

Use of Biosimilars in Paediatric Inflammatory Bowel Disease: A Position Statement of the ESPGHAN Paediatric IBD Porto Group

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ABSTRACT

Because the patents for biopharmaceutical monoclonal antibodies have or soon will expire, biosimilars are coming to the market. This will most likely lead to decreased drug costs and so easier access to these expensive agents. Extrapolation, however, of the limited available clinical data from adults with rheumatologic diseases to children with inflammatory bowel disease

(IBD) should be done with caution and needs some considerations. Post-marketing surveillance programs for efficacy, safety, and immunogenicity should become mandatory in children with IBD using biosimilars, as for all biological drugs.

Key Words: biosimilar, inflammatory bowel disease, infliximab, paediatric, position paper

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Biological medicines are complex protein-based compounds derived from a biological source as defined by the European Medicines Agency (EMA) (1). These proteins have a much larger molecular structure than the standard pharmacological preparations. When such small molecule drugs' patents expire, generic products are introduced. Because of both their structure and biological activity, however, the counterpart of generics in terms of biologicals is called biosimilars (1). The World Health Organization has defined these as "a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product" (2). Because of the structure of the biological molecules and trade secrets of the companies producing the original products, the new versions are very similar but not exactly identical to the originator drug.

These products do not need to go through the same complex licensing process for approval as new small molecules, thereby bringing down their cost (Fig. 1) (3). Biosimilars may also be cheaper because it is possible to produce molecules which are almost identical to the original product through alternative methods. The pricing difference, however, may be less pronounced than when producing generics because of the complex manufacturing process which large-molecule biosimilars require (4,5). Overall, a lower price should result, allowing wider access to this expensive class of medications.

Agencies including the US Food and Drug Administration (FDA) and EMA decided that for biosimilars, documentation of efficacy is not needed for all of the indications of the original molecule. Extrapolation may be acceptable provided that the pharmacokinetic (PK) and pharmacodynamic properties have been demonstrated in studies of all levels (in vitro, animal models, and clinical trials) in some of the indications, (3).

Because biosimilars have now come to the market in some countries, an overview is given on behalf of the paediatric inflammatory bowel disease (IBD) Porto group on the use of biosimilars in paediatric IBD (PIBD). The PIBD Porto group is a group of PIBD experts from European Society for Paediatric Gastroenterology, Hepatology, and Nutrition whose goals are to generate collaborative

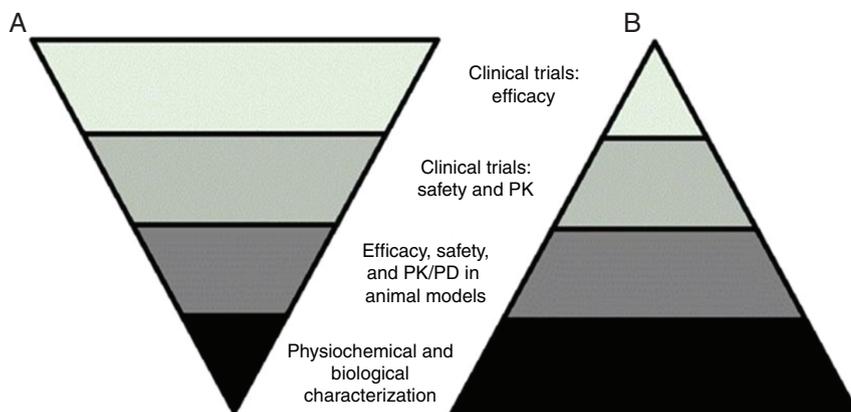


FIGURE 1. Biosimilar principle. A, Process development of new drug (original). B, Process development of biosimilar: reversed engineering and body of evidence. Although a new drug development starts with some physiochemical and biological characterization, the emphasis is on clinical trials. This is the other way around for the development of a biosimilar, in which the emphasis is on the proof of similarity (physiochemical and biological characterization). Revision of figure, derived from (3).

international research and to provide a leadership role with regards to current diagnosis and management of IBD in children. Children with IBD on average have a more severe disease phenotype than in adult-onset IBD, potentially requiring antitumour necrosis factor (anti-TNF) treatment for even longer duration. Therefore, in addition to the European Crohn's and Colitis Organisation position statement on the use of biosimilars in the treatment of IBD, we hereby provide consensus-based recommendations specifically for paediatric gastroenterologists treating children with IBD (6).

