Drug survival of biologics in the treatment of psoriasis

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Statement of originality

This thesis is submitted to the University of Sydney in fulfilment of the requirements for the Degree of Master of Philosophy

This is to certify that to the best of my knowledge, this thesis is my own work, and that all sources of assistance have been acknowledged. This thesis has not been submitted for any degree or diploma at this or any other institution.

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Chapter 2 of this thesis is published as: ‘Ting S, Lowe P, Smith A, Fernández-Peñas P. Drug survival of biologics in psoriasis: An Australian multicentre retrospective study. Australas J Dermatol. 2024 Mar 21’. Samantha Ting (ST) developed and conducted this study with the assistance of Pablo Fernandez-Peñas (PFP), Patricia Lowe (PL) and Annika Smith (AS). ST co-designed the study with the co-authors, collected the data, performed and interpreted the analysis, and drafted the manuscript. All the co-authors contributed intellectually to the manuscript.

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

Samantha Ting

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

Professor Pablo Fernandez-Peñas

Glossary

ADA – Anti-Drug Antibodies

BMI – Body Mass Index

CLA – Cutaneous Lymphocyte-associated Antigen

CPP – Chronic Plaque Psoriasis

DLQI – Dermatology Life Quality Index

HLA – Human Leukocyte Antigen

IL - Interleukin

IBD – Inflammatory Bowel Disease

IFN - Interferon

Ig - Immunoglobulin

IV - Intravenous

JAK/STAT – Janus Kinase/Signal Transducers and Activators of Transcription

MHC – Major Histocompatibility Complex

NBUVB – Narrowband Ultraviolet-B

PASI – Psoriasis Area and Severity Index

PBS - Pharmaceutical Benefits Scheme

PPP – Palmoplantar psoriasis

PSORS – Psoriasis Susceptibility Gene

PUVA – Psoralen plus Ultraviolet-A

RCT – Randomised controlled trial

SC – Subcutaneous

TGA - Therapeutics Goods Administration

TNF – Tumour necrosis factor

Th – T helper cell

T_{reg} – Regulatory T cell

T_{RM}– Resident Memory T cell

UV – Ultraviolet

Thesis Abstract

Psoriasis is a chronic inflammatory skin disease with a global prevalence of 2-3%. It causes significant disability through its cutaneous manifestations and psychosocial impacts. The past decade has seen significant progress in the management of moderate-to-severe psoriasis through the development of biologic treatments. Drug survival, which refers to the time from treatment initiation to discontinuation, is commonly used as a proxy to measure the safety and efficacy of treatment in a real-world setting. This thesis investigates the drug survival of the currently available biologics in Australia, and the factors contributing to drug discontinuation. This thesis also aims to provide further guidance on the management of psoriasis. Another avenue that warrants further investigation is guidance on biologic-switching if initial treatment fails. Therefore, this thesis also examines the patterns of care across two tertiary dermatology centres in Sydney, Australia, to elucidate ideal treatment sequencing.

Chapter one of this thesis reviews psoriasis and the current evidence pertaining to drug survival of biologics in psoriasis. Chapter two investigates the drug survival of biologics currently approved for the treatment of psoriasis in Australia, and the factors leading to treatment discontinuation. This study provides information on the safety and efficacy of novel biologics in a real-world setting and demonstrates the utility of the newer biologics. Chapter three explores the patterns of care across two tertiary Australian dermatology centres to provide insight into ideal treatment sequencing of biologics. The factors related to biologic-switching are also examined. The study of local patterns of care demonstrated a high uptake of the newer biologics as they became available, which is likely related to their rapid onset of action and clinical efficacy.

Chapter 1: Introduction

1.1 Overview of psoriasis

Psoriasis is a chronic immune-mediated disease that has an estimated global prevalence of 2-3% (1-4). Although psoriasis encompasses a range of clinical phenotypes, the predominant phenotype is psoriasis vulgaris which accounts for 85-90% of patients affected by the disease (5). Psoriasis vulgaris is characterised by erythematous cutaneous plaques that are covered with white or silver scales (6). These plaques, which are most commonly observed on the extensor surfaces of the limbs and on the scalp, are often pruritic or painful (6). However, the physical manifestations of psoriasis represent only a single aspect of the disease. Psoriasis is also associated with a number of comorbidities including cardiovascular and inflammatory bowel disease (7). Moreover, psoriasis has significant psychosocial sequelae. The conspicuous nature of the disease is a widely reported source of embarrassment for patients and is associated with greater rates of anxiety, depression and stigmatization (8-11). These broad impacts of psoriasis as a disease have spurred research to improve on existing management (5, 12).

The treatment of psoriasis is an area that has seen significant evolution in the preceding decades. These advances have been primarily a product of a vastly improved knowledge of the pathogenesis of psoriasis. Although the exact cause of psoriasis is still not yet fully elucidated, it is now well-established that psoriasis is an inflammatory disease mediated by T helper (Th) cells of the Th1, Th17, and Th22 subtypes and their associated cytokines (13-15). Treatments have evolved from this knowledge and are aimed at downregulating these mediators that drive the immune response. However, many of the traditional systemic therapies in use for moderate-to-severe psoriasis are limited by unwanted side-effects and significant toxicity (16-18). Attempts to improve on this have led to the development of biologic therapies, which target key immune pathways with greater precision and thus result in fewer side effects. In Australia, biologics have now been approved for use in the treatment of moderate to severe psoriasis in patients who have either not responded to conventional systemic treatment, or phototherapy, or who have been affected by either the acute or cumulative toxicity of those treatments (19). In the time since these treatments have been approved, the theoretical

benefits of biologic therapies have been realised, with an overall improvement in patients' signs and symptoms, and less toxicity (20-22).

The increasing numbers of available biologics on the market have led to questions regarding the sequencing of treatment, the criteria by which biologics should be chosen and metrics to gauge long-term therapeutic success. Drug survival has emerged as a metric of particular importance and is defined as the time of initiation to the time of discontinuation of a drug. In conjunction with clinical guidelines, drug survival provides a key piece of information to clinicians to select an appropriate biologic that aligns with their patients' expectations. This is a metric that we will focus on in this review.

This review will also provide a brief overview of the aetiology and pathogenesis of psoriasis. The various biologic therapies available in the treatment of moderate to severe psoriasis, and the current evidence in the literature regarding drug survival of these biologics, will be discussed. This will be valuable because psoriasis treatment is constantly evolving, and there are limited reviews on all the new biologic treatments that are currently available. Furthermore, data on drug survival is limited due to the novelty of many of the biologics. This review will therefore aim to explore the current evidence available in the literature with regards to this.

1.2 Clinical features of psoriasis

Psoriasis encompasses a variety of clinical phenotypes which can affect the skin, nails, and joints. Psoriasis vulgaris is the most common phenotype, accounting for 85-90% of cases (23). Other associated clinical phenotypes which include palmoplantar pustulosis, flexural psoriasis, and psoriatic arthritis will also be outlined in this review (24-28). Generalised pustular psoriasis and guttate psoriasis are additional recognised clinical variants of psoriasis. However, they present unique challenges that warrant separate consideration and will therefore not be covered in detail as they are beyond the scope of this study.

1.2.1 Psoriasis vulgaris

Psoriasis vulgaris, also known as chronic plaque psoriasis (CPP), is clinically diagnosed by the appearance of well-circumscribed erythematous cutaneous plaques covered by white and silver scales (29). These plaques follow a symmetric distribution across the trunk, extensor surfaces of the upper and lower limbs, and scalp. Its severity varies from single lesions to a generalised spread, and it often follows a relapsing and remitting course (23). Patients who suffer from psoriasis vulgaris frequently report symptoms such as pain and pruritus associated with psoriatic plaques. Although the diagnosis of psoriasis is typically made clinically, a skin biopsy can occasionally be helpful in select cases that may be challenging to diagnose clinically (30).

The clinical severity of psoriasis can be categorised as mild, and moderate to severe (31). The Psoriasis Area and Severity Index (PASI) is an objective scoring system for clinical severity that assesses body surface area affected by psoriatic lesions and the severity of the lesions (32). The body is divided into four areas: head, trunk, arms and legs (33). Psoriatic lesions are rated on a scale of 0 to 4 to assess the severity of erythema, induration, and scaling in each of the areas (33). The percentage of each of the areas affected by psoriatic lesions is assessed and scored on a scale of 0 to 6 (33). A coefficient is applied to each area and the scores are summed to provide a final PASI score between 0-72 (33). An improvement of at least 75% from a patient's baseline PASI score (PASI-75), is generally considered an indicator of therapeutic success (34). However, there is substantial evidence that using PASI alone is insufficient to achieve optimal clinical outcomes (2, 35, 36). Therefore, health-related quality of life instruments such as the Dermatology Life Quality Index (DLQI) are commonly used alongside PASI to guide clinical decision-making (37). The DLQI consists of 10 questions that assess aspects of the quality of life including symptoms, daily activities, leisure, work or school, personal relationships, and side effects from treatment (38). According to the guidelines by the Australasian College of Dermatologists, mild psoriasis is defined as PASI $\leq$ 10, and a DLQI $\leq$ 10; and moderate to severe psoriasis is defined as PASI > 10 and/or DLQI >10 (31). Scores of 0 or 1 in DLQI indicate a lack of impact of the skin disease on the quality of life of the patient.

1.2.2 Flexural psoriasis

Flexural psoriasis, which is also commonly known as inverse psoriasis, has a predilection for intertriginous areas such as the inguinal folds, axillae and genitalia (25). Flexural psoriasis affects approximately 8-36% of patients with psoriasis (25). Lesions often have an erythematous shiny appearance with less scaling compared to CPP (39). Due to the location of these lesions, they are often prone to maceration and fungal infections which further exacerbate symptoms of pain, itch, and erythema (39). This is particularly debilitating for patients with genital psoriasis due to the deleterious effect on patients' quality of life and sexual function (39).

1.2.3 Palmoplantar pustulosis

Palmoplantar pustulosis (PPP) affects approximately 12-16% of people with psoriasis, and it tends to be more common among females (39). Palmoplantar pustulosis is characterised by painful fissures, hyperkeratotic plaques, scales, and occasional sterile pustules on the palms and soles (40). Palmoplantar pustulosis is a source of distress for many patients due to the pain that restricts their activities of daily living, making PPP disabling for patients despite the relatively small surface area that it affects compared to CPP (40). There is evidence in the literature that suggests a genetic variation between PPP and CPP, as PPP does not share the same strong genetic association with PSORS1 which is found in CPP (41). Nevertheless, there is a significant overlap in the treatment of PPP and CPP, possibly due in part to their shared histological similarities (41). However, PPP presents a therapeutic challenge due to a lack of standardised therapy and significant variability in its response to treatment (42). Thus, biologic treatment is typically reserved for severe and recalcitrant cases of PPP, with ongoing research focused on developing targeted therapies (42, 43).

1.2.4 Psoriatic arthritis

Psoriatic arthritis is a significant feature of psoriasis which affects 20-30% of patients with psoriasis and is a frequently cited problem in patients' quality of life (44). It causes chronic pain and disability, which leads to a significant decrease in productivity (44, 45). Psoriatic arthritis is a seronegative arthritis that is characterised by peripheral and axial joint inflammation, enthesitis, tenosynovitis, and dactylitis (46). There are several different subtypes of psoriatic arthritis which have a range of different clinical presentations and clinical courses (45). Although the cutaneous manifestations of psoriatic arthritis tend to precede the joint symptoms,

15% of cases may experience joint symptoms before or at the same time as their psoriasis (45, 47). Its diagnosis is therefore based on clinical and radiographic findings where at least three of the following five criteria are met: a personal or family history of psoriasis, psoriatic nail dystrophy, a negative test for rheumatoid factor, a history of dactylitis, and radiographic evidence of juxta-articular new bone formation on the hand or the foot (47). The main goals of treatment in psoriatic arthritis are to reduce joint inflammation and associated pain. Depending on the severity of the disease, this can range from the use of nonsteroidal anti-inflammatories to the use of biologics where there is significant overlap with the treatment of chronic plaque psoriasis (45).

1.3 Aetiology and epidemiology of psoriasis

The precise aetiology of psoriasis is unknown. However, population studies have demonstrated a clear genetic component in the development of psoriasis (48). Relatives of patients have been shown to have a significantly higher incidence of psoriasis compared to the general population (48). Furthermore, twin studies of disease concordance have demonstrated that the risk of psoriasis in monozygotic twins was 62-70% compared to 21-23% in dizygotic twins (48).

In examining specific genetic factors, genetic linkage analyses have identified psoriasis susceptibility 1 (PSORS1), in the MHC portion of chromosome 6p21.3, as a significant factor in the pathogenesis of psoriasis, accounting for 35-50% of the heritability of the disease (23, 49). This region was further found to code for several genes involved in the immune response, including HLA-Cw6 (23, 50). This is significant as HLA-C plays an important role in the process of antigen presentation to CD8+ T lymphocytes, which has led to hypotheses that HLA-Cw6 may bind to psoriasis autoantigens (50, 51). Furthermore, the HLA-Cw6 allele is present in over 60% of patients with psoriasis, and significantly increases the risk of psoriasis (52). Previous studies have also identified single nucleotide polymorphisms near genes associated with IL-23 signalling in patients with psoriasis, including IL12B (which encodes the shared p40 subunit of IL-12 and IL-23), IL-23A (encodes p19 subunit of IL-23), and IL23R (encodes subunit of IL-23 receptor) (53, 54).

Despite a clear genetic component which is linked to the pathogenesis of psoriasis, no single genetic variant has been identified that is responsible for the development of psoriasis. This suggests that the pathogenesis of psoriasis is multifactorial, with a number of genetic and environmental factors which contribute to the disease process (55). Common environmental triggers associated with psoriasis include lack of UV exposure, medications, smoking, localised trauma (Koebner phenomenon), streptococcal infections, alcohol intake, and obesity (56-61). These environmental factors contribute to epigenetic modifications, which have been commonly found in psoriasis. These include increased DNA methylation in peripheral blood mononuclear cells (PBMC), hypoacetylation of histones in PBMCs, and the over-expression of skin-specific miRNA in patients with psoriasis (62).

1.4 Pathogenesis of psoriasis

Psoriasis was previously considered a primary keratinocyte disorder, but there is now compelling evidence that psoriasis is an immune-mediated disease, with a strong interaction observed between the innate and adaptive immune systems (63). This assertion is supported by the presence of increased serum levels of cytokines in patients with psoriasis compared to healthy controls, increased populations of cytokines associated with the Th1 pathway found in psoriatic lesions, the efficacy of cyclosporin A in the treatment of psoriasis, and the noted clearance of psoriasis in patients who had received bone marrow transplants (13, 64, 65).

The defining features of psoriasis are chronic plaques that are erythematous and scaly. These plaques are the result of increased proliferation of keratinocytes and high epidermal turnover which causes altered epidermal differentiation and epidermal thickening (29, 66). This high cellular turnover time observed in the pathogenesis of psoriasis leads to the abnormal maturation of keratinocytes, characterised by parakeratosis, and a diminished granular layer. Furthermore, keratinocytes are proangiogenic, leading to increased numbers of dermal capillaries, which contributes to the erythema that is observed in psoriasis (66). This increased vascularity stimulates inflammation, and drives a T-cell response, resulting in elevated levels of mixed CD4+ and CD8+ populations in psoriatic plaques (67).

1.4.1 Molecular pathogenesis

The molecular pathway by which hyperproliferation of keratinocytes occurs is complex (Figure 1.1). The process begins with LL-37 cathelicidin, an antimicrobial peptide which is released from keratinocytes in response to skin injury, and forms part of the innate immunity (68, 69). It is complexed with DNA through toll-like receptor 9 to activate plasmacytoid dendritic cells (69). Plasmacytoid dendritic cells are typically found in peripheral blood and secondary lymphoid organs, but are known to infiltrate psoriatic skin (70). The activation of plasmacytoid dendritic cells results in the release of IFN- α, which induces a strong T cell response and the release of cytokines such as IFN-γ, TNF-α, IL-1β, and IL-6 (71). This leads to the activation of myeloid dendritic cells (72). Activated myeloid dendritic cells, in conjunction with the auto-RNA-LL-37 complex, produce TNF-α, IL-6, IL-20, IL-1, IL-12 and IL-23 (15). These myeloid dendritic cells then migrate to lymph nodes to stimulate the differentiation of naïve CD4+ T cells into Th1, Th17 and Th22, which triggers the release of their associated cytokines (Figure 1.1), and thus the hyperproliferation of keratinocytes (15).

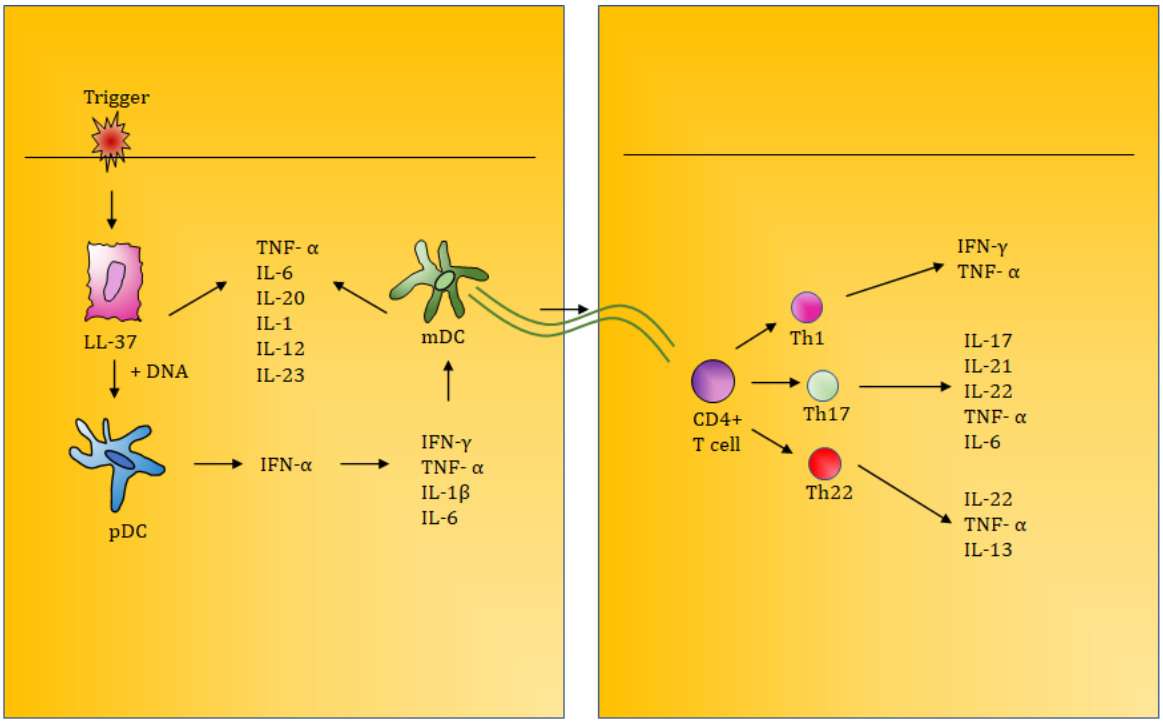

Figure 1.1 Pathogenesis of psoriasis. LL-37 is released from keratinocytes in response to an insult. It is complexed with DNA to activate plasmacytoid dendritic cells, leading to the release of IFN-γ, TNF-α, IL-1β and IL-6. This leads to the activation of myeloid dendritic cells, which migrate to lymph nodes and stimulate the differentiation of naïve CD4+ T cells into Th1, Th17, and Th22. The resultant downstream cytokines trigger the hyperproliferation of keratinocytes.

