Biosimilars in inflammatory bowel disease

Cost savings are welcome but evidence supporting equivalence of biosimilar and originator drugs is currently limited

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The management of inflammatory bowel disease has undergone major changes in the last decade with the availability on the Pharmaceutical Benefits Scheme (PBS) of targeted biological therapies. The first of these was the anti-tumour necrosis factor α (anti-TNF-α) monoclonal antibody infliximab, followed by another anti-TNF-α antibody adalimumab, and, more recently, the first gut-specific T-cell trafficking inhibitor vedolizumab, an anti-α-4 β-7 integrin monoclonal antibody. These drugs have resulted in a shift in the management paradigm from symptom control and the minimisation of exposure to corticosteroids to now aiming for healing of the intestinal mucosa, prevention of damage and subsequent disability.[1]

The development of biologic medication is comparatively long and the manufacturing process very expensive, resulting in a high cost for these agents.[2] In Australia, the most expensive single drug in absolute dollar value for the 2015 financial year was adalimumab, with biologic agents making up five of the top eight most costly drugs and accounting for over 12% of the total PBS spend.[3] Given the increasing incidence of diseases that may be best managed by biologic agents, and the prolonged duration of therapy involved, the costs of these drugs are rising annually. These cost increases could pose a significant risk to the sustainability of the PBS system.

The patents for the initial biologic agents are starting to expire, which has led to the development of what are known as biosimilar versions of the originator product. These competitor drugs have created pressure to reduce the cost for the health system. The first biosimilar to infliximab was listed on the PBS in December 2015.

Biologic therapies are very different from chemically synthesised drugs, typically being large protein-containing agents produced from recombinant DNA and cell culture techniques, with complex post-translational modification and glycosylation. The technique of production can result in significant variability even between batches of production and requires strict quality assurance and in vitro assessments.[4] The Therapeutic Goods Administration (TGA) has harmonised with and adopted a number of the guidelines of the European Medicines Agency regarding the assessment and approval of biosimilar medicines. To be considered a biosimilar medicine in Australia, the new product must have "demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety".[4] Despite this, these drugs are not considered to be identical or to have demonstrated bioequivalence with the originator biological medicine.

The major difference in the approval process between an originator drug and a biosimilar is that if the originator drug has more than one indication, the efficacy and safety

of the biosimilar may only need to be demonstrated in one indication and this will be extrapolated to the other disease indications in which the originator drug is approved. The randomised controlled trials for the biosimilar infliximab CT-P13 (now commercially available in Australia) were only required in ankylosing spondylitis and rheumatoid arthritis and not Crohn disease or ulcerative colitis.[5,6] The listing for the biosimilar infliximab on the PBS covers all the indications of the originator infliximab.

Cost savings accompany the listing of biosimilar agents on the PBS, with a mandated 16% drop in the PBS rebate and a move from the F1 to F2 formulary, where the drugs are then subject to application of the PBS price disclosure policy. This assesses the actual cost of supplying the drug to retail pharmacies and results in further adjustment and reduction of the PBS rebate over time to more accurately reflect the cost price.[7]

Despite the welcome cost reductions that have accompanied the arrival of the first biosimilars, unanswered questions remain about their long term interchangeability with the originator product. All biologics are immunogenic and can result in antibody formation, reactions, and loss of efficacy with time. Up to 20% of patients on maintenance therapy may develop antibodies to anti-TNF-α monoclonal antibodies.[8] Given

