania, Australia. *Intern Med J* 2019; 49: 622–630.

8 Ng SC, Kaplan GG, Tang W, et al. Population density and risk of inflammatory bowel disease: a prospective population-based study in 13 countries or regions in Asia-Pacific. *Am J Gastroenterol* 2019; 114: 107–115.

9 Jones GR, Lyons M, Plevris N, et al. IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. *Gut* 2019; 68: 1953–1960.

10 City of Canada Bay Council. Welcome to the City of Canada Bay: community profile. Updated Oct 2016. http://profile.id.com.au/canada-bay/about (viewed Nov 2016).

11 Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; 19 (Suppl A): 5A–36A.

12 Munkholm P. Crohn's disease: occurrence, course and prognosis. An epidemiologic cohort-study. *Dan Med Bull* 1997; 44: 287–302.

13 Langholz E. Ulcerative colitis. An epidemiological study based on a regional inception cohort, with special reference to disease course and prognosis. *Dan Med Bull* 1999; 46: 400–415.

14 Levine A, Koletzko S, Turner D, et al. European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014; 58: 795–806.

15 Ahmad OB, Boschi-Pinot C, Lopez AD, et al. Age standardization of rates: a new WHO standard (GPE Discussion paper series: No. 31). Geneva: World Health Organization, 2001. http://who.int/healthinfo/paper31.pdf (viewed Sept 2019).

16 Keyfitz N. Sampling variance of standardized mortality rates. *Hum Biol* 1966; 38: 309–317.

17 Gearry RB, Richardson A, Frampton C, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis* 2006; 12: 936–943.

18 Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol* 2006; 101: 1559–1568.

19 Bitton A, Vutcovici M, Patenaude V, et al. Epidemiology of inflammatory bowel disease in Quebec: recent trends. *Inflamm Bowel Dis* 2014; 20: 1770–1776.

20 Jacobsen BA, Fallingborg J, Rasmussen HH, et al. Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978–2002. *Eur J Gastroenterol Hepatol* 2006; 18: 601–606.

21 Loftus CG, Loftus EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis* 2007; 13: 254–261.

22 Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol* 2007; 5: 1424–1429.

23 Ng SC, Bernstein CN, Vatn MH, et al; Epidemiology and Natural History Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD). Geographical variability and environmental risk factors in inflammatory bowel disease. *Gut* 2013; 62: 630–649.

24 Soon IS, Molodecky NA, Rabi DM, et al. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. *BMC Gastroenterol* 2012; 12: 51.

25 Selinger CP, Andrews J, Dent OF, et al. Cause-specific mortality and 30-year relative survival of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2013; 19: 1880–1888.

26 Pudipeddi A, Kariyawasam V, Haifer C, et al. Safety of drugs used for the treatment of Crohn's disease. *Expert Opin Drug Saf* 2019; 18: 357–367.

27 Kariyawasam VC, Kim S, Mourad FH, et al. Comorbidities rather than age are associated with the use of immunomodulators in elderly-onset inflammatory bowel disease. *Inflamm Bowel Dis* 2018; 25: 1390–1398.

28 Tan M, Holloway RH, Lange K, et al. General practitioners' knowledge of and attitudes to inflammatory bowel disease. *Intern Med J* 2012; 42: 801–807.

29 Vavricka SR, Spigaglia SM, Rogler G, et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; 18: 496–505. ■

Supporting Information

Additional Supporting Information is included with the online version of this article.

APPENDIX 3. **Pudipeddi A**, Ko Y, Paramsothy S, Leong R. Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Therap Adv Gastroenterol* 2022; Mar 8;15:17562848221080793.

Ther Adv Gastroenterol
2022, Vol. 15: 1–17
DOI: 10.1177/17562848221080793

Vedolizumab has longer persistence than infliximab as a first-line biological agent but not as a second-line biological agent in moderate-to-severe ulcerative colitis: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study

Aviv Pudipeddi, Yanna Ko, Sudarshan Paramsothy and Rupert W. Leong, for the PANIC Study Group – Persistence in Australian National IBD Cohort

Abstract

Background: The choice between infliximab (IFX) and vedolizumab (VED) as a first-line biological agent in moderate-to-severe ulcerative colitis (UC) can be difficult. Second-line vedolizumab (VED) efficacy may decline following prior infliximab (IFX) treatment failure in UC patients. However, it is not known whether second-line IFX efficacy declines after failure of first-line VED.

Aims: We aimed to compare first-line and second-line persistence of IFX and VED, in particular whether second-line IFX persistence declines after failure of first-line VED.

Methods: Persistence of IFX and VED was analysed from the Australian Pharmaceutical Benefits Scheme registry data as either first- or second-line treatment in UC. Propensity score matching (1:1) was conducted in the comparison of first-line treatments. Cox proportional hazard regression analysis was used to identify significant predictors and expressed as a hazard ratio (HR and 95% CI).

Results: There were 420 subjects with moderate-to-severe UC who received either first-line IFX ($n = 251$) or VED ($n = 169$), with 774 patient-years of follow-up. First-line VED had significantly longer persistence than first-line IFX (>50.2 *versus* 22.2 months, $p = 0.001$). Fifty-three subjects failed first-line IFX and swapped to second-line VED (IFX→VED group). Twenty-two subjects failed first-line VED group and swapped to second-line IFX (VED→IFX group). First-line VED persistence was significantly longer than second-line VED (>50.2 *versus* 32.0 months, $p = 0.03$), but first-line IFX persistence was not statistically significantly different to second-line IFX (27.6 months *versus* >38.6 months, $p = 0.30$). Immunomodulator co-therapy was significantly associated with a lower risk of nonpersistence of first-line VED (HR: 0.55, 95% CI: 0.33–0.89, $p = 0.02$) and IFX (HR: 0.63,95%CI: 0.33–0.92, $p = 0.02$).

Conclusion: VED had a significantly longer persistence than IFX as first-line biological agent but does not disadvantage second-line IFX use in moderate-to-severe UC. VED after IFX is associated with significantly poorer persistence. VED, therefore, should be considered as the first-line biological agent of choice in UC.

Keywords: infliximab, sequencing, ulcerative colitis, vedolizumab

Received: 19 October 2021; revised manuscript accepted: 28 January 2022.

Correspondence to:
Rupert W. Leong
Gastroenterology and Liver Services, Concord Repatriation General Hospital, Hospital Road, Concord, Sydney, NSW 2139, Australia

Faculty of Medicine and Health, Concord Clinical School, The University of Sydney, Sydney, NSW, Australia.
rupertleong@outlook.com

Aviv Pudipeddi
Yanna Ko
Sudarshan Paramsothy
Gastroenterology and Liver Services, Concord Repatriation General Hospital, Sydney, NSW, Australia

Faculty of Medicine and Health, Concord Clinical School, The University of Sydney, Sydney, NSW, Australia

Introduction

Ulcerative colitis (UC) is an increasingly prevalent chronic inflammatory bowel disease (IBD) with 15% of patients having an aggressive disease course.[1,2] The cumulative risk of relapse is 70–80% at 10 years[2] and as such, many patients require maintenance treatment with an advanced therapy.[3] Recent guidelines recommend the use of infliximab (IFX) or vedolizumab (VED) as a first-line biological agent for patients with moderate-to-severe UC who are naïve to biological therapy.[4] However, 10–40% of patients have a primary nonresponse to IFX, while 23–46% of patients have a secondary loss of response to IFX at 12 months after induction.[5] Furthermore, 35% of patients lose response to VED at 12 months.[6] Therefore, many patients will switch to a second-line biological agent. VED may be less effective in those who have failed prior anti-tumour necrosis factor-alpha (anti-TNFα) therapy including IFX.[7,8] The effectiveness of second-line IFX after failure of VED, however, is less well-known. The optimal sequencing of these agents as first- and second-line agents is a key knowledge gap that requires addressing to reduce disease burden.[9]

Treatment persistence measures continuing medication prescription based on ongoing therapeutic efficacy in the absence of significant adverse effects.[10] Persistence reflects willingness by patient and their physician to continue a medication in the absence of therapeutic failure or a better treatment alternative.[11] Importantly, it reflects real-world practice that allows for treatment optimisation including dose-adjustment, addition of temporary induction treatments and other strategies. The rate of failure and duration of persistence for various drugs are different and provide important comparative efficacy data given the paucity of head-to-head trials of advanced therapies in UC.[10,12]

Persistence data, in some respects, may be even more informative than head-to-head trials. Population-based persistence data are cost-efficient and might include sufficient statistical power to identify clear clinical differences through long-term follow-up. Persistence data may be similar to clinical drug trials in that both have strict inclusion and exclusion eligibility criteria, collect data prospectively, include data on prior or ongoing use of conventional and biological agents, and are multicentre and generalizable. The Persistence in Australian National IBD Cohort (PANIC) is a large real-world national population-based registry with 8219 patient-years of follow-up, in which biological agents were fully funded without stipulated hierarchical prescribing order.[13] Hence, this database allows for an objective comparison of persistence between biological agents.

The primary aim of this population-based prospective study was to compare the persistence of IFX and VED as first- and second-line therapies, including second-line IFX following VED failure *versus* first-line IFX use. Factors affecting the persistence of these biological agents were examined.

Methods

Study population

Consecutive adult subjects (aged ⩾18 years) prescribed IFX or VED for the treatment of moderate-to-severe UC were included. The diagnosis of moderate-to-severe UC had to be definite using the Copenhagen diagnostic criteria[14] and we excluded biological agents prescribed to treat acute severe UC, Crohn's disease or rheumatological/dermatological indications.

Study design and data source

The Persistence Australian National IBD Cohort (PANIC) study used prospective script data, including co-therapy with immunomodulators, collected from the Australian Pharmaceutical Benefits Scheme (PBS) database from December 2014 to September 2019. The PBS subsidises treatment with biological agents under the National Health Act 1953. Patients with UC and a partial Mayo score of ⩾6 are provided biological agents at no cost if they fail to achieve adequate treatment response following a 3-month course of mesalazine and either 3 months of thiopurine (or shorter due to toxicity) or at least a 6-week course of a corticosteroid.[15] Following induction therapy, demonstration of response to PBS subsidised treatment must be conducted 6-monthly in order to continuing maintenance treatment. The PBS does not enforce hierarchical prescribing order so there is no need to prescribe anti-TNFα agents or biosimilars prior to VED. Script data were linked to the patients' unique Medicare number. Data were analysed using a 10% random sample, which is a standardised accepted strategy.[13] PBS data were acquired and collated by an independent provider (Model Solutions, Australia) and

validated through a second provider to ensure robustness of data. All analyses, however, were performed by the researchers.

Study definitions

Persistence was defined as the duration of time from initiation to discontinuation of biological therapy for moderate-to-severe UC.[11] Nonpersistence was defined as discontinuation of that agent and represented objectively as a switch in or out of biological class or complete cessation. Persistence rate was the proportion of patients who continued on a biological agent at a particular time point. Immunomodulator co-therapy was defined as the concurrent use of a thiopurine or methotrexate during the period of biological agent use.

Sample size calculation

Sample size calculation was based on results from a retrospective real-world study that found a persistence rate of 78% for VED patients and 64% for IFX patients with IBD at 24 months.[16] Assuming a two-sided alpha of 0.05 and a power of 80%, a total of 249 IFX and 166 VED patients would be required at a ratio of three IFX patients to every two VED patients. The 3:2 ratio of IFX:VED was based on PBS biological agent prescription use for UC in Australia.[17]

Study outcomes, propensity score matching and statistical analysis

Baseline characteristics of continuous variables were described as medians with interquartile ranges (IQR). Categorical variables were described as percentages. Outcomes comparing the persistence of first-line and second-line IFX and VED were analysed using unadjusted Kaplan–Meier survival curves and statistically significant differences in persistence were identified using the log-rank test. Cox proportional hazard regression was used to identify factors affecting persistence, adjusting for covariates and described as hazard ratios (HR) and 95% confidence intervals (CI). Secondary outcomes included comparing the persistence rates between each biological agent at 12, 24, 36 and 48 months using chi-square testing. We also analysed the persistence of first-line IFX and VED stratified by immunomodulator co-therapy using unadjusted Kaplan–Meier survival curves and log-rank testing. Propensity score matching was also performed in first-line therapy comparisons to control for age and gender as possible confounders of medication persistence. Using the propensity scores, first-line VED patients were matched with first-line IFX patients using a 1:1 matching algorithm, with a proximity calliper of 0.1. A p value of <0.05 was considered statistically significant. Bonferroni correction was applied in the setting of multiple comparisons during analysis of persistence rates. Statistical analysis was performed using IBM SPSS software version 27.0 (SPSS Inc., Chicago, IL, USA).

Ethics approval

The study was approved by the Services Australia External Request Evaluation Ethics Committee with approval number RMS1531. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

Results

Study population and baseline characteristics

In total, 420 patients were prescribed either IFX (251 patients) or VED (169 patients) as a first-line biological agent for moderate-to-severe UC, equating to 774 person-years of follow-up. Males comprised 54.2% (136/251) of the IFX group and 49.7% (84/169) of the VED group ($p=0.38$). The median age of the VED group (44.0 years, IQR: 33.0–56.0) was older than the IFX group (37.0 years, IQR: 28.0–54.0, $p=0.003$). The baseline characteristics of the study population are shown in Table 1.