One of the first studies that demonstrated the central role that T-cells play in the pathogenesis of psoriasis showed the resolution of psoriatic plaques with the selective inhibition of activated T lymphocytes using denileukin diftitox (73). This is further supported by the observation that cyclosporin, through its role in T-cell suppression, has been effective in the treatment of psoriasis (55). It has subsequently been well-established in the literature that T-cells play a key role in the initiation and maintenance of psoriasis (74-76). Psoriatic lesions are characterised by numerous features including lymphocytic infiltrate, with increased numbers of CD4+ and CD8+ T-cells (74, 75). These T-cells express LFA-1 and CD2 which interact with antigen-presenting cells. T-cells subsequently infiltrate the skin through the expression of cutaneous lymphocyte antigen (CLA) and chemokine receptors which interact with adhesion molecules such as E-selectin on endothelial cells (76). Thus, one of the earlier biologic treatments for psoriasis, efalizumab, targeted LFA-1 to down-regulate T-cell activation in psoriatic skin (76). However, after three patients developed progressive multifocal leukoencephalopathy in association with efalizumab, it was withdrawn from the market (77, 78). Further research into the role of T-cells in the pathogenesis of psoriasis has also revealed the specific CD4+ subsets that are involved, based on the cytokine populations that are present in human psoriatic lesions (14). This includes Th1, Th17 and Th22 that correspond to T cells that produce IFN- γ, IL-17 and IL-22 respectively (14).

1.4.2 The IL-23/Th17 axis

Recent studies have demonstrated the crucial role that the IL-23/Th17 axis plays in the pathogenesis of psoriasis (79). As previously outlined, cytokines such as IL-17 that are produced by Th17 are responsible for keratinocyte proliferation and the local inflammation that is characteristic of psoriatic skin lesions (15). This pathway is often implicated in both chronic plaque psoriasis and palmoplantar psoriasis (63).

The differentiation of Th17 and the subsequent release of its cytokines is driven by IL-23 through JAK2/TYK2 and STAT3 signalling (80, 81). IL-23 is a heterodimeric protein which is composed of two subunits, IL-23p19 and IL-12p40 (82). It is released by activated dendritic cells in response to a cutaneous insult and binds to IL-23 receptors (IL-23R) which are found on multiple immune cells including natural killer cells, Th17 cells, retinoic acid receptor-related orphan receptor (ROR)γ^+ innate lymphoid cells and γδ T cells

(55, 80). The resultant activation of the signal transducer and activator of transcription (STAT3) leads to the expansion of Th17 cells that release IL-17A and IL-17F (55, 83, 84). IL-17A and IL-17F are isoforms of 1L-17 that activate the same receptor, which triggers a downstream activation of intracellular kinases (55). This results in the release of chemokines which drive a positive feedback loop involving the recruitment of further Th17 and dendritic cells and the resultant inflammatory response seen in psoriatic skin (80).

IL-23 drives the pathogenesis of psoriasis through other pathways. It induces the differentiation of cutaneous $Foxp3^+$ regulatory T-cells (T_{reg}) into Th17-like T_{reg} cells which causes a downstream release of IL-17A through $ROR\gamma^+$ signalling (85). Indeed, the ex-vivo stimulation of T_{reg} cells derived from the peripheral blood of patients with severe psoriasis resulted in the production of IL-17A-producing cells (86). This response was notably increased further in the presence of IL-23 (86). Furthermore, animal studies have demonstrated a decrease in skin thickness and populations of Th17-like T_{reg} cells among IL-23-treated mice that received antibodies against TNF-α and IL-23p19 (85).

Tissue resident memory cells (T_{RM}) typically reside in tissues to mount a localised response to previously exposed pathogens and thus play a key role in host defence (87). However, in the context of psoriasis, it is thought that T_{RM} cells are produced in response to self-antigens and continue to persist in the skin, causing a localised psoriasiform dermatitis in response to a trigger (84, 88, 89). Indeed, histological studies have confirmed the presence of IL-17A-producing memory T-cells in non-lesional skin of patients with psoriasis (90, 91). Murine studies have demonstrated the essential role of IL-23 in the maintenance and proliferation of pathogenic T_{RM} cells (89). It was further found that anti-IL-23 therapy resulted in a decrease in T_{RM} cells in both lesional human and murine skin, which led to the clinical appearance of skin clearance (89). Therefore, these findings demonstrate the central role of the IL-23/Th17 axis in the pathogenesis of psoriasis, highlighting potential immunological targets in the treatment of psoriasis.

1.4.3 TNF-α

Another key pro-inflammatory factor involved in psoriasis is TNF-α. TNF-α drives the inflammatory response in both psoriasis and psoriatic arthritis (92). It induces the expression of adhesion molecules on endothelial

cells and keratinocytes, which leads to the recruitment of leukocytes (77,78). This contributes to the leukocytic infiltration that is found in psoriatic lesions as well as the joints (93, 94). The presence of TNF-α in lesional skin also results in the release of other cytokines such as IL-1 and IL-8 which directly contribute to keratinocyte proliferation (95). Finally, as outlined above, TNF-α plays a significant role in the activation of myeloid dendritic cells and the resultant activation of the IL-23/Th17 pathway (65). This thereby highlights the pivotal role TNF-α plays in the inflammatory cascade seen in psoriasis (71). Together, this leads to keratinocyte hyperproliferation, increased production of pro-inflammatory cytokines, and further growth and invasiveness of dermal fibroblasts that are found in psoriasis.

1.5 Management of psoriasis

The approach to treating psoriasis is stepwise, depending on its severity. First line therapy, which is used for mild psoriasis, comprises topical treatments such as corticosteroids, emollients, salicylic acid, retinoids, vitamin D3 analogues, and calcineurin inhibitors (29). The next line of treatment for moderate to severe plaque psoriasis is either phototherapy and/or non-biologic systemic treatment, such as methotrexate, cyclosporin, acitretin, apremilast and deucravacitinib which will be outlined below (96).

The beneficial effect of sunlight on psoriasis is a well-known phenomenon which has led to the clinical use of ultraviolet (UV)-based therapy (97, 98). It is hypothesised that the exposure of UV radiation to psoriatic skin results in the apoptosis of keratinocytes and the down-regulation of keratinocyte proliferation (99). This occurs through the suppression of key cytokines such as IL-8, IL-9, IL-17, IL-22, IL-23 and TNF-α (99). Narrowband UV-B (NBUVB) and psoralen UVA (PUVA) are used in the treatment of moderate-to-severe psoriasis prior to consideration of biologic treatments (100). Almutawa et al. performed a systematic review examining the efficacy of different phototherapies, and found that PUVA had a PASI-75 of 73% compared to NBUVB which had a PASI-75 of 62% (100). Despite this, NBUVB is the preferred form of phototherapy due to its relative safety profile compared to PUVA which is associated with an increased risk of skin cancer and needs whole-day skin and eye protection from sun UV light due to the psoralen (56, 100). While UV-based

therapy remains a favourable option, it can affect patient compliance due to the time commitment required, as patients have to present for phototherapy three times a week for several months (101).

Methotrexate is the most commonly used systemic agent in psoriasis and is also effective in psoriatic arthritis (102). It is a folate-antagonist which inhibits DNA synthesis in the Synthesis (S) phase of the cell cycle (102). It is thus hypothesised that methotrexate is effective in psoriasis because it targets psoriatic skin cells that have a shorter cell cycle, and which therefore tend to be in the S phase of the cell cycle (103). Methotrexate has been demonstrated to be effective compared to placebo, where PASI-75 was achieved in 36% of patients with moderate to severe psoriasis, as compared to 19% in the placebo arm after 16 weeks (104). However, treatment with methotrexate requires frequent monitoring due to its toxic effects on the liver and bone marrow (102).

Cyclosporin is a polypeptide calcineurin inhibitor that has a similar efficacy to methotrexate (105, 106). It inhibits T cells and thereby mediates the release of inflammatory factors associated with psoriasis (107). However, it is not generally used for the long-term treatment of psoriasis due to the adverse effects associated with it such as irreversible nephrotoxicity, hypertension and a higher risk of cutaneous malignancies (102, 108).

Acitretin is an oral retinoid. Its exact mechanism of action in psoriasis is unknown, but it is thought to mediate gene transcription of cells in the epidermis, thereby minimising the scaling, erythema and induration that is characteristically found in psoriasis (109). Acitretin used as monotherapy in chronic plaque psoriasis has been demonstrated to be efficacious in 34% of patients, who achieved PASI-75 after 12 months (109, 110). Acitretin is generally well-tolerated at low doses. However, it has teratogenic effects and is therefore contraindicated in pregnancy and women who are planning pregnancy (109). Acitretin is also associated with hyperlipidaemia and hepatotoxicity, and lipid studies and liver function tests need to be regularly monitored in patients who are on acitretin (109).

In addition to traditional systemic treatments, further research is being conducted on targeted therapies in psoriasis, aiming to overcome therapeutic challenges associated with contraindications and the need for ongoing laboratory monitoring. Oral small molecules have emerged as viable alternatives, providing good safety profiles and ease of administration. Apremilast and deucravacitinib are examples of oral small molecules approved for the treatment of psoriasis in Australia.

Apremilast is a phosphodiesterase (PDE) 4 inhibitor which is used in the management of psoriasis and psoriatic arthritis (111, 112). The inhibition of PDE4 leads to the accumulation of intracellular cyclic AMP (cAMP), resulting in an increase in the expression of the anti-inflammatory cytokine IL-10, while suppressing the production of pro-inflammatory cytokines including TNF-α, IFN-γ and IL-23 (111, 113). Studies that examined the efficacy of apremilast demonstrated 33.1% of patients achieved PASI-75 at week 16 with apremilast compared to 5.3% of patients on placebo (112). Apremilast is generally well-tolerated with minimal associated adverse effects (114). Thus, apremilast provides a safe option for patients with psoriasis.

More recently, deucravacitinib, a tyrosine kinase (TYK) 2 selective inhibitor, has been developed in the treatment of psoriasis (115). Deucravacitinib exerts its downstream effects by binding allosterically to the pseudokinase domain of TYK2, resulting in the down-regulation of IL-23, IL-12 and type I interferon pathways (116, 117). Efficacy results for deucravacitinib have been promising, with 58.4% of patients achieving PASI-75 at week 16, surpassing both placebo (12.7%) and apremilast (35.1%) groups (118). Notably, deucravacitinib's high selectivity for TYK2 suggests a superior safety profile compared to other Janus kinase (JAK) inhibitors which tend to be associated with infections, cytopenia, hyperlipidaemia, and renal and liver toxicity (115). Indeed, clinical trials have reported few adverse events associated with the use of deucravacitinib (119). Despite its reported safety profile, regular laboratory monitoring is still required, and its use is contraindicated in patients with immunosuppression (115).

Biologic therapies, which were first introduced for the treatment of psoriasis in 2003, have less systemic and cumulative toxicity than conventional systemic treatments and have demonstrated better response rates (20). Biologics refer to bioengineered targeted therapies which come in the form of monoclonal antibodies or

receptor fusion proteins (16). Due to their large molecular weight, they are injected either intravenously or subcutaneously (16). In psoriasis, biologics target different players in the immune pathway such as TNF-α, IL-17, IL-23, and IL-12 (Table 1.1). Patients who are switched from traditional systemic treatment to biologics generally experience an improvement in PASI and health-related quality of life measures (20). Indeed, studies have shown that patients on biologic therapy for psoriasis demonstrate the highest levels of satisfaction with treatment compared to other forms of treatment (120). Therefore, the advent of biologic therapy has provided patients with safe and effective options to assist them in achieving their treatment goals.

The current guidelines in Australia recommend the use of phototherapy and traditional systemic treatments as first-line therapies in moderate-to-severe psoriasis (31). Pharmaceutical Benefits Scheme (PBS) subsidised biologic therapies are only approved once patients with psoriasis have failed at least two traditional treatments, either with a PASI >15 or severe psoriasis affecting the face, palms or soles, following 6 weeks of treatment (19). These restrictions are largely due to the higher cost of biologics, as they are significantly more expensive than systemic therapies (121).

Table 1.1 Biologics approved for the treatment of psoriasis in Australia, their immunological targets, and their routes of administration (16, 19).

Target	Biologic drug	Administration
TNF-α	Etanercept	SC weekly
	Infliximab	IV 8-weekly or SC 2-weekly
	Adalimumab	SC fortnightly
IL-17A	Secukinumab	SC 4-weekly
	Ixekizumab	SC 4-weekly
IL-17A/IL-17F	Bimekizumab	SC 8-weekly
IL-23	Guselkumab	SC 8-weekly
	Tildrakizumab	SC 12-weekly
	Risankizumab	SC 12-weekly
IL-12/IL-23 p40	Ustekinumab	SC 12-weekly

SC: subcutaneous; IV: intravenous

1.5.1 TNF-α inhibitors

TNF-α inhibitors dampen the activation of myeloid dendritic cells which produce IL-23 and contribute to the differentiation of naïve CD4+ T cells to Th17 cells (15). The inhibition of this pathway, in turn, down-regulates the production of pro-inflammatory cytokines which drive psoriasis (15). Several randomised controlled trials have demonstrated the efficacy and safety of TNF-α inhibitors (122, 123). More specific example of TNF-α inhibitors that have been approved for use in the treatment of psoriasis are discussed below.

Etanercept

Etanercept is a human fusion protein that consists of an extracellular TNF receptor and an Fc portion of human IgG (124). Etanercept inhibits the binding of TNF-α to cell surface receptors, thus rendering TNF-α

biologically inactive (124). It also modulates the downstream proinflammatory effects of TNF-α. It is administered subcutaneously, and it has been demonstrated to be effective in the treatment of psoriasis and psoriatic arthritis.

Phase III studies that examined the PASI-75 response in patients demonstrated 34% and 49% in the 25 mg and 50 mg twice weekly dosing arms respectively, compared to 4% in placebo at the 12-week mark (122, 123). After 24 weeks of treatment, clinical efficacy improved, with 59% of patients who received 50 mg of etanercept twice weekly, and 44% of patients who received 25 mg of etanercept twice weekly achieving PASI-75 respectively (122). Etanercept has also demonstrated efficacy in treating joint and tendon manifestations, with up to 74% improvement from baseline in the physician's global assessment after 24 weeks of treatment (125).

Etanercept is generally well-tolerated, and it has a proven good safety profile. There have been rare reports of exacerbation of demyelinating disorders, allergic reactions, and aplastic anaemia (126). However, the most common adverse events that have been described across multiple studies were injection site reactions, headaches and upper respiratory tract infections (122), which are seen with most biologic therapies. TNF-α plays an important role in the protection against the development of mycobacterial infection, and thus the role of TNF-α inhibitors in tuberculosis has been investigated (127). There have been variable associations between different TNF-α inhibitors and tuberculosis, with infliximab and adalimumab displaying a stronger association with tuberculosis compared to etanercept (127). However, although no strong causal or temporal link has been made between etanercept and the development of tuberculosis, screening for tuberculosis and other infectious diseases is routinely performed before the commencement of all TNF-α inhibitors (127).

Infliximab

Infliximab is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody, comprising of a murine portion and a human portion, which binds to and neutralizes both receptor-bound and soluble TNF-α (124, 128). Infliximab was originally administered intravenously, and has more recently been available in a subcutaneous

formulation. It is used in the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, and Crohn's disease (129, 130).

A randomised double-blind trial comprising 835 patients across the United States, Canada, and Europe, showed that infliximab has a rapid onset of clinical efficacy, with patients achieving PASI-75 as early as two weeks into treatment (131). At week 10, PASI-75 was achieved by 70.3% and 75.5% of patients who had received 3 mg/kg of infliximab and 5 mg/kg of infliximab respectively, compared with 1.9% of patients in the placebo group (131). Another phase III multicentre, placebo-controlled trial, with 378 patients, demonstrated that at week 10, 80% of patients on 5 mg/kg of infliximab achieved PASI-75 compared to 3% in the placebo group (132). Complete clearing of skin was seen in 26% patients of patients who were treated with 5 mg/kg of infliximab. A similar rapid effect was observed in this study, with significant differences in clinical efficacy between the treatment group and placebo seen after 2 weeks of treatment. At week 50, 61% of patients treated with 5 mg/kg of infliximab maintained a PASI-75 response. Blood samples were also collected from 169 patients to measure serum concentrations of infliximab before and after infusions at weeks 10 and 50, and antibodies to infliximab at weeks 0, 46, and 66. The study showed evidence that the maintenance of clinical response was associated with serum infliximab concentrations above 1.0 μg/mL. It was also shown that antibodies to infliximab were associated with a higher likelihood of treatment failure, with only 39% of antibody-positive patients maintaining a PASI-75 response from week 10 through to week 50, compared to 81% of antibody-negative patients (132).

Several adverse events have been reported with the administration of infliximab including immediate infusion reactions characterised by chest pain, hypotension or hypertension, and dyspnoea; delayed hypersensitivity reactions due to serum sickness from neutralizing antibodies to infliximab; and the development of tuberculosis (124). Approximately 24.4 cases of tuberculosis per 100,000 were observed in patients on infliximab for rheumatoid arthritis compared to a background rate of 6.2 cases per 100,000 in patients with rheumatoid arthritis who were not on infliximab (133).

Adalimumab

Adalimumab is a fully human monoclonal IgG1 antibody that binds and neutralizes soluble and membrane-bound TNF-α, by inhibiting the interaction between TNF-α and p55 and p75 TNF cell surface receptors (134). In addition to moderate to severe plaque psoriasis, adalimumab has been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa and Crohn's disease (135, 136).

The REVEAL study was a multicentre, randomised, controlled phase III study conducted in 67 centres across the United States and Canada (134). It demonstrated that 71% of patients treated with an 80 mg loading dose of adalimumab, followed by 40 mg every other week over 16 weeks, achieved a PASI-75 response compared to 7% of placebo-treated patients (134). In a double-blind, randomised, placebo-controlled trial which examined the efficacy of adalimumab on patients with psoriatic arthritis, it was found that the PASI-75 response rate was 59% after 24 weeks of treatment with adalimumab compared to 1% in the placebo group (137). In the CHAMPION study, it was revealed that adalimumab showed greater clinical efficacy than methotrexate, with 79.6% of patients in the adalimumab group achieving PASI-75, compared to 35.5% in the methotrexate group, after 16 weeks of treatment (138). Furthermore, a pooled analysis of three major randomised and placebo-controlled trials of adalimumab revealed that adalimumab reduces symptoms of psoriatic arthritis, and reduces the risk of psoriatic arthropathy adverse events (139).

Data from the REVEAL trial also revealed a statistically significant improvement in health-related quality of life measures with the treatment of adalimumab. After 16 weeks of treatment, patients treated with adalimumab had an 8.4 point decrease in DLQI, compared to 1.9 points among placebo-treated patients (140). Patients reported improvements in symptoms such as pain and itch, and they also demonstrated improvements in work-related activities, and activities of daily living.

Adalimumab is generally well tolerated. Common adverse events that have been observed in the previously mentioned studies among patients treated with adalimumab include upper respiratory tract infections, nasopharyngitis, sinusitis, and injection-site reactions (134, 138). Although the risks of these common adverse

events are comparable to placebo-treated patients, patients on adalimumab are potentially at an increased risk of more serious infections such as tuberculosis. 13 cases of tuberculosis have been reported in clinical trials (141). It is however worth noting that in the CHAMPION study, the rates of adverse events among patients who received adalimumab, methotrexate, and placebo, were comparable. Adverse events leading to discontinuation were greatest among patients who received methotrexate, due to deranged liver enzymes (138).