HOW BIOSIMILARS MAY DIFFER FROM CURRENT BIOLOGICS

Although the generic version of a small molecule drug is identical to the original product with respect to its structural and therapeutic identity, this cannot be said for biosimilars:

1. The reference biopharmaceuticals are characterised by marked molecular heterogeneity because of a variety of factors (ie, the interplay of primary, secondary, and higher-order protein structures, and intramolecular/intermolecular interactions and posttranslational modifications) leading to a magnitude of chemical forms.
2. Because biopharmaceuticals are made in living cell lines, they are sensitive to changes in the manufacturing process such as growth conditions, purification processes, formulation, or storage conditions (5).

The large and complex structure of monoclonal antibodies (mAbs) makes the synthesis of biosimilars more complicated than a biosimilar of small proteins. Moreover, even the original product drifts over time and is not fully identical to the drug that was licensed. Therefore, specific European guidelines published by the EMA do not refer to structural identity, rather they mandate that biosimilar mAb cannot have clinically meaningful differences from the reference product in terms of "quality, safety, or efficacy" (7,8). According to the FDA, there should not be any clinically meaningful differences in "safety, purity, and potency" (9).

Proof of Biosimilarity

The primary goal of biosimilar development is to establish biosimilarity (10):

1. In vitro characterisation studies are required, in which the biosimilar and the reference product are compared in terms of binding and function. In vivo testing may be required if there are concerns identified in in vitro studies, such as alterations in receptor binding or stability, potentially resulting in altered safety or clinical efficacy. Clinical evaluations are required to evaluate PKs, pharmacodynamics, efficacy, and safety.
2. Analytical tools currently available remain limited in the ability to characterise all possible chemical variants of biologics. Therefore, the absence of detectable differences does not necessarily imply biosimilarity (11).
3. Because the manufacturing process of the originator product remains a trade secret even after patent expiration, there is no information on process steps (ie, vector, host cell expression system, cell expansion procedure, protein recovery mechanism, purification process, or formulation of the therapeutic protein into a drug) (12).
4. Changes in manufacturing over the years of production with subsequent incremental differences among multiple biological medicines, either original authorised products or biosimilars, have to be considered (13–15). Even after the demonstration of biosimilarity at the time of approval, a biosimilar and a reference medicine could then diverge over time. Therefore, demonstration of comparability between subsequent biosimilar products and the initial biosimilar is also necessary.

Because of the vast molecular structural heterogeneity and differences in manufacturing, biosimilars are unlikely to be identical with their reference products.

EXISTING BIOSIMILARS DESTINED FOR IBD AND CURRENT CLINICAL DATA ON EFFICACY

There are no randomised controlled trials (RCTs) published on the use of infliximab (IFX) or other anti-TNF biosimilars in IBD to date. The only data on the efficacy can be derived from 2 published RCTs in adult patients with rheumatoid arthritis (PLANETRA) and ankylosing spondylitis (PLANETAS) (16,17). Data from long-term extensions of both studies are available as abstracts (18,19).

Recently, a Hungarian IBD cohort treated with the biosimilar IFX is published as an abstract (20).

PLANETAS

PLANETAS was a randomised, double-blind, multicentre prospective study comparing the PKs, safety, and efficacy of biosimilar CT-P13 (an immunoglobulin G1 chimeric human-murine mAb IFX biosimilar) and IFX in patients with ankylosing spondylitis (16). The primary endpoint was PK equivalence at steady state and the observed maximal serum concentration assessed between weeks 22 and 30. Efficacy was a secondary endpoint.

Of the 250 randomised patients, 229 completed the 30-week study period. PK analyses included 223 patients. Efficacy and safety analyses were performed in all 250 patients. Patients were randomly assigned 1:1 to receive either 5 mg/kg of CT-P13 (Celltrion Inc, Incheon, Republic of Korea) or IFX (Janssen Biotech Inc, Horsham, PA), at weeks 0, 2, 6, and thereafter every 8 weeks until week 30. Steady-state PK was equivalent for CT-P13 and IFX in the overall PK population. Efficacy was highly similar between the 2 groups. No statistically significant difference in immunogenicity between the CT-P13 and IFX treatment groups was observed.

PLANETAS Extension

Of the 210 patients who completed PLANETAS, 174 patients entered the extension phase for an additional 48 weeks: 88 were continuously treated with CT-P13 (maintenance group) and 86 were switched from IFX to CT-P13 (switch group) (18). During the extension, disease activity scores were similar in the maintenance group and the switch group.