that biosimilar drugs are not identical, there is a theoretical risk that switching between agents may result in the development of neutralising anti-drug antibodies (ADAs) and subsequent loss of response. At present, there are some reassuring data from the open label extension studies of the PLANETAS and PLANETRA studies, where there were no significant differences in the rate of ADA formation between patients who continued on the biosimilar product and those who had a single switch from originator infliximab to the biosimilar infliximab at 1 year; however, trough drug levels were not reported.[9,10] ADAs in the presence of low or absent drug levels are strongly associated with clinical loss of efficacy.[11] Since the introduction of the biosimilar infliximab in Europe, several countries have mandated a single switch. The early data are reassuring but, as yet, only reported in small numbers and in abstract form, and a large Norwegian randomised controlled trial has recently been completed (https://clinicaltrials.gov/ct2/show/NCT02148640). Further reassuring data were seen in the cross-reactivity of ADA from patient sera to the originator infliximab having near identical binding to the biosimilar infliximab CT-P13; however, this has not been demonstrated in reverse.[12] The vast majority of ADAs to anti-TNF-α monoclonal antibodies appear to be against the fragment antigen-binding region and may be neutralised by the addition of TNF-α. This reaction to TNF-α would be expected to be identical for originator and biosimilar agents and less prone to interference due to glycosylation and conformational changes.[13]

At present, studies have investigated a single switch between the originator and the biosimilar anti-TNF-α agent, whereas multiple switch and switch-back strategies have not been assessed. The Australian government has stated that biosimilar and originator anti-TNF-α agents can be considered interchangeable at the point of dispensing from the pharmacy, as is the case with small-molecule generic medicines. This practice known as "a-flagging" and requires patient consent.[4] This may result in patients electing to receive a different anti-TNF-α agent at each time point of dispensing. Under the legislation, the only way a prescriber can ensure that a patient is continued on the initially prescribed biologic agent, be that either a biosimilar or an originator biologic, is to tick the "brand substitution not permitted" box on the prescription.

This decision has caused the greatest concern for prescribing clinicians and representative bodies. The absence of data to suggest adverse reactions or the development of ADA from multiple switching does not imply safety.

At the point of registration, biosimilars are required to satisfy the criteria of similarity to the originator, but the TGA has stated that it is "inevitable that reference and biosimilar medicines will diverge to some degree after comparability has been established".[14] In theory, this increases the chance of antigenic changes developing, and no clinical studies have assessed this to date. There has been no additional pharmacovigilance program instituted to monitor the outcomes of a-flagging, with only the drug sponsor required to develop a risk management plan and a reliance on voluntary reporting by prescribers of adverse outcomes to the TGA. This could be considered equivalent to conducting a clinical trial on the Australian public without the means to accurately capture data such as loss of response, requirement for corticosteroid therapy, or milder adverse reactions that may not result in reporting. However, a consultation process by the government on this with relevant stakeholders is ongoing.

Infliximab is only given intravenously, but the next biologic agents to come off patent that will result in biosimilars entering the market will be self-injectable (for example, etanercept and adalimumab for rheumatoid arthritis). The parenteral administration of these agents is far more complex than the taking of an oral agent and requires familiarity and ability to use the delivery devices. Further, many patients utilise and are dependent on patient support programs that are supplied by third party providers while being funded by the pharmaceutical companies. The viability of these important programs for patients who are potentially undergoing switches between biologic products is unknown.

A significant number of inflammatory bowel disease patients also require dose escalation to maintain clinical response, beyond the fixed dosing regimens funded by the PBS. At present, the compassionate access programs of the pharmaceutical companies provide these additional doses, with the PBS recently rejecting a submission to provide dose tailoring. With the potential for a patient to receive multiple versions of the same biologic, where there are no safety data supporting this practice, the provision of compassionate doses is also under threat.

The arrival of biosimilars is welcomed by clinicians for the cost savings they bring to our health system, but ongoing studies and pharmacovigilance are required in a framework that captures clinical response data. The decision to allow a-flagging in this area of limited evidence has caused concerns for clinicians and patients alike. Ongoing education of prescribers, pharmacists and patients is required, and the minimisation of unnecessary switches until more safety data are available is recommended.

Competing interests: I am the current chair of the Australian Inflammatory Bowel Disease Association of the Gastroenterological Society of Australia, a board member of Crohn's & Colitis Australia, and have been on advisory boards and/or received speaker fees from the following manufacturers of biological medicines: AbbVie, Janssen, Hospira and Takeda.

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