No evidence or no alternative? Taking responsibility for off-label prescribing

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ABSTRACT

Recombinant activated factor VII (rFVIIa) is registered for patients with rare haematological disorders, but is used 'off-label' in many other situations, including intracranial haemorrhage, cardiac surgery, trauma, transplantation and prostatectomy. Lack of systematic evidence to support these off-label uses has not slowed the growth of off-label prescribing of rFVIIa. We use the case of rFVIIa to illustrate the issues raised by off-label prescribing, and the kind of impasse that can arise when views about evidence, expertise and clinical necessity are in conflict. We argue that clinicians, hospital drug committees and regulators all need to acknowledge the complexity of prescribing decisions, and ensure that decisions to prescribe off-label are sufficiently justified.

Introduction

'Off-label prescribing' refers to the prescription of a pharmaceutical agent in a manner that is not consistent with indications approved by a regulatory agency, such as the Food and Drug Administration in the United States or the Therapeutic Goods Administration (TGA) in Australia. The distinction between on-label and off-label prescribing is essentially a statement about evidence and authority. 'On-label' uses are those that have been determined following formal assessment of safety and efficacy data from clinical trials according to standards demanded by the drug regulator. When a clinician prescribes a medication contrary to approved indications (i.e. for a different indication, patient age range, dose or route), this constitutes an off-label use.1

In recent years, off-label prescribing has attracted significant debate. On the one hand, it is argued that off-label prescribing can promote clinical innovation and provide options for patients for whom there are no other alternatives.2,3 Arguments in favour of off-label prescribing also note that adding new information to a label is a costly and time-consuming process. Thus, while it is often in a drug company's interests to extend the indications for its products, information that could be beneficial to physicians and patients might in some cases be of only limited value to the pharmaceutical industry, and therefore unlikely to ever be added to the label. Indeed, in some cases supporting research into off-label indications may be counterproductive to the industry as more controlled studies might negate the

efficacy claims that smaller, less formalised studies may make. On the other hand, a number of concerns have been raised about off-label prescribing, including that it is not (always) evidence based, that it undermines the regulatory system, that it is costly, that it puts patients at risk2,3 and that it results from the promotional activities of pharmaceutical companies anxious to extend the market for their product.4 It is also claimed, although very difficult to prove, that excessive off-label drug use could impact on pharmaceutical innovation as physicians may be less likely to enrol patients in clinical trials of investigational drugs if patients have off-label treatment options.5 Those with concerns about off-label prescribing have generally supported robust controls of off-label drug promotion and advertising, and have called for measures to further restrict the ability of physicians to prescribe drugs off-label.6,7

Off-label prescribing is not an uncommon event,1,8 with recent research demonstrating extensive off-label prescribing of agents, including anti-epileptics (used as mood stabilisers and to treat neuropathic pain), anti-psychotics (used to treat delirium) and anti-rejection medications used for (non-transplant-related) immunological conditions. An extensive study of office-based physicians in the United States examined prescribing patterns for 160 medicines and showed that 21% of all prescriptions were off-label, 73% of which were classified by the authors as having little or no scientific support.8 In a study of a specialist oncology centre in Australia, 35% of prescriptions were found to be off-label.9 Off-label prescribing is also common in geriatric medicine10 and obstetrics,11 and in the treatment of patients with rare diseases.12 Off-label prescribing is particularly common in paediatrics, with one study suggesting that well over half of all paediatric prescriptions are off-label.13 This is not surprising given that many medicines are not tested in children and cannot, therefore, be formally registered for paediatric indications.

In many instances, clinicians may not be aware that they are engaging in off-label prescribing. A study aimed at testing the knowledge of prescribers about off-label indications of commonly-prescribed drugs found that in only just over 50% of cases could physicians accurately identify an off-label use and that in 41% of cases, physicians believed that at least one drug-indication pair that had uncertain or no supporting evidence was regulator approved.14

The case of off-label prescribing of recombinant factor VIIa (rFVIIa) provides a good illustration of these issues, and of the impasse that can result from disagreements about off-label prescribing.