1.5.2 IL-12/IL-23 inhibitor

Ustekinumab

Ustekinumab is a human monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23, and thus inhibits interaction with the IL12Rβ1 receptor (142).

The phase III PHOENIX 1 and PHOENIX 2 trials examined the efficacy and safety of ustekinumab in moderate to severe plaque psoriasis (143). In PHOENIX 1, patients were randomly assigned to receive either 45 mg or 90 mg of ustekinumab at weeks 0, 4, then every 12 weeks, or a placebo (143). Half of the patients who were initially assigned placebo were re-randomised again at week 12 to receive either 45 mg of ustekinumab or 90 mg of ustekinumab (143).

At week 12 in PHOENIX 1, 67.1% of patients on 45 mg of ustekinumab achieved PASI-75, compared to 66.4% on 90 mg ustekinumab, and 3.1% in the placebo group (143). In week 28, 71.2% of patients on 45 mg of ustekinumab achieved PASI-75 compared to 78.6% on 90 mg of ustekinumab (143). In PHOENIX 2, 67% of patients on 45 mg of ustekinumab and 76% on 90 mg of ustekinumab achieved PASI-75 at week 12 (144). Most of the patients who remained on the same doses of ustekinumab past 12 weeks, showed a sustained long-term PASI-75 response over 3 years (144). There was also a noted rapid response to ustekinumab, with patients responding to treatment and achieving PASI-50 by week 2 (144). After 28 weeks of treatments in the PHOENIX 1 trial, 58.6% of patients on 45 mg of ustekinumab reported a DLQI of 0 or 1, and 69% of patients on 90 mg reported a DLQI 0 or 1 (143).

Pooled safety data across three clinical trials were examined over 5 years (145). The most commonly reported adverse effects were nasopharyngitis, upper respiratory tract infections, headaches and arthralgia (143, 145). It was also found that there was no statistically significant increase in the rates of malignancy and serious infections for patients on ustekinumab. Rates of cardiovascular events were low across all treatment groups. It is recommended that screening and monitoring for tuberculosis is performed on patients on ustekinumab, as it has been found that patients with IL-12 and IL-23 deficiencies are more susceptible to infections such as mycobacterium, salmonella, nocardiosis, and bacillus Calmette-Guerin (146, 147).

1.5.3 IL-17 inhibitors

Secukinumab

Secukinumab is a fully human recombinant IgG1 monoclonal antibody that binds to and neutralizes IL-17A. It has been approved for use in severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis.

Two multicentre phase III, randomised, placebo-controlled, double-blind trials were conducted over 52 weeks – ERASURE and FIXTURE (148). The combined results of the ERASURE and FIXTURE trials were examined and showed that 81.6% of patients who were treated with 300 mg of secukinumab achieved PASI-75 after 12 weeks, compared to 71.6% who were treated with 150 mg of secukinumab, and 4.5% of patients who were in the placebo group (148). Furthermore, it was found that treatment with secukinumab resulted in a significant improvement in PASI regardless of patients' baseline PASI, as compared with placebo and etanercept (148). Secukinumab has also demonstrated improved efficacy, and faster response rates compared to ustekinumab. In a head-to-head trial, 79% of patients on secukinumab achieved PASI 90 at week 16 compared to 57.6% on ustekinumab (149).

A pooled analysis of 10 phase II and phase III clinical trials demonstrated that secukinumab has a favourable safety profile overall (150). The most common adverse effects recorded were infections such as nasopharyngitis and upper respiratory tract infections. There were no recorded cases of reactivation of latent tuberculosis across any of the studies. Mucocutaneous candidiasis was observed more frequently among patients on secukinumab as compared to any other treatment group, however, they did not lead to

discontinuation of treatment. The rates of malignancy were comparable across all treatment groups, with the majority of malignancies being recorded as non-melanoma skin cancers. There were no recorded cases of lymphoma (150).

In summary, the advent of newer biologics such as secukinumab, which exerts a more targeted impact on systemic immunity compared to TNF-α inhibitors, has brought with it improved safety profiles, higher response rates and improved clinical efficacy. This stands in contrast to systemic treatments such as methotrexate that has a number of adverse effects and requires monitoring. Furthermore, when compared to TNF-α inhibitors, concerns regarding systemic infection, multiple sclerosis, lymphoma and reactivation of tuberculosis underscore the favourable safety profile of novel biologics such as secukinumab (151).

Ixekizumab

Ixekizumab is a high-affinity IgG4-κ monoclonal antibody which selectively targets IL-17A, and thus regulates the inflammatory response that is driven by IL-17A (152). It has been approved for the treatment of moderate to severe plaque psoriasis.

The results of three large, multicentre, randomised phase III trials examining the efficacy and safety of ixekizumab compared to placebo and etanercept, have previously been reported (153). In the UNCOVER-1 trial, 1296 patients were randomly assigned to receive either 80 mg of ixekizumab every 2 weeks or every 4 weeks, after a starting dose of 160 mg of ixekizumab in week 0, or a placebo, over the course of 12 weeks (153). In the UNCOVER-2 and UNCOVER-3 trials, patients were randomly assigned to a placebo group, 80 mg of ixekizumab 2-weekly, or 4-weekly, after a starting dose of 160 mg at week 0, or 50 mg of etanercept twice weekly, for a total of 12 weeks of treatment (154). In the UNCOVER-3 trial, all patients were given 80 mg of ixekizumab every 4 weeks from weeks 12-60 (154).

The efficacy rate of ixekizumab was noted to be higher than etanercept and placebo, with patients in both ixekizumab groups achieving PASI-75 as early as week 1. After 12 weeks, in the UNCOVER-1, UNCOVER-2 and UNCOVER-3 trials, 82.6%, 77.5% and 84.2% of patients on ixekizumab every 4 weeks achieved PASI-

75, compared to 89.1%, 89.7% and 84.2% of patients on ixekizumab every 2 weeks, 3.9%, 2.4% and 7.3% of placebo, and 41.6% and 53.4% of patients who were assigned to etanercept (153). In a separate study, patients from the UNCOVER-3 trial who had received 80 mg of ixekizumab 2-weekly up to week 12 and were subsequently on 80 mg ixekizumab 4-weekly, were monitored over the course of 3 years. It was found that 80.5% of these patients maintained PASI-75 after 3 years of treatment (155). Furthermore, sustained resolution of nail, palmoplantar, and scalp psoriasis were also observed in the 3-year study. PASI-75 response rates with ixekizumab were also found to be comparable in patients who were biologic naïve vs patients who had previously been on a different biologic (154). DLQI at 12 weeks showed an improvement of 7.8% among patients who received placebo, compared to 43.7% on etanercept, 63.7% on ixekizumab every 4 weeks, and 64.7% of patients on ixekizumab every 2 weeks (154).

Infections and injection-site reactions were more common among patients who were given ixekizumab compared to etanercept and placebo. Infections commonly seen included nasopharyngitis, sinusitis, and upper respiratory tract infections (154). Localised candida infections, neutropenia, Crohn's disease and ulcerative colitis, and rare cases of major adverse cardiovascular events and malignancies have also previously been reported (152, 156).

Bimekizumab

Bimekizumab is a human monoclonal IgG1 antibody that was recently approved in Australia for the treatment of psoriasis (157). It selectively inhibits both IL-17A and IL-17F, leading to suppressed cytokine production, lowered pro-inflammatory gene expression, and reduced inflammatory cell migration, compared to the sole inhibition of IL-17A (157). This dual inhibition is thought to exert a synergistic effect in the treatment of psoriasis (158).

Multiple phase III randomised, placebo-controlled and active comparator trials have been performed, comparing bimekizumab to other biologics (159-161). In the BE SURE, BE VIVID, and BE RADIANT trials, bimekizumab demonstrated greater clinical efficacy compared to adalimumab, ustekinumab and secukinumab, respectively (159-161).

Participants in the BE SURE trial were randomly allocated to 320 mg of bimekizumab every 4 weeks for 56 weeks; 320 mg of bimekizumab every 4 weeks for 16 weeks, then every 8 weeks till week 56; or 80 mg of adalimumab at week 0, 40 mg at week 1, then 40 mg every 2 weeks till week 24 when patients were transitioned to bimekizumab every 4 weeks till week 56 (161). After 16 weeks, 86.2% of patients treated with bimekizumab achieved PASI-90 compared to 47.2% of patients who received adalimumab (161). At week 56, patients on bimekizumab maintained their clinical response, with 84.8% of patients on 4-weekly dosing, and 82.6% of patients on 4-weekly then 8-weekly dosing, achieving PASI-90 (161). For patients who were initially on adalimumab, 51.6% achieved PASI-90 at week 24, a proportion that increased to 81.8% after switching to bimekizumab by week 56 (161). Furthermore, a higher percentage of patients who were on bimekizumab achieved low DLQI scores of 0 or 1 (67.1%, 67.1%) compared to those on adalimumab (47.8%) (161). The long-term efficacy of bimekizumab was further assessed up to 2 years in the BE BRIGHT open label extension, with patients recruited from the BE SURE trial (162). At 104 weeks, 91.2% of patients on 4-weekly bimekizumab and 89.7% of patients on 8-weekly bimekizumab maintained PASI-90 (162).

The BE VIVID trial was a placebo-controlled, active-comparator trial that assessed the efficacy of bimekizumab compared to ustekinumab and placebo (159). Patients were randomly allocated to 320 mg of bimekizumab every 4 weeks; 45 mg (for patients ≤100 kg) or 90 mg (for patients ≥100 kg) of ustekinumab at weeks 0, 4, then every 12 weeks; or placebo (159). At week 16, 85% of patients on bimekizumab achieved PASI-90 compared to 50% of patients on ustekinumab, and 5% who received the placebo (159). Patients' clinical responses were sustained through week 52, with 82% of patients on bimekizumab and 56% of patients on ustekinumab maintaining PASI-90 (159).

The BE RADIANT trial compared the efficacy of bimekizumab to secukinumab (160). Patients were randomised to receive either 320 mg of bimekizumab 4-weekly or 300 mg of secukinumab weekly at week 0-4, then 4-weekly (160). At week 16, patients on bimekizumab were re-randomised to either continue on 4-weekly bimekizumab or to reduce their dosing frequency to 8-weekly (160). At week 16, 61.7% of patients on bimekizumab achieved PASI-100, compared to 48.9% of patients on secukinumab (160). At week 48, 73.5% of patients who continued a 4-weekly dosing of bimekizumab had a PASI-100 response as compared to 66.0%

of patients on 8-weekly bimekizumab, and 48.3% of patients on secukinumab (160). Additionally, 77.7% of patients on bimekizumab achieved a DLQI of 0 or 1, compared to 70.3% of patients on secukinumab (160).

In the collective analysis of the BE SURE, BE VIVID, and BE RADIANT trials, the frequency of adverse events among patients on bimekizumab was comparable to that of other biologics (159-161). Upper respiratory tract infections were the most commonly reported adverse events (159-161). However, it is noteworthy that higher rates of oral candidiasis were observed among patient on bimekizumab compared to the other biologics (159-161).

1.5.4 IL-23 inhibitors

Guselkumab

Guselkumab is a fully human IgG λ monoclonal antibody that binds to the p19 subunit of IL-23 and thereby blocks signalling through the IL-23 receptor (163). It has been approved for use in moderate to severe plaque psoriasis.

VOYAGE I and VOYAGE II were phase III randomised, double-blind placebo-controlled, adalimumab-comparator-controlled trials which examined the efficacy of guselkumab vs. adalimumab vs. placebo (164). Patients were allocated to guselkumab 100 mg at weeks 0, 4, 12, then every 8 weeks; or adalimumab 80 mg at week 0, 40 mg at week 1 then 40 mg every 2 weeks; or placebo (164). After 16 weeks of treatment, in the VOYAGE I and VOYAGE II trials, 91.2% and 86.3% of patients treated with guselkumab achieved PASI-75, compared to 73.1% and 68.5% of patients who received adalimumab, and 5.7% and 8.1% who were in the placebo group. This response was sustained through to the end of the VOYAGE I trial in week 48, as 87.8% of patients on guselkumab maintained a PASI-75 response, and 62.6% of patients on adalimumab maintained their PASI-75 response (164). In the VOYAGE II trial, patients who were on adalimumab, and did not achieve PASI-90 by week 28 were treated with guselkumab. It was also found that patients who were on guselkumab experienced a significant improvement in absolute DLQI scores compared to the placebo group, with a mean change of -11.2 among patients on guselkumab compared to -0.6 in the placebo group (164).

Overall, guselkumab has a favourable safety profile, with similar rates of adverse events across all treatment groups in the clinical trials (165). The most commonly reported side effects were nasopharyngitis and upper respiratory tract infections (165, 166).

Tildrakizumab

Tildrakizumab is a human IgG1/Igκ monoclonal antibody which selectively binds to the p19 subunit of IL-23, and blocks IL-23 action (167).

The combined results of two phase III clinical trials has previously been reported (168). Participants in the reSURFACE1 clinical trial were assigned to tildrakizumab 200 mg at weeks 0 and 4, then every 12 weeks; tildrakizumab 100 mg at weeks 0 and 4, then every 12 weeks; and placebo (168). Patients in the placebo group were subsequently randomised to receive either 100 mg or 200 mg of tildrakizumab after week 12, and every 12 weeks thereafter. The reSURFACE2 clinical trial was a placebo-controlled, active-comparator clinical trial that also compared etanercept to tildrakizumab (168). Patients were randomly assigned to either 100 mg or 200 mg of tildrakizumab at weeks 0 and 4, then every 12 weeks; etanercept 50 mg twice a week until week 12, then once a week till week 28; or placebo (168).

At week 12, in reSURFACE1, PASI-75 was achieved in 62% of patients on 100 mg tildrakizumab, 64% for patients on 200 mg tildrakizumab; 6% on placebo (168). At week 12 in reSURFACE2, 66% of patients on 200 mg tildrakizumab achieved PASI-75, compared to 61% on 100 mg tildrakizumab, 6% on placebo and 48% on etanercept (168). After 28 weeks, 82% of patients on 200 mg of tildrakizumab achieved PASI-75, compared to 80% on 100 mg of tildrakizumab in reSURFACE1, and 73% of patients on 200 mg of tildrakizumab achieved PASI-75, compared to 73% of patients on 100 mg of tildrakizumab in reSURFACE2 (168). Long term data for tildrakizumab also showed a positive response, with most patients improving or maintaining a good clinical response over 3 years (169).

The most reported adverse effect from treatment with tildrakizumab was nasopharyngitis. There was one reported death in the reSURFACE2 trial – the participant was on 100 mg of tildrakizumab, his cause of death

was not determined (168). There was no significant difference between the adverse events observed in patients on tildrakizumab compared to the other treatment groups (168).

Risankizumab

Risankizumab is a humanised IgG1 monoclonal antibody which targets the p19 subunit of IL-23, and thus inhibits the pro-inflammatory action of IL-23 (170).

The UltIMMA-1 and -2 trials were phase III randomised, placebo-controlled and active-comparator clinical trials that were performed across 139 sites worldwide (171). Patients were randomised to receive 150 mg of risankizumab, 45 or 90 mg of ustekinumab, based on their body weight, or placebo, over a 16-week period. In UltIMMA-1 and -2, 75.3% and 74.8% of patients on risankizumab achieved PASI-90 after 16 weeks of treatment, compared to 42% and 47.5% of patients on ustekinumab, and 4.9% and 2% of patients in the placebo group (171). The percentage of patients who achieved PASI 90 at week 52 were 81.9% and 80.6% of patients on risankizumab, compared to 44% and 50.5% of patients on ustekinumab. 86.8% and 88% of patients on risankizumab achieved PASI 75 at week 12 compared to 70% and 69.7% on ustekinumab, and 9.8% and 8.2% on placebo (171). It was also found that 65.8% and 66.7% of patients on risankizumab achieved a DLQI of 0 or 1 at week 16, compared to 43% and 46.5% of patients on ustekinumab and 7.8% and 4.1% of patients on placebo (171). In a separate phase II/III study based in Japan, approximately 14% of all 1079 patients who were treated with risankizumab developed neutralizing antibodies to risankizumab (142).

The most commonly reported adverse events were upper respiratory tract infection and diarrhoea (171). Two cases of non-melanoma skin cancers were reported in patients on risankizumab across both trials, and there was one death among the risankizumab group due to an unknown cause (171). Two cases of latent TB were reported in the patients who were treated with risankizumab (171).

1.6 Drug survival

The previously discussed randomised controlled trials (RCTs) are a valuable repository of information on the safety and efficacy of various biologics. However, RCTs have inherent limitations leading to a lack of external validity (172). Firstly, certain demographics of patients, including older patients and patients with co-morbidities, are often precluded from RCTs (172). Furthermore, RCTs do not reflect sufficient long-term outcomes due to limitations on follow-up times (173). Therefore, drug survival has emerged as an approach in the field of dermatology to measure the long-term efficacy and safety of biologic treatment in a real-world setting (174).

Drug survival refers to the time from initiation of a drug to its discontinuation (175, 176). It is assessed using the statistical method of survival analysis to measure the occurrence of drug discontinuation for patients with differing follow-up times (175). This approach is widespread due to the relative ease of using retrospective data for analysis, which demands fewer resources (172). Furthermore, drug survival reflects the treatment patterns of a diverse range of patients, and accounts for the varying reasons for drug discontinuation that extend beyond the considerations of RCTs (173). Drug survival has therefore become an increasingly meaningful source of real-world evidence that guides clinicians in their choice of treatment (173, 176).

While drug survival provides clinical insight in a real-world setting, it has its limitations (177). Firstly, there is significant variability in the way drug survival is reported across different studies, as there is no strict definition of drug discontinuation (172). For example, there is heterogeneity in the literature, where drug discontinuation has been defined as a gap in treatment anywhere between 60 and 365 days across a range of different studies (172, 177).

There is also variability across different patients and clinicians in terms of their willingness to tolerate more side effects, or their thresholds to switch drugs (175). For instance, patients' concerns about potential side effects or lack of clinical efficacy, regardless of whether these concerns are empirically grounded, can lead to premature discontinuation of biologics. Conversely, other patients with a higher risk tolerance may choose to

switch biologics more readily. Clinicians are equally shaped by their varying risk tolerances, which can lead to heterogeneity in clinical decision-making. Due to the introduction of multiple new biologics over the past decade which offer potentially superior outcomes, clinicians may be influenced to switch biologic therapies in pursuit of higher clinical efficacy (177). Furthermore, in a local setting, clinicians may be influenced by external regulations. In Australia, patients who fail to respond to three biologics are ineligible for further biologic treatment for a minimum of five years (178). This may pose a barrier for clinicians when considering switching their patients to a newer biologic or to report drug failure. Additionally, recent changes to the PBS guidelines allow patients to qualify for biologic treatment after failure of two, instead of the previous requirement of three, conventional therapies. Thus, it is possible that patients who were started on biologic treatment before this policy change suffered from more severe psoriasis which could potentially impact drug survival analyses.

Patients' life circumstances such as family planning and the recent COVID-19 pandemic have also influenced the drug survival landscape (179). Current guidelines regarding the use of biologics in pregnancy recommend that TNF-α inhibitors should not be used in the second or third trimesters of pregnancy, and that secukinumab and ustekinumab should be discontinued in pregnancy (180). Guidelines regarding the use of newer biologics such as risankizumab, guselkumab and tildrakizumab in pregnancy are limited (180). Therefore, family planning considerations often lead to the interruption of treatment. Furthermore, the COVID-19 pandemic led to reduced access to biologic treatments and their healthcare practitioners. Studies examining biologic discontinuation during the COVID-19 pandemic demonstrated that adherence to treatment was affected by patients' perceptions of an increased risk of infection while on biologic therapy (180, 181). Furthermore, patients with over three co-morbidities were less likely to adhere to biologic treatment during the pandemic (179).

