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SPECIAL ARTICLE

ECCO position statement: The use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD)

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Abstract

Biologics have become key agents for the management of Crohn's disease and ulcerative colitis. Biosimilars are biological medicines similar to previously authorized biologics and are already available in some countries. This ECCO Position Statement defines the collective view of European specialist in inflammatory bowel disease (IBD) concerning biosimilars. Biosimilars are not comparable to generic small molecules, since both efficacy and toxicity are difficult to predict due to subtle molecular changes that can have profound effects on clinical efficacy and immunogenicity. Direct evidence of safety and benefit from clinical trials in IBD, post-marketing pharmacoviligance, and unequivocal identification of the product as a biosimilar should be requirements before approval. Switching from an established biologic to a biosimilar to save costs is likely to be as inappropriate and inefecctive as switching between current biologics that act on the same target, except when there is loss of response.

Contents

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1. Introduction

Biological medicines are comprised of proteins or other substances derived from a biological source.[1] Biosimilar medicines ('biosimilars') are biological medicines similar to other, already authorized, biological medicines, that are able to enter the market once the patent for the original product, the reference product, has expired.[1] Biosimilar medicines can be broadly categorized into three categories:

1) products very similar to natural body substances, often used as replacement therapy, or to enhance the body's innate response;
2) monoclonal antibodies;
3) engineered proteins.

Biological medicines are generally more complex and much larger in size than chemical medicines (sometimes called 'small molecules'), therefore their precise properties and characteristics are largely dependent upon the manufacturing process used.[2] Biological medicines are produced by living systems, such as cell lines, and are therefore subject to considerable variability in structure and characteristics. Even after patent expiration, manufacturing processes do not have to be disclosed, so there are likely to be appreciable differences in the manufacturing processes of biosimilars and their reference product.[3] Biosimilar products are not generic medical products, so it is therefore likely that these differences in the manufacturing process will lead to subtle differences between similar biological medicines.[2]

Biosimilars should be distinguished from new generation biological medicines, sometimes called 'me too' biologics. New generation biological medicines are agents that may have a similar target to the first-generation product, but are manufactured independently as new products that are subject to conventional proof of efficacy and licensing procedures.

In the EU, biological medicines need to be authorized by the European Medicines Agency (EMA). The EMA established a specific legal pathway for approval of biosimilars in 2005, in which it is recognized that biosimilars cannot be identical to the primary compound, but must be similar to the original EU-approved molecules in terms of quality, safety, and efficacy.[1]

To date, a total of 19 biosimilar medicines have been evaluated and 14 authorized in the EU. All currently authorized biosimilars fall within three product classes: human growth hormones, erythropoietins and granulocyte colony stimulating factors.[4]

2. Why biosimilars?

Use of biological agents is increasing, with new indications and increased patient demand. Notably, in 2012, it was estimated that seven of the world's top ten selling drugs were biological medicines. Sales of biological medicines are expected to continue to grow at least twice the rate of sales of small molecules.[5,6]

Biosimilars have been viewed as potentially cost saving compared to the reference product, in a manner similar to the cost savings associated with generic versions of chemical medicines. However, while generic chemical medicines and biosimilars have an important role to play in terms of increasing competition in the marketplace, price reductions for biosimilars are unlikely to be as substantial as those seen for generics. This is because biological medicines, including biosimilars, are more costly to produce and develop than chemical medicines and their generics. Furthermore, the regulatory process based on clinical trials of bioequivalence necessary for the approval of either biological medicines or biosimilars is more involved and therefore more costly. If regulatory authorities stipulate the necessity for a safety registry for biosimilars, this will further add to baseline costs. Nevertheless, it can still be expected that biosimilars will be priced below their reference product, which can therefore be expected to have an impact on the affordability and availability of biological medicines, making them more accessible to patients.[6]

3. Biosimilars in inflammatory bowel disease

- The patent on the monoclonal antibody infliximab is due to expire in the EU
  - o two biosimilar infliximabs have already filed for EMA regulatory approval, one of which is now licensed in South Korea
- Special considerations for TNF-alpha antagonists in IBD
  - o Mechanism of action not completely understood
  - o No suitable surrogate endpoints to act as pharmacodynamic markers
  - o Downstream effects contributing to efficacy remain unclear
  - o Concomitant medications (e.g. oral immunomodulators) affect pharmacokinetics and pharmacodynamics
  - o Methods and interpretation of drug levels and anti-drug antibodies in IBD remain to be standardized