The story of off-label rFVIIa

rFVIIa (NovoSeven – NovoNordisk; generic name: epticog alpha) is a powerful coagulant. It is registered by the therapeutic goods administration (TGA) for the treatment of haemorrhage in factor VII deficiency, Glanzmann's thrombasthaenia, and in patients with haemophilia with inhibitors to factor VIII or IX. Because factor VII is a protein that is involved in normal coagulation, rFVIIa is also widely used off-label in a broad range of settings in which prevention or control of bleeding is paramount, such as cardiac surgery, intracerebral haemorrhage, postpartum haemorrhage and thoraco-abdominal trauma.15–19 Recent studies in the United States have noted a dramatic increase in off-label use of rFVIIa, which was almost non-existent in 2000 and now constitutes more than 97% of usage of rFVIIa.20 The story of this dramatic rise in off-label prescribing – and the involvement of its

manufacturer – is illustrative. In 1999, a research letter was published in the Lancet, which reported that traumatic bleeding had been successfully treated with rFVIIa.21 Referenced in this letter was a symposium held the same year by the manufacturers of the drug (Novo Nordisk) on the treatment of bleeding and thrombotic disorders. At this symposium it was reported that rFVIIa had been used for a range of indications, including cardiac surgery. In the following years, a series of articles touting the effectiveness of rFVIIa in controlling bleeding in traumatic haemorrhage,22 some cardiac surgery,23 and severe bleeding associated with disseminated intravascular coagulation24 were published. Around this time, the off-label prescribing of rFVIIa began to rise dramatically.20 Published studies of the efficacy of off-label rFVIIa were conflicting, with some studies suggesting that rFVIIa was effective in the management of intracerebral haemorrhage, and bleeding in cardiac surgery, liver surgery, postpartum haemorrhage and trauma, and others suggesting that it had no benefit.25,26 Early studies of the safety of off-label rFVIIa, particularly with respect to its likelihood of causing thromboembolic events, were also contradictory.27,28 Despite uncertainty regarding the risks and benefits of rFVIIa, off-label prescribing has risen dramatically over the last decade, with some estimates suggesting that off-label prescribing of rFVIIa has increased 140-fold over this time.20

Importantly, however, recent systematic reviews and meta-analyses of the off-label use of rFVIIa for cardiac surgery, intracranial haemorrhage, trauma, liver transplant and prostatectomy, have shown that it does not lead to a reduction in overall mortality,29,30 but may be associated with a small (and generally non-significant) reduction in haematoma expansion in intracerebral haemorrhage and adult respiratory distress syndrome in trauma. These reviews have also noted an increase in the risk of arterial thromboembolism when rFVIIa is used off-label – particularly in cardiac surgery and intracerebral haemorrhage.29 While most studies included in these reviews have been conducted in the United States and Western Europe, the results are relevant to practice in Australia and New Zealand as research from Australia has established that rFVIIa is widely prescribed in Australian hospitals – particularly in cardiac surgery and trauma.31

The authors of the most recent systematic review29 and the editorial that accompanied it32 concluded that off-label use of rFVIIa is unwarranted and that rFVIIa should only be prescribed off-label in the context of clinical trials. This conclusion, however, has been met with significant resistance from a subset of clinicians.33,34 The arguments given for and against off-label use of rFVIIa illustrate both the reasons why physicians might prescribe off-label and the limitations of systems of evidence that fail to take account of the reasons why physicians prescribe the medications they do.

Arguments for and against off-label use of rFVIIa

Those in favour of off-label prescribing of rFVIIa generally argue that they and their colleagues have observed clinical benefit when using rFVIIa, that surrogate end-points, such as reductions in re-operation or blood loss may be as significant as overall mortality, and that observations made in specific clinical contexts might be more relevant than the composite results of clinical trials. They also make reference to the fact that they have little else to offer their patients in situations of overwhelming blood-loss, and that ‘even if the safety data from existing randomised trials do apply . . . this risk is likely dwarfed by the risk of allowing blood loss to continue unabated’.33 Opponents of off-label prescribing of rFVIIa, on the other hand, argue that evidence-based medicine should trump both ‘emotion’ and clinical experience, and that composite evidence provided by a systematic review should