Antidrug antibody formation was comparable between the 2 groups, and positivity was maintained throughout the study. Patients without anti-drug antibody formation achieved better responses compared with patients with anti-drug antibody formation, whereas there were no differences between the maintenance and switch groups.

PLANETRA

PLANETRA was a randomised, double-blind, multicentre prospective study comparing CT-P13 and IFX, both coadministered with methotrexate in adult patients with active rheumatoid arthritis (17).

Patients with active rheumatoid arthritis were randomly assigned 1:1 to receive 3 mg/kg of CT-P13 or IFX at weeks 0, 2, and 6 and thereafter every 8 weeks until week 30. The primary endpoint was to demonstrate equivalent efficacy of CT-P13 to IFX at week 30, as determined by rheumatological disease activity scores. Of the 606 randomised patients, 494 completed the study without protocol violations. Discontinuation was primarily because of adverse events (8.9%) and patient withdrawal of consent (4.1%). Clinical responses at week 30 were equivalent (60.9% and 58.6%) between treatment groups according to the intention-to-treat analysis for CT-P13 and IFX, respectively, as were the PK profile and immunogenicity.

PLANETRA Extension

Out of the 455 patients who completed the PLANETRA study, 302 patients were entered into the open-label extension for an additional 48 weeks (19). Patients either continued CT-P13 (n = 158) or switched from IFX to CT-P13 (n = 144). Through week 102, clinical response rates were maintained and similar within each group. Antidrug antibody formation positivity was comparable between both groups and did not increase significantly during year 2 while on CT-P13.

Biosimilar IFX in an IBD Cohort

Geese et al (20) describe the first prospective nationwide cohort examining the efficacy and safety of the biosimilar IFX in adult IBD patients. In total, 90 CD and 51 UC patients have been treated with the biosimilar IFX (total number of infusions not reported). A total of 26% of patients had previous exposure to anti-TNF treatment. Patients were followed for 52 weeks but only results until week 14 have been reported to date. Early clinical response and remission rates were comparable to previously reported original IFX trials.

These studies have shown that the efficacy between the biosimilar CT-P13 and IFX was comparable both in ankylosing spondylitis and rheumatoid arthritis patients until week 102. Switching from IFX to CT-P13 was efficacious during 2 years in both patient groups. Extrapolation of these data to children with IBD, however, should be done with caution and needs some considerations.

First, it needs to be taken into account that biological medicines such as IFX are used to treat IBD. IBD and rheumatoid arthritis are not identical in pathogenesis, and there are several examples of biologics which are effective in rheumatoid arthritis but ineffective (21) or even harmful in IBD (22). In vitro studies show substantial differences in the mechanism of action among the anti-TNF drugs currently used (23). Therefore, extrapolation of the biosimilar agent to be approved across the indications for which the reference agent is approved is not well established, and this should be weighed in the decision to support approval. Moreover, pharmacodynamic markers as surrogate endpoints for efficacy, such as the absolute neutrophil count for granulocyte-colony stimulating factor (G-CSF) therapy, are lacking for TNF antagonists.

The second consideration pertains to the differences in doses. The dose of IFX for IBD, 5 mg/kg, differs from that used for rheumatoid arthritis, 3 mg/kg. The third consideration is that children with IBD are often treated with monotherapy, or combination therapy with concomitant immunosuppressive agents for short periods of time, yet the authorisation studies were in those on combination therapy. The presence of drug antibodies to anti-TNFs correlates with shorter duration of response and higher incidence of infusion reactions (24,25): immunosuppressive medications are known to reduce the risk of the development of neutralising antibodies against anti-TNFs (26). Therefore, the concomitant use of methotrexate in the phase III study may compromise the validity of extrapolation of safety and efficacy data to children with IBD who are not receiving concomitant methotrexate.

EXISTING BIOSIMILARS DESTINED FOR IBD AND CURRENT CLINICAL DATA ON SAFETY

Data concerning the safety of biosimilars is available only from the PLANETAS and PLANETRA trials and their extensions described above (16,17). In the PLANETAS trials, infusion reactions occurred in 3.9% of patients receiving CT-P13 and in 4.9% of patients treated with IFX. Patients who developed antidrug antibodies were 27.4% and 22.5% in the CT-P13 and IFX group, respectively. In the PLANETRA study, drug-related adverse events were observed in 35.3% versus 35.9% whereas antidrug antibodies were developed in 48.4% versus 48.2%, respectively. In both trials, the majority of adverse events were mild to moderate in severity. In patients with rheumatoid arthritis, the most common reported treatment-related adverse events in CT-P13 and reference IFX were latent tuberculosis, raised alanine aminotransferase/aspartate aminotransferase, urinary tract infection, flare in rheumatoid arthritis