Figure 1 illustrates the PBS prescription of IFX and VED as first-line and second-line biological agents. From the 251 patients who used IFX as a first-line biological agent, 53 used VED as a second-line biological agent (IFX→VED group). From the 169 patients who used VED as a first-line biological agent, 22 used IFX as a second-line biological agent (VED→IFX group). The baseline characteristics of the IFX→VED and VED→IFX groups are shown in Table 2. The median ages of the IFX→VED and VED→IFX groups were 38.0 years (IQR: 28.5–55.0) and 41.5 years (IQR: 29.5–58.8), respectively ($p=0.30$). About 67.9% (36/53) of the IFX→VED group were treated with immunomodulator co-therapy during first-line biological agent use,

Table 1. Baseline characteristics of moderate-to-severe UC patients using first-line and second-line infliximab or vedolizumab.

Biological agent	Infliximab $n = 251$	Vedolizumab $n = 169$	*p*-value
Male, *n* (%)	136 (54.2%)	84 (49.7%)	0.38
Median age, years (IQR)	37.0 (28.0–54.0)	44.0 (33.0–56.0)	0.003
Immunomodulator co-therapy, *n* (%)	160 (63.7%)	80 (47.3%)	0.001
Thiopurine, *n* (%)	145 (57.8%)	75 (44.4%)	0.01
Methotrexate, *n* (%)	21 (8.4%)	7 (4.1%)	0.09
Time on combination therapy between biological agent and immunomodulator, months (IQR)	17.3 (5.1–27.6)	13.3 (3.6–17.5)	0.03

IQR, interquartile range; UC, ulcerative colitis.

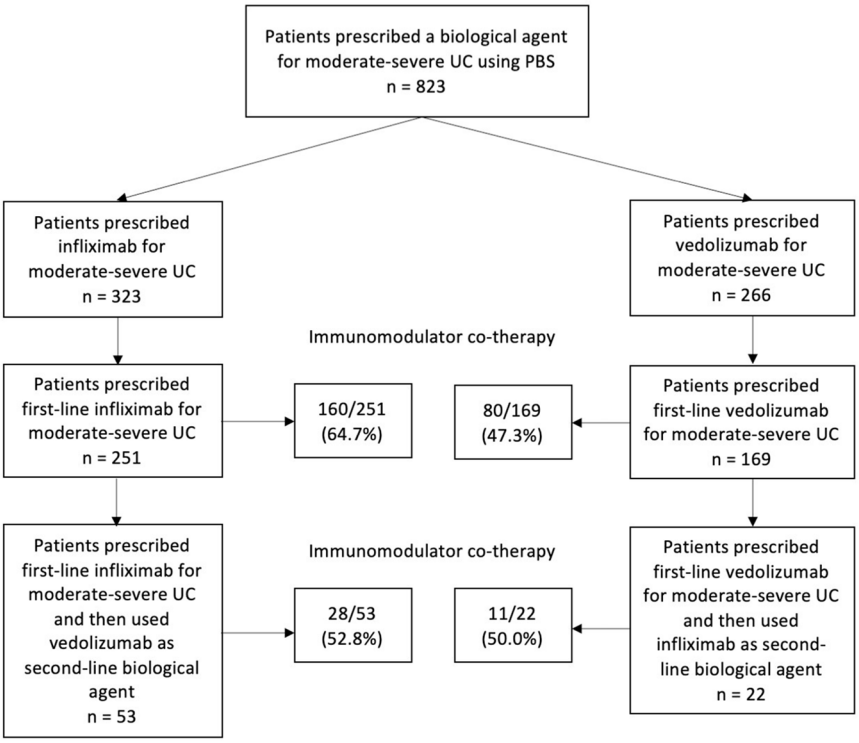


Figure 1. Flow diagram of infliximab and vedolizumab choice in moderate-to-severe UC from PBS.

compared with 36.4% (8/22) of the VED→IFX group ($p = 0.01$). About 52.8% (28/53) of the IFX→VED group were treated with immunomodulator co-therapy during second-line biological agent use, compared with 50.0% (11/22) of the VED→IFX group ($p = 0.82$).

Persistence of infliximab and vedolizumab as first-line biological agents in moderate-to-severe UC

VED had a significantly longer persistence than IFX when used as a first-line biological agent in moderate-to-severe UC [>50.2 months *versus*

Table 2. Baseline characteristics of moderate-to-severe UC patients using second-line vedolizumab or infliximab (IFX→VED and VED→IFX groups, respectively).

Biological agent	IFX→VED $n = 53$	VED→IFX $n = 22$	*p*-value
Male, *n* (%)	32 (60.4%)	14 (63.6%)	0.79
Median age, years (IQR)	38.0 (28.5 – 55.0)	41.5 (29.5 – 58.8)	0.30
First-line immunomodulator co-therapy	36 (67.9%)	8 (36.4%)	0.01
Second-line immunomodulator co-therapy	28 (52.8%)	11 (50.0%)	0.82

IFX, infliximab; IQR, interquartile range; UC, ulcerative colitis; VED, vedolizumab.

27.6 months (95% CI: 18.7–36.6), $p = 0.004$] (Figure 2). VED use was associated with a 43% lower risk of nonpersistence than IFX (HR: 0.57, 95% CI: 0.41–0.80, $p = 0.001$) (Table 3). Persistence rates and their 95% CIs at 12, 24, 36 and 48 months are reported in Figure 2. Immunomodulator co-therapy use was higher in the IFX group (63.7%, 160/251) than the VED group (47.3%, 80/169; $p = 0.001$) and was associated with a 44% lower risk of nonpersistence of first-line biological therapy (HR: 0.56, 95% CI: 0.42–0.77, $p < 0.001$).

Using propensity score matching, 169 IFX patients were matched with 169 VED patients using age and gender as covariates. VED had a significant longer persistence than IFX as a first-line biological agent (>50.2 months *versus* 22.2 months, $p = 0.001$) (Figure 3).

Persistence of infliximab and vedolizumab as second-line biological agents in moderate-to-severe UC

There was no significant difference between the persistence of second-line IFX in the VED→IFX group *versus* second-line VED use in the IFX→VED group (>38.6 months *versus* 32.0 months, $p = 0.37$, Figure 4). However, there were numerically higher persistence rates with second-line IFX in the VED→IFX group compared with second-line VED in the IFX→VED group at 12 and 24 months (Figure 4). No significant predictors of nonpersistence were identified (Table 3).

Persistence comparison between first-line vedolizumab and second-line vedolizumab

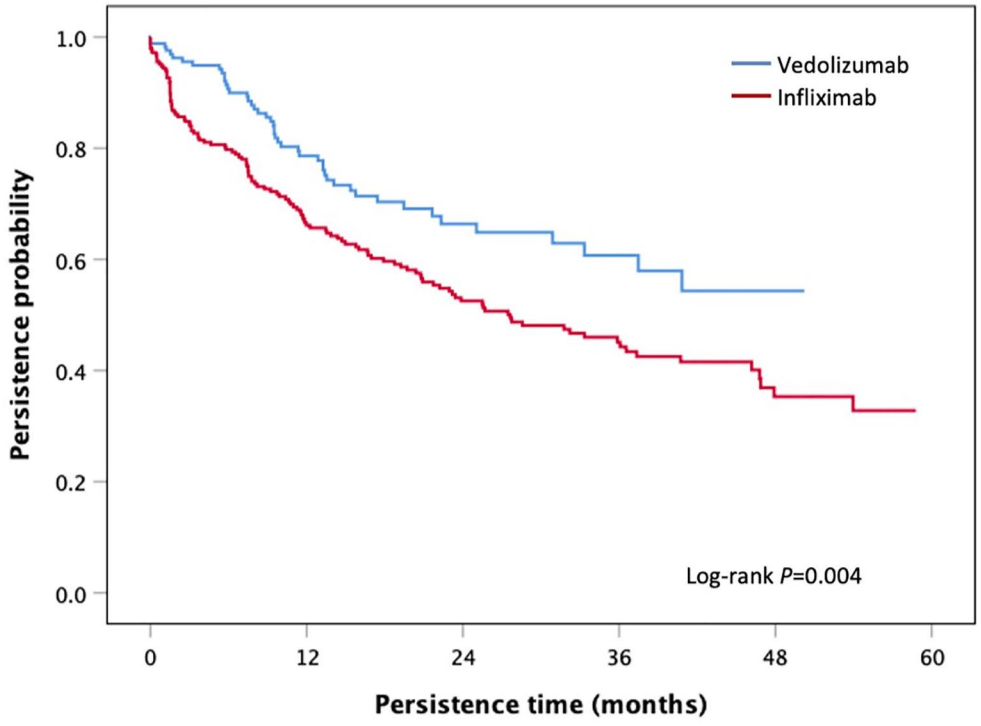
First-line VED use had a significantly longer persistence than when used as a second-line biological agent (>50.2 months *versus* 32.0 months, $p = 0.03$, Figure 5). First-line VED use was associated with a 44% lower risk of nonpersistence compared with second-line VED use (HR: 0.56, 95% CI: 0.34–0.92, $p = 0.02$). Persistence rates at 12, 24 and 36 months between first-line VED and second-line VED are shown in Figure 5. Immunomodulator co-therapy occurred in 47.3% (80/169) of the first-line VED group *versus* 52.8% (28/53, $p = 0.49$) of the second-line VED group, and was associated with a 45% lower risk of nonpersistence of VED therapy (HR: 0.55, 95% CI: 0.33–0.89, $p = 0.02$).

Persistence comparison between first-line infliximab and second-line infliximab

There was no significant difference between first-line IFX and second-line IFX persistence [27.6 months (95% CI: 18.7–36.6) *versus* >38.6 months, $p = 0.30$, Figure 6]. The use of IFX as a first- *versus* second-line agent did not significantly predict for nonpersistence (HR: 1.49, 95% CI 0.61–3.67, $p = 0.39$). Immunomodulator co-therapy occurred in 64.7% (160/251) of the first-line IFX group *versus* 50.0% (11/22, $p = 0.20$) of the second-line IFX group and was associated with a 37% lower risk of nonpersistence of IFX therapy (HR: 0.63, 95% CI: 0.44–0.92, $p = 0.02$).

Persistence of infliximab and vedolizumab stratified by immunomodulator use

First-line IFX and first-line VED had a significantly longer persistence when used in combination with an immunomodulator compared with monotherapy [36.0 months (95% CI: 22.4–49.8) *versus* 17.9 months (95% CI: 8.8–26.9), $p = 0.003$



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
Infliximab	66.1 (60.0-72.1)	52.5 (46.3-58.7)	45.1 (38.9-51.3)	35.3 (29.4-41.2)	27.6 (18.7–36.6)
Vedolizumab	78.6 (72.3-84.8)	66.4 (59.3-73.5)	60.7 (53.3-68.1)	54.3 (46.8-61.8)	> 50.2*
P-value†	0.01‡	0.01‡	0.001‡	<0.001‡	

CI, confidence interval

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

†Based on Bonferroni correction, statistical significance defined as $P<0.0125$

‡Statistically significant values

Figure 2. Kaplan–Meier curve for persistence of first-line infliximab and vedolizumab in moderate-to-severe UC.

for IFX group; > 50.2 months *versus* 40.8 months (95% CI: 10.3–71.3), $p = 0.02$ for VED group, Figures 7 and 8]. There was no significant difference in persistence between second-line IFX ($p = 0.95$) and VED ($p = 0.30$) when stratified by immunomodulator co-therapy (Figures 9 and 10).

Discussion

In this large population-based prospective registry providing 774 patient-years of real-world follow-up, the persistence of VED was significantly longer than IFX as a first-line biological agent in moderate-to-severe UC. Persistence of second-line IFX after VED exposure was not significantly

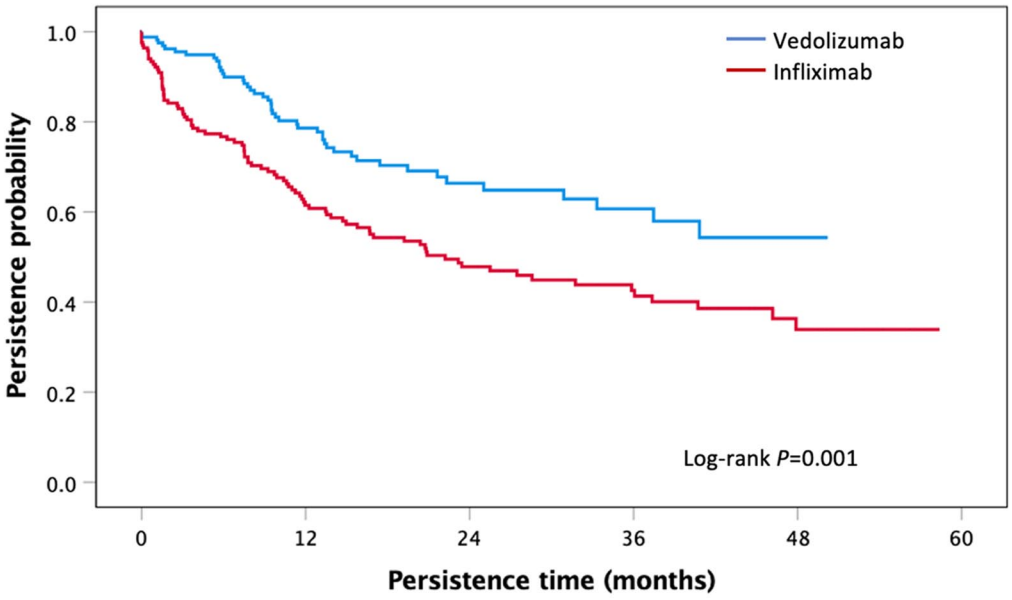
Table 3. Predictors of medication nonpersistence.