Finally, some biologics have longer half-lives and dosing intervals compared to others which results in longer survival times (172, 177). It has thus been proposed that criteria for gaps in treatment should be adjusted to account for biologics with differing half-lives (172).

Despite these limitations, drug survival remains a valuable tool for clinicians (182). Indeed, studies of real-world evidence have reinforced RCT findings in patient populations that were excluded from clinical trials (173). Furthermore, real-world studies have provided useful data on patient outcomes when treatment was adjusted to suit patients' lifestyles and needs (173, 183). This has provided clinicians and patients with practical information on optimal treatment plans to improve patient satisfaction.

1.6.1 Reasons for drug discontinuation

To further understand drug survival, it is important to be aware of the factors affecting drug survival. The most common reasons for drug discontinuation include treatment failure, patient satisfaction, and adverse events, which will be discussed in the following section (184).

Treatment failure

Treatment failure refers to a lack of clinical efficacy (185). Treatment failure can be categorised as primary failure and secondary failure (186, 187). Primary failure of a drug refers to an inadequate initial response, whereas secondary failure refers to loss of drug efficacy over time after initial treatment success (186). The mechanisms behind primary failure remain poorly understood. However, it is theorised that in secondary failure, a process known as immunogenicity occurs where the helper T-cell humoral response is mounted against the biologic, resulting in the formation of anti-drug antibodies (ADA) (188). This can have neutralising effects, as ADA bind to antigen-specific sites on the drug, leading to lower serum concentrations of the biologic and increased drug clearance (175, 188). In addition to a decrease in clinical efficacy, neutralising ADA are associated with higher rates of adverse reactions, as seen in the case of infliximab, where patients who are ADA-positive tend to have higher rates of infusion reactions (188).

Neutralising ADA have been found among patients treated with TNF-α inhibitors such as adalimumab and infliximab, and to a smaller extent, newer biologics such as ustekinumab and tildrakizumab (189-193). Studies performed on these biologics have shown that the presence of neutralising ADA was generally associated with lower serum concentrations of the corresponding drug (189, 191, 193, 194). However, this correlation has not been consistently reflected among the other newer biologics, and the long-term impact of ADA in these

biologics requires further investigation (190, 195-197). It is also worth noting that clinical efficacy is still possible in the presence of ADA, as long as therapeutic levels of the active drug are reached (192). Higher doses and increased dosing frequencies of biologic treatments have thus been shown to improve clinical efficacy (188, 189). In the case of infliximab and ustekinumab, higher doses were associated with lower frequencies of ADA-positive patients (192).

In comparison, non-neutralising ADA that bind to epitopes apart from the drug-binding site, do not appear to have a significant effect on clinical efficacy (192). Non-neutralising ADA have only been observed in etanercept (192).

Several studies into immunogenicity have recommended the routine monitoring of ADA to predict clinical outcomes (188, 189). However, ADA levels are dependent on several different factors, such as the ADA's affinity or isotype (192). Furthermore, there is currently no standard guideline for interpreting ADA assays (198). It is worth noting that the monitoring of serum drug levels has been adopted in the treatment of Crohn's disease, and may serve as a useful clinical predictor of treatment response (192). Therefore, further consideration is required to investigate the utility of monitoring serum drug or ADA levels to predict patients' treatment response.

Patient satisfaction

Patient satisfaction and preference are important determinants of drug survival. The most common target for treatment success in psoriasis is PASI-75, and with the advent of new biologics, PASI-90 has become a realistic target for many patients (198-200). However, patients' preferences extend beyond numerical measures such as PASI, encompassing nuanced considerations such as psychosocial factors, symptoms of itch, pain, or location of plaques in sensitive areas such as the face, genital regions, or plantar surfaces, that the PASI does not account for (201). This has therefore led to the use of dermatology-specific quality-of-life instruments such as DLQI or Skindex-29, to guide clinical decision-making (202).

Another important consideration in patient satisfaction is the compatibility of treatment with patients' lifestyles. Patients who work full-time are more likely to prefer treatments that have lower dosing frequencies, a rapid onset of action and a convenient treatment location (120, 203, 204). As previously outlined, in Table 1.1, the dosing frequency and route of administration of the biologics differ. For instance, infliximab may be given intravenously compared to the other biologics, which are administered subcutaneously. Therefore, patients on intravenous infliximab need to attend an infusion centre, usually in a major hospital, at regular intervals to receive their treatment. This is generally perceived to be less desirable compared to a subcutaneous route of administration (203). Some patients are also more likely to adhere to treatment regimens with longer dosing intervals such as ustekinumab, tildrakizumab and risankizumab which are given every 12 weeks.

Patients' demographics also affect their treatment preferences. Younger patients tend to place more value on the probability of treatment efficacy (120). Conversely, older patients were less concerned with the probability of PASI-50 or PASI-90 and were instead concerned about adverse effects (120, 203). Males were found to value treatment efficiency more than females, whereas females generally preferred lower dosing frequencies (203). In assessing patients' preferences, consideration also needs to be given to their co-morbidities. It has been shown that patients with cardiovascular disease are generally more concerned about adverse events, whereas patients with severe psoriasis place less of an emphasis on side effects and are instead more concerned with treatment efficacy (120). Overall, this highlights the importance of involving patients in a robust discussion when selecting an appropriate biologic to improve patient satisfaction and compliance.

1.6.2 Predictors of drug survival

In addition to identifying the common reasons for drug discontinuation, it is important to understand the factors that may influence treatment response. Several studies have examined the predictors of drug survival to determine ways to further optimise treatment (205-209). Modifiable risk factors such as obesity and smoking have been associated with a poorer response to biologic treatment.

Obesity

There is an established link between obesity and psoriasis which has been demonstrated by multiple epidemiological studies (208, 210-212). In a systematic review and meta-analysis with a total of 2.1 million participants, it was found that patients with psoriasis were significantly more likely to be obese, with a pooled odds ratio of 1.66 (213). Furthermore, in a large prospective study of 78,826 women over a 14-year period, it was found that participants with a higher body mass index (BMI) had an increased risk of incident psoriasis (214). This supports the notion that obesity is an independent risk factor for psoriasis (210).

While the exact mechanism behind the link between obesity and psoriasis is unknown, it is hypothesised that adipokines released by white adipose tissue leads to a pro-inflammatory state which is similarly found in psoriasis (210). These adipokines produce cytokines such as IL-6, IL-10 and TNF-α, which potentially contributes to the pathogenesis of psoriasis (215). As a result of this pro-inflammatory state, obesity is also associated with a decreased clinical response to biologic treatment, as increased BMI was generally associated with lower response rates of PASI-75 for multiple different biologics (216). It is noteworthy that weight loss has been associated with improved skin clearance, and improved response rates to biologic treatment (217). Therefore, it is worthwhile for clinicians to encourage weight loss to optimise patients' treatment response.

Smoking

There is compelling evidence linking smoking with an increased risk of developing psoriasis and exacerbating its severity (209, 211, 218). It is theorised that free radicals that are produced from smoking leads to the activation of multiple intracellular signalling pathways such as mitogen-activated kinase, nuclear factor kappa B and JAK/STAT pathways (209, 219). The resultant cytokines from smoking and nicotine use such as TNF-α, IL-12, IL-17 and IL-23 thereby lead to worsening psoriasis (209, 219).

Several studies have reported a dose-dependent relationship between smoking and the risk of psoriasis, where a higher number of pack-years has been associated with an increased risk of developing psoriasis (209, 220, 221). A pooled analysis revealed a correlation between daily cigarette consumption and psoriasis risk, as individuals that smoked ≥25 cigarettes a day were twice more likely to develop psoriasis compared to non-

smokers (222). This effect was particularly pronounced among women, with an odds ratio (OR) of 3.2 among women who smoked ≥15 cigarettes/day compared to 1.6 in men (223). Furthermore, higher smoking intensity correlates with more clinically severe psoriasis (224). It has been reported that patients who smoked more than 20 cigarettes a day were twice more likely to suffer from severe psoriasis (224). Furthermore, multiple studies have reported a higher mean PASI among smokers compared to non-smokers and ex-smokers (224-226).

The impact of smoking on treatment response remains less clear due to a limited number of studies. A meta-analysis performed by Zhou et al. showed that smokers treated with biologics experienced decreased treatment efficacy at 6 months (209). This finding was further supported by a large-scale observational study which found that previous and current smoking were associated with decreased odds of achieving PASI-90 after 6 months of biologic therapy (227). In contrast, some studies suggest no clear effect of smoking on treatment outcomes (208, 228, 229). Thus, while smoking is known to be associated with a higher risk of developing and exacerbating psoriasis, its specific effect on clinical response remains equivocal due to limited and varied study findings. Nevertheless, given the detrimental effects of smoking on disease severity and the incidence of psoriasis, dermatologists should counsel patients on smoking cessation.

Gender

Female gender is associated with poorer drug survival (184, 230-232). However, it is not known why females have a higher drug discontinuation rate than males, as males tend to suffer from more severe psoriasis as reflected by their higher PASI scores (233). It has been hypothesized that females may be more prone to developing anti-drug antibodies, although there have not been any specific studies that have verified this (232). A likely contributing factor to poorer drug survival among females, is that women tend to express lower rates of treatment satisfaction than men (234). One of the reported reasons for lower satisfaction among women was increased rates of fungal and herpes infections in women on biologics (234). Furthermore, women tend to experience higher levels of discomfort and lower self-esteem, which impacts their mental health and affects their satisfaction (235).

Biologic-naivete

Multiple studies have suggested that previous failure of biologic treatment is associated with higher rates of drug discontinuation and lower rates of complete skin clearance (236-239). A study by van Lumig et al. comprising 85 patients on adalimumab demonstrated that biologic-naïve patients had higher rates of PASI-75 compared to biologic-experienced patients (237). However, longer-term PASI-75 response rates at weeks 24-48 were not statistically different (237). Similarly, Gniadecki et al. examined 882 treatment courses which demonstrated lower drug survival rates of TNF-α inhibitors with previous failure of another TNF-α inhibitor (238). Switching from a TNF-α inhibitor to ustekinumab was also associated with decreased drug survival compared to biologic-naïve patients (240). Patients who had previously failed on ustekinumab generally had lower drug survival rates when they were switched to almost all biologics except for guselkumab (240). It has also been reported that the proportion of biologic-naïve patients with improved DLQI scores whilst on secukinumab were higher compared to biologic-experienced patients (241).

There are several possible explanations for the higher drug survival rates seen among biologic-naïve patients. Firstly, the development of ADA in response to an initial biologic may result in drug tolerance, thus increasing the threshold required for an optimal response with subsequent treatment. As previously discussed, prior failure in response to a TNF-α or ustekinumab has been associated with poorer drug survival with subsequent treatment, except for patients who were switched to guselkumab (208, 237, 238, 240). To support this hypothesis, neutralising ADA have been found in patients on TNF-α and ustekinumab (189-191). However, the role of ADA among patients on ustekinumab is less certain, as the rate of ADA formation to ustekinumab is generally low (242, 243). Furthermore, there is no evidence of a link between ADA to ustekinumab and lower serum drug levels (242).

Secondly, patients who are biologic-experienced are more likely to have more complex disease with other co-morbidities such as cardiovascular disease or psoriatic arthritis. Therefore, the options for an appropriate biologic may be more limited. Additionally, it is thought that these patients are resistant to treatment (208, 244). Studies have revealed that treatment-refractory patients are more likely to be overweight, and patients who were more responsive to treatment had fewer co-morbidities (208).

It is important to note that, as previously outlined, PASI-75 response rates were comparable between biologic-naïve and biologic-experienced patients on ixekizumab in the UNCOVER-2 and -3 trials (154). The lack of significant differences in outcomes between biologic-naïve and biologic-experienced patients may be explained by the rare occurrence of ADA formation in IL-17 inhibitors, resulting in an equally efficacious response among biologic-experienced patients (245). However, these findings were reported at week 12, and should thus be interpreted with caution as it offers limited insight into long-term drug survival (154). Indeed, a large-scale real-world study demonstrated poorer drug survival among biologic-experienced patients on ixekizumab compared to biologic-naïve patients, postulating that these patients on ixekizumab had more complex psoriasis that was difficult to treat (240).

Lastly, one of the main factors contributing to treatment interruption is patient compliance (246). It is therefore important that clinicians counsel patients on the importance of adherence to treatment and explore patients' needs and concerns prior to the commencement of therapy.

1.6.3 Drug survival studies

As outlined above, there are multiple different factors that can affect clinical efficacy and treatment outcomes. Data on PASI-75 outcomes does not always reflect patient satisfaction or treatment success (247-249). Drug survival data, which reflects the subjective reasons for drug discontinuation, can therefore provide further insight and guidance on a tailored approach for treatment selection.

Based on the currently available long-term data, several studies have shown that ustekinumab has superior drug survival compared to the TNF-α inhibitors (184, 250, 251). A meta-analysis performed by Lin et al. demonstrated that ustekinumab had the best overall drug survival at 4 years of 56% compared to etanercept (41%), adalimumab (47%) and infliximab (42%) (252). To support these findings, a large-scale international study comprising 12,095 patients from 2007 to 2013 demonstrated significantly longer drug survival times for patients on ustekinumab for first-, second-, and third-line treatment compared to infliximab, adalimumab and etanercept (253).

Multiple newer biologic therapies have been introduced in recent years, starting with secukinumab in 2015, followed by ixekizumab, tildrakizumab, guselkumab, and risankizumab respectively (254). Since then, there have been further investigations into the drug survival of IL-17 and IL-23 inhibitors (236, 240, 255-258). A number of studies have shown that secukinumab and ustekinumab have comparable survival (255, 256). Yiu et al. reported in a large-scale prospective study of 9652 patients a 1-year drug survival of 0.88 for both secukinumab and ustekinumab (255). Similarly, a study from the Austrian Psoriasis Registry comprising 4348 patients revealed comparable survival rates between secukinumab, ixekizumab and ustekinumab at 1 year and beyond, after the analysis was adjusted for biologic-naivete (236). A longer-term multicentre study conducted by Torres et al. demonstrated superior 24-month drug survival rates of ustekinumab (82.8%) compared to secukinumab (74.1%) and ixekizumab (79.1%) (257). The 12-month drug survival rates of ustekinumab, secukinumab and ixekizumab were similar, which aligns with the aforementioned studies (257). A possible explanation for this is that the drug survival analysis was not time-adjusted in this study, which could result in longer drug survival for ustekinumab. Further studies are required to elucidate the long-term survival of the IL-17 inhibitors.

Torres et al. also reported high drug survival rates among the IL-23 inhibitors compared to the other biologics, which was sustained until 18 months - the drug survival rate of guselkumab was 0.911, risankizumab: 0.964, ixekizumab: 0.820, secukinumab: 0.790 and ustekinumab: 0.861. (257). Despite the modest number of patients on IL-23 inhibitors, these findings are broadly consistent with other studies that compared the drug survival of guselkumab to the older biologics (240, 257, 259). Indeed, another large-scale prospective study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) comprising 16122 treatment courses demonstrated the highest drug survival rates among patients who were on guselkumab, with a 2-year survival function of 0.80 compared to 0.61 for patients on ixekizumab, 0.66 for patients on secukinumab, and 0.73 for patients on ustekinumab (240). Survival data pertaining to risankizumab and tildrakizumab are still limited due to their novelty, which leaves scope for future studies.

Overall, the IL-23 inhibitors have shown promising results in terms of drug survival compared to the other biologics. There are several possible explanations for this. Firstly, as previously discussed, IL-23 plays an

important role in the maintenance and proliferation of pathogenic T_{RM} cells (89). Thus, targeting IL-23 may result in long-term disease modification through the down-regulation of T_{RM} cells (84). Furthermore, IL-23 mediates the release of IL-17A and IL-17F which leads to the release of inflammatory cytokines that drive the pathogenesis of psoriasis. Therefore, blocking IL-23, which is an upstream target, has a broader impact on dampening the inflammatory response in psoriasis.

1.6.4 Other considerations in drug selection for the management of psoriasis

Patients' co-morbidities

Despite these promising findings, there are several other considerations when tailoring a treatment to a patient's needs (198, 260). Many of the biologics used in psoriasis are also used to treat other diseases such as psoriatic arthritis and inflammatory bowel disease (IBD) (261). For example, TNF-α inhibitors have a proven efficacy in the treatment of psoriatic arthritis with significant long-term data and they have therefore been considered first-line treatment for several years (262). More recently, studies have also demonstrated the efficacy of ixekizumab and secukinumab in the treatment of psoriatic arthritis (263-265). Ixekizumab was found to be more efficacious than adalimumab, with 60.1% of patients reaching PASI-100, compared to 46.6% in adalimumab, and 50.5% improvement from baseline in psoriatic arthritis with ixekizumab compared to 47% in adalimumab (263). However, IL-17 inhibitors should be avoided among patients with IBD as they can exacerbate the disease (263, 266). This briefly illustrates the complexities involved in selecting an appropriate biologic for psoriasis. Therefore, patients' co-morbidities need to be taken into account and treatments should be tailored to the patient's needs (267).

Speed of treatment response

Treatment goals should also be discussed with the patient prior to the commencement of therapy as patients' expectations may not align with their clinicians. A study in Japan by Okubo et al. supports this notion, as 67.9% of patients and their clinicians were found to have a misalignment in their treatment goals (268). Another treatment goal that patients commonly value is the speed of response to treatment (269-271). Several studies have examined the speed of response of biologics and have demonstrated that IL-17 inhibitors - particularly ixekizumab - resulted in the most rapid skin clearance compared to the other biologics (272-274).

Furthermore, a recent head-to-head randomised, double-blind 24-week trial comparing the efficacy of guselkumab vs. ixekizumab was performed (IXORA-R) (166). At week 12, 41% of patients on ixekizumab achieved PASI-100 compared to 25% of patients on guselkumab (275). By week 24, 50% of patients on ixekizumab achieved PASI-100 compared to 52% of patients on guselkumab (275). There was also no significant difference between the number of patients who reported a DLQI of 0 or 1 between the two groups (275). Thus, the IL-17 inhibitors offer significant potential in terms of excellent and rapid skin clearance, which should be a consideration for clinicians. However, data from most of these studies were based on RCTs, and thus there is still a lack of real-world evidence pertaining to this aspect of treatment. It would be valuable for further studies to focus on the speed of treatment response in a real-world setting.

Biologic-switching

Lastly, it is hypothesised that early disease control is associated with improved long-term clinical response (276-278). In support of this hypothesis, multiple post hoc analyses have shown that shorter disease duration is associated with an improved PASI response (276, 279, 280). Furthermore, early intervention minimises suffering for the patient and ameliorates the chronic inflammatory response which can lead to other co-morbidities including cardiovascular disease (281, 282). However, some clinicians and patients are hesitant to cease a first-line biologic despite a partial response only, which potentially leads to sub-optimal outcomes. Indeed, with the availability of multiple new biologics with proven safety and efficacy, the possibility of PASI-90 or PASI-100 is likely attainable (198, 199). Furthermore, multiple studies have reported positive clinical outcomes after switching biologics. It has also been found that the overall drug survival rate of second-line biologic therapy is comparable to first-line biologics (251). Therefore, biologic-switching is common in clinical practice. However, there are no guidelines on the ideal sequencing of treatment or the safety and efficacy of switching from one biologic to another.