activity, nasopharyngitis, and headache. Infusion reactions occurred in 6.6% of patients in the CT-P13 group and in 8.3% of the patients in the reference IFX group. Serious adverse events occurred in 10.0% of the rheumatoid arthritis patients receiving CT-P13 and 7.0% receiving IFX. Three cases of active tuberculosis occurred in the CT-P13 group and none in the reference IFX group. Two patients in the IFX group withdrew from the trial because of malignancy. In patients with ankylosing spondylitis, serious treatment-related adverse events occurred in 4.7% of patients receiving CT-P13 and 6.4% of patients receiving reference IFX. In both trials, there were no deaths. Safety data of the Hungarian IBD cohort treated with the biosimilar IFX is limited to the report of allergic reactions which were found in 2.8% of cases (all previously anti-TNF treated patients) (20).

CT-P13 is now being produced in Korea, and commercialised under the name Remsima by Celltrion Healthcare and Inflectra by Hospira (Lake Forest, IL). In September 2013, EMA approved both Remsima and Inflectra for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, as well as for adult IBD and PIBD. Until now, no postmarketing data on the safety of these agents have been published (27).

CONCERNS REGARDING THE INTRODUCTION OF BIOSIMILARS

It appears that the experience so far with the introduction of biosimilar therapeutic mAb is encouraging with regards to drug safety and effectiveness in rheumatology. Even minor alterations, however, in the production process of biologics may lead to changes in cell behaviour and cause differences in structure, stability, or other quality aspects of the end product, commonly because of differences in glycosylation patterns. Any of these differences may affect the treatment's safety, efficacy, and, most importantly with biologics, the immunogenicity (28). In children, the risk of developing immunogenicity to anti-TNF treatment is even more worrisome than in adult patients because children both have more severe disease and potentially need anti-TNF treatment for a longer period.

Previous studies have shown that these differences in glycosylation and protein structure between the original drugs and biosimilar products do occur. For instance, in a study comparing 7 brands of recombinant human G-CSF, potency differences of 82% to 105% were noted, as well as significant differences in the level of purity among various brands of G-CSF and erythropoietin biosimilars (29). Following a change in the stabilizer used in subcutaneous erythropoietin (Eprex, Janssen Cilag, High Wycombe, UK) syringes (ie, the originator drug), an unprecedented rise in the incidence of pure red-cell aplasia was noted between 1998 and 2003, with ~200 cases reported in patients with chronic renal failure. An interaction of the stabilizer with the rubber cap acted as an adjuvant that induced an immune response to erythropoietin that in turn attacked erythroblasts and caused red-cell aplasia (30). A study comparing the structure of 2 original erythropoietins and 2 erythropoietin biosimilars found considerable differences in structure and potency (31). Concerns about these experiences led to the development of EMA guidelines on biosimilar development in general (32) and specifically on mAb biosimilars (7).

Despite the potential for altered efficacy, increased immunogenicity, and adverse effects, generally the introduction of most biosimilars has turned out to be safe. In the largest study to date, with a total of 904 patients using a biosimilar G-CSF (520 with Ratiograstim [Ratiopharm, Ulm, Germany]/Tevagrastim [Pharmachemie, Haarlem, the Netherlands], 384 with Zarzio [Sandoz, Holzkirchen, Germany]), the adverse effect profile was comparable to historic controls treated with the originator G-CSF (34).

Erythropoietin biosimilars such as HX575 were generally safe in most studies (31). Immunogenicity was not more than expected in some studies (30), whereas other studies did show increased prevalence of neutralizing antibodies in individuals who experienced a loss of response (35).

Still, monoclonal anti-TNF-antibody biosimilars may pose more concerns for immunogenicity and safety because these are much larger than proteins such as erythropoietin (148,000 Da vs 18,464 Da, respectively). Gaining a clear understanding of the immunogenicity impact of nonanti-TNF agents has taken several years. As stated before, immunogenicity is clinically a very relevant phenomenon with both IFX and adalimumab, and affects anti-TNF drug levels and clinical efficacy in both Crohn disease and ulcerative colitis (36–43). Therefore, there is no guarantee that our understanding of immunogenicity of the originator biological will easily be extrapolated to the biosimilar that may be subtly different in molecular structure. New assays need to be developed and studies undertaken to explore and understand the immunogenicity of the biosimilars.

