

ABSTRACTED SCIENTIFIC CONTENT

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Investigating the validity of biosimilar extrapolation and interchangeability

The European Medicines Agency's (EMA) decision to approve the use of CPT-13, an infliximab biosimilar, in the treatment of inflammatory bowel disease (IBD), has proven controversial. In two papers, Professor Fernando Gomollón [1, 2] has reviewed and summarized opinions on the current use and extrapolation of biosimilars for the treatment of IBD.

Biologics are defined as 'a medicinal product or vaccine that consists of, or has been produced by the use of living organisms' [3]. They are difficult to make and expensive, with a year of treatment for one patient costing upward of Euros 10–20,000. This is attracting more and more businesses to the idea of making copies of biologics, called biosimilars, that can be brought to market when the 'innovator' patent has expired [3]. With this in mind, Gomollón highlights the key question that is asked by clinicians, pharmacists and patients, 'Are these biosimilars reliable?'

Inflammatory bowel disease and biosimilars

IBD can be treated using infliximab, a biological monoclonal antibody, first used in the effective treatment of rheumatoid arthritis. It was soon picked up and is now key to successful management of Crohn's disease (CD) and ulcerative colitis (UC). At present, a number of other biologics are also used to treat refractory CD, perianal CD and severe UC.

In the IBD field, the infliximab biosimilar CPT-13, marketed as Inflectra® and Remsima®, was approved by EMA in 2013. Following expiration of the innovator infliximab Remicade® patent [4], this product has gone on sale in many European countries. EMA made its approval based on preclinical studies that showed high similarity to the innovator infliximab Remicade®, and on data from two clinical trials concerning the treatment of those with ankylosing spondylitis and rheumatoid arthritis. From the clinical trial data, EMA 'extrapolated' that the infliximab biosimilar could also be used for treatment of all conditions approved for the original infliximab, including CD and UC. In his recently published reviews [1, 2], Gomollón set out to investigate how appropriate this extrapolation is, and how this is viewed by clinicians, pharmacists and patients.

The controversy behind extrapolation

For a biosimilar to gain EMA approval it must demonstrate high 'comparability' of three different main parameters: reliability in manufacturing and high product quality, non-clinical comparability, and clinical comparability. If these criteria are met, the product will be considered 'highly similar' and this can mean less stringent requirements for clinical trials as compared to the innovator. This is where the reasoning for accepting 'extrapolation' comes into effect in accordance with EMA statement that 'if clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indication(s) of the reference product may be possible under certain conditions' [5, 6]. Despite evidence in support of this, and EMA's strict rules on pharmacovigilance, Gomollón highlights that there is considerable resistance to extrapolation among the scientific community.

A recent survey conducted by the European Crohn's and Colitis Organisation (ECCO) has shown that two out of three member clinicians are not confident in the use of biosimilars in the treatment of IBD [7]. Gomollón suggests that the reasons for this

lie in the fact that there is a lack of information on the strict regulatory procedures of EMA and that confidence in regulatory authorities is low.

ECCO released a position statement in which they outlined the necessity for clinical trials of the infliximab biosimilar to be carried out in CD and UC patients [8]. This gave a number of reasons for their lack of confidence in the extrapolation of the biosimilar for the treatment of these patients, which included: (1) biologics do not always work in treatment of all indications, as is demonstrated in the case of etanercept which has efficacy in RA treatment but not in treatment of CD; (2) immunogenicity is not the same between diseases, and the pathophysiology of immunogenicity from monoclonal antibodies is, at present, not clear and unpredictable; (3) intestinal immunology is very complex and specific pathophysiological mechanisms could account for theoretical differences between drugs; (4) clinical experience of CD and UC could reveal differences that have not previously been observed in other diseases; (5) in IBD patients, the innovator drug is often administered in combination with thiopurines and considerable interaction has been seen between the two, there is no evidence that this is the case with the biosimilar; (6) RA is probably not the most sensitive model and a condition that is likely to show greater differences should have been used.

Although EMA defended its decision to extrapolate usage, the lack of clinical trial data prevented initial approval of the biosimilar for treatment of CD and UC in Canada. Here, concerns over the differences in afucosylation and how this could affect pathophysiological routes important in IBD, were raised. This was rebutted by Ebbers who stated that, 'differences in glycosylation are not known to have a relevant impact on the pharmacokinetic behavior of monoclonal antibodies, so it is unlikely that microheterogeneity will affect pharmacokinetic behavior of the biosimilar' [9, 10]. Despite regulatory approval of the infliximab biosimilar in Europe, a CD clinical trial is underway and results are expected in 2017.

