

**USE OF BIOSIMILARS IN
PAEDIATRIC INFLAMMATORY BOWEL DISEASE:
A POSITION STATEMENT OF THE ESPGHAN paediatric IBD Porto GROUP**

Societal paper

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Abstract

Since 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. However, extrapolation 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.

Keywords: Biosimilar; Infliximab; Position paper; Inflammatory Bowel Disease; Paediatric

Abbreviations

EMA European Medicines Agency

FDA Food and Drug Administration

G-CSF Granulocyte-Colony Stimulating Factor

IBD Inflammatory bowel disease

mAb monoclonal antibodies

PK Pharmacokinetics

RCT Randomized controlled trial

TNF Tumour necrosis factor

WHO World Health Organisation

Introduction

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. However, due to both their structure and biological activity, the counterpart of generics in terms of biologicals are called biosimilars[1]. WHO have defined these as “a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product”[2]. Due to the structure of the biological molecules as well as 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 (Figure 1). Biosimilars may also be cheaper because it is possible to produce molecules which are almost identical to the original product through alternative methods. However the pricing difference may be less pronounced than when producing generics due to the complex manufacturing process which large molecule biosimilars require [3, 4]. 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 and pharmacodynamic properties have been demonstrated in studies of all levels (*in vitro*, animal models, and clinical trials) in some of the indications, [5].

Since biosimilars have now come to the market in some countries, an overview is given on behalf of the paediatric IBD Porto group on the use of biosimilars in paediatric

inflammatory bowel disease (IBD). The paediatric IBD Porto group is a group of paediatric IBD (PIBD) experts from ESPGHAN whose goals are to generate collaborative 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 anti-TNF treatment for even longer duration. Therefore, in addition to the ECCO 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].

(Figure 1)

How biosimilars may differ from current biologics

While 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*:

- a) The reference *biopharmaceuticals* are characterised by marked molecular heterogeneity due to a variety of factors (i.e. the interplay of primary, secondary and higher-order protein structures as well as intra-/inter-molecular interactions and post-translational modifications) leading to a magnitude of chemical forms.
- b) Since 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 [4].

The large and complex structure of *monoclonal antibodies* (mAb) 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]:

- a) *In vitro* characterisation studies are required, where 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, e.g. alterations in receptor binding or stability, potentially resulting in altered safety or clinical efficacy. Clinical evaluations are required to evaluate pharmacokinetics, pharmacodynamics, efficacy and safety.
- b) 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].
- c) Because the manufacturing process of the originator product remains a trade secret even after patent expiration, there is no information on process steps (i.e. vector, host cell expression system, cell expansion procedure, protein recovery mechanism, purification process or formulation of the therapeutic protein into a drug) [12].
- d) 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 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.

Due to 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 (RCT) published on the use of infliximab (IFX) or other anti-tumour necrosis factor (TNF) biosimilars in IBD to date. The only data on efficacy can be derived from two 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 infliximab is published as an abstract [20].

PLANETAS

PLANETAS was a randomised, double-blind, multicentre prospective study comparing the pharmacokinetics, safety, and efficacy of biosimilar CT-P13 (an IgG1 chimeric human-murine mAb IFX biosimilar) and IFX in patients with ankylosing spondylitis [16]. The primary endpoint was pharmacokinetic (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 five mg/kg of CT-P13 (CELLTRION INC, Incheon, Republic of Korea) or IFX (Janssen Biotech Inc, Horsham, Pennsylvania, USA), at weeks 0, 2, 6 and thereafter q8 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 two 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.

Anti-drug antibody formation was comparable between the two 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 while there were no differences between the maintenance and switch groups.

PLANETRA

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

Patients with active rheumatoid arthritis were randomly assigned 1:1 to receive three mg/kg of CT-P13 or IFX at weeks 0, 2 and 6 and thereafter q eight 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 due to 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 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. Anti-drug antibody formation positivity was comparable between both groups and did not increase significantly during year two while on CT-P13.

Biosimilar infliximab in IBD cohort

Gecse et al [20] describe the first prospective nationwide cohort examining the efficacy and safety of the biosimilar infliximab in adult IBD patients. In total, 90 CD and 51 UC patients have been treated with the biosimilar infliximab (total number of infusions not reported). Twenty-six% of patients had previous exposure to anti-TNF treatment. Patients will be 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 infliximab 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 over two years in both patient groups.