	HR (95% CI)	*p*-value
First-line biological therapy of vedolizumab and infliximab		
Female *versus* male gender	1.03 (0.76–1.39)	0.84
Age	1.00 (0.99–1.01)	0.67
VED *versus* IFX	0.57 (0.41–0.80)	0.001
Immunomodulator co-therapy	0.56 (0.42–0.77)	<0.001
Second-line biological therapy of infliximab (VED→IFX group) and vedolizumab (IFX→VED) group		
Female *versus* male gender	0.61 (0.25–1.49)	0.28
Age	0.98 (0.96–1.01)	0.34
VED *versus* IFX	1.66 (0.63–4.40)	0.31
Immunomodulator co-therapy	0.66 (0.30–1.47)	0.31
Vedolizumab use as a first-line or second-line biological therapy		
Female *versus* male gender	0.85 (0.52–1.39)	0.51
Age	1.00 (0.98–1.01)	0.59
First-line VED *versus* second-line VED	0.56 (0.34–0.92)	0.02
Immunomodulator co-therapy	0.55 (0.33–0.89)	0.02
Infliximab use as a first-line or second-line biological therapy		
Female *versus* male gender	0.86 (0.59–1.25)	0.43
Age	1.00 (0.99–1.01)	0.90
First-line IFX *versus* second-line IFX	1.49 (0.61–3.67)	0.39
Immunomodulator co-therapy	0.63 (0.44–0.92)	0.02

CI, confidence interval; HR, hazard ratio; IFX, infliximab; VED, vedolizumab.

impaired when compared against second-line VED after IFX exposure. First-line VED persistence had significantly longer persistence than second-line VED. There was no significant difference in persistence between first-line IFX and second-line IFX. These data support the use of VED as first-line biological treatment in moderate-to-severe UC given the longer persistence when used first-line and the decline in persistence when used second-line. Conversely, IFX persistence when used as a second-line agent after switch from VED was not impaired.

There is a lack of data on the long-term effectiveness of biological agents in UC, and persistence data provide an indirect approach for assessing the long-term therapeutic benefit and safety of therapies.[19] The VARSITY (An Efficacy and Safety Study of Vedolizumab Intravenous [IV] Compared to Adalimumab Subcutaneous [SC] in Participants With Ulcerative Colitis) study recently demonstrated that VED was superior to adalimumab in achieving clinical remission and endoscopic improvement; however, there are no direct comparisons between IFX and VED.[12] In the absence of head-to-head comparisons between IFX and VED, real-world persistence data act as a surrogate marker for treatment efficacy, safety and acceptability by patients and physicians.[19] Our results demonstrate significantly greater persistence of



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
Infliximab	61.5 (52.0-71.0)	47.9 (38.1-57.7)	43.8 (34.1-53.5)	33.9 (24.6-43.2)	22.2 (12.7–31.7)
Vedolizumab	78.6 (72.3-84.8)	66.4 (59.3-73.5)	60.7 (53.3-68.1)	54.3 (46.8-61.8)	> 50.2*
P-value†	<0.001‡	<0.001‡	<0.001‡	<0.001‡	

CI, confidence interval

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

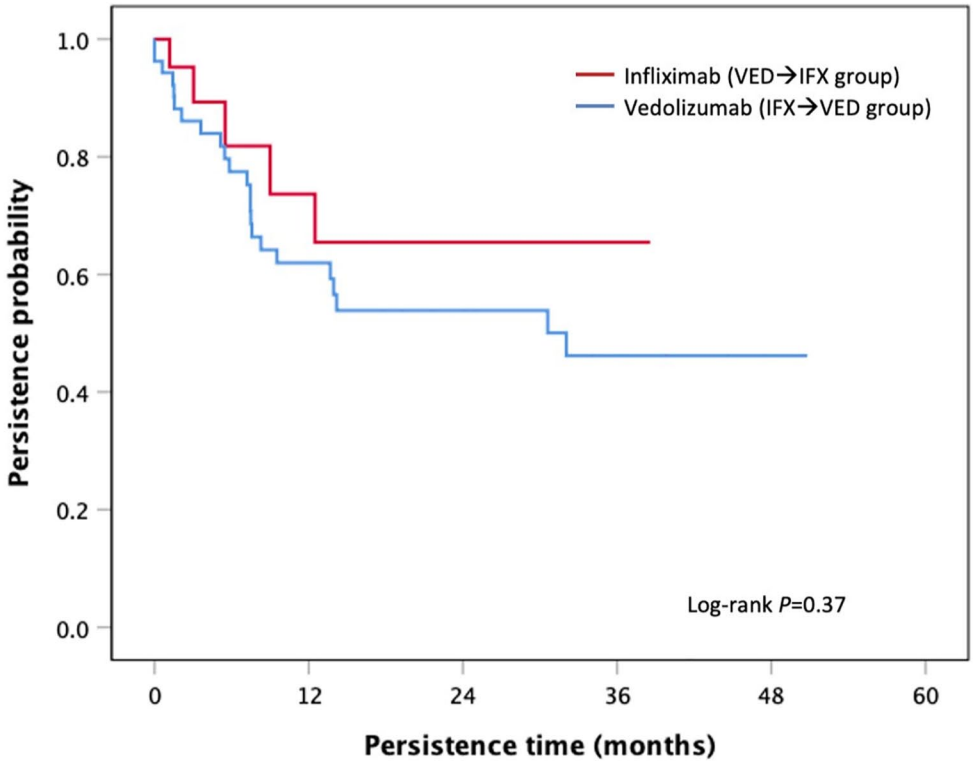
†Based on Bonferroni correction, statistical significance defined as $P<0.0125$

‡Statistically significant values

Figure 3. Kaplan–Meier curve for persistence of first-line infliximab and vedolizumab in moderate-to-severe UC using propensity score matching.

first-line VED over first-line IFX in both short term (12 months) and long term (24, 36 and 48 months) (Figure 2). The results from this PANIC study are supported by a retrospective study which also demonstrated that VED had higher persistence rates than IFX in biological-naïve IBD patients.[16] The addition of propensity score matching was relevant due to the significant increased age of VED subjects compared with IFX in the PANIC registry. We previously demonstrated the increasing age of IBD subjects in developed countries[1] and for age to be a significant determinant in the deciding a biological agent in IBD.[20] Therefore, propensity score matching was performed to reduce the selection bias associated with older age and the risk of adverse effects.[21]

Consistent with other studies,[7,8] we found VED had significantly longer persistence when used as a first-line agent *versus* second-line use following IFX failure. To our knowledge, however, there are no data comparing second-line biological agents in IFX→VED with VED→IFX sequences. There is a need to explore the correct positioning



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
Infliximab	73.7 (68.3-79.1)	65.5 (59.6-71.4)	65.5 (59.6-71.4)	-	> 38.6*
Vedolizumab	62.0 (54.7-69.3)	53.9 (46.4-61.4)	46.2 (38.7-53.7)	46.2 (38.7-53.7)	32.0^
P-value†	0.39	0.48	0.15	n/a	

IFX, infliximab; VED, vedolizumab; CI, confidence interval; n/a, not applicable

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

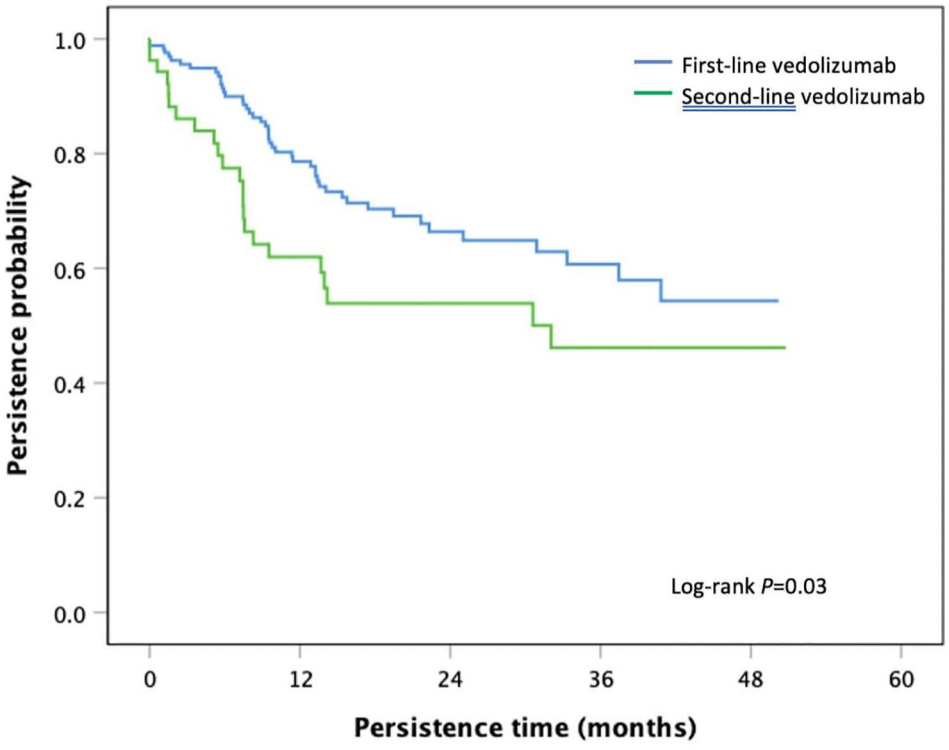
^Unable to compute confidence interval when event rate is higher than 45%

†Based on Bonferroni correction, statistical significance defined as $P<0.017$

Figure 4. Kaplan–Meier curve for persistence of second-line infliximab and vedolizumab in VED → IFX and IFX → VED groups, respectively.

of biological agents, as less than half of all UC patients continue their first-line biological agent after 1 year.[19] The persistence of second-line IFX (after VED exposure) of 65.5% (95% CI: 59.6–71.4%) compared against second-line VED of 46.2% (95% CI: 38.7–53.7%) at 36 months ($p=0.15$, Figure 3) suggests a trend of IFX being a better second-line agent than VED. There have been no studies that evaluated persistence up to 3 years previously with others limited to only 6 months of follow-up.[22,23] The persistence of IFX was not dissimilar when used first-line or second-line following VED.

First-line VED use did not impair the effectiveness of second-line IFX use, as supported by the



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	Time in months (95% CI)
First-line VED	78.6 (72.4-84.8)	66.4 (59.3-73.5)	60.7 (53.3-68.1)	54.3 (46.8-61.8)	> 50.2*
Second-line VED	62.0 (48.9-75.1)	53.9 (40.5-67.3)	46.2 (32.8-59.6)	-	32.0^
P-value†	0.02	0.13	0.04	n/a	

CI, confidence interval; VED, vedolizumab; n/a, not applicable

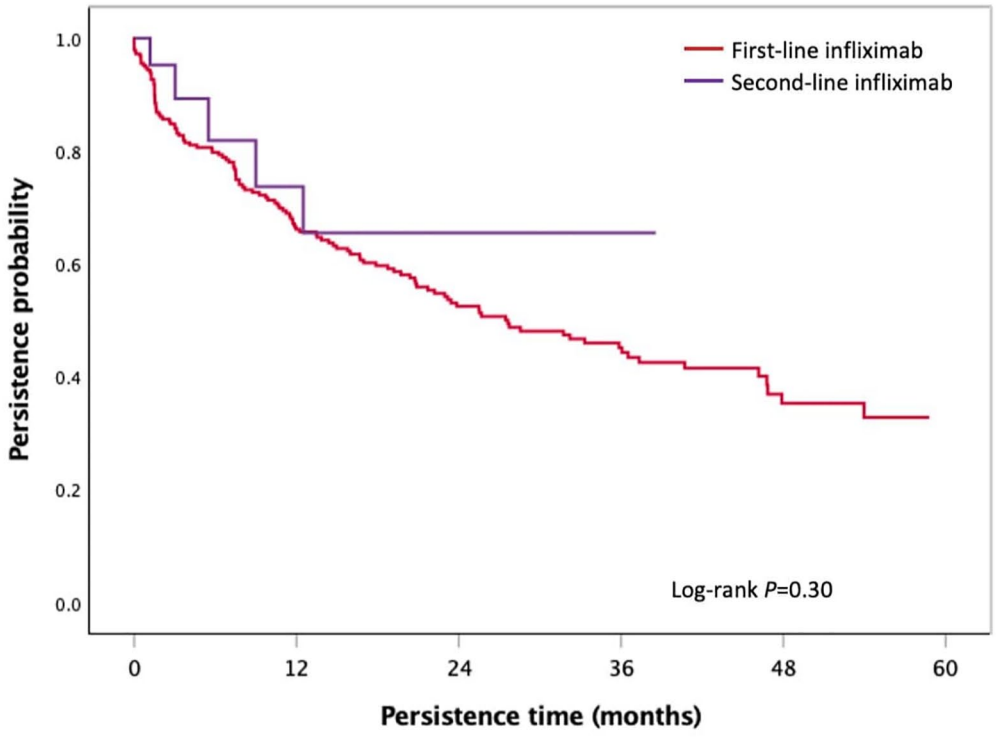
*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

^Unable to compute confidence interval when event rate is higher than 45%

†Based on Bonferroni correction, statistical significance defined as $P<0.017$

Figure 5. Kaplan–Meier curve for persistence of first-line vedolizumab compared with second-line vedolizumab in moderate-to-severe UC.