1.6.5 Intra-class switching

Intra-class switching between TNF-α inhibitors has had proven efficacy due to the distinct pharmacokinetics and mechanisms of action between each TNF-α inhibitor (283, 284). There is a significant body of evidence in the literature supporting the efficacy of switching from other TNF-α inhibitors to adalimumab (285-287). A

16-week double-blind RCT showed that 61.7% of patients who had previously been on a TNF-α inhibitor achieved PASI-75 after 16 weeks of treatment with adalimumab (287). Etanercept was one of the first biologics to be approved for the treatment of psoriasis (186). There is therefore less data regarding switching from other biologics to etanercept. However, there have been smaller studies that reported a clinical improvement in switches from infliximab or adalimumab to etanercept (288, 289). Lastly, most of the studies regarding switching to infliximab were conducted on patients who did not respond adequately to etanercept (290, 291). Gottlieb et al. demonstrated that 51.7% of patients who switched from etanercept to infliximab achieved PASI-75 by week 10 (290). Hence, intra-class switching between TNF-α inhibitors is a reasonable option for clinicians provided this aligns with their patients' expectations and treatment goals.

Recent studies have also reported on intra-class switching between IL-17 inhibitors. Lockshin et al. examined the clinical outcomes of patients treated with ixekizumab, who had previously been on secukinumab vs. other biologics (292). It was found that patients who had previously been treated with secukinumab were still able to achieve a meaningful clinical response after switching to ixekizumab, although the response rates among patients who had been on other biologics were higher (292). These findings are supported by a systematic review and meta-analysis which examined clinical outcomes of intra-class switching in IL-17 inhibitors and found short-term PASI-75 response rates of between 77-89% (293). However, most of the studies that were included in the analysis were focused on switching to ixekizumab (293). Thus, further studies are required to confirm the long-term safety and efficacy of intra-class switching between other IL-17 inhibitors.

Finally, data on the IL-23 inhibitors is still limited due to their novelty. Studies focusing on intra-class switching between IL-23 inhibitors will undoubtedly be of interest.

1.6.6 Inter-class switching

Several studies have reported the benefits of inter-class switching of biologics (186, 198, 251, 294). A large-scale real-world study demonstrated higher rates of drug survival among patients who switched from a TNF-α inhibitor to ustekinumab as compared to an intra-class switch (251). Data from several RCTs have also shown

a general improvement when switching from other biologics - which were mostly TNF-α inhibitors - to both IL-17 inhibitors, secukinumab and ixekizumab (144, 154, 294-296).

Switches from TNF-α inhibitors to IL-23 inhibitors are similarly well-described (297, 298). Patients who did not respond adequately to adalimumab achieved PASI-90 by week 48 when switched to guselkumab (66.1%), and by week 44 when switched to risankizumab (66.0%) (168, 297). The NAVIGATE trial reported on the outcomes of patients who did not respond to ustekinumab by week 16 (299). These patients were randomised to receive either guselkumab or to continue ustekinumab (299). It was found that by week 52, 51.1% of patients on guselkumab achieved PASI-90 as compared to 24.1% of patients on ustekinumab (299). Interestingly, a recent study found that ustekinumab-refractory patients had higher rates of clinical and histological clearance in response to secukinumab as compared to guselkumab, suggesting an IL-23 independent pathway in the pathogenesis of psoriasis (300).

1.7 Discussion

This review has covered in-depth the evidence surrounding the efficacy and safety of the currently available biologics in Australia and provided insight into factors that determine biologic drug survival.

Psoriasis is accompanied by significant psychosocial and economic burdens (8-10). There are various efficacious lines of treatment available which has resulted in an improvement in patients' quality of life. This is particularly true with the advent of biologic therapy which has demonstrated superior efficacy to conventional systemic treatment, with minimal side effects (232). As more novel biologic therapies are being developed, more information on their efficacy and safety is required.

Current studies have shown favourable clinical efficacy of the newer biologics, with many patients achieving complete skin clearance (301). Based on current information, IL-23 inhibitors have demonstrated superior drug survival, and IL-17 inhibitors have shown the most rapid onset of action compared to the other biologics (240, 257, 301). However, there is still limited long-term data on these newer biologics. Most of the

information on efficacy and safety is limited to clinical trials which are not representative of a real-world setting (173, 176). Furthermore, there are limited drug survival studies in Australia that reflect the local experience. Therefore, further long-term data is required to assess the overall drug survival of the different biologics in an Australian setting. This thesis will thus aim to address the following objectives:

1. To assess the drug survival of the currently available biologics in Australia
2. To assess the reasons for drug discontinuation
3. To examine the patterns of care in local tertiary institutions
4. To provide preliminary data on biologic-switching

Chapter 2: Drug survival of biologics in psoriasis: An Australian multicentre retrospective study

Abstract

Drug survival, which refers to the time from treatment initiation to discontinuation, provides a surrogate measure of the effectiveness of a biologic in a real-world setting (175). The aim of this study was to determine the drug survival of biologics that are currently available in Australia. We also analysed the treatment efficacy of these biologics, and reasons for discontinuation.

Retrospective data from outpatient Dermatology biologic clinics in Westmead Hospital and Royal Prince Alfred Hospital (Sydney, Australia) from April 2006 to December 2020 were collected. Kaplan-Meier analysis was used to calculate drug survival.

A total of 312 patients who underwent 577 treatment courses were analysed. Guselkumab was observed to have the longest drug survival, with cumulative drug survival rates of 94.2% ± 4.0 at 1- and 5-years. This was followed by ixekizumab which had a 1-year survival rate of 87.2% ± 4.5 and a 5-year survival rate of 59.4% ± 9.5. Ixekizumab and guselkumab were also noted to have superior treatment efficacy compared to other biologics, with PASI-75 rates of 94.9% and 93.8% respectively. The most common reasons for treatment discontinuation were a lack of initial efficacy to treatment, and a loss of efficacy over time despite an initial response, respectively.

To our knowledge, this is the first Australian study to report on the outcomes of multiple new biologics that are currently in use for the treatment of chronic plaque psoriasis. Overall, this study provides insight into patterns of care from a local experience that may help guide the management of moderate-to-severe psoriasis.

2.1 Introduction

Psoriasis is a chronic immune-mediated disease that has an estimated global prevalence of 2-3% (1-3). In recent years, the use of biologic therapy has shifted the paradigm in the management of psoriasis, offering high efficacy and good safety profiles in comparison to traditional systemic therapies (16). Although biologics have demonstrated significant promise in clinical trial settings, real-world data on their efficacy and safety is still lacking.

Drug survival, which refers to the time from drug initiation to drug discontinuation, reflects drug efficacy and safety in a real-world setting (175). Several reported factors impact drug survival including primary failure, secondary failure, a lack of initial efficacy in response to treatment, a loss of efficacy over time despite an initial positive response, adverse reactions, and patients' individual preferences (253, 302).

There is currently limited Australian data reporting on the drug survival of biologics in psoriasis and a paucity of data in the literature on the drug survival of newer biologics such as the IL-17 and IL-23 inhibitors. Reporting on drug survival data will guide clinicians in the choice of a biologic to meet patients' expectations and to avoid frequent biologic-switching (236, 253).

The current study therefore aimed to investigate the drug survival of all biologics that are currently approved for use in Australia, their treatment efficacy, and the factors contributing to treatment discontinuation.

2.2 Methods

Data was retrospectively collected on patients who were seen in the outpatient psoriasis biologic clinics of two tertiary centres in Sydney, Australia (Royal Prince Alfred Hospital, Westmead Hospital). Inclusion into the study required: (i) Patients to be above the age of 18; (ii) A diagnosis of moderate-to-severe chronic plaque psoriasis; (iii) Patients must have had a review in the biologic clinics between April 2006 and December 2020.

To qualify for PBS subsidised biologic treatment in Australia, patients must have either moderate-to-severe chronic plaque psoriasis (defined as having a Psoriasis Area and Severity Index (PASI) of ≥15), or severe palmoplantar psoriasis, for over 6 months. Patients must also have previously either had contraindications or failed to achieve a PASI below 15 with a minimum of two systemic treatments or phototherapy. Treatment

efficacy was determined by assessing rates of PASI-75, -90, and -100, as measured by a 75, 90, and 100% reduction in PASI compared to their baseline.

The follow-up protocol for patients who were started on a new biologic during the study period was routinely reviewed at least 12 weeks after the commencement of the drug, then every 6 months thereafter, following the regulatory requirements for biologics prescription. This study was approved by the Western Sydney Local Health District ethics committee (HREC reference number 2019/ETH13159).

2.2.1 Data collection

Data on age, gender, psoriasis subtype, concurrent treatment of psoriasis with medications other than their primary course of biologic, treatment duration, PASI at every visit, the number of co-morbidities and the presence of psoriatic arthritis were collected. Biologics investigated in this study included adalimumab, infliximab, etanercept, ustekinumab, secukinumab, ixekizumab, guselkumab, and risankizumab. Each treatment course was analysed separately. Treatment courses with alefacept, efalizumab and brodalumab were excluded, as they are not currently approved for use in Australia. Treatment courses with tildrakizumab were also excluded from the analysis due to the limited number of patients who were on the drug.

Drug survival was calculated from the time of drug initiation to drug discontinuation. For patients who were lost to follow-up, their last date of contact was utilised as the date of discontinuation. Patients who had a gap of > 90 days in treatment were considered to have discontinued the drug. Reasons for drug discontinuation were classified as primary failure, secondary failure, lack of efficacy, loss of efficacy, adverse effects, psoriatic arthritis flare, lost to follow-up, and others. Primary failure was defined as patients who did not achieve PASI-75 at their initial 3-month follow-up, and secondary failure was defined as patients who failed to achieve PASI-75 despite an initial response. A lack of efficacy refers to a lack of clinical response to treatment during the initial 3-month follow-up visit, despite achieving PASI-75. A loss of efficacy refers to an initial response to treatment that was lost over time, despite maintaining PASI-75 throughout the treatment course. These patients were further stratified into biologic-naïve and biologic-experienced. Patient data was excluded from analysis if the date of initiation was unknown and could not be extrapolated.

2.2.2 Statistical analysis

Drug survival was determined using Kaplan-Meier analysis to generate survival curves. A P value of <0.05 was considered statistically significant. Data was analysed using the SPSS statistical software (SPSS, Chicago, IL, USA) and R (version 4.2.1).

2.3 Results

2.3.1 Baseline characteristics

The baseline characteristics of the patients in the current study are summarised in Table 2.1. In total, 306 patients who received a total of 566 treatment courses were included in our analysis. This included 97 treatment courses on adalimumab (17.1%), 70 on infliximab (12.4%), 26 on etanercept (4.6%), 143 on ustekinumab (25.3%), 100 on secukinumab (17.7%), 59 on ixekizumab (10.4%), 35 on guselkumab (6.2%), and 36 on risankizumab (6.4%) (Table 2.1).

The mean overall age of the cohort was 44.7 years with 215 treatment courses (38.0%) administered to female patients (Table 2.1). The mean baseline PASI at treatment initiation was 22.3. There were also higher proportions of patients on concurrent methotrexate with their prescribed biologic among those on infliximab (22.9%) and adalimumab (21.6%) (Table 2.1). The trend of baseline PASI over the years was also examined (Figure S1). A Wilcoxon rank-sum test was conducted to compare the median baseline PASI before and after January 1, 2015. No statistically significant difference between the groups was found (W=9486, p-value = 0.448).

Table 2.1: Baseline characteristics of participating patients across all treatment courses

	Adalimumab (n=97)	Infliximab (n=70)	Etanercept (n=26)	Ustekinumab (n=143)	Secukinumab (n=100)	Ixekizumab (n=59)	Guselkumab (n=35)	Risankizumab (n=36)	Overall (n=566)
Age, mean (SD)	43.9 (12.3)	45.6 (13.6)	44.8 (15.2)	45.5 (13.5)	45.3 (13.9)	41.1 (14.1)	46.4 (12.9)	45.1 (15.7)	44.7 (13.6)
Gender, no. (%)									
Females	47 (48.5%)	23 (32.9%)	10 (38.5%)	52 (36.4%)	39 (39.0%)	24 (40.7%)	10 (28.6%)	10 (27.8%)	215 (38.0%)
Males	50 (51.5%)	47 (67.1%)	16 (61.5%)	91 (63.6%)	61 (61.0%)	35 (59.3%)	25 (71.4%)	26 (72.2%)	351 (62.0%)
BMI, mean (SD)*	32.1 (9.23)	32.1 (8.53)	30.2 (9.45)	32.9 (8.85)	31.8 (8.47)	32.3 (8.80)	33.5 (8.20)	35.1 (9.85)	32.5 (8.85)
Baseline PASI, mean (SD)†	21.4 (7.19)	22.8 (6.69)	22.1 (8.67)	22.6 (7.52)	21.5 (6.35)	23.7 (7.94)	21.5 (7.98)	23.1 (7.61)	22.3 (7.31)
Comorbidities, mean (SD)	1.55 (1.70)	1.94 (1.69)	2.19 (2.08)	1.71 (1.67)	1.70 (1.61)	1.41 (1.53)	1.63 (1.55)	1.97 (1.86)	1.71 (1.68)
Smoker, no. (%)									
Never smoked	40 (41.2%)	32 (45.7%)	14 (53.8%)	75 (52.4%)	47 (47.0%)	38 (64.4%)	18 (51.4%)	21 (58.3%)	285 (50.4%)
Current/Previous smoker	43 (44.3%)	34 (48.6%)	11 (42.3%)	62 (43.4%)	44 (44.0%)	19 (32.2%)	13 (37.1%)	14 (38.9%)	240 (42.4%)
Missing	14 (14.4%)	4 (5.7%)	1 (3.8%)	6 (4.2%)	9 (9.0%)	2 (3.4%)	4 (11.4%)	1 (2.8%)	41 (7.2%)
Palmoplantar psoriasis, mean (SD)	4 (4.1%)	1 (1.4%)	1 (3.8%)	7 (4.9%)	1 (1.0%)	1 (1.7%)	1 (2.9%)	1 (2.8%)	17 (3.0%)
Psoriatic arthritis, mean (SD)	61 (62.9%)	36 (51.4%)	10 (38.5%)	59 (41.3%)	51 (51.0%)	25 (42.4%)	13 (37.1%)	14 (38.9%)	269 (47.5%)
Concurrent therapy, no. (%)									
Methotrexate	21 (21.6%)	16 (22.9%)	4 (15.4%)	14 (9.8%)	13 (13.0%)	6 (10.2%)	2 (5.7%)	0 (0%)	76 (13.4%)
Topical corticosteroids	30 (30.9%)	19 (27.1%)	8 (30.8%)	45 (31.5%)	32 (32.0%)	5 (8.5%)	8 (22.9%)	1 (2.8%)	147 (25.9%)
Phototherapy	0 (0%)	0 (0%)	1 (3.8%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.3%)
Cyclosporine	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.8%)	2 (0.3%)
Acitretin	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (1.0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)

Missing data: *142, †38

2.3.2 Drug survival

Across all treatment courses, the median follow-up time was 50.4 months (IQR 19.8-101.3 mo). A summary of the cumulative 1- to 5-year survival rates for 566 treatment courses is presented in Table 2.2. Guselkumab had the highest 1-year survival rate (94.2% ± 4.0) which was consistently sustained up to 5 years. This was followed by ixekizumab which had a 1-year survival rate of 87.2% ± 4.5 and 5-year survival rate of 59.4% ± 9.5. In comparison, etanercept had the lowest survival rate at 1 year (57.7% ± 9.7) and at 5 years (30.3% ± 9.1). A Kaplan-Meier analysis demonstrating drug survival of each biologic is shown in Figure 2.1. The number at risk is detailed in supplementary table 1 (Table S1; see Supporting Information).

Table 2.2 Cumulative drug survival rates at years 1, 2, 3, and 5. The drug survival rates of each biologic at years 1, 2, 3, and 5 are listed.

	1-year survival % (SE)	**2-year survival % (SE)**	**3-year survival % (SE)**	**5-year survival % (SE)**
Adalimumab	70.1 (4.7)	55.8 (5.3)	50.6 (5.4)	32.2 (5.3)
Infliximab	82.6 (4.6)	69.1 (5.6)	60.0 (6.0)	50.4 (6.2)
Etanercept	57.7 (9.7)	46.2 (9.8)	34.6 (9.3)	30.3 (9.1)
Ustekinumab	81.2 (3.3)	70.7 (4.1)	61.7 (4.5)	46.7 (5.0)
Secukinumab	85.7 (3.5)	70.5 (4.8)	51.1 (5.5)	33.1 (6.6)
Ixekizumab	87.2 (4.5)	74.2 (6.2)	66.0 (7.9)	59.4 (9.5)
Guselkumab	94.2 (4.0)	94.2 (4.0)	94.2 (4.0)	94.2 (4.0)
Risankizumab	NR	NR	NR	NR

NR (Not Reached)

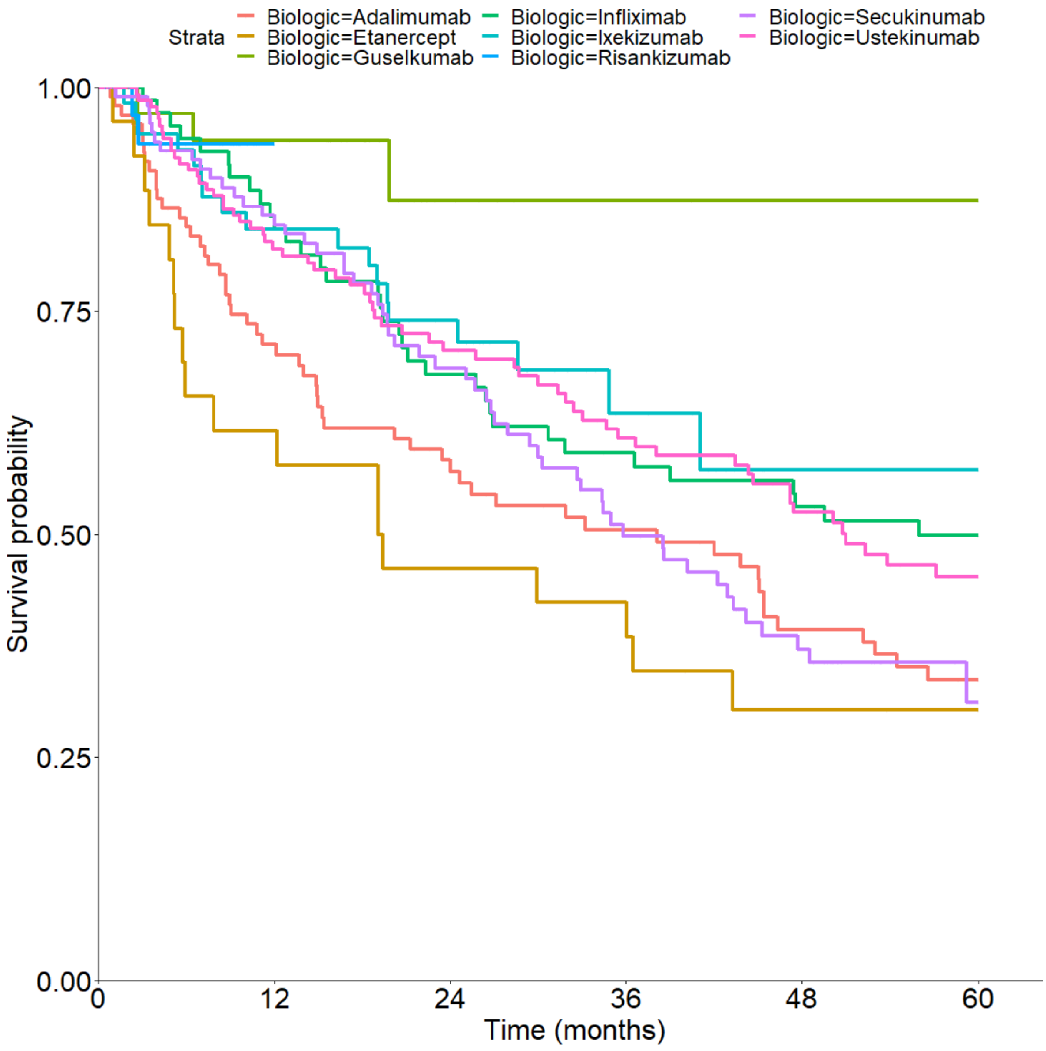

Figure 2.1. Drug survival curve of patients with chronic plaque psoriasis on biologic therapy. The drug survival of each biologic is presented, up to 5 years of follow-up.