4. Regulatory requirements in Europe

In 2005, EMA established a specific legal pathway for the authorization of biosimilars. While EMA recognizes that it is not possible for biosimilars to be identical to the reference compound, it is necessary for such agents to be similar in terms of efficacy and safety, as well as quality.[1] Assessment by EMA of applications for biosimilars is conducted in accordance with the guidelines of the Committee for Human Medicinal Products (CHMP), which highlight the studies necessary for demonstrating similarity of the proposed biosimilar to the reference product. These studies include pharmacokinetic and pharmacodynamic studies, both in vitro and animal models, as well as studies conducted in patients.[2,7,8] EMA allows for a

biosimilar agent to be approved across the indications for which the reference product is approved, based on the extrapolation of data obtained in these indications for the reference product. Following approval of biosimilars, rigorous pharmacovigilance is necessary to obtain full information regarding the safety profile of biosimilar agents, both to detect unexpected reactions and to identify any increase in frequency of predictable adverse events (such as sepsis or reactivation of tuberculosis) resulting from any lower threshold for treatment. It is noted that EMA guidelines (EMEA/CHMP/BMWP/42832/2005) state that "Within the authorisation procedure….Pharmacovigilance systems (as defined in the current EU legislation) and procedures (including traceability as described in the current EU guidelines) to achieve this monitoring should be in place when a marketing authorisation is granted…The compliance of the marketing authorisation holder with commitments (where appropriate) and their pharmacovigilance obligations will be closely monitored."

5. Position

ECCO believes that the safest and most effective treatments should be readily available to appropriate patients at the lowest possible cost. The principal driver of decisions should, in all cases, be sound scientific evidence and a "patient first" approach.[9] In the very specific case of biosimilars in IBD, decisions regarding therapeutic equivalence and interchangeability should be taken into consideration and guide principles, which include the following:

- The molecular size and complex structure of biological medicines (and biosimilars) make it extremely difficult to predict therapeutic equivalence, because even subtle changes during development can cause profound differences in clinical efficacy or immunogenicity. Such differences can occur even within the same biological medicine if different manufacturing processes are used (e.g. different cell lines).
- Rules applied to the production of generic chemical medicines cannot be transferred to biosimilars
- Different biological and biosimilar medicines targeting the same molecule are neither identical in efficacy nor toxicity, even in the same clinical entity.
- A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective.
- Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis
- Clinical trials should be of large enough size to detect common adverse events and powered to show equivalence with a reference biological agent, or conventional superiority
- Post-marketing collection of data in both children and adults is necessary to confirm safety by recording less common but important potential adverse effects, as well as identifying any increase in frequency of predictable adverse events contingent on wider access to treatment.
- Any decision to substitute a product should only be made with the prescribing health care provider's specific approval and patient's knowledge[10]
- Names of biosimilars need clearly to differ from their reference biological medicine in order to facilitate the collection of data on safety and efficacy, which would be impossible if confusion between names will occur

6. Conclusion

The overall position of ECCO is that the use of most biosimilars in patients with IBD will require testing in this particular patient population, with comparison to the appropriate innovator product. Although wider access to appropriate use of biological therapy in IBD and potential direct cost savings are important, rigorous testing is necessary in patients with IBD to ensure that appropriate efficacy and safety standards are met. Final clinical decisions should always be made on an individual basis, taking into account both circumstances of the individual patient and prescribing physician.

Conflict of interest

Silvio Danese has served as a speaker, a consultant and an advisory board member for Schering-Plough, Abbott Laboratories, Merck & Co, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson and Johnson. F. Gomollón has acted as consultant for MSD, ABBVIE, PHARMACOSMOS, and FAES-FARMA; has received investigational grants from MSD; and received support for travelling and congress assistance from MSD, ABBVIE, FAES-PHARMA, and SHIRE.

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References

1. European Medicines Agency. Questions and answers on biosimilar medicines (similar biological medicinal products). 2012 18 January 2013. Available from:, http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500020062.
2. EuropeanMedicines Agency. Guideline on similar biological medicinal products. 2005 18 January 2013. Available from:, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c.
3. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues. 2012 18 January 2013. Available from:, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c.
4. European Medicines Agency. Human medicines — biosimilars. 2013 18 January 2013. Available from:, http://www.ema.europa.eu/ema/.
5. Biologic drugs set to top 2012 sales. *Nat Med* 2012;**18**(5):636.

6. McCamish M, Woollett G. Worldwide experience with biosimilar development. *MAbs* 2011;**3**(2):209–17.
7. Jelkmann W. Biosimilar epoetins and other ""follow-on" biologics: update on the European experiences. *Am J Hematol* 2010;**85**(10): 771–80.
8. Reichert JM. Next generation and biosimilar monoclonal antibodies. Essential considerations towards regulatory acceptance in Europe. *MAbs* 2011;**3**:223–40.
9. Miletich J, Eich G, Grampp G, Mounho B. Biosimilars 2.0. Guiding principles for a global "patients first" standard. *MAbs* 2011;**3**:318–25.
10. Lee EO, Emanuel EJ. Shared decision making to improve care and reduce costs. *N Engl J Med* 2013;**368**:6–8.