Biosimilars: what's around the corner?

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Infliximab is an effective treatment for patients with refractory inflammatory bowel disease (IBD) and is well established in treatment algorithms. Biosimilar infliximab will become available in the UK from early 2015 as the patent for originator infliximab (Remicade) ends. Potentially this is a time of uncertainty for IBD teams and patients as, although biosimilar infliximab is approved for the same indications as the originator product, there is a lack of high-quality data supporting its use in IBD. The attraction of biosimilars is that they will result in a significant reduction in the price of infliximab which it is hoped will ease patient access to anti-tumour necrosis factor (TNF) therapy.

Biologics are medications that are manufactured in or derived from a biological product. A biosimilar is a medicinal product based on the same design as a biological drug. However, the production of biosimilars is vastly more complicated than that of simple generic molecules and, as a result, biosimilars must meet strict specifications regarding their efficacy and safety laid down by regulatory authorities such as the FDA and EMA (box 1).

Manufacturing a biosimilar involves replication of complex process, small changes in which could alter the molecular structure of the molecule. As the manufacturing process of the originator product is not in the public domain, production of biosimilar infliximab will inevitably involve a degree of variability compared with manufacture of the originator product. Such variability, however, also occurs in the manufacture of the originator product over time. Accordingly, extensive preclinical testing of biosimilars both in vitro and in animal models is required to demonstrate that their physicochemical, pharmacokinetic and pharmacodynamic properties are

highly similar to the reference product before clinical testing is permitted. The EMA has a series of characteristics that must be demonstrated in the biosimilars: these pharmacological properties have a range or window that lies within the range or window of the originator. Thus in the laboratory, biosimilar infliximab has properties that match a typical batch of Remicade.

Two clinical trials have been carried out demonstrating the efficacy and safety of biosimilar infliximab (CT-P13) for rheumatological disorders. The first trial was conducted in patients with ankylosing spondylitis (PLANETAS) and compared originator infliximab and CT-P13, both given as monotherapy at a dose of 5 mg/kg.¹ The second trial (PLANETRA) was carried out in rheumatoid arthritis and compared 3 mg/kg of originator and biosimilar infliximab in combination with methotrexate.² The outcomes of both studies in terms of immunogenicity, efficacy and safety demonstrated equivalence between the two products.

The EMA have accepted extrapolation from these rheumatology studies to IBD indications whereas, interestingly, Health Canada has not. Health Canada accepted extrapolation for rheumatological indications but cited potential differences noted in afucosylation, receptor binding and in vitro antibody assays for not allowing extrapolation for any IBD indication (see http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_remsima_160195-eng.php, accessed 21 May 2014). Biosimilars of erythropoietin and growth hormone are widely used, but these are much less complex molecules than infliximab which limits the ability to draw too many conclusions from their successful introduction. Biosimilar infliximab is the most complicated biosimilar approved to date and may in some ways act as a 'proof of principle' for other complex biosimilar

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Box 1 Definitions of a biosimilar from the FDA and EMA

FDA definition:

- ▶ Highly similar to the reference product notwithstanding minor differences in clinically inactive compounds. No clinically meaningful differences between the biological product and reference product in terms of safety, purity and potency.

EMA definition:

- ▶ A copy version of an already authorised biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.

mediations that will follow. Biosimilars have transformed oncology enabling countless patients to receive effective therapy at an affordable price.

The challenge for clinical health professionals now that biosimilar status has been granted for CT-P13, marketed in the UK as Remsima (Napp for Celltrion) and Inflectra (Hospira), is how to use it in practice? While there is a small amount of preliminary data regarding biosimilar infliximab in patients with IBD, the drugs will be available to prescribe before a significant body of IBD literature is available although trials including patients with IBD are underway (ClinicalTrials.gov Identifier: NCT02066272 and NCT02148640).³ Preliminary IBD clinical studies have also been reported as abstracts recently too.⁴ Accordingly, the British

Box 2 Summary of key recommendations on biosimilars from the British Society of Gastroenterology (BSG) (December 2014)

1. Prescribing by brand name.
2. Avoidance of switching from parent drug to biosimilar, or vice versa at least until we have safety data.
3. The use of a prospective registry of all biological use in inflammatory bowel disease (IBD) to capture safety data, rare and new side effects. We recommend the BSG-hosted Registry.
4. Discussion with patients about the choice of anti-tumour necrosis factor (TNF).
5. A substantial discount in line with Norway (39%) and Poland (31%),³ to facilitate market access by the biosimilar in order to gain real-world experience. However, any apparent cost benefit must be balanced against the unknown risk from the biosimilar. Product specific data (from IBD trials) will mitigate against this concern.

Society of Gastroenterology has issued provisional guidance on the use of biosimilars (box 2).

While further data are awaited, it seems sensible to first use biosimilar infliximab in TNF-naïve patients. As our experience of their use grows, assuming that they fulfil their promise, it is likely that they will be considered in other clinical situations including switching. However, competitive pricing models will mean that many funders will be keen that we accelerate this process. Those of us who switch should be encouraged to collect data and report their real-life experiences.

In summary, the introduction of biosimilar infliximab offers a great opportunity to make significant financial savings. However, their introduction must be carefully monitored to ensure that patient outcomes are truly similar.

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