2.3.4 Reasons for treatment discontinuation

The reasons for treatment discontinuation are summarised in Supplementary Table 2. There was a total of 279 drug discontinuations out of 566 treatment courses (48.4%), of which 22.2% were on adalimumab, 17.6% were on infliximab, 7.2% on etanercept, 24.7% on ustekinumab, 19.7% on secukinumab, 6.8% on ixekizumab, 1.0% on guselkumab, and 0.7% on risankizumab (Table S2; see Supporting Information).

The most common reasons for treatment discontinuation overall were a lack of initial efficacy to treatment (14.3%) and loss of efficacy over time (9.9%) (Table S2). The highest rates of discontinuation due to a lack of initial efficacy to treatment were seen among patients on etanercept

(42.3%), followed by adalimumab (22.7%). Patients who were on secukinumab (18.0%) had the highest rates of treatment discontinuation due to loss of efficacy over time, followed by infliximab (14.3%). Patients who were biologic-experienced were more likely to discontinue therapy due to a lack of initial efficacy as compared to biologic-naïve patients who had higher rates of discontinuation due to a loss of efficacy over time. The highest rates of primary and secondary failure were seen among biologic-naïve patients on etanercept (7.7%, 7.7%).

The overall rate of adverse reactions across 566 treatment courses was 4.2% (Table S2). The highest rates of adverse reactions were seen among patients who were on infliximab (8.6%), followed by adalimumab (7.3%). Among patients who were on infliximab and who discontinued treatment due to an adverse event, there were three reported cases of infusion reactions, two allergic reactions - one of which was an anaphylactic response, and one reported case of a myocardial infarction. Among patients who were on adalimumab, five of them had minor reactions which included rash, allergic reaction, and headaches. There was one reported case of possible adalimumab-induced neuropathy and sarcoidosis. Guselkumab, risankizumab and ustekinumab had relatively low rates of adverse events (Table S2).

2.3.5 Treatment efficacy

The rates of PASI-75, PASI-90, and PASI-100 across all treatment courses are summarised in Table 2.3.

Ixekizumab had the highest rate of PASI-75 (94.9%) followed by guselkumab (93.8%) and the lowest rates were seen in risankizumab (69.4%) and etanercept (73.1%) respectively. The rate of PASI-75 was higher in all drugs for patients who were biologic-naïve. The median time to PASI-75 was highest for adalimumab (84 days) and longest for infliximab (130 days).

Ixekizumab had the highest rate of PASI-90 (84.7%), followed by guselkumab (78.1%) with the lowest rate of PASI-90 seen in etanercept (42.3%). The fastest median time to PASI-90 was seen in guselkumab (85 days) and the longest median time was seen with infliximab (222 days).

A lower number of patients across all the different biologics achieved a PASI-100 with the highest number achieved in ixekizumab (71.2%). The lowest rates of PASI-100 were seen in patients who were on etanercept (19.2%). Ixekizumab reflected the shortest time to PASI-100 with a median time of 90.5 days, whilst infliximab required the longest median time to reach PASI-100 with a time of 413 days.

Table 2.3. Treatment efficacy of currently available biologics. The rates of PASI-75, -90, and -100 for each biologic, and the median time taken to achieve this clinical endpoint is presented. Treatment courses are further stratified into biologic-naïve and biologic-experienced.

Biologic	PASI-75	Median time to PASI-75 (days)	PASI-90	Median time to PASI-90 (days)	PASI-100	Median time to PASI-100 (days)
Adalimumab (n=97)	83 (85.6%)	84.0	56 (57.7%)	111.5	33 (34.0%)	231.0
BN (n=51)	48 (94.1%)		35 (68.6%)		20 (39.2%)	
BE(n=46)	35 (76.1%)		21 (45.7%)		13 (28.3%)	
Infliximab (n=70)	59 (84.3%)	130.0	46 (65.7%)	222.0	27 (38.6%)	413.0
BN (n=44)	41 (93.2%)		35 (79.5%)		21 (47.7%)	
BE (n=26)	18 (69.2%)		11 (42.3%)		6 (23.1%)	
Etanercept (n=26)	19 (73.1%)	91.0	11 (42.3%)	250.0	5 (19.2%)	237.0
BN (n=20)	15 (75.0%)		8 (40.0%)		5 (25.0%)	
BE (n=6)	4 (66.7%)		3 (50.0%)		0 (0.0%)	
Ustekinumab (n=143)	124 (86.7%)	112.0	101 (70.6%)	150.0	57 (39.9%)	203.0
BN (n=86)	74 (86.0%)		64 (74.4%)		40 (46.5%)	
BE (n=57)	50 (87.7%)		37 (64.9%)		17 (29.8%)	
Secukinumab (n=100)	88 (88.0%)	89.0	76 (76.0%)	98.0	41 (41.0%)	99.0
BN (n=48)	44 (91.7%)		40 (83.3%)		24 (50.0%)	
BE (n=52)	44 (84.6%)		36 (69.2%)		17 (32.7%)	
Ixekizumab (n=59)	56 (94.9%)	86.5	50 (84.7%)	90.0	42 (71.2%)	90.5
BN (n=23)	23 (100.0%)		21 (91.3%)		19 (82.6%)	
BE (n=36)	33 (91.7%)		29 (80.6%)		23 (63.9%)	
Guselkumab (n=32)	30 (93.8%)	87.5	25 (78.1%)	85.0	15 (46.9%%)	401.0
BN (n=9)	9 (100.0%)		9 (100.0%)		5 (66.7%)	
BE (n=23)	21 (91.3%)		16 (69.6%)		10 (43.4%)	
Risankizumab (n=36)	25 (69.4%)	89.0	18 (50.0%)	92.0	10 (27.8%)	93.5
BN (n=5)	3 (60.0%)		2 (40.0%)		1 (20.0%)	
BE (n=31)	22 (71.0%)		16 (51.6%)		9 (29.0%)	

BN: Biologic-naïve; BE: Biologic-experienced.

2.4 Discussion

The current study demonstrated the drug survival of all biologics that are currently approved in Australia for the treatment of moderate-to-severe chronic plaque psoriasis. To our knowledge, this is the first Australian study that has examined the drug survival of newer biologic therapies in psoriasis. This study adds to long-term data pertaining to the survival of these novel therapies, of which there is limited literature outside the clinical trial setting.

In the current study, guselkumab had the highest drug survival that was sustained for up to 5 years, followed by ixekizumab. Etanercept had the lowest drug survival over a 5-year period. However, the survival rates observed among patients on etanercept may be partially explained by the abrupt withdrawal of efalizumab in 2003, as patients with severe rebound effects transitioned to etanercept. This transition may have led to higher reported failure rates and thus skewed the data on its long-term survival rates. Despite recommendations for the concurrent use of methotrexate with biologics such as infliximab and adalimumab to reduce the development of ADAs, this study did not demonstrate enhanced survival rates for patients on these biologics (303).

Our overall findings are largely consistent with previous studies which demonstrated relatively high survival of guselkumab and ixekizumab compared to other biologics (1, 2). To compare, one of the largest studies to date investigated the drug survival of adalimumab, ustekinumab, secukinumab, guselkumab and ixekizumab, utilising data from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) (240). It was demonstrated that in a cohort of 16,122 treatment courses, guselkumab had the highest drug survival (two-year survival function = 0.80). However, their findings differed slightly from the current study as ustekinumab had the second-highest drug survival rate (two-year survival function = 0.73). Secukinumab and ixekizumab had comparable survival with survival functions at two years of 0.66 and 0.61 respectively.

Another large study that reflected our findings was a meta-analysis performed by Lin et al. (2018) of 32,631 subjects (252). The meta-analysis reported a superior drug survival of ustekinumab (four-year survival rate = 0.56) compared to etanercept which had a four-year survival rate of 0.41 (252). These findings are broadly similar to the outcome of the present study. Few studies regarding the drug survival of newer biologics have been published to date. Most recently, a multi-country study performed by Torres et al. (2021) examined the drug survival of the novel IL-23, IL-17 and IL-12/23 inhibitors (257). Guselkumab had a drug survival rate of 90.2% after two years of follow-up, followed by ustekinumab (82.8% at two years) and ixekizumab (79.1% at two years). It is noteworthy that risankizumab demonstrated the highest drug survival until 18 months of follow-up, with a survival

rate of 96.4%. Similarly, our study demonstrated high survival rates among patients on risankizumab, although 12-month follow-up data was lacking (Figure 2.1).

The difference in drug survival of ixekizumab in the present study compared to the aforementioned studies may be partially explained by the larger proportion of biologic-naïve patients in our study population. Notably, the proportion of biologic-naïve patients on ixekizumab in the current study was 38.9% compared to 18.2% and 16.6% in Yiu et al. and Torres et al.'s studies respectively (240, 257). The relatively high proportion of biologic-naïve patients on ixekizumab in the current study may have led to more favourable drug survival rates. This hypothesis is supported by the finding in the study by Yiu et al. (2022) that drug survival rates of biologic-naïve patients were comparable among individuals on guselkumab and ixekizumab (240). It has also been further established in the literature that biologic-naïve patients on IL-17 inhibitors have better drug survival rates than biologic-experienced patients (240, 304). Another possible explanation for the observed discrepancy is the differing patterns of prescribing across different centres. Due to the availability of several new biologic therapies and the resultant possibility of complete skin clearance, clinicians may have a lower threshold for switching therapy. However, given the relatively high rates of skin clearance among patients on ixekizumab in this study, it is more likely that the discrepancy is due to a relatively high proportion of biologic-naïve patients on ixekizumab.

This is the first and largest study reflecting the drug survival of novel biologic therapies from any centre in Australia (305). The results broadly reflect and confirm the findings of larger international experiences in other countries (240, 252, 257). The study has also added to the literature in confirming the real-world efficacy of the newest biologics including guselkumab, risankizumab, and ixekizumab, as real-world data pertaining to these therapies is still scarce.

However, this study had the following limitations. Firstly, the size of the study was modest which limited a detailed analysis of possible confounding factors. Drug survival is influenced by many different factors including patient factors such as age and comorbidities, treatment naivety, treatment efficacy, side effects, and safety. Indeed, there were higher rates of biologic-experienced patients on

guselkumab and risankizumab in the current study's cohort. Whilst some prior studies were able to elucidate factors that affected survival in multivariate analysis, the current study did not have the statistical power to analyse these factors (240). Additionally, although the highest rates of discontinuation due to adverse effects were observed among patients on TNF-α inhibitors such as infliximab and adalimumab, the lower discontinuation rates associated with newer biologics such as guselkumab, risankizumab and ustekinumab may be due to the shorter cumulative exposure of patients to the newer biologics. The results for the newest biologics such as risankizumab were also limited to short follow-up times due to its recent approval for use in Australia. As none of the patients in our cohort who were on risankizumab reached one year of follow-up, the rates of PASI-75 were skewed. Nevertheless, with the paucity of published data worldwide, the current study still provides early insight into the effectiveness of these newest biologics in the real-world setting. Finally, the results are limited by the retrospective nature of this study, which makes it more susceptible to selection bias.

There are several potential future avenues of study evolving from the current study. The first is the further contextualisation of drug survival with the use of instruments such as the Dermatology Life Quality Index (DLQI) or Skindex-29 which accounts for the significant psychosocial impact of psoriasis and its effects on treatment adherence (37). Another area that would be of great interest is the optimal sequencing of biologics for the management of psoriasis. The process of choosing a biologic is complex and involves considering patients' co-morbidities, characteristics, and preferences (263). With the influx of many novel biologics with varying mechanisms of action, clear guidelines on biologic-switching and optimal treatment sequencing are still lacking. It is well-known that biologic-experience can be a negative predictor of drug survival (240, 257, 304). Therefore, determining the optimal sequence of utilisation could be of great clinical benefit to patients.

In conclusion, this is the first Australian study to report on the drug survival of multiple new biologics. The findings of the study broadly confirm the international experience and validate current Australian guidelines on the use of biologics in psoriasis.

Supporting Information

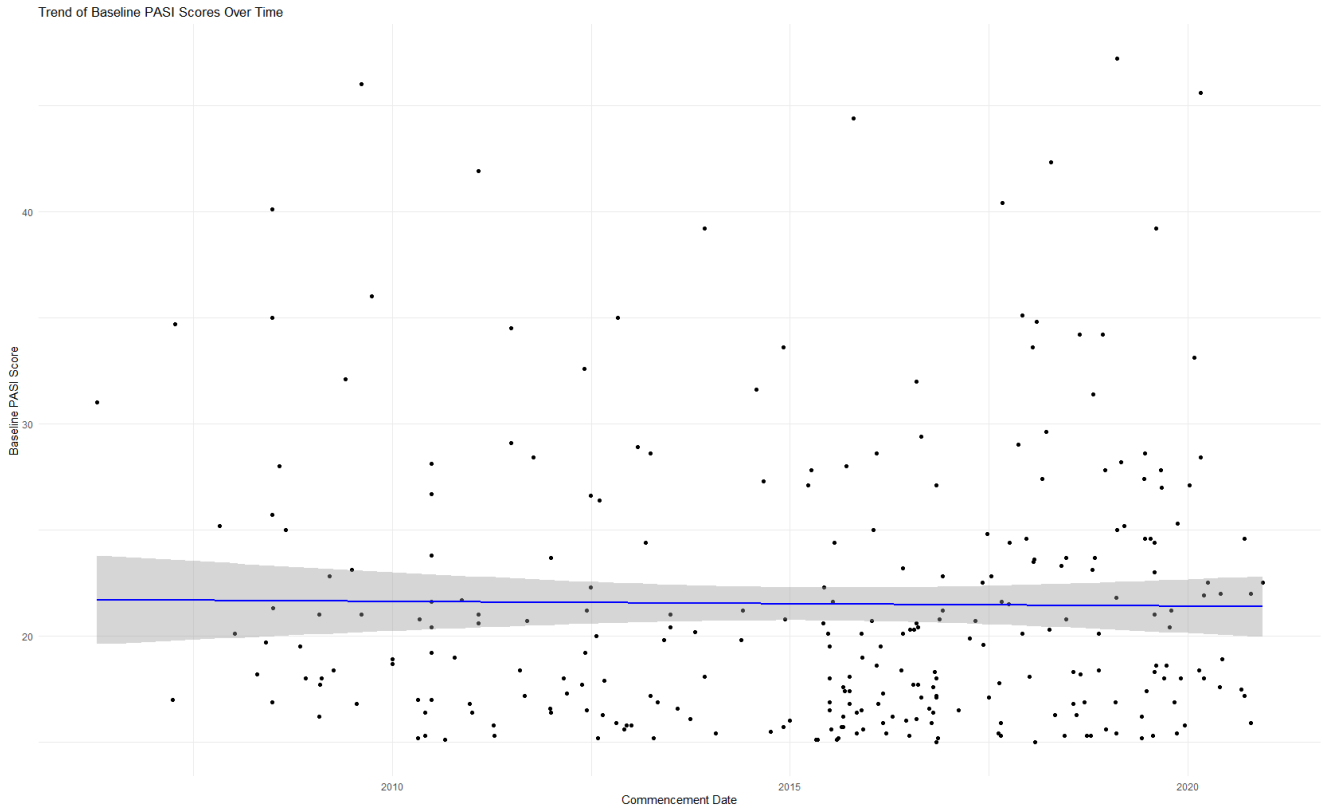

Figure S1. Baseline severity over time. This scatter plot displays the baseline PASI of all biologic-naïve patients on the y-axis plotted against the commencement date of biologic treatment on the x-axis. Each plot represents an individual patient's baseline PASI at the beginning of treatment. The blue line indicates a linear trend line, while the shaded grey area represents the 95% confidence interval for this trend.

Table S1. Number at risk

Biologic	0 months	12 months	24 months	36 months	48 months	60 months
Adalimumab	97	62	45	37	28	23
Infliximab	70	57	46	39	35	32
Etanercept	26	16	12	11	7	6
Ustekinumab	143	107	75	61	49	35
Secukinumab	100	81	56	38	25	5
Ixekizumab	59	45	32	12	3	3
Guselkumab	35	28	8	4	3	3
Risankizumab	36	0	0	0	0	0

Table S2: Reasons for discontinuation

Reasons for discontinuation	Adalimumab N = 97		Infliximab N = 70		Etanercept, N = 26		Ustekinumab, N = 143		Secukinumab, N = 100		Ixekizumab, N = 59		Guselkumab, N = 35		Risankizumab, N = 36		Overall, N=566	
	BN (n=51)	BE (n=46)	BN (n=44)	BE (n=26)	BN (n=20)	BE (n=6)	BN (n=86)	BE (n=57)	BN (n=48)	BE (n=52)	BN (n= 23)	BE (n=36)	BN (n=12)	BE (n=23)	BN (n=5)	BE (n=31)	BN (n=289)	BE (n=277)
Primary failure	1 (1.0%)	4 (4.1%)	0 (0.0%)	1 (1.4%)	2 (7.7%)	0 (0.0%)	5 (3.5%)	1 (0.7%)	1 (1.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	9 (1.6%)	9 (1.6%)
Secondary failure	4 (4.1%)	3 (3.1%)	2 (2.9%)	1 (1.4%)	2 (7.7%)	0 (0.0%)	1 (0.7%)	4 (2.8%)	3 (3.0%)	0 (0.0%)	1 (1.7%)	3 (5.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (2.3%)	11 (1.9%)
Lack of efficacy	10 (10.3%)	12 (12.4%)	6 (8.6%)	3 (4.3%)	8 (30.8%)	3 (11.5%)	9 (6.3%)	14 (9.8%)	3 (3.0%)	9 (9.0%)	1 (1.7%)	3 (5.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	37 (6.5%)	44 (7.8%)
Loss of efficacy	0 (0.0%)	4 (4.1%)	8 (11.4%)	2 (2.9%)	3 (11.5%)	0 (0.0%)	10 (7.0%)	6 (4.2%)	9 (9.0%)	9 (9.0%)	1 (1.7%)	4 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (5.5%)	25 (4.4%)
Psoriatic arthritis flare	3 (3.1%)	0 (0.0%)	1 (1.4%)	3 (4.3%)	0 (0.0%)	1 (3.8%)	6 (4.2%)	4 (2.8%)	3 (3.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	13 (2.3%)	11 (1.9%)
Adverse reactions	5 (5.2%)	2 (2.1%)	3 (4.3%)	3 (4.3%)	0 (0.0%)	1 (3.8%)	1 (0.7%)	0 (0.0%)	1 (1.0%)	3 (3.0%)	2 (3.4%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	12 (2.1%)	12 (2.1%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.4%)	2 (2.0%)	1 (1.0%)	1 (1.7%)	1 (1.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.9%)	5 (0.9%)
Others	6 (6.2%)	8 (8.2%)	13 (18.6%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	5 (3.5%)	4 (4.0%)	3 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	24 (4.2%)	18 (3.2%)
Total discontinued (n=279)	29 (29.9%)	33 (34.0%)	34 (48.6%)	15 (21.4%)	15 (57.7%)	5 (19.2%)	33 (23.1%)	36 (25.2%)	26 (26.0%)	29 (29.0%)	6 (10.2%)	13 (22.0%)	1 (2.9%)	2 (5.7%)	0 (0.0%)	2 (5.6%)	144 (25.4%)	135 (23.9%)

Chapter 3: Treatment sequencing and the factors contributing to biologic-switching

Abstract

The introduction of biologics to the management of psoriasis has resulted in a new treatment paradigm due to the relative safety and efficacy of biologic treatment. As newer biologics emerge, biologic-switching has become more common as patients and clinicians pursue higher levels of skin clearance and improved clinical outcomes. However, there is limited guidance on treatment sequencing. Data in an Australian setting is particularly sparse. This study thus describes the patterns of care across two tertiary dermatology centres in Australia and examines the factors that contribute to biologic-switching.