EVOLVE study which also found that anti-TNF effectiveness may not be compromised by prior VED exposure.[24] However, our study found that IFX therapy impaired subsequent VED persistence.[7,8] A possible explanation is a pharmacokinetic impact of prior IFX exposure on VED trough levels, with one study noting lower VED trough levels at week 6 compared with biological-naïve patients (22.5 *versus* 36.0 µg/ml, $p = 0.03$).[25] Previous research has also demonstrated that MAdCAM-1 is downregulated by TNFα blockade, so prior IFX-exposed patients may need higher doses of vedolizumab to bind a higher target burden.[26] These detectable biological changes, therefore, support VED to be used as first-line biological agent in moderate-to-severe UC, followed by IFX as a second-line agent.



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
First-line IFX	66.1 (60.2-71.9)	52.5 (46.3-58.7)	45.1 (38.9-51.3)	35.3 (29.4-41.2)	27.6 (18.7–36.6)
Second-line IFX	73.7 (55.3-92.1)	65.5 (45.6-85.4)	65.5 (45.6-85.4)	-	> 38.6*
P-value†	0.53	0.32	0.09	n/a	

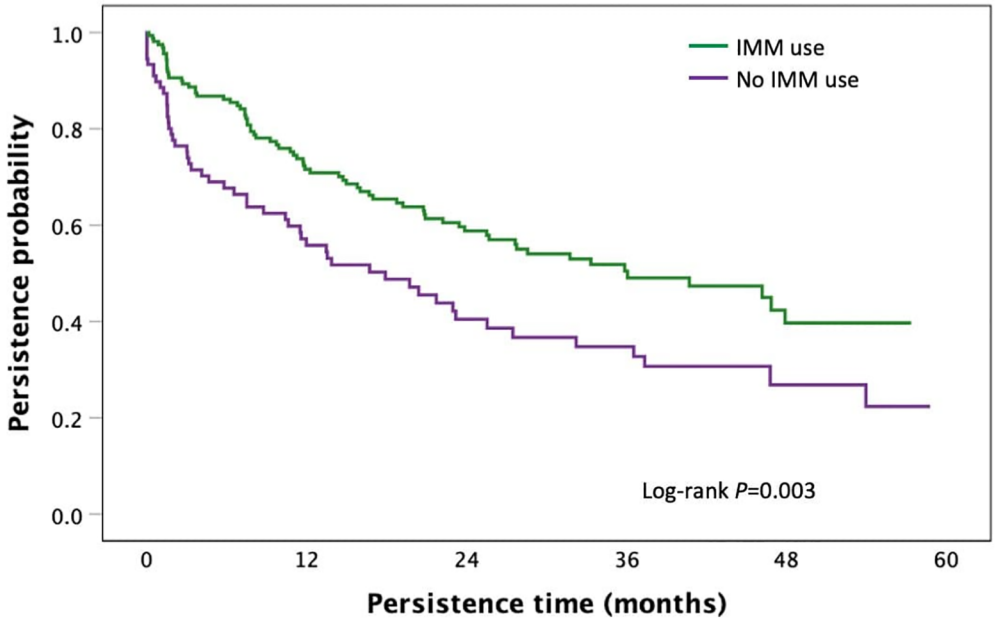
CI, confidence interval; IFX, infliximab; n/a, not applicable

*The median survival or its confidence interval cannot be exactly calculated when event rate is higher than 50%.

†Based on Bonferroni correction, statistical significance defined as $P<0.017$

Figure 6. Kaplan–Meier curve for persistence of first-line infliximab compared with second-line infliximab in moderate-to-severe UC.

Immunomodulator use improved the persistence of first-line IFX and first-line VED. Immunomodulator co-therapy is known to reduce immunogenicity and improve the persistence and effectiveness of IFX.[13] However, the benefit of combination immunotherapy with VED is less clear. This is the first study to demonstrate the increased persistence of first-line VED when combined with immunomodulators through the use of prospectively collected data for immunomodulators in our PANIC registry. We found larger differences in persistence rates between combination VED and immunomodulator co-therapy *versus* VED monotherapy after 12 months of VED use (Figure 8), suggesting a greater benefit with long-term follow-up. Other studies suggest a lack of advantage of combination therapy *versus* monotherapy but were limited to 6–12 months of data and may not have verified ongoing



	Persistence Percentage (95%CI) (%)				Median survival
	12 months	24 months	36 months	48 months	time in months (95% CI)
IMM use	71.6 (62.8-80.4)	58.8 (49.2-68.4)	50.5 (40.7-60.3)	39.7 (30.1-49.3)	36.0 (22.4-49.8)
No IMM use	55.8 (46.4-65.2)	40.5 (30.9-50.1)	34.8 (25.5-44.1)	26.9 (18.2-35.6)	17.9 (8.8-30.0)
P-value†	0.04	0.03	0.07	0.06	

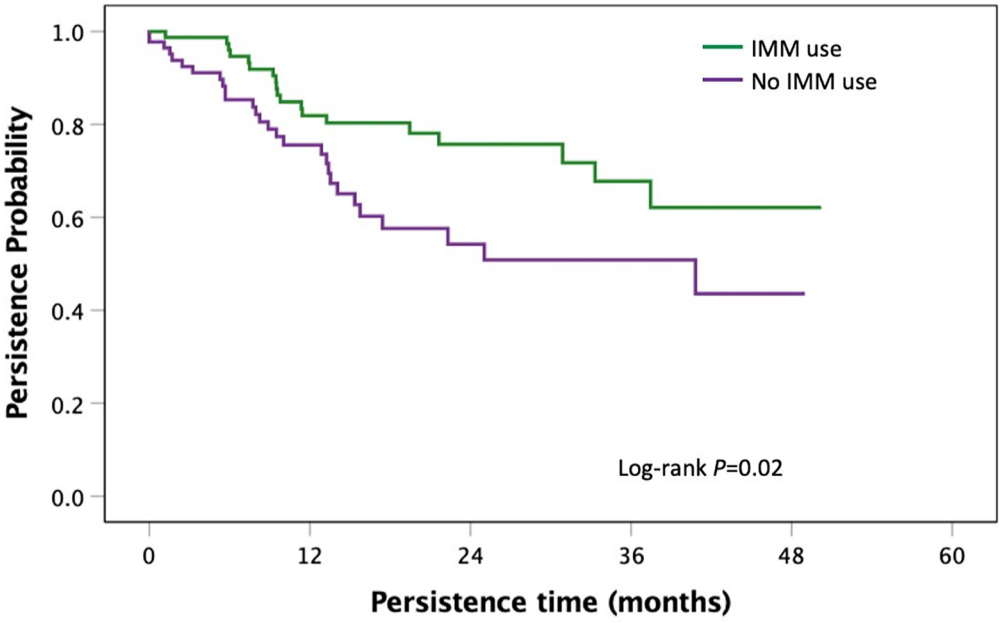
CI, confidence interval; IMM, immunomodulator;

†Based on Bonferroni correction, statistical significance defined as $P<0.0125$

Figure 7. Kaplan–Meier curve for persistence of first-line infliximab stratified by immunomodulator co-therapy in moderate-to-severe UC.

immunomodulator use.[27] The smaller sample size of the EVOLVE study (22 patients in the combination group) identified numerically higher persistence in the combination group at 18 and 24 months but might be underpowered to demonstrate statistical significance.[28] It is possible that newer monoclonal antibodies, although less immunogenic than older anti-TNFα agents, are still complex glycoproteins that may result in the eventual development of antibodies. Additive anti-inflammatory effects of immunomodulators with VED are also possible. A prospective study primarily focusing on the benefits of combination therapy with VED is recommended.

This study has limitations. First, this study was not a randomised controlled trial controlling for patient characteristics and disease severity. However, there is no proposed randomised controlled trial of IFX *versus* VED currently planned, and it would not be possible to include a sufficient sample size and follow-up duration to be able to follow-up those that require switching to a second-line treatment. Real-world evidence with



	Persistence Percentage (95%CI) (%)				Median survival time in months
	12 months	24 months	36 months	48 months	
IMM use	81.9 (74.7-89.4)	75.7 (67.3-84.1)	67.8 (58.7-77.0)	62.1 (52.6-71.6)	> 50.2*
No IMM use	75.6 (67.2-84.0)	54.2 (44.4-64.0)	50.8 (41.0-60.6)	43.6 (33.9-53.3)	40.8 (10.3-71.3)
P-value†	0.62	0.17	0.25	0.26	

CI, confidence interval; IMM, immunomodulator;

*The median survival or its confidence interval cannot be calculated when event rate is higher than 50%.

†Based on Bonferroni correction, statistical significance defined as $P<0.0125$

Figure 8. Kaplan–Meier curve for persistence of first-line vedolizumab stratified by immunomodulator co-therapy in moderate-to-severe UC.

sufficient patient-years of follow-up may address these data gaps. Second, the clinical, biochemical, and endoscopic outcomes are not known. Although patients with acute severe UC were excluded, it is possible that patients were prescribed IFX as they had a more severe phenotype, hence biasing the results. However, as only experienced gastroenterologists prescribe these agents in Australia, it is expected that relevant clinical information would be incorporated into any decision to continue or discontinue treatment. The population-based database also means data are not limited to specialised centres so that data can be generalised. Third, data on therapeutic drug monitoring and corticosteroid use are unknown. However, current conventional practice allows for treatment escalation of IFX and VED to be provided under compassionate access at no cost to the hospitals or subjects so it is likely that dose optimisation is performed prior to treatment switching. Whereas clinical trials might deem such dose escalations as treatment failure on intention-to-treat, persistence data allow these subjects to be included and provide a more realistic comparison of treatment efficacy. Ideally, correcting for clinical characteristics beyond age in

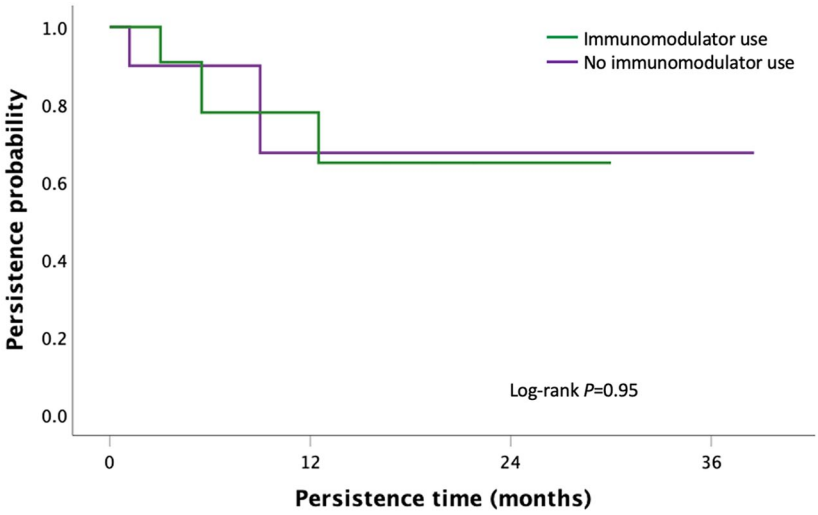


Figure 9. Kaplan–Meier curve for persistence of second-line infliximab stratified by immunomodulator co-therapy in moderate-to-severe UC.