take precedence over the results of individual studies. Indeed, Jerry Avorn and Aaron Kesselheim, the authors of an editorial accompanying the systematic review in the Annals of Internal Medicine argued that, in light of emerging evidence, 'physicians who persist in (using rFVIIa off-label) in the face of clear evidence of inutility and harm could be subject to civil action by the affected patients or their heirs.'32 In their editorial Avorn and Kesselheim, like others before them, also made note of the high costs of rFVIIa (in Australia, the current price of rFVIIa is $1169 per 1 mg, and doses range from 50 to 100 mcg/kg, so for a 70 kg man a single dose of rFVIIa would cost between $4091 and $8183, and two doses would cost $8183 to $16 366) and the possible role of the manufacturer (Novo Nordisk) in promoting off-label use of rFVIIa. Novo Nordisk was sanctioned by Medicines Australia in 2004 for inappropriate marketing of rfVIIa35 and recently settled (for $25 million) a civil lawsuit for improper marketing of rFVIIa, appearing to vindicate Avorn's and Kesselheim's contention that in this case, as in many others, off-label prescribing may occur as a direct result of the promotional activities of the pharmaceutical industry.36 A recent study published in 2010 by Spurling et al. supports this view, having observed a correlation between industry promotion and prescribing patterns.37

Implications: taking responsibility for off-label prescribing

The case of rFVIIa illustrates that debates about off-label prescribing are not simply a matter of different interpretations of data from clinical trials, but occur as a result of the complex interplay of different influences on prescribing. It is unlikely that the debate about off-label prescribing will ever be fully resolved as clinical trials and regulatory labels will never be able to capture all possible uses of a medicine for all possible patient groups.

What matters more is that all stakeholder groups are aware of the issues surrounding off-label prescribing, and of their responsibilities for ensuring that off-label prescribing is as safe, effective and cost-effective as possible.

First, professional bodies have a responsibility for identifying instances of off-label prescribing and generating clinical practice guidelines that take account of off-label uses of medicines. However, just as it would be impossible to approve a drug for all the medical conditions it might treat, so too it would be impossible to develop clinical guidelines for every possible off-label use. For this reason, clinicians and hospital drug committees also have an important role to play.

Clinicians need to be conscious of the fact that they often prescribe off-label and that all such decisions can have serious implications – particularly when evidence of efficacy and/or safety is lacking. Once this has been acknowledged, clinicians will be in a better position to reflect on their own prescribing practices and ask themselves: 'Am I privileging the values of evidence-based medicine, or am I privileging other factors, such as common professional practice, clinical impression, physiological rationale?' And 'To what degree has my decision to prescribe this agent been influenced by drug company marketing?' Whatever the answer, it is then the clinician's responsibility to acknowledge the implications of his or her decision for the patient as well as for the healthcare system and (re)consider whether their off-label use of this medication is justifiable. The clinician also needs to consider whether and how the patient is informed about off-label use – a complex ethical and legal issue given that some off-label uses are supported by substantial bodies of evidence whereas others are closer to being 'experimental'.1 In this regard, it is noteworthy that legal analysis suggests that although off-label prescribing may increase the chance of liability, this can be reduced by taking appropriate measures such as: informing the patient that the drug is being used

off-label; ensuring the motivation for use is in the best interest of the patient; basing the decision on sound expert opinion; supporting use with reputable peer-reviewed literature; and ensuring the decision would be generally supported by local colleagues.12,38 Given these complexities, some have argued that the role of clinical pharmacologists should be strengthened as they are best positioned to make a judgement about the most appropriate and cost-effective treatment options.39

There is also an important role for hospital drug committees. While drug committees currently provide an important check on off-label prescribing of medications, particularly expensive medications, there is a pressing need to clarify and standardise the criteria for assessment of requests for off-label prescribing. And, as is the case with the decisions made by individual clinicians, these criteria must acknowledge that published evidence is not always complete or adequate (i.e. that lack of evidence is not evidence of lack) and that off-label prescribing is driven not only by evidence but by clinical necessity, physiological and therapeutic rationale and by the drive both to innovate and to provide care for people for whom there are few alternatives. But while clinicians and hospital drug committees are immediately responsible for the day to day decisions about off-label prescribing, it is also up to regulators to take a broader view and to ensure that off-label prescribing in the absence of high quality evidence and/or another compelling rationale is managed appropriately. The civil lawsuit against Novo Nordisk underscores the need for better monitoring of off-label drug uses and pharmaceutical industry promotion of off-label prescribing. This should aim at identifying and investigating any dramatic unexplained increases in off-label prescribing before such practices diffuse throughout, and become entrenched within, the system. The medical community and health regulators could work together to establish such mechanisms.

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