3.1 Introduction

Psoriasis affects 2.3%-6.6% of the population in Australia and poses a significant physical and psychosocial burden on patients affected by the disease (306). Biologics have shifted the landscape in the management of moderate-to-severe psoriasis over the past two decades. As newer biologics emerge, we have observed improved patient outcomes in terms of both skin clearance and patient-reported symptoms. This has resulted in a shift in patients' and clinicians' expectations, as goals of treatment have evolved to aim for complete skin clearance (198).

Previous studies into drug survival have demonstrated the safety and efficacy of various biologics in a real-world setting. However, when treatment failure occurs, there is limited guidance on the subsequent choice of biologic treatment (198). Due to the availability of multiple new biologics with excellent safety profiles, there are various possible options (198). The choice of sequencing may have therapeutic implications on efficacy and patients' quality of life. Thus, it would be beneficial to utilise real-world data to guide our choice of biologic treatment.

Overall, this study aims to provide insight into the patterns of care across two tertiary dermatology centres in Australia, and to provide preliminary evidence on treatment sequencing with the currently available biologics. The present study will also examine the factors that may contribute to biologic-switching, such as the absolute PASI on drug discontinuation, the velocity of treatment response, and the reasons for biologic-switching.

3.2 Methods

Data was retrospectively collected on patients who were seen in the outpatient psoriasis biologic clinics of two Dermatology clinics in Sydney, Australia (Royal Prince Alfred Hospital, Westmead Hospital). Inclusion into the study required: (i) Patients to be above the age of 18; (ii) A diagnosis of moderate-to-severe chronic plaque psoriasis; (iii) Patients must have had a review in the biologic clinics between April 2006 and December 2020.

Biologics investigated in this study included adalimumab, infliximab, etanercept, ustekinumab, secukinumab, ixekizumab, guselkumab, tildrakizumab and risankizumab. Each treatment course was

analysed separately. A treatment course is defined as a distinct period during which a patient received continuous treatment on a single unique biologic. A 'switch' was defined as patients who transitioned from one treatment course to another. These patients either switched to another biologic within the same drug class, referred to as an intra-class switch, or switched to a biologic from a different drug class, termed an inter-class switch. Patients who either remained on the same treatment or discontinued treatment were classified as those who did not switch treatment courses. Patients who had a gap of ≥90 days in treatment were also considered to have discontinued the drug. Treatment courses with alefacept, efalizumab and brodalumab were excluded, as they are not currently approved for use in Australia. Patients who were on clinical trials and patients with missing baseline PASI data were also excluded.

The follow-up protocol for patients who were started on a new biologic during the study period was routinely reviewed at least 12 weeks after commencement of the drug, then every 6 months thereafter.

Reasons for biologic-switching were classified as lack of efficacy, loss of efficacy, adverse effects, psoriatic arthritis flare, others, and pregnancy. A sample of patients paused biologic treatment as they were either anticipating pregnancy or were pregnant. A lack of efficacy refers to a lack of adequate clinical response to treatment during the initial 12-week follow-up visit, despite achieving PASI-75. A loss of efficacy refers to an initial response to treatment that was lost over time, despite maintaining PASI-75 throughout the treatment course.

This study was approved by the Western Sydney Local Health District ethics committee (HREC reference number 2019/ETH13159).

3.2.1 Statistical analysis

Sankey diagrams were used to represent biologic-prescribing patterns using R (version 4.2.1). The initial three lines of treatment were analysed. The Sankey diagrams reflect switches between biologics, continuation of treatment, and cessation of treatment.

Secukinumab was approved by the Therapeutics Goods Administration (TGA) for use in moderate-to-severe psoriasis in 2015. Therefore, the Sankey diagrams reflecting patterns of biologic-switching were further stratified into pre-2015 and post-2015. The last recorded PASI for each treatment course was analysed and stratified by drug class, biologic-naivete and whether the patient had discontinued or was still on the drug.

The velocity of treatment response was determined by assessing the number of patients who achieved PASI-75, -90, and -100 at the earliest possible time point. This analysis was performed until 180 days of treatment.

3.3 Results

3.3.1 Baseline characteristics

The baseline characteristics of the patients in the present study are summarised in Table 3.1. Data was collected from 340 patients across two centres, of which 264 patients met the inclusion criteria. The mean overall age of the cohort was 44.1 years, with females comprising 34.1% of the cohort. The mean baseline PASI at treatment initiation was 21.4. Patients who did not switch biologics had a higher mean age (45.3±14.4) compared to those who switched biologics (42.7±14.2). Furthermore, the baseline PASI of patients who did not switch biologics was 20.7±6.3 compared to 22.3±7.2 among patients who switched biologics. Notably, the rate of psoriatic arthritis was higher among patients who switched biologics (48.4%) compared to patients who did not switch biologics (24.6%).

Out of 476 treatment courses, 44.5% of patients switched biologic agents. The highest proportion of biologic-switching was observed among patients who were on TNF-α inhibitors (62.8%), followed by IL-12/23 inhibitors (43.7%) (Table 3.2).

There were 153 treatment courses on TNF-α inhibitors, 126 on IL-12/23 inhibitors, 135 on IL-17 inhibitors and 62 on IL-23 inhibitors (Table 3.2).

Table 3.1. Baseline characteristics of all patients from April 2006 to December 2020. Switch refers to patients who switched biologics; no switch refers to patients who did not switch biologics.

	Switch (n=122)	No switch (n=142)	Overall (n=264)
Age, mean (SD)	42.7 (14.2)	45.3 (14.4)	44.1 (14.4)
BMI, mean (SD)	33.2 (8.9)	29.6 (6.5)	31.3 (7.9)
Gender, no. (%)			
Male	75 (61.5)	99 (69.7)	174 (65.9)
Female	47 (38.5)	43 (30.3)	90 (34.1)
Baseline PASI, mean (SD)	22.3 (7.2)	20.7 (6.3)	21.4 (6.8)
Co-morbidities, mean (SD)	1.8 (1.8)	1.6 (1.6)	1.7 (1.7)
Smoker, no. (%)	48 (39.3)	62 (43.7)	110 (41.7)
Psoriatic arthritis, no. (%)	59 (48.4)	35 (24.6)	94 (35.6)

Table 3.2. Biologic switching patterns by drug class from April 2006 to December 2020.

Biologic-switching is represented by their different drug classes. Intra-class switch refers to the number of treatment courses that switched within the same drug class and inter-class switch refers to the number of treatment courses that switched from one drug class to another. No switch refers to the number of treatment courses that did not switch biologics.

Biologic by drug class	Intra-class switch, no. (%)	Inter-class switch, no. (%)	No switch, no. (%)	Total no. of treatment courses
TNF-α	26 (17.0)	70 (45.8)	57 (37.3)	153
IL-12/23	4 (3.2)	51 (40.5)	71 (56.4)	126
IL-17	9 (6.7)	48 (35.6)	78 (57.8)	135
IL-23	2 (3.2)	2 (3.2)	58 (93.6)	62

TNF: tumour necrosis factor; IL: interleukin;

3.3.2 Biologic-switching patterns across all treatment courses

Ustekinumab (n=80) and adalimumab (n=51) were the most commonly prescribed first-line drugs respectively across all treatment courses (Figure 3.1). Most of the biologic-naïve patients who were started on ustekinumab either continued treatment or were switched to either one of the IL-17 inhibitors (Figure 3.2). All biologic-naïve patients who were on guselkumab and risankizumab continued with their treatment (Figure 3.1)

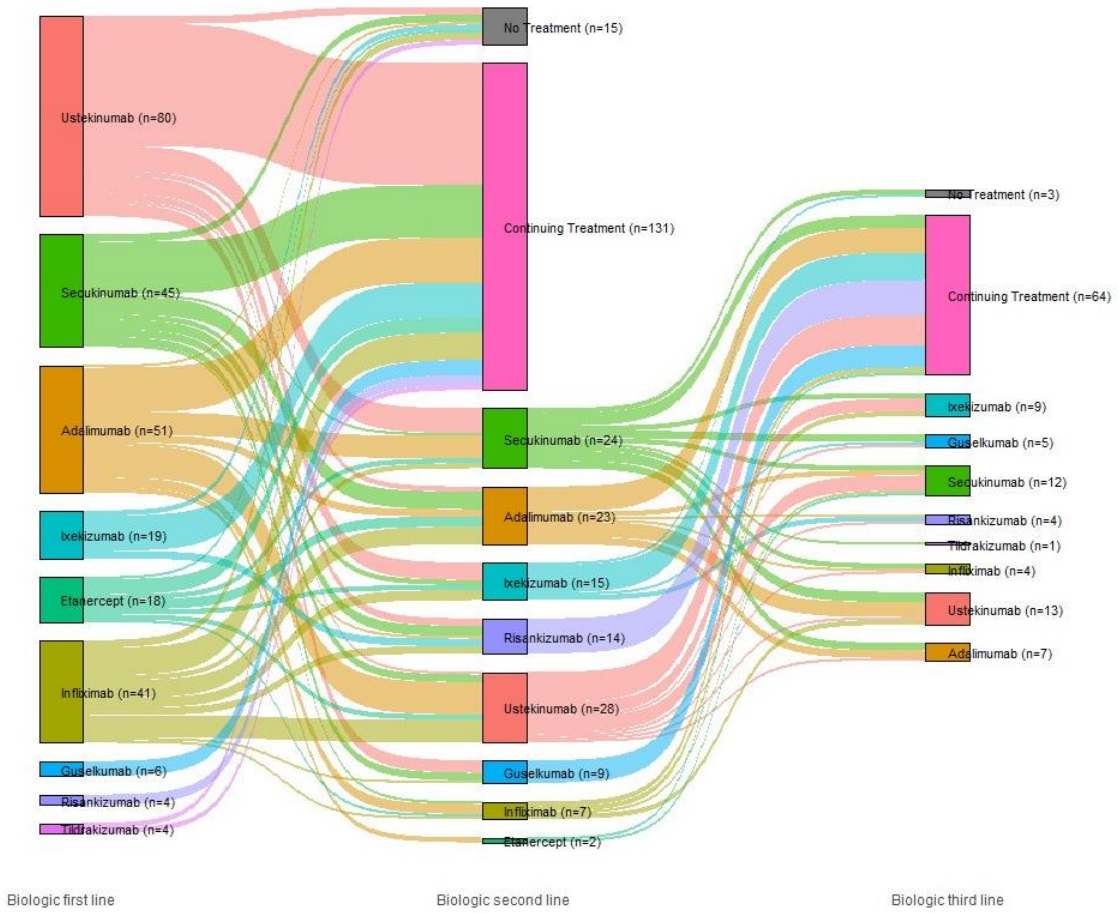

Figure 3.1. Sankey diagram representing patterns of care for all treatment courses from April 2006 to December 2020. Each column represents a line of treatment. Each bar represents the number of patients on each biologic. Continuing treatment refers to patients who continued their treatment. No treatment refers to patients who discontinued treatment but did not switch to another biologic.

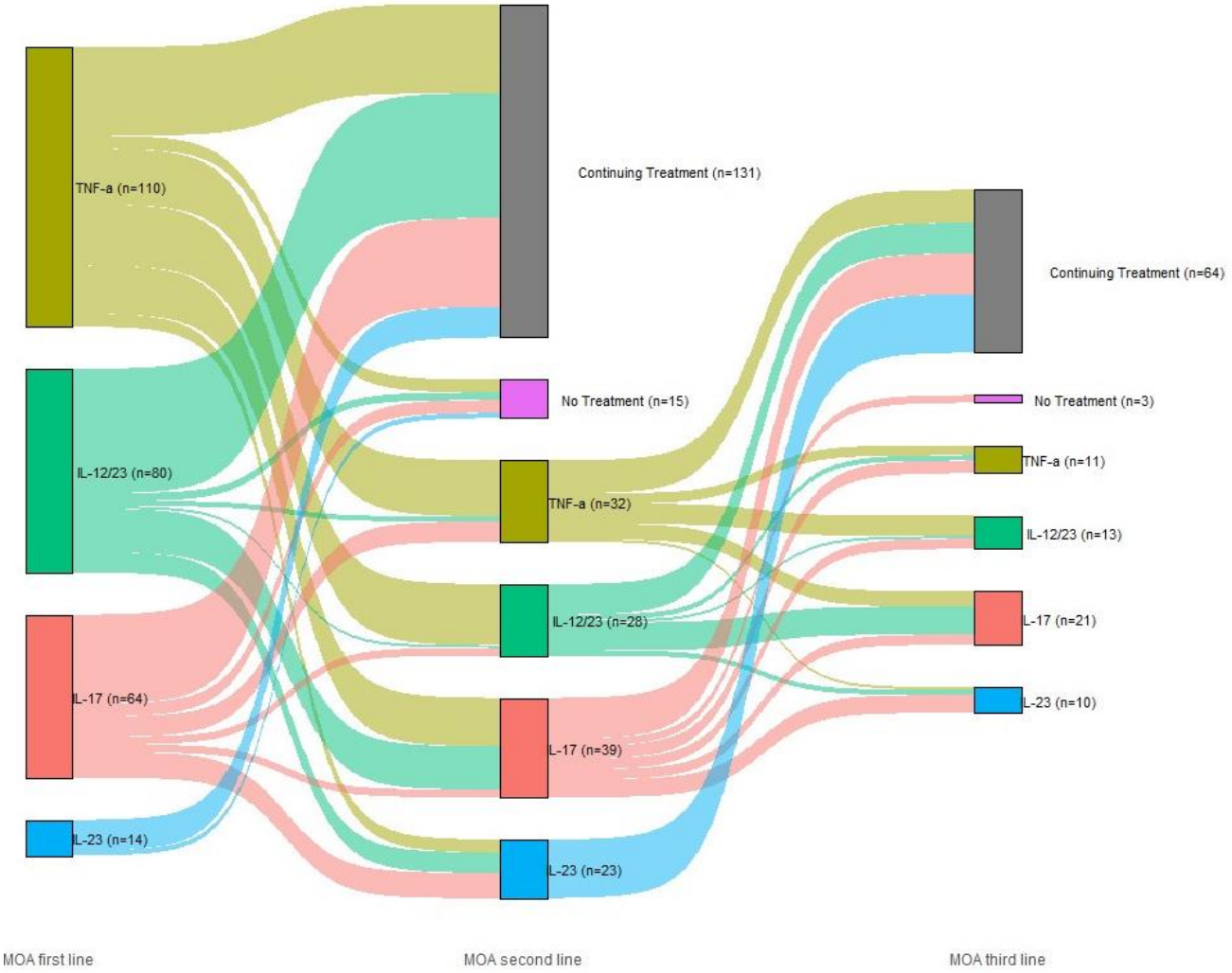

Figure 3.2. Sankey diagram representing patterns of care by the drug's mechanism of action across all treatment courses from April 2006 to December 2020. Each column represents a line of treatment. Each bar represents the number of patients treated with the listed drug class.

Among the biologic-naïve patients who discontinued therapy, patients who were on IL-23 inhibitors had the lowest absolute median PASI on discontinuation (2.0, IQR 1.4) (Table 3.3). Among the biologic-experienced patients who discontinued therapy, patients on IL-17 inhibitors had the lowest absolute median PASI on discontinuation (3.6, IQR 4.2). Among all the patients who continued their last recorded treatment, biologic-experienced patients on IL-17 inhibitors had the lowest absolute median PASI of 0.0. Of the 19 biologic-experienced patients on IL-17 inhibitors who continued their treatment and whose last recorded PASI was 0, 79.0% of these patients were on ixekizumab.

Table 3.3 Median absolute PASI on drug discontinuation vs continuation by drug class for all treatment courses. The median PASI of each drug class on discontinuation and on continuation are presented with their respective interquartile ranges.

Biologic class	**Median PASI on discontinuation (IQR)**		**Median PASI on continuation (IQR)**	
	BN	BE	BN	BE
TNF-α	3.2 (3.9)	3.6 (8.0)	1.2 (1.6)	1.2 (1.8)
IL-12/23	3.4 (4.6)	3.7 (5.1)	0.3 (1.7)	0.9 (1.8)
IL-17	3.0 (4.3)	3.6 (4.2)	0.7 (1.5)	0.0 (2.1)
IL-23	2.0 (1.4)	4.2 (12.0)	0.9 (1.4)	1.2 (2.4)

BN = Biologic-naïve; BE = Biologic-experienced; TNF=tumour necrosis factor; IL: interleukin; IQR: interquartile range.

3.3.3 Reasons for biologic-switching

The most common reasons for switching biologic treatment were a lack of efficacy, followed by a loss of efficacy (Table 3.4). The highest number of adverse events was seen among patients who were on TNF-α (n=13), followed by IL-17 inhibitors (n=5). Most patients who experienced adverse events from treatment with a TNF-α inhibitor underwent an inter-class biologic switch. Intra-class switching was less common among patients on IL-17 and IL-23 inhibitors. A breakdown of adverse effects leading to biologic switching is provided in Table S3.

Table 3.4 Reasons for switching biologics across all treatment courses. The reasons for biologic-switching are listed below and categorised by intra- vs. inter-class switching.

	Lack of efficacy	**Loss of efficacy**	**Adverse events**	**Psoriatic arthritis flare**	**Others**	**Pregnancy**
Intra-class switch						
TNF-α	10	2	2	2	4	6
IL-17	0	4	0	1	2	2
IL-23	1	0	0	0	1	0
IL-12/23	0	0	0	0	2	2
Inter-class switch						
TNF-α to						
IL-12/23	9	15	4	0	5	0
IL-17	9	8	5	2	5	0
IL-23	1	3	2	0	2	0
IL-12/23 to						
TNF-α	3	1	0	1	0	0
IL-17	14	11	0	6	1	0
IL-23	8	4	0	1	1	0
IL-17 to						
TNF-α	6	3	2	2	1	0
IL-12/23	4	3	2	1	0	0
IL-23	5	18	1	0	0	0
IL-23 to						
TNF-α	0	1	0	0	0	0
IL-12/23	0	0	0	0	0	0
IL-17	0	0	1	0	0	0
Total (n=212) no. (%)	70 (33.0)	73 (34.4)	19 (9.0)	16 (7.6)	24 (11.3)	10 (4.7)

3.3.4 Biologic-switching before and after 2015

Between 2006 and 2015, 81.1% of biologic-naïve patients were treated with TNF-α inhibitors (Figure 3.3a). No preference was observed for intra- or inter-class switching after treatment with a TNF-α inhibitor, as a similar number of patients were switched to either another TNF-α inhibitor or an IL-12/23 inhibitor. After 2015, the proportion of biologic-naïve patients on TNF-α inhibitors decreased to 16.5% in favour of IL-12/23 and IL-17 inhibitors (Figure 3.3b). Intra-class switching of biologic-naïve patients on TNF-α inhibitors decreased from 27.9% before 2015, to 6.9% after 2015.