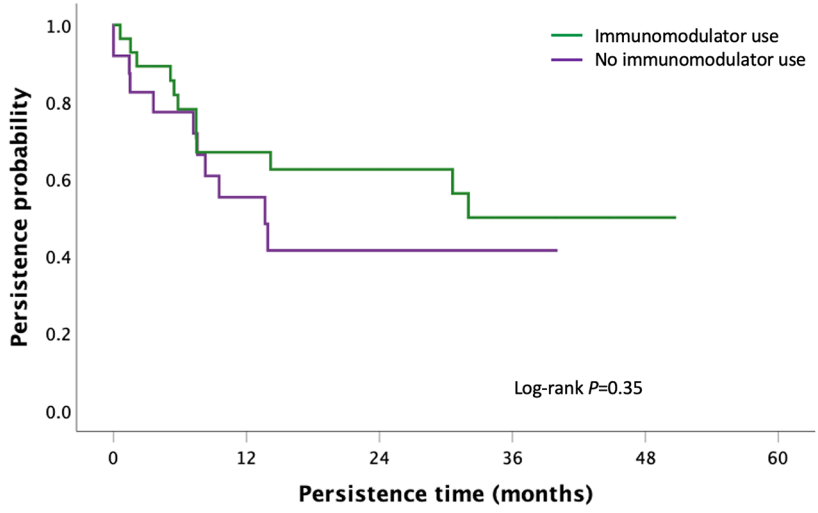


Figure 10. Kaplan–Meier curve for persistence of second-line vedolizumab stratified by immunomodulator co-therapy in moderate-to-severe UC.

propensity score matching might further reduce bias in comparing subjects on VED *versus* IFX. However, age was the most important factor identified previously[18] and subjected to propensity score matching. Also, there was a relatively small number of patients in the second-line groups which may impact on the results. However, there is limited available data on second-line use (particularly IFX) so our results will be beneficial. Finally, only a randomly selected 10% of the population database could be used for analysis due to national ethical criteria for data accessibility. However, this was a random sampling without selection bias and similar publications were deemed robust given the large patient-years of follow-up.[29]

Strengths include the use of a large, national, population-based study where biological agents are prescribed without a hierarchical prescribing order and are fully reimbursed indefinitely. All subjects had verified Mayo scores of $\geqslant$6 which

indicates consistency of disease severity. All data were collected prospectively with clinical remission being an absolute requirement for ongoing treatment. Whether treatment escalation was performed or concurrent immunomodulator was used was decided between the clinician and patients consistent with real-world practice. Furthermore, individual switches to other biological agents and immunomodulator co-therapy are prospectively recorded and long-term follow-up data beyond 4 years is an advantage over clinical trials that have relatively short durations of follow-up. The population-based data also mean the results are more generalizable. In the absence of large head-to-head studies with long-term follow-up, population-based persistence data can effectively compare the efficacy of IFX *versus* VED.

Conclusion

In summary, the PANIC cohort with real-world data set of nonhierarchical prescribing of biological agents supports the use of VED over IFX as a first-line biological agent in moderate-to-severe UC. Following failure of VED, there is no impact on IFX persistence when used second-line. Immunomodulator treatment significantly increases the persistence of VED, but further prospective data are required to confirm this observation. Our findings will assist in the positioning of biological therapies in moderate-to-severe UC.

Acknowledgements

We acknowledge Services Australia for providing the Pharmaceutical Benefits Scheme data for this research project.

Author contributions

Aviv Pudipeddi: Data curation; Formal analysis; Methodology; Resources; Software; Writing – original draft; Writing – review & editing.

Yanna Ko: Formal analysis; Writing – review & editing.

Sudarshan Paramsothy: Conceptualisation; Writing – review & editing.

Rupert Leong: Conceptualisation; Data curation; Formal analysis; Resources; Supervision; Visualisation; Writing – review & editing.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Aviv Pudipeddi has received speaker fees from Takeda. Yanna Ko reports no conflicts. Sudarshan Paramsothy is a consultant for Finch Therapeutics and received speaker fees from Ferring, Janssen and Takeda. Rupert Leong reports advisory board fees from AbbVie, Aspen, Celgene, Ferring, Gilead, Hospira, Janssen, MSD, Pfizer and Takeda; research fees from Gastrointestinal Society of Australia (GESA), Endochoice, Janssen, National Health and Medical Research Council of Australia, Shire and Takeda; and speaker fees from Emerge Health, Ferring, Janssen, Shire and Takeda.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Rupert W. Leong https://orcid.org/0000-0001-5944-3488

Data

The data underlying this article was provided by Services Australia by permission. Deidentified individual participant data will be shared on request to the corresponding author with permission from Services Australia.

Supplemental material

Supplemental material for this article is available online.

References

1. Pudipeddi A, Liu J, Kariyawasam V, *et al.* High prevalence of Crohn disease and ulcerative colitis among older people in Sydney. *Med J Aust* 2021; 214: 365–370.
2. Fumery M, Singh S, Dulai PS, *et al.* Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clin Gastroenterol Hepatol* 2018; 16: 343–356.
3. Jeong DY, Kim S, Son MJ, *et al.* Induction and maintenance treatment of inflammatory bowel disease: a comprehensive review. *Autoimmun Rev* 2019; 18: 439–454.
4. Feuerstein JD, Isaacs KL, Schneider Y, *et al.* AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology* 2020; 158: 1450–1461.

5. Ben-Horin S, Kopylov U and Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev* 2014; 13: 24–30.
6. Schmidt E, Kochhar G, Hartke J, *et al.* Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. *Inflamm Bowel Dis* 2018; 24: 2461–2467.
7. Feagan BG, Rubin DT, Danese S, *et al.* Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol* 2017; 15: 229–239.
8. Narula N, Peerani F, Meserve J, *et al.* Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY Consortium. *Am J Gastroenterol* 2018; 113: 1345.
9. Danese S, Fiorino G and Peyrin-Biroulet L. Positioning therapies in ulcerative colitis. *Clin Gastroenterol Hepatol* 2020; 18: 1280–1290.
10. Patel H, Lissoos T and Rubin DT. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn's disease in the United States. *PLoS One* 2017; 12: e0175099.
11. Cramer JA, Roy A, Burrell A, *et al.* Medication compliance and persistence: terminology and definitions. *Value Health* 2008; 11: 44–47.
12. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, *et al.* Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med* 2019; 381: 1215–1226.
13. Ko Y, Paramsothy S, Yau Y, *et al.* Superior treatment persistence with ustekinumab in Crohn's disease and vedolizumab in ulcerative colitis compared with anti-TNF biological agents: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Aliment Pharmacol Ther* 2021; 54: 292–301.
14. Langholz E. Ulcerative colitis. An epidemiological study based on a regional inception cohort, with special reference to disease course and prognosis. *Dan Med Bull* 1999; 46: 400–415.
15. Australian Government, Services Australia. Ulcerative colitis – adult patient, 2020, https://www.servicesaustralia.gov.au/organisations/health-professionals/forms/pb127 (accessed 20 March 2020).
16. Patel H, Latremouille-Viau D, Burne R, *et al.* Comparison of real-world treatment outcomes with vedolizumab versus infliximab in biologic-naïve patients with inflammatory bowel disease. *Crohns Colitis 360* 2019; 1: otz022.
17. Pharmaceutical Benefits Scheme. Analysis of medicines used to treat ulcerative colitis: drug utilisation sub-committee (DUSC), 2017, https://www.pbs.gov.au/industry/listing/participants/public-release-docs/2017-06/ulcerative-colitis-dusc-prd-2017-06.pdf (accessed 5 November 2020).
18. Von Elm E, Altman DG, Egger M, *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007; 335: 806–808.
19. Chen C, Hartzema AG, Xiao H, *et al.* Real-world pattern of biologic use in patients with inflammatory bowel disease: treatment persistence, switching, and importance of concurrent immunosuppressive therapy. *Inflamm Bowel Dis* 2019; 25: 1417–1427.
20. Chan W, Kariyawasam V, Kim S, *et al.* Gastroenterologists' preference and risk perception on the use of immunomodulators and biological therapies in elderly patients with ulcerative colitis: an international survey. *Eur J Gastroenterol Hepatol* 2020; 32: 976–983.
21. Pudipeddi A, Kariyawasam V, Haifer C, *et al.* Safety of drugs used for the treatment of Crohn's disease. *Expert Opin Drug Saf* 2019; 18: 357–367.
22. Ritter T, Fourment C, Kuten SA, *et al.* Second-line biologic therapy after vedolizumab. *Am J Gastroenterol* 2019; 114(Suppl.): S429–S430.
23. Bressler B, Yarur A, Kopylov U, *et al.* Clinical effectiveness of first-line anti-TNF therapies and second-line anti-TNF therapy post-discontinuation in patients with ulcerative colitis or Crohn's disease. *Am J Gastroenterol* 2019; 114(Suppl.): S373.
24. Bressler B, Yarur A, Silverberg M, *et al.* Vedolizumab and anti-TNFα real-world outcomes in biologic-naïve inflammatory bowel disease patients: results from the EVOLVE study. *J Crohns Colitis* 2021; 15: 1694–1706.
25. Liefferinckx C, Minsart C, Cremer A, *et al.* Early vedolizumab trough levels at induction in inflammatory bowel disease patients with treatment failure during maintenance. *Eur J Gastroenterol Hepatol* 2019; 31: 478–485.
26. Biancheri P, Di Sabatino A, Rovedatti L, *et al.* Effect of tumor necrosis factor-α blockade on mucosal addressin cell-adhesion molecule-1 in Crohn's disease. *Inflamm Bowel Dis* 2013; 19: 259–264.
27. Yzet C, Diouf M, Singh S, *et al.* No benefit of concomitant immunomodulator therapy on efficacy of biologics that are not tumor necrosis

factor antagonists in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2020; 19: 668–679.

28. Bressler B, Yarur A, Kopylov U, *et al*. P419 Clinical effectiveness and safety of first-line biologic vedolizumab as a monotherapy or combination therapy in ulcerative colitis and Crohn's disease patients: results from the EVOLVE study. *J Crohns Colitis* 2020; 14(Suppl. 1): S381–S382.
29. Simons LA, Ortiz M and Calcino G. Persistence with a single pill versus two pills of amlodipine and atorvastatin: the Australian experience, 2006-2010. *Med J Aust* 2011; 195: 134–137.

APPENDIX 4. **Pudipeddi A**, Fung C, Christensen B, Bryant RV, Subramaniam K, Chetwood J, Paramsothy S, Leong R. Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologist vs pathologists. *World J Gastroenterol* 2023; 29(2):378-389.

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 January 14; 29(2): 378-389

DOI: 10.3748/wjg.v29.i2.378

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologists *vs* pathologists

Aviv Pudipeddi, Caroline Fung, Britt Christensen, Robert V Bryant, Kavitha Subramaniam, John Chetwood, Sudarshan Paramsothy, Rupert W Leong

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Exbrayat JM, France; Iizuka M, Japan; Xing HC, China

Received: September 11, 2022
Peer-review started: September 11, 2022
First decision: October 22, 2022
Revised: November 4, 2022
Accepted: December 23, 2022
Article in press: December 23, 2022
Published online: January 14, 2023

Aviv Pudipeddi, John Chetwood, Sudarshan Paramsothy, Rupert W Leong, Gastroenterology and Liver Services, Concord Repatriation General Hospital, Sydney 2139, Australia

Aviv Pudipeddi, Sudarshan Paramsothy, Rupert W Leong, Faculty of Medicine and Health, Concord Clinical School, University of Sydney, Sydney 2138, Australia

Caroline Fung, Department of Anatomical Pathology, Concord Repatriation General Hospital, Sydney 2139, Australia

Britt Christensen, Department of Gastroenterology, Royal Melbourne Hospital, Melbourne 3050, Australia

Britt Christensen, Department of Medicine, University of Melbourne, Melbourne 3052, Australia

Robert V Bryant, Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital, Adelaide 5011, Australia

Kavitha Subramaniam, Gastroenterology and Hepatology Unit, Canberra Hospital, Canberra 2605, Australia

Kavitha Subramaniam, Australian National University Medical School, Australian National University, Canberra 2601, Australia

Sudarshan Paramsothy, Rupert W Leong, Faculty of Medicine and Health Sciences, Macquarie University Hospital, Sydney 2109, Australia

Corresponding author: Aviv Pudipeddi, FRACP, MBBS, Doctor, Gastroenterology and Liver Services, Concord Repatriation General Hospital, Level 1West ACE Unit, Concord Repatriation General Hospital, Hospital Road, Concord, Sydney 2139, Australia.
avivpudipeddi@gmail.com

Abstract

BACKGROUND

Histological remission is increasingly accepted as a treatment endpoint in the

management of ulcerative colitis (UC). However, the knowledge of histology guidelines and the attitudes towards their use in clinical practice by gastroenterologists and pathologists is unknown.

AIM

To evaluate the knowledge of histology guidelines and attitudes towards the use of histology in UC by gastroenterologists and pathologists.

METHODS

A prospective, cross-sectional nationwide survey of gastroenterologists and pathologists who analyse UC specimens was conducted. The survey consisted of 34 questions to assess gastroenterologists' and pathologists' knowledge (score out of 19) and attitudes towards histological assessment in UC. Survey questions were formulated using the European Crohn's and Colitis position paper on histopathology and the British Society of Gastroenterology biopsy reporting guidelines. It included knowledge of histological assessment of disease activity and dysplasia, knowledge of histological scoring systems for ulcerative colitis, uptake of histology scoring systems in routine practice, attitudes towards the role of histological activity, and the use of histological activity in clinical scenarios.