Gomollón points out that CD and UC are very complex diseases and that monoclonal antibodies themselves are hugely complex. Clinicians are used to meta-analysis and evidence-based medicine supported by clinical trials. As such, they find it difficult to trust the biochemical and biological experimental evidence that supports biosimilars and their extrapolation. Clinical comparability studies include pharmacokinetics (PK) and, when possible, pharmacodynamics (PD). Gomollón expresses concern that these concepts are not well understood by clinicians and suggests that further education is needed to explain the justification of extrapolation. This idea is further discussed in the paper of Kurki [11].

Gomollón also stresses the importance of the forthcoming results from the CD clinical trials, in increasing clinicians' understanding of, and supporting the use of biosimilars. Gomollón also believes that improved collaboration between regulators and scientific societies could act to increase confidence in biosimilars. A recent GaBI roundtable discussion on biosimilars was held in Brussels, Belgium on 12 January 2016, with participation by European regulators and medical societies, to facilitate such collaborations [12].

The IBD biosimilar financial landscape

Biologics are expensive and are the main drivers of the cost of IBD treatment. They have been shown to account for 64%

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of expenses associated with CD treatment, and 31% of those associated with UC treatment [13]. Biosimilars are cheaper alternatives to originator biologicals and some estimates claim that biosimilars of the infliximab monoclonal antibody could reduce the cost of IBD treatments by 25–40% per mg. With the advent of innovator patent expiry, many companies have made note of the potential financial gain that could be made from biosimilars, and are now working towards their development. However, Gomollón is quick to point out that the market for biosimilars is still uncertain and notes that it will be interesting to assess their position relative to biologicals in the years to come.

Although the use of biosimilars in the treatment of IBD could offer some financial relief to patients and healthcare authorities, clinicians are reluctant to adopt their use for this reason alone. Gomollón notes that clinicians see biosimilars as a low-cost option to replace existing medications with proven efficacy. Here, the reduction in cost does not outweigh the concerns over extrapolation and the desire for proof regarding the safety and efficacy of biosimilars.

Interchangeability and product names

In both reviews, Gomollón highlights that there is also controversy surrounding the interchangeability and naming of biosimilars. In relation to this, Gomollón states that, 'Being "highly similar" does not mean that switching is a good idea', and recommends that patients do not switch to the biosimilar until clinical trial data are available. He also points out that clinicians, who have more patient contact, are more reluctant than pharmacists to recommend a change.

When it comes to the naming of biosimilars, there are arguments for and against nomenclature that is similar to the innovator product [14]. Interestingly, Gomollón notes that biosimilar companies prefer to use generic names, whereas those who manufacture the original product use brand names. As is true for innovators, he stresses that, 'For adequate pharmacovigilance, the brand name and a complete registry of batches should always be registered, as unexpected changes in the manufacturing process can have big molecular consequences'.

Concluding remarks

With respect to the infliximab biosimilar, Gomollón states that there is no doubt that this is bioequivalent to the original Remicade®. However, he asks the question, 'Can I be as confident as with Remicade in all the indications I have been using it in my IBD patients?'. And in answer to that, clinicians are calling for adequate clinical trials, which should be carried out to provide direct clinical evidence for its efficacy in the treatment of those with CD and UC.

In his discussion of the controversies surrounding the use of biosimilars in the treatment of IBD, Gomollón touches on issues related to regulation, economics, extrapolation, interchangeability and product naming. He notes that a lack of confidence in the extrapolation of biosimilars for the treatment of IBD may be due to a lack of understanding and education, and a lack of collaboration between scientific societies and regulators. The adoption of biosimilars is seen to be financially beneficial which has led to skepticism amongst clinicians as they do not want to be seen to cut costs at the expense of effective and safe patient treatment. He concludes that the results from infliximab biosimilar CPT-13 clinical trials for the treatment of CD and UC are likely to support extrapolation and the future use of biosimilars for IBD treatment.

Editor's comment

Following the publication of Gomollón's reviews, the infliximab biosimilar, Inflectra®, was approved for the treatment of CD and UC in Canada. Regarding this, the pharmaceutical manufacturer stated, 'The addition of CD, fistulising CD and UC to the approved indications was granted on the basis of similarity between INFLECTRA® and the reference product, Remicade®, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and on clinical experience with the reference product'. See link: http://www.pfizer.ca/node/7526#_ftn1

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