Among 176 biologic-naïve patients since 2015, 37.5% (n=66) were commenced on an IL-17 inhibitor. Biologic-experienced patients at this time were mostly switched to either an IL-23 inhibitor or an IL-17 inhibitor for their second and third lines of treatment.

Notably, since the IL-23 inhibitor, guselkumab, was approved for use in moderate-to-severe chronic plaque psoriasis in 2019, 30.4% (n=14) of biologic-naïve patients from 2019 onwards were commenced on an IL-23 inhibitor.

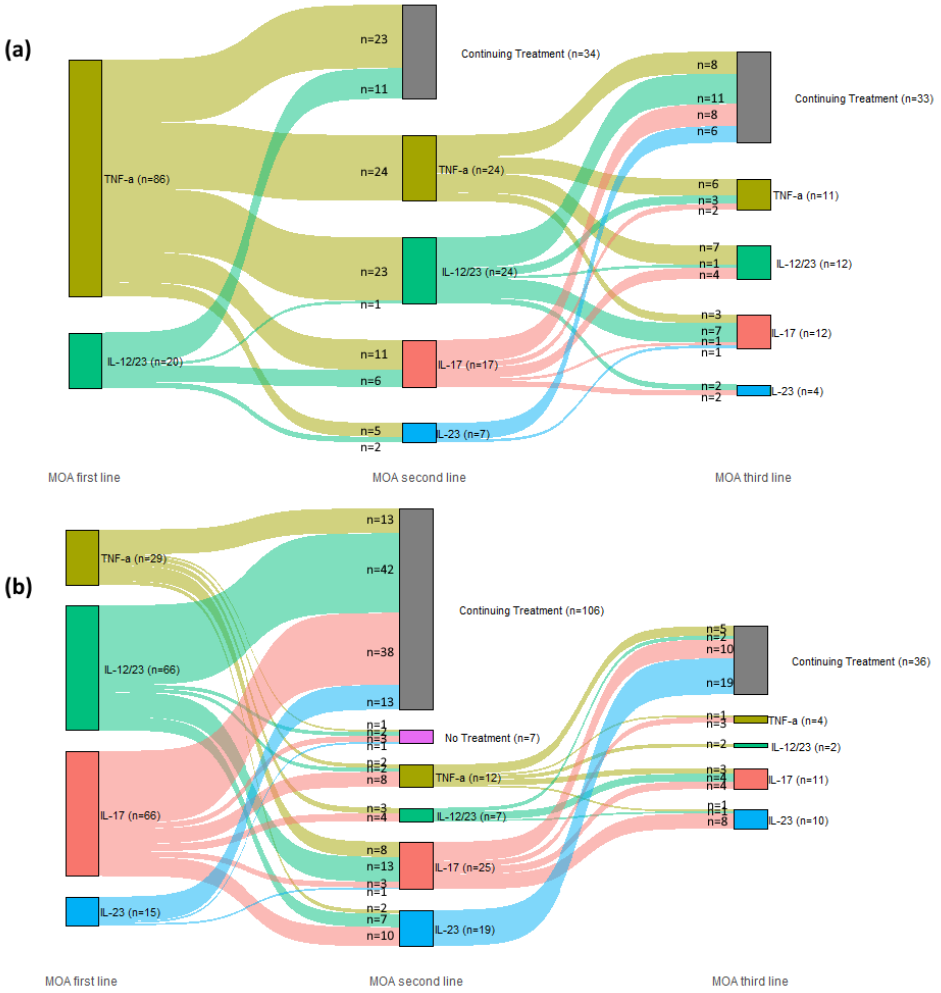

Figure 3.3. Sankey diagram reflecting biologic-switching patterns by the drug's mechanism of action. Each column represents a line of treatment. The diagram reflects up to three lines of treatment, and it reflects biologic-switching patterns, patients who continued treatment, and patients who stopped treatment **(a)** Sankey diagram of biologic-switching between 2006 and2015. **(b)** Sankey diagram of biologic-switching after 2015.

3.3.5 Speed of treatment response

Patients who were on IL-17 inhibitors, regardless of whether they were biologic-naïve or experienced, demonstrated the most rapid short-term response as measured by PASI-75, -90, and -100 (Figure 3.4). Biologic-experienced patients who were on IL-23 inhibitors also displayed a relatively rapid response as measured by PASI-75 and PASI-90 (Fig 4b & 4d). Patients on IL-12/23 inhibitors generally demonstrated the slowest response to treatment.

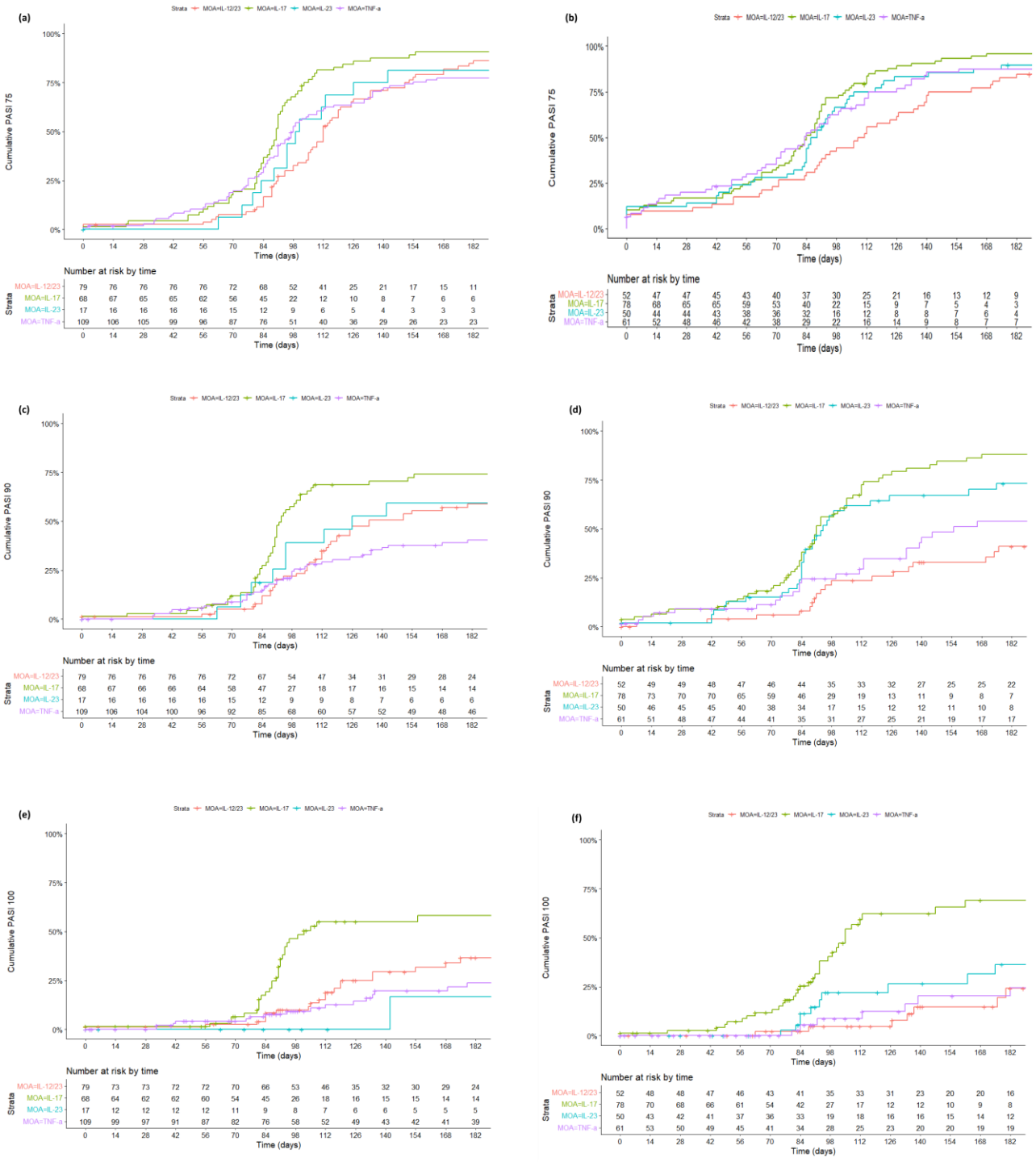

Figure 3.4 Velocity of treatment response as measured by PASI-75, -90, and -100. (a) Velocity of treatment response as measured by PASI-75 among biologic-naïve patients. **(b)** Velocity of treatment response as measured by PASI-75 among biologic-experienced patients. **(c)** Velocity of treatment response as measured by PASI-90 among biologic-naïve patients. **(d)** Velocity of treatment response as measured by PASI-90 among biologic-experienced patients. **€** Velocity of treatment response as measured by PASI-100 among biologic-naïve patients. **(f)** Velocity of treatment response as measured by PASI-100 among biologic-experienced patients.

3.4 Discussion

This study demonstrates for the first time the sequencing of biologics in the treatment of psoriasis within an Australian setting. This significantly expands on prior literature in this area, particularly regarding the newer biologics. The study also provides guidance on sequencing by demonstrating the factors related to biologic-switching such as the relative velocities of each drug class and their clinical efficacy. Due to the paucity of information regarding treatment sequencing in the literature, this study offers real-world patterns of care that will provide insight into possible sequencing options.

The present study examined the patterns of care across two major tertiary centres in Australia. In this study we demonstrated clinicians' preferences and the shift in patterns of care as newer biologics became available. Overall, ustekinumab and adalimumab were the most frequently prescribed first-line biologics. Patients on these biologics were subsequently mostly switched to IL-17 inhibitors (Fig 1). Prior to 2015, majority of the biologic-naïve patients were treated with TNF-α inhibitors (Fig 3a). However, after the introduction of secukinumab in 2015, we observed an increase in the proportion of biologic-naïve patients who were instead commenced on either ustekinumab or an IL-17 inhibitor (Fig 3b). Furthermore, most patients who failed their first line of treatment were switched to the IL-17 and IL-23 inhibitors over the TNF-α inhibitors and ustekinumab. Notably, after 2015, the IL-17 inhibitors were the most frequently prescribed in the second and third lines of treatment. This reflects patients' and clinicians' willingness to switch biologic therapies as newer biologics become available, in keeping with recommendations from the literature (186, 198, 307). A previous large-scale study in France comprising 2153 patients across 41 French dermatology centres demonstrated similar findings (308). After the introduction of the IL-17 inhibitors in France, there was a similar increase in uptake of IL-17 inhibitors, and a concomitant decrease in the prescription of TNF-α inhibitors (308).

A preference for switching to the newer biologics may also be partially explained by their excellent clinical efficacy and safety profile. Indeed, the clinical outcomes for patients who were on IL-17 inhibitors were promising. Biologic-experienced patients who were treated with IL-17 inhibitors and who have continued with their current treatment had a median absolute PASI of 0 (Table 3.3). Furthermore, the IL-17 inhibitors have demonstrated the most rapid treatment response, as patients on

IL-17 inhibitors achieved PASI-75, -90, and -100 in the shortest timeframe compared to the other drug classes (Figure 3.4). These findings are consistent with other studies in the literature, as IL-17 inhibitors such as ixekizumab have demonstrated shorter clinical response times compared to other biologics including the IL-23 inhibitors (273, 309, 310). However, the data from these studies were derived from clinical trials. This study therefore adds to the literature as it illustrates an important clinical parameter within a real-world setting. To our knowledge, this is the first Australian study that has compared the speed of treatment response of the currently available biologics. Although this factor is often overlooked, it is clinically meaningful, as patients frequently cite short clinical response times as a valuable treatment goal (269, 311, 312). Furthermore, a rapid clinical response is useful in the management of acute cases of psoriasis, to provide quick symptomatic relief.

The IL-23 inhibitors also showed a relatively rapid clinical response rate among biologic-experienced patients. However, biologic-naïve patients on IL-23 inhibitors had a slower clinical response compared to ustekinumab and IL-17 inhibitors. This discrepancy may be due to our small sample size of biologic-naïve patients on IL-23 inhibitors. Furthermore, our analysis of the Sankey diagrams indicates that both biologic-naïve and biologic-experienced patients who were on IL-23 inhibitors had low attrition rates, which is consistent with our previous drug survival studies. This may reflect the IL-23 inhibitors' good long-term clinical efficacy and safety. However, further longitudinal data is required to fully elucidate the long-term efficacy and safety of these newer biologics.

This study has also assessed the reasons for biologic-switching. It was demonstrated that most of the patients who underwent an intra-class switch with a TNF-α inhibitor experienced an initial lack of efficacy. However, patients who experienced a loss of efficacy over time were more likely to switch to another drug class. One possible reason for this may be related to immunogenicity. It is theorised that a loss of clinical response occurs with TNF-α inhibitors due to the development of anti-drug antibodies (192, 313). Biologic-switching to a second TNF-α inhibitor has subsequently been associated with poorer outcomes (313). This observation has been extensively investigated in the fields of rheumatology and gastroenterology, with similar outcomes (314-316). Intra-class switching was notably uncommon among IL-17 inhibitors, as most patients were switched to IL-23 inhibitors

due to a loss of efficacy. Previous studies have demonstrated that patients who switched from one IL-17 inhibitor to another were able to achieve a meaningful clinical response (293). However, no known comparisons have been made from examining the outcomes of intra- and inter-class switching from an IL-17 inhibitor. Thus, further studies are required to investigate the safety and effectiveness of intra- and inter-class switching in IL-17 inhibitors. It is also noteworthy that the median absolute PASI on discontinuation generally exceeded 3.0, while on continuation it was less than 1.2. This likely reflects patients' limited tolerance for a PASI above 3.0, and a threshold of 1.2, where patients consider treatment adequate.

This study had the following limitations. Firstly, we were limited by a small sample size, and we were therefore unable to characterise the patterns of care past three lines of treatment. Our analysis of treatment sequencing was thus primarily classified by mechanism of action. Secondly, there was limited information on some of the newer biologics such as the IL-17 and IL-23 inhibitors. Therefore, future studies can be focused on larger-scale and long-term data which includes the currently available biologics to elucidate ideal treatment sequencing for the use of clinical guidelines.

To our knowledge, this is the first Australian study that characterises the patterns of care in the treatment of moderate-to-severe psoriasis, involving the newest biologics. We have demonstrated that biologic-switching is a common practice in our centres, and there has been a favourable uptake of the new IL-17 and IL-23 inhibitors. We have also shown that the IL-17 inhibitors have a more rapid onset of action compared to the other biologics, with excellent skin clearance. Rapid skin clearance is often cited by patients as an important treatment goal (269, 270, 311). Patients and clinicians often have incongruent views of treatment goals, leading to patient dissatisfaction and poor adherence to treatment (268). Thus, the data from this study can be used to inform decisions about biologic-switching in keeping with patients' treatment goals. This study also serves as a source of preliminary information for further larger-scale studies in the future which will shape clinical guidelines on treatment sequencing.

Supporting information

Table S3: Description of adverse events leading to biologic-switching by mechanism of action

Adverse events	**TNF-α**	**IL-17**	**IL-23**
Cardiac and vascular disorders			
Myocardial infarction	1	0	0
Immune system disorders			
Allergic reaction	5	0	0
Sarcoidosis	1	0	0
Skin and subcutaneous tissue disorders			
Rash	3	2	0
Erythema nodosum		1	0
Vitiligo	1	0	0
Hidradenitis suppurativa	0	0	1
Investigations			
Eosinophilia	0	2	0
Elevated double-stranded DNA	1	0	0
Nervous system disorders			
Demyelinating event	1	0	0

Chapter 4: Summary and future directions

The main objective of this thesis was to assess the drug survival of the currently available biologics for the treatment of moderate-to-severe psoriasis in an Australian setting. Drug survival data guides clinical management as it reflects the safety and efficacy of biologics in a real-world setting. Furthermore, there is a paucity of data reflecting outcomes from a local cohort. Expanding on our study of the management of psoriasis in an Australian setting, the present study also examined the patterns of care across two tertiary centres. The findings encapsulated by this thesis provide insight into biologic-switching and may serve as preliminary data for future studies to expand on, to inform clinical guidelines on treatment sequencing.

4.1 Summary of findings

This thesis showed that guselkumab, followed by ixekizumab, consistently demonstrated the highest survival rates from the first year of follow-up through to the fifth year. The rates of adverse events were also low among the newer biologics. This confirms the safety and efficacy of the newer biologics in a real-world setting.

Furthermore, ixekizumab, followed by guselkumab, demonstrated the highest rates of PASI-75, -90, and -100. The IL-17 inhibitors, followed by the IL-23 inhibitors also demonstrated the most rapid skin clearance. This provides objective evidence of their clinical efficacy.

Lastly, this thesis demonstrated a shift in patterns of care as the IL-17 inhibitors became available, reflecting clinicians' willingness to trial newer biologics. Patients who were biologic-experienced and switched to an IL-17 inhibitor demonstrated the highest rates of complete skin clearance. Hence, this illustrates the safety and effectiveness of switching to the newer biologics.

Overall, the findings of this thesis are significant because clinicians rely on drug survival data to guide their practice. This study has also demonstrated objective evidence of the safety and clinical efficacy of the newer biologics in a real-world setting. Furthermore, the present study adds to the literature as data on treatment sequencing is sparse. This thesis has thus provided evidence of the safety and efficacy of biologic-switching to the newer biologics.

4.2 Strengths and limitations

To our knowledge, this is the first Australian study that demonstrates the drug survival of the newer biologics. The data was extracted from two tertiary centres translating to a relatively large cohort in the local setting. This larger data set was able to provide greater insights to clinicians and patients. Prior to this study, data on treatment sequencing particularly in the context of newer biologics was sparse. This study contributes valuable information on the effectiveness of switching to the newly available biologics.

However, this study had the following limitations. Firstly, the study was limited by a small sample size which affected its statistical significance. Secondly, there was a lack of long-term data on the more recently available biologics due to their novelty. Thirdly, this thesis looked at data in a retrospective manner compared to a prospective study and was therefore more prone to bias. Finally, this study had a significant focus on objective clinical outcomes. However, patients' subjective opinions on their symptoms and experiences play a central role in clinical decision-making. Therefore, although drug survival data broadly reflects patients' experiences, it would be helpful to incorporate quality-of-life measures into their drug survival studies.

4.3 Future directions

In view of the considerations above, there are several avenues for future studies to expand upon. Firstly, larger-scale and longer-term data would provide more clarity on the drug survival of some of the newer biologics such as risankizumab and tildrakizumab. Secondly, future studies could contextualise drug survival studies with the use of quality-of-life instruments. Lastly, our study into biologic-switching of the newer biologics has provided preliminary data for future studies to build upon. Further work in this area with larger datasets could potentially lead to the development of guidelines for ideal treatment sequencing.

4.4 Conclusions

Drug survival data provides clinicians with useful information on the safety and efficacy of drugs in a real-world setting. We have examined the drug survival of the most recently available biologics and

contextualised this data to an Australian population. The factors affecting drug survival and the choice of biologic has also been assessed further in this thesis.

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