RESULTS

Of 89 responders (77 gastroenterologists, 12 pathologists), there was almost universal acceptance that histological assessment should form part of UC evaluation [95% gastroenterologists, 92% pathologists]. However, gastroenterologists reported that 92% of their pathologists do not use a histological scoring system. Utilisation of a formal histological scoring system was preferred by 77% of gastroenterologists and 58% of pathologists. Both groups lacked awareness of the Geboes Score, Nancy Index and Robarts Histopathological Index scoring systems with 91%, 87%, and 92% of gastroenterologists respectively; and 83%, 83%, and 92% pathologists respectively, being uncertain of scoring systems' remission definitions. Histology knowledge score was not significantly different between gastroenterologists and pathologists [9/19 (IQR: 8-11) *vs* 8/19 (IQR: 7-10), $P = 0.54$]. Higher knowledge scores were predicted by hospital attending gastroenterologists ($P = 0.004$), participation in inflammatory bowel disease (IBD) multidisciplinary teams ($P = 0.009$), and self-declared IBD sub-specialist ($P = 0.03$).

CONCLUSION

Histological remission is a recognised target for both gastroenterologists and pathologists. Despite this, knowledge of histological scoring systems and their utilisation is poor.

Key Words: Histology; Scoring system; Ulcerative colitis; Survey

Core Tip: This manuscript describes, for the first time, the knowledge and attitudes of gastroenterologists and pathologists towards the use of histology in clinical practice. Given the increasing literature and use of histology in trials, there is a need to understand the current perceptions of using histology in the real-world. Using a novel Inflammatory Bowel Disease Knowledge score, we demonstrate that although histology is an accepted endpoint, knowledge is poor, particularly relating to histological scoring systems. As such, these results illustrate a pressing need and opportunity to improve knowledge around histology scores amongst gastroenterologists and pathologists and develop consensus agreements on a reporting approach.

Citation: Pudipeddi A, Fung C, Christensen B, Bryant RV, Subramaniam K, Chetwood J, Paramsothy S, Leong RW. Knowledge and attitudes towards the use of histological assessments in ulcerative colitis by gastroenterologists *vs* pathologists. *World J Gastroenterol* 2023; 29(2): 378-389
URL: https://www.wjgnet.com/1007-9327/full/v29/i2/378.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i2.378

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease characterised by a relapsing and remitting course[1]. Disease activity is typically evaluated using clinical, biochemical and endoscopic assessments.

Treatment goals have evolved over time, and current consensus guidelines from the Selecting Therapeutic Targets in Inflammatory Bowel Disease initiative (STRIDE-II) recommend achieving clinical and endoscopic remission[2]. However, up to 40% of patients who achieve these therapeutic endpoints may have persistent histological inflammatory activity[3,4].

Despite endoscopic normalization, ongoing active histological activity may be associated with poorer clinical outcomes including higher clinical relapse rates, corticosteroid requirement, hospitalization, colectomy and development of colorectal neoplasia[3-7]. Although histological remission is currently not a formal treatment target by consensus expert-opinion, STRIDE-II guidelines do recommend that formal histological assessment take place to determine the depth of remission and help prognosticate patient outcomes. Further, it is increasingly incorporated into clinical drug trials, with central reading to reduce bias, to provide objective scoring of inflammatory activity[2]. Standardized histological scoring systems with varying levels of validity have been developed to quantify the degree of microscopic inflammatory activity and provide a more accurate assessment of mucosal inflammation[8-12]. The three most commonly used are the Geboes score, Nancy index and Robarts histopathology index due to evidence of their content validity and reliability in evaluating histological features[13].

Although accepted in modern clinical drug trials and research settings, histological disease activity and scoring systems have not been incorporated in routine clinical practice. It is not known whether gastroenterologists understand these scoring systems or if they welcome their incorporation into routine clinical care. Achieving consensus in a formal reporting scoring system will require agreement by pathologists, but their knowledge of these scoring systems and willingness to use them is also unknown. Many pathologists use written descriptions of UC activity in their reports. Whether this translates to a numerical value, if they favour a particular scoring system, or their attitude towards synaptic reporting of histological activity, is not known. This cross-sectional survey study evaluated gastroenterologist and pathologist knowledge of histological findings and scoring systems, together with their attitudes towards the role of histology in UC management. We hypothesised that based on their dedicated training, knowledge of histological scoring systems would be significantly higher in pathologists than gastroenterologists.

MATERIALS AND METHODS

Study cohort

This was a prospective cross-sectional survey of Australian gastroenterologists and pathologists from July 2021 to January 2022. Gastroenterologists were contacted by proxy through the Gastroenterological Society of Australia, and pathologists who review UC specimens were contacted by their associated gastroenterologists to participate in the survey.

Survey questionnaire and inflammatory bowel disease histology knowledge score

A survey was developed to explore the knowledge and attitudes towards the use of histology in inflammatory bowel disease (IBD) for both gastroenterologists and pathologists. The European Crohn's and Colitis Organisation (ECCO) position paper on histopathology and the British Society of Gastroenterology (BSG) biopsy reporting guidelines were utilised to formulate questions and quantify knowledge[14,15]. The structured survey was designed by a focus group of three gastroenterologists and comprised of 34 questions. It included knowledge of histological assessment of disease activity and dysplasia, knowledge of histological scoring systems for ulcerative colitis, uptake of histology scoring systems in routine practice, attitudes towards the role of histological activity, and the use of histological activity in clinical scenarios (Supplementary Data 1). Questionnaire language and ambiguity were evaluated by the focus group. A novel IBD Histology Knowledge Score was created that was derived from the survey as a tool to measure overall performance and tested for construct validity and discriminant ability (Supplementary Table 1). The IBD Histology Knowledge Score was calculated as the sum of correct responses to survey questions that aligned with the ECCO position paper on histopathology and the BSG reporting guidelines on IBD biopsies[14,15]. The maximum possible score was nineteen. For construct validity, a high-performance score had to represent a good understanding of histological findings. During the development phase, the survey was administered to senior gastroenterologists and pathologists not directly involved in designing the study, and they were deemed as criterion standards. The survey was then administered to gastroenterology fellows, junior resident medical officers and non-medical staff. Senior staff scored significantly higher (P = 0.001) than junior doctors, establishing content validity. Discriminant validity compared the knowledge scores of those who followed published guidelines *vs* those who did not.

Statistical analysis

The IBD Histology Knowledge Score was analysed as a non-parametric continuous variable, described as medians with interquartile ranges and compared using Mann-Whitney *U*-test and Kruskal-Wallis test. Parametric continuous variables were described as means and compared using the *t*-test and ANOVA test. Predictors of the IBD histology knowledge score were determined using linear regression

with backward elimination regression modelling. A *P*-value of < 0.05 was deemed statistically significant. Statistical analyses were performed with SPSS version 27 (SPSS Inc, Chicago, IL, United States).

Ethics approval

The study was approved by the Sydney Local Health District Human Research Ethics Committee (HREC CH62/6/2021-055).

RESULTS

Study cohort

A total of 89 responses were obtained, comprising 77 gastroenterologists and 12 pathologists. The response rate for gastroenterologists was 25% (n = 77/310). Subspecialty breakdown of gastroenterologists is shown in Figure 1. Gastroenterologists listed their predominant work as 31% public hospital staff specialists, 30% private practice, 21% trainee gastroenterologists, 17% visiting medical officers and 1% research-based gastroenterologist. Ninety-four percent of respondents saw > 2 IBD patients each week and 30% saw > 10 patients each week. Forty-five percent of gastroenterologists were involved in a regular IBD multidisciplinary team. Full study cohort characteristics are shown in Table 1.

Of the 12 surveyed pathologists, 83% worked in tertiary teaching hospitals and 17% were solely in private practice. Half of all pathologists were involved in regular IBD multidisciplinary meetings. Full study cohort characteristics are shown in Table 1.

Attitudes towards histology and scoring systems in UC

Histological activity was considered to have an 'emerging' or 'established' role in UC by 40% and 55% of gastroenterologists respectively. Proportions for pathologists were 33% and 58% respectively. Histological remission was considered more important to achieve than endoscopic remission by 65% of gastroenterologists ('somewhat agree' and 'agree') (Table 2).

The proportion of gastroenterologists who want to use a histological scoring system at least 'sometimes' or 'always' was 59%, and 50% for pathologists. Gastroenterologists reported that 92% of their pathologists do not routinely use a histological scoring system, whilst 83% pathologists report not routinely using a scoring system. More than half of gastroenterologists (64%) and pathologists (58%) did not know which scoring systems had undergone the most validation (Table 2).

For the Geboes score, 91% of gastroenterologists and 83% of pathologists did not know the defined histological remission score of '< 2.1'[14]. For the Nancy index, 87% of gastroenterologists and 83% of pathologists did not know the defined histological remission score of '0'[14]. For the Robarts histopathology index (RHI), 92% of gastroenterologists and pathologists did not know the defined histological remission score of '≤ 3'[14] (Table 2 and Figure 2).

Impact of histological activity on treatment decisions in clinical scenarios

The impact of histological disease activity on gastroenterologists' decisions to escalate treatment or de-escalate in particular scenarios is summarized in Table 3. In the setting of clinical and endoscopic remission, but histological activity alone, 10% of gastroenterologists would escalate therapy ('often' or 'always'). When combined with an elevated faecal calprotectin, 30% of gastroenterologists would escalate treatment. A greater proportion of gastroenterologists would de-escalate treatment if two consecutive colonoscopies showed endoscopic and histological remission, compared with a single episode of endoscopic and histological remission (53% *vs* 19% respectively). A greater proportion of gastroenterologists would aim for histological remission if a patient with UC had other risk factors for colon cancer (71%).

IBD histology knowledge score

Gastroenterologists and pathologists had similar IBD histology knowledge scores [8.0 (IQR: 6.5-10.0) *vs* 9.0 (IQR: 7.8-11.0), P = 0.54] (Table 4). Within gastroenterologists, IBD sub-specialists had higher knowledge scores compared with other gastroenterologists [10.5 (IQR: 7.3-14) *vs* 9.0 (IQR: 7.8-10.0), P = 0.02] (Figure 3A). Public hospital staff specialists had higher knowledge scores than visiting medical officers [11.0 (IQR: 9.0-13.0) *vs* 8.0 (IQR: 8.0-9.0), P = 0.003] and those in private practice [11.0 (IQR: 9.0-13.0) *vs* 8.0 (IQR: 6.3-9.8), P = 0.002] (Figure 3B). Gastroenterologists with a PhD had higher knowledge scores than those whose highest level of education was a bachelor degree [11.0 (IQR: 7.0-14.0) *vs* 9.0 (IQR: 8.0-10.0), P = 0.01] (Figure 3C). Involvement in an IBD multidisciplinary team was associated with a higher knowledge score [9.5 (IQR: 8.0-11.0) *vs* 8.0 (IQR: 6.0-10.0), P = 0.002] (Figure 3D).

On univariate analysis, subspecialty type (P = 0.005), predominant practice (p=0.004), involvement in an IBD multidisciplinary team (P = 0.002) and a higher level of education (P = 0.02) were all significantly associated with higher IBD histology knowledge scores (Table 5). On multivariate analysis, subspecialty type (P = 0.03), predominant practice (P = 0.005) and involvement in an IBD multidisciplinary team (P =

Table 1 Demographics and study cohort characteristics, *n* (%)

	Gastroenterologists (*n* = 77)	Pathologists (*n* = 12)
Age (yr)		
< 30	4 (5.2)	0 (0.0)
30-40	30 (39.0)	1 (8.3)
41-50	15 (19.5)	4 (33.3)
51-60	19 (24.7)	4 (33.3)
> 60	9 (11.7)	3 (25.0)
Location		
New South Wales	46 (59.7)	8 (66.7)
Victoria	11 (14.3)	2 (16.7)
Queensland	11 (14.3)	2 (16.7)
Western Australia	8 (10.4)	0 (0.0)
Australian Capital Territory	1 (1.3)	0 (0.0)
Highest level of education		
Bachelor of medicine/bachelor of surgery	51 (66.2)	11 (91.7)
Masters	10 (13.0)	0 (0.0)
PhD	16 (20.8)	1 (8.3)
What is your predominant practice		
Staff specialist	24 (31.2)	10 (83.3)
University academic work	1 (1.3)	0 (0.0)
Visiting medical officer	13 (16.9)	0 (0.0)
Private practice	23 (29.9)	2 (16.7)
In training program	16 (20.8)	0 (0.0)
How many IBD patients do you see each week		
0-1	5 (6.5)	N/A
2-5	31 (40.3)	N/A
6-10	18 (23.4)	N/A
> 10	23 (29.9)	N/A
Involved in regular IBD multidisciplinary meeting		
Yes	35 (45.5)	6 (50.0)
No	42 (54.5)	6 (50.0)

IBD: Inflammatory bowel disease; N/A: Not applicable.

0.009) remained significant predictors for higher IBD histology knowledge scores (Table 5).