Emerging study results on Remicade (Merck Sharp & Dohme, Kenilworth, NJ) biosimilars have been reassuring. Cross-reactivity between antibodies to Remicade and the biosimilar Remsima was recently investigated by Ben-Horin et al (published as an abstract) (44). They describe a cross-immunogenicity study in IBD patients. In total, 124 sera of Remicade-treated IBD patients with measurable antibodies to Remicade were tested by anti- λ enzyme-linked immunosorbent assay (ELISA) for their cross-reactivity to 2 batches of Remsima. Sera negative for anti-Remicade antibodies were tested in parallel as controls. All 68 positive anti-Remicade IBD sera were cross-reactive with Remsima. In negative controls (16 healthy individuals, 40 IBD patients), there was a slightly higher background signal in the enzyme-linked immunosorbent assay for Remsima compared with Remicade. Anti-Remicade antibodies of IBD patients ($n=10$) exerted a similar functional inhibition on Remsima and Remicade TNF α -binding capacity (P = not significant for all points on the inhibition curves). Antibodies to adalimumab in adalimumab-treated IBD patients ($n=7$) did not cross-react with neither Remicade nor Remsima. Ben-Horin et al (44) concluded that antibodies to Remicade in Remicade-treated IBD patients recognize Remsima to a similar extent, suggesting shared immunodominant epitopes on these 2 IFX agents. These currently available studies have included only adult patients, whereas no data are available in children. So far, the results suggest a strong similarity between the originator and the biosimilar product. An important implication of these findings is that patients who received Remicade and developed antibodies to IFX would not be candidates for IFX biosimilar therapy.

RESEARCH GAPS IN BIOSIMILAR RESEARCH IN IBD

Clinical trials in the IBD population could help ease concerns. The technical aspects of designing these trials of biosimilars for the treatment of IBD need careful consideration. Noninferiority trials are probably the best design, even though they are not often feasible given the required large sample size. It has been estimated that 1500 patients would be required to conclude with 95% confidence that the biosimilar would not be >7.5% inferior than the originator (45). Therefore, it is possible that regulatory decisions may be made based on trials of smaller size, increasing the likelihood of failure to detect small but clinically significant difference in therapeutic effect. Another important issue is whether regulatory agencies will require both induction and maintenance data or only induction data. We have learnt from existing TNF antagonists that attenuation of response with maintenance therapy is a key issue, and

it will be important to know whether the biosimilars will have similar performance characteristics in both the induction and maintenance phases of treatment. On the contrary, a lengthy approval pathway including prolonged IBD maintenance studies may result in significant delay of the introduction of biosimilars into the market and thus will result in continued elevation of therapy-related health expenditure.

Postmarketing surveillance programs for efficacy, safety, and immunogenicity should become mandatory in children with IBD using biosimilars and when using all biological drugs. For this purpose, the PIBD community recently established an international platform (PIBD-net). PIBD-net is a nonprofit organization founded in September 2014. The aim is to advance the care of children with IBD globally through investigator and industry initiated research, the development of optimal treatment plans, and monitoring safety and effectiveness of current and emerging treatments (46).

CONCLUSIONS

Concerns remain about the introduction of biosimilars, particularly in PIBD. These concerns should spark debates in the medical arena, and this information should be available to physicians who have to make the decisions about the welfare of their patients. In contrast, the introduction of biosimilars to the market will likely decrease the costs of anti-TNF drugs by $\geq 30\%$, thereby lowering the threshold of use of these highly effective but expensive drugs in IBD. Because of the absence of published trials on the use of biosimilars in adult IBD and PIBD, the following statements cannot be used as recommendations for management. They reflect expert opinion designed to inform paediatric gastroenterologists and to promote consensus on the proper usage of these agents in children with IBD. The statements are accompanied by the percentage of voting members of the PIBD Porto group expressing agreement: 83% (30/36) of all members voted.

The European Medicines Agency approved the use of biosimilars for infliximab for all indications, including adult and paediatric inflammatory bowel disease (IBD). The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition paediatric IBD Porto group advocates giving high priority to performing paediatric trials with long-term follow-up to support this decision: 97% agreement

Treatment of a child with sustained remission on a specific medication should not be switched to a biosimilar until clinical trials in IBD are available to support the safety and efficacy of such a change: 94% agreement

Postmarketing surveillance programs for efficacy, safety, and immunogenicity in children with IBD should be a mandatory requirement for the marketing of biologics and biosimilars with respective indications: 100% agreement

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