DISCUSSION

Therapeutic goals in UC have evolved from achieving clinical response to attaining objective targets of resolution of inflammation beyond symptoms such as biochemical and endoscopic remission. However, histological remission outside of the research setting has yet to be adopted by gastroenterologists and pathologists. Our study revealed firstly that histological activity is a recognised treatment goal for gastroenterologists who wish to use histology results in combination with other endpoints to guide management decisions. Secondly and conversely, despite this awareness and use of histology, there is a poor knowledge of histological scoring systems in UC not only by gastroenterologists, but by pathologists as well. As such there is an opportunity to develop consensus guidelines incorporating

Table 2 Attitudes towards histology and histological scoring systems, *n* (%)

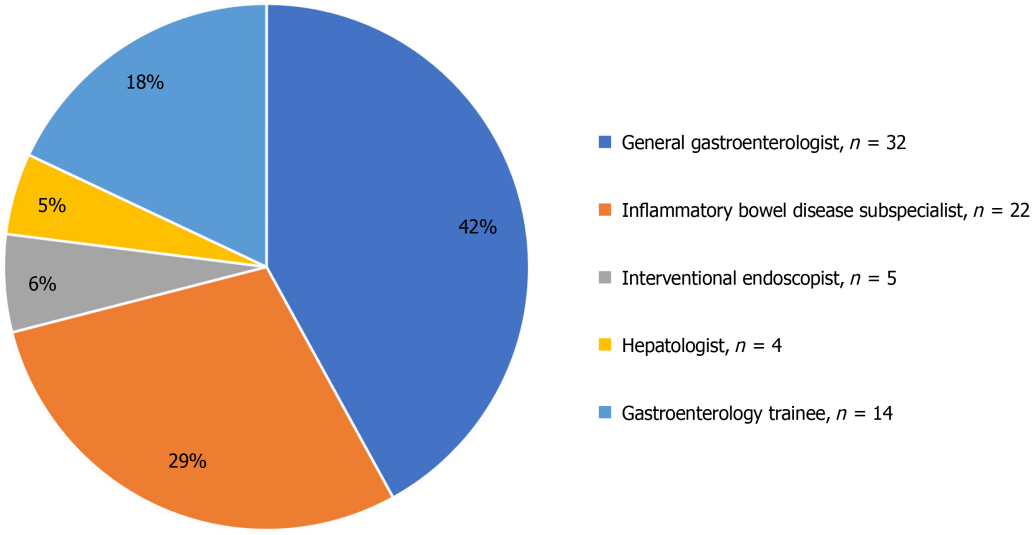
	Gastroenterologists (*n* = 77)	Pathologists (*n* = 12)
The role of histological activity in IBD is		
Not established	3 (3.9)	1 (8.3)
Preliminary	1 (1.3)	0 (0.0)
Emerging	31 (40.3)	4 (33.3)
Established	42 (54.5)	7 (58.3)
Histological remission is more important to achieve than endoscopic remission		
Disagree	4 (5.2)	N/A
Somewhat disagree	13 (16.9)	N/A
Neither agree nor disagree	10 (13.0)	N/A
Somewhat agree	36 (46.8)	N/A
Agree	14 (18.2)	N/A
What histological scoring system does your pathologist routinely or frequently use in their reports		
Geboes	2 (2.6)	0 (0.0)
Nancy index	3 (3.9)	1 (8.3)
RHI	1 (1.3)	0 (0.0)
They do not routinely use a scoring system	71 (92.2)	10 (83.3)
Other		IBD-DCA score (*n* = 1)
I would like to use a histological scoring system for my IBD patients		
Never	8 (10.4)	4 (33.3)
Rarely	10 (13.0)	1 (8.3)
Occasionally	14 (18.2)	1 (8.3)
Sometimes	23 (29.9)	3 (25.0)
Always	22 (28.6)	3 (25.0)
Which scoring systems have undergone the most validation		
Modified Riley score	1 (1.3)	1 (8.3)
Geboes score	13 (16.9)	3 (25.0)
Nancy index	20 (26.0)	5 (41.7)
RHI	9 (11.7)	3 (25.0)
Truelove and Richards score	5 (6.5)	0 (0.0)
Not sure	49 (63.6)	7 (58.3)
What Geboes score is considered histological remission		
< 1.1	2 (2.6)	1 (8.3)
< 2.1	7 (9.1)	2 (16.7)
< 3.1	4 (5.2)	0 (0.0)
< 4.1	1 (1.3)	0 (0.0)
Not sure	63 (81.8)	9 (75.0)
What Nancy index is considered histological remission		
0	10 (13.0)	2 (16.7)
≤ 1	4 (5.2)	3 (25.0)

≤ 2	0 (0.0)	0 (0.0)
≤ 3	0 (0.0)	0 (0.0)
Not sure	63 (81.8)	7 (58.3)
What Robarts histopathology index is considered histological remission		
≤ 2	4 (5.2)	1 (8.3)
≤ 3	6 (7.8)	1 (8.3)
≤ 4	0 (0.0)	0 (0.0)
≤ 5	0 (0.0)	1 (8.3)
Not sure	67 (87.0)	9 (75.0)

RHI: Robarts histopathology index; IBD: Inflammatory bowel disease; N/A: Not applicable.

Table 3 Impact of histological disease activity on treatment management in clinical scenarios, *n* (%)

Scenario	Never	Not often	Sometimes	Often	Always
If a patient is in clinical and endoscopic remission, but has histological activity, then I will escalate medical therapy	14 (18.2)	35 (45.5)	20 (26.0)	5 (6.5)	3 (3.9)
If a patient is in clinical and endoscopic remission, but has an elevated faecal calprotectin (> 100 μg/g) and histological activity, then I will escalate medical therapy	4 (5.2)	18 (23.4)	31 (40.3)	19 (24.7)	5 (6.5)
If a patient is in clinical, endoscopic and histological remission, (but prior colonoscopy showed Mayo 1 endoscopic disease), then I will de-escalate medical therapy	7 (9.1)	19 (24.7)	36 (46.8)	15 (19.5)	0 (0.0)
If a patient is in clinical remission, with their last 2 colonoscopies showing endoscopic and histological remission, then I will de-escalate medical therapy	2 (2.6)	2 (2.6)	31 (40.3)	38 (49.4)	4 (5.2)
If a patient with ulcerative colitis has other risk factors for colon cancer, then I will aim to achieve histological remission	0 (0.0)	7 (9.1)	14 (18.2)	27 (35.1)	29 (37.7)



DOI: 10.3748/wjg.v29.i2.378

Figure 1 Subspeciality characteristics of gastroenterologists.

gastroenterologists and pathologists that are adopted by the respective societies to further this evolving field.

Our study showed 95% of gastroenterologists believe histological activity plays a role in the management of UC, with 76% wanting to use a histological scoring system in clinical practice. Further evidence on the role of UC histological activity scores is required as only a small proportion of gastroenterologists currently make treatment decisions based solely on histological activity. In UC patients with clinical and endoscopic remission but ongoing histological disease activity, 10% of gastroenterologists

Table 4 Inflammatory bowel disease histology knowledge scores

	Gastroenterologists (*n* = 77)	Pathologists (*n* = 12)
IBD histology knowledge score [median (IQR)]	9.0 (7.8-11.0)	8.0 (6.5-10.0)
Type of subspecialist		
General gastroenterologist	8.0 (7.0-9.0)	N/A
IBD subspecialist	10.5 (7.3-14)	N/A
Interventional endoscopist	9.0 (4.5-9.8)	N/A
Hepatologist	10.5 (8.5-11)	N/A
Gastroenterology trainee	8.5 (6.0-10.0)	N/A
Predominant practice		
Staff specialist	11.0 (9.0-13.0)	N/A
Visiting medical officer	8.0 (8.0-9.0)	N/A
Private practice	8.0 (6.3-9.8)	N/A
In training program	8.5 (6.0-10.0)	N/A
Highest level of education		
Bachelor degree	9.0 (8.0-10.0)	N/A
Masters	8.0 (7.0-11.0)	N/A
PhD	11.0 (7.0-14.0)	N/A
Involved in regular IBD multidisciplinary meeting	35 (45.5%)	6 (50.0%)
Yes	9.5 (8.0-11.0)	N/A
No	8.0 (6.0-10.0)	N/A

IQR: Interquartile range; N/A: Not applicable; IBD: Inflammatory bowel disease.

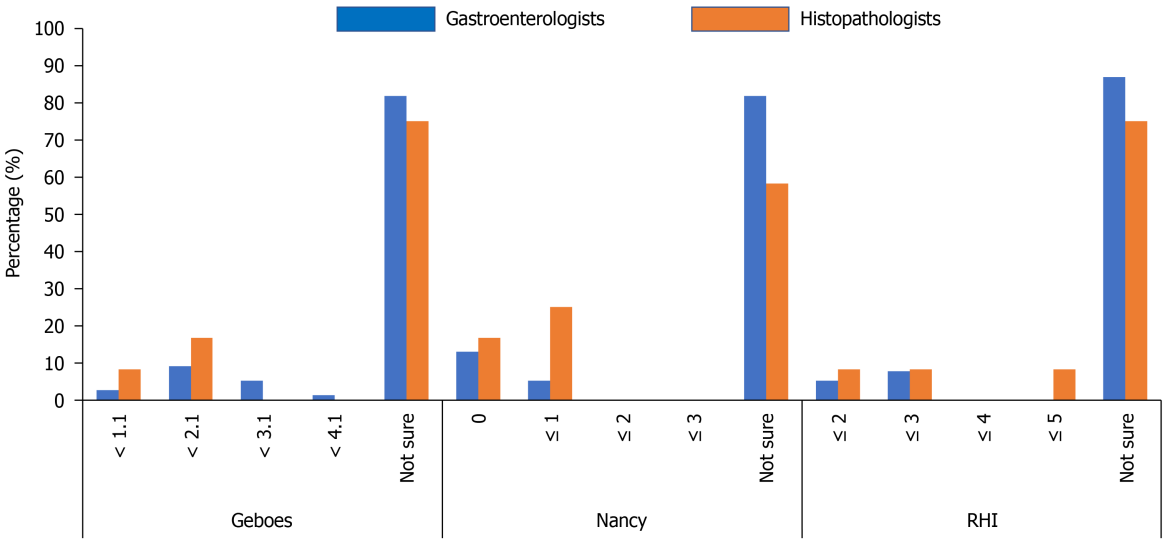
Table 5 Significant predictors of inflammatory bowel disease histology knowledge score for gastroenterologists on univariate and multivariate analyses

	Univariate analysis *P* value	Multivariate analysis *P* value
Type of subspecialty	0.005	0.03
Predominant practice	0.004	0.005
Involvement in IBD MDT	0.002	0.009
Highest level of education	0.02	

IBD: Inflammatory bowel disease; MDT: Multidisciplinary team.

would escalate medical therapy. However, when histological activity coincides with elevated faecal calprotectin, 30% were prepared to escalate treatment. These decisions match the current STRIDE-II guidelines given that histological activity is not currently an accepted target, but shows that gastroenterologists are prepared to include this endpoint as a treatment target[2]. Histological remission becomes even more important if a patient with UC had other risk factors for colon cancer, with 72% prepared to escalate treatment, given that histological activity increases the risk of colorectal neoplasia (odds ratio 3.0, 95%CI: 1.4-6.3)[5]. Therefore, when UC subjects have greater colonic disease extent, more prolonged duration of UC, presence of primary sclerosing cholangitis, or presence of a family history of colorectal cancer, gastroenterologists might escalate treatment in the presence of histological disease activity irrespective of symptoms.

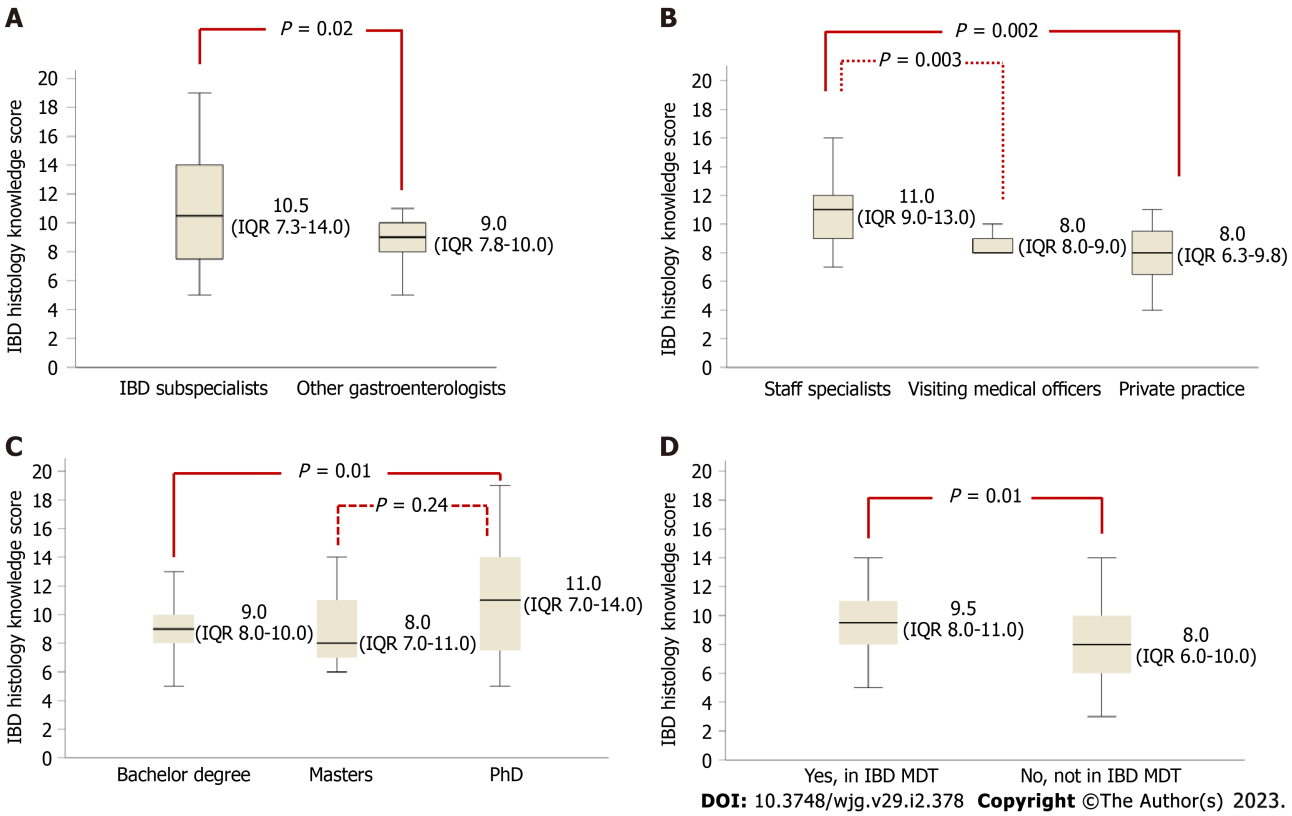
Despite the awareness of the importance of histology in UC, our survey demonstrated a lack of knowledge of histological scoring systems by gastroenterologists. Clinical trials have used Nancy index, RHI and the Geboes score but recent European Crohn's and Colitis Organisation (ECCO) guidelines recommended the use of the Nancy index and RHI for randomised clinical trials, and the Nancy index for clinical practice given its ease of use[14]. Gastroenterologists did not know which scoring systems



Percentage of gastroenterologists	2.6	9.1	5.2	1.3	81.8	13	5.2	0	0	81.8	5.2	7.8	0	0	87
Percentage of histopathologists	8.3	16.7	0	0	75	16.7	25	0	0	58.3	8.3	8.3	0	8.3	75

DOI: 10.3748/wjg.v29.i2.378

Figure 2 Knowledge of histological remission definitions for scoring systems by gastroenterologists and pathologists. RHI: Robarts histopathology index.



DOI: 10.3748/wjg.v29.i2.378

Figure 3 Comparisons of inflammatory bowel disease histology knowledge score for gastroenterologists. A: Subspecialty type; B: Predominant practice; C: Highest education level; and D: Involvement in inflammatory bowel disease multidisciplinary team. IBD: Inflammatory bowel disease; IQR: Interquartile range; MDT: Multidisciplinary team.

had undergone the most validation, or were unaware of the histological remission scores for the Geboes score (91%), Nancy index (87%) and RHI (92%). Despite the increasing interest and evolving role of histological scoring systems in UC, there is an opportunity to educate gastroenterologists about these

scoring systems and how to apply them in clinical practice. Predictors for higher knowledge included employment as a public hospital staff specialist and involvement in an IBD multidisciplinary team. As such, it is likely working in public hospitals within an IBD team would lead to increased exposure to the understanding of common histological scoring systems in UC. Conversely, gastroenterologists working in private practice would have less exposure to these scoring systems and their utility in UC management, contributing to lower knowledge scores.

Few studies have evaluated pathologists' views on histological activity, but most believe that they have a role in evaluating UC. However, pathologists' knowledge of UC histology was comparable to gastroenterologists [median knowledge score 8.0 (IQR: 6.5-10.0) *vs* 9.0 (IQR: 7.8-11.0) $P = 0.54$]. Similar to gastroenterologists, they also lacked knowledge of histological scoring systems and their remission definitions. There is an opportunity, therefore, to improve the utilisation of histological activity scoring for both pathologists and gastroenterologists. A harmonised approach to histological assessment in UC is lacking[16]. Future directions should include the development of histology consensus guidelines in consultation with pathologists to ensure homogeneity in reporting across hospitals to permit comparability of mucosal biopsies across different sites.

This study has several limitations. First, responder bias may have played a role, whereby responders having greater knowledge were more likely to take part on the survey. However, this would indicate a greater unawareness of histological activity scoring in the assessment of UC and a greater need for education and a harmonized approach towards the adoption of a scoring system. Secondly, a smaller respondent number for pathologists was surveyed. However, we demonstrated statistically that pathologists did not differ in their knowledge of histological scoring systems in UC despite expertise in reading biopsy histology. Thirdly, the results may lack worldwide generalisability given the survey was sent to Australian health professionals.

Strengths of this study included: (1) Being the first to report gastroenterologists' knowledge and attitudes towards the use of histology in UC; (2) recruitment of pathologists to compare their awareness against gastroenterologists; and (3) to target respondents nationwide to demonstrate generalisability.

CONCLUSION

The study highlights that while there is an acknowledgment of the importance of histological assessment in UC, there is a lack of knowledge of histological scoring systems. It indicates areas of educational need in the field of UC histology, and the importance of including pathologists in developing future consensus guidelines on the use of histology in clinical practice.

ARTICLE HIGHLIGHTS

Research background

The role of histology in ulcerative colitis has evolved over time. Histological activity despite endoscopic remission is associated with poorer clinical outcomes, and various histological scoring systems have been developed. However, the knowledge and attitudes towards the use of histology in the management of ulcerative colitis by gastroenterologists and pathologists is unknown.

Research motivation

Although there has been an increasing literature into the use of histology in ulcerative colitis, it is unknown whether this has translated into knowledge and use by gastroenterologists and pathologists in clinical practice.

Research objectives

The main objective was to evaluate the knowledge of histology guidelines and attitudes towards the use of histology in ulcerative colitis by gastroenterologists and pathologists.

Research methods

A prospective, cross-sectional survey of gastroenterologists and pathologists was conducted in Australia. The survey was formulated by using peer-reviewed guidelines.

Research results

Of 89 responders (77 gastroenterologists, 12 pathologists), there was almost complete acceptance that histological assessment should form part of ulcerative colitis evaluation (95% gastroenterologists, 92% pathologists). However, the majority of both groups lacked awareness of the Geboes score, Nancy index and Robarts histopathological index. Higher knowledge scores were predicted by public hospital attending gastroenterologists and involvement in an inflammatory bowel disease meeting.

Research conclusions

Histological remission is a recognised target for both gastroenterologists and pathologists. However knowledge of histological scoring systems was poor.

Research perspectives

Future research should involve the development of consensus guidelines in consultation with pathologists on the use of histology in ulcerative colitis management. This should include an agreement on a standardised scoring system to ensure homogenity in reporting across hospitals to permit comparability of biopsies.

FOOTNOTES

Author contributions: Pudipeddi A and Leong RW designed the research study. Pudipeddi A, Chetwood J, Paramsothy S and Leong RW performed the research and collected data. Pudipeddi A, Chetwood J and Leong RW analysed the data. Pudipeddi A drafted the manuscript. Fung C, Christensen B, Bryant RV and Subramaniam K edited the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The study was approved by the Sydney Local Health District Human Research Ethics Committee (HREC CH62/6/2021-055).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest.

Data sharing statement: The data underlying this article will be shared on reasonable request to the corresponding author.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Australia

ORCID number: Aviv Pudipeddi 0000-0002-3664-2246; Robert V Bryant 0000-0002-8106-1280; Kavitha Subramaniam 0000-0001-9867-4094; John Chetwood 0000-0002-8947-9817; Sudarshan Paramsothy 0000-0002-9097-6028; Rupert W Leong 0000-0001-5944-3488.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

REFERENCES

1 **Ungaro R**, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2017; **389**: 1756-1770 [PMID: 27914657 DOI: 10.1016/S0140-6736(16)32126-2]

2 **Turner D**, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, Bettenworth D, Sandborn WJ, Sands BE, Reinisch W, Schölmerich J, Bemelman W, Danese S, Mary JY, Rubin D, Colombel JF, Peyrin-Biroulet L, Dotan I, Abreu MT, Dignass A; International Organization for the Study of IBD. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021; **160**: 1570-1583 [PMID: 33359090 DOI: 10.1053/j.gastro.2020.12.031]

3 **Park S**, Abdi T, Gentry M, Laine L. Histological Disease Activity as a Predictor of Clinical Relapse Among Patients With Ulcerative Colitis: Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2016; **111**: 1692-1701 [PMID: 27725645 DOI: 10.1038/ajg.2016.418]

4 **Christensen B**, Hanauer SB, Erlich J, Kassim O, Gibson PR, Turner JR, Hart J, Rubin DT. Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes. *Clin Gastroenterol Hepatol* 2017; **15**: 1557-1564.e1 [PMID: 28238954 DOI: 10.1016/j.cgh.2017.02.016]

5 **Gupta RB**, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, Bodian C, Ullman T. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007; **133**: 1099-

105; quiz 1340 [PMID: 17919486 DOI: 10.1053/j.gastro.2007.08.001]
6 **Hefti MM**, Chessin DB, Harpaz NH, Steinhagen RM, Ullman TA. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. *Dis Colon Rectum* 2009; **52**: 193-197 [PMID: 19279411 DOI: 10.1007/dcr.0b013e31819ad456]
7 **Wang H**, Fewings I, Bornman L, Shadbolt B, Fadia M, Subramaniam K. Histologic Remission (NANCY Index) is Superior to Endoscopic Mucosal Healing in Predicting Relapse Free Survival in Patients With Ulcerative Colitis in Clinical and Endoscopic Remission. *J Clin Gastroenterol* 2022 [PMID: 35220375 DOI: 10.1097/mcg.0000000000001681]
8 **Geboes K**, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000; **47**: 404-409 [PMID: 10940279 DOI: 10.1136/gut.47.3.404]
9 **Riley SA**, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991; **32**: 174-178 [PMID: 1864537 DOI: 10.1136/gut.32.2.174]
10 **Marchal-Bressenot A**, Salleron J, Boulagnon-Rombi C, Bastien C, Cahn V, Cadiot G, Diebold MD, Danese S, Reinisch W, Schreiber S, Travis S, Peyrin-Biroulet L. Development and validation of the Nancy histological index for UC. *Gut* 2017; **66**: 43-49 [PMID: 26464414 DOI: 10.1136/gutjnl-2015-310187]
11 **Mosli MH**, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, Shackelton LM, Walker CW, Nelson S, Vandervoort MK, Frisbie V, Samaan MA, Jairath V, Driman DK, Geboes K, Valasek MA, Pai RK, Lauwers GY, Riddell R, Stitt LW, Levesque BG. Development and validation of a histological index for UC. *Gut* 2017; **66**: 50-58 [PMID: 26475633 DOI: 10.1136/gutjnl-2015-310393]
12 **Chateau T**, Feakins R, Marchal-Bressenot A, Magro F, Danese S, Peyrin-Biroulet L. Histological Remission in Ulcerative Colitis: Under the Microscope Is the Cure. *Am J Gastroenterol* 2020; **115**: 179-189 [PMID: 31809296 DOI: 10.14309/ajg.0000000000000437]
13 **Mosli MH**, Parker CE, Nelson SA, Baker KA, MacDonald JK, Zou GY, Feagan BG, Khanna R, Levesque BG, Jairath V. Histologic scoring indices for evaluation of disease activity in ulcerative colitis. *Cochrane Database Syst Rev* 2017; **5**: CD011256 [PMID: 28542712 DOI: 10.1002/14651858.cd011256.pub2]
14 **Magro F**, Doherty G, Peyrin-Biroulet L, Svrcek M, Borralho P, Walsh A, Carneiro F, Rosini F, de Hertogh G, Biedermann L, Pouillon L, Scharl M, Tripathi M, Danese S, Villanacci V, Feakins R. ECCO Position Paper: Harmonization of the Approach to Ulcerative Colitis Histopathology. *J Crohns Colitis* 2020; **14**: 1503-1511 [PMID: 32504534 DOI: 10.1093/ecco-jcc/jjaa110]
15 **Feakins RM**; British Society of Gastroenterology. Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. *J Clin Pathol* 2013; **66**: 1005-1026 [PMID: 23999270 DOI: 10.1136/jclinpath-2013-201885]
16 **Vespa E**, D'Amico F, Sollai M, Allocca M, Furfaro F, Zilli A, Dal Buono A, Gabbiadini R, Danese S, Fiorino G. Histological Scores in Patients with Inflammatory Bowel Diseases: The State of the Art. *J Clin Med* 2022; **11**: 939 [PMID: 35207211 DOI: 10.3390/jcm11040939]