However, extrapolation of these data to children with IBD 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 G-CSF therapy, are lacking for TNF antagonists.

The second consideration pertains to the differences in doses. The dose of IFX for IBD, five mg/kg, differs from that used for rheumatoid arthritis, three mg/kg. The third consideration is that children with IBD are often treated with monotherapy, or combination therapy with concomittant 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]: immnuosuppressive 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 concomittant 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 anti-drug 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% vs 35.9% whereas anti-drug antibodies were developed in 48.4% vs 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 ALT/AST, 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 8.3% of patients in the reference IFX group. Serious adverse events occurred in 10.0% of 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 AS, 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 infliximab 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 commercialized under the name Remsima[®] by Celltrion Healthcare and Inflectra[®] by Hospira. In September 2013 EMA approved both Remsima[®] and Inflectra[®] for treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis as well as for adult and paediatric IBD. Until now no post-marketing data on the safety of these agents have been published [27].

Concerns regarding the introduction of biosimilars

It appears that experience so far with the introduction of biosimilar therapeutic monoclonal antibodies is encouraging with regards to drug safety and effectiveness in rheumatology.

However, even minor alterations 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 due to 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 since 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 seven brands of recombinant human Granulocyte-Colony Stimulating Factor (G-CSF), potency differences of 82-105% 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®) syringes (i.e. the originator drug), an unprecedented rise in incidence of pure red cell aplasia was noted between 1998 to 2003, with some 200 cases reported in patients with chronic renal failure. An interaction of the stabilizer with the rubber cap acted as 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 two original erythropoietins and two 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 monoclonal antibody biosimilars [33].

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®/Tevagrastim, 384 with Zarzio®), the side 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] while other studies did show increased prevalence of neutralizing antibodies in individuals who experienced loss of response [35].

Still, monoclonal anti-TNF-antibody biosimilars may pose more concerns for immunogenicity and safety as these are much larger than proteins such as erythropoietin (148,000 daltons vs. 18,464 daltons, respectively). Gaining a clear understanding of the immunogenicity impact of non-anti-TNF agents has taken several years. As stated before, immunogenicity is clinically a very relevant phenomenon with both IFX and adalimumab, and impacts anti-TNF drug levels and clinical efficacy in both Crohn's 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® 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]. The authors 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-lambda ELISA for their cross-reactivity to two 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 ELISA assay for Remsima compared to Remicade. Anti-Remicade antibodies of IBD patients (n=10) exerted a similar functional inhibition on Remsima and Remicade TNF α -binding capacity (P=NS 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. The authors concluded that antibodies-to-Remicade in Remicade-treated IBD patients recognize Remsima to a similar extent, suggesting shared immuno-dominant epitopes on these two infliximab agents [44]. These currently available studies have included only adult patients, while 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 infliximab would *not* be candidates for infliximab 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. Non-inferiority 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 more than 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 other hand, a lengthy approval pathway including prolonged IBD maintenance studies may result in significant delay of biosimilars introduction into the market and thus will result in continued elevation of therapy-related health expenditure.

Post-marketing surveillance programs for efficacy, safety and immunogenicity should become mandatory in children with IBD using biosimilars, as well as when using all biological drugs. For this purpose, the paediatric IBD community recently established an international platform (PIBD-net). PIBD-net is a non-profit 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 paediatric IBD. These concerns should spark debate in the medical arena, and this information should be available to physicians who have to make the decisions about the welfare of their patients. On the other hand, the introduction of biosimilars to the market will likely decrease the costs of anti-TNF drugs by at least 30%, thereby lowering the threshold of use of these highly effective but expensive drugs in IBD. Due to the absence of published trials on the usage of biosimilars in adult and paediatric IBD, the following statements cannot be used as

recommendations for management. They reflect expert opinion designed to inform paediatric gastroenterologists and to promote consensus on proper usage of these agents in children with IBD.

The statements are accompanied by the percentage of voting members of the paediatric IBD Porto group expressing agreement: 83% [30/36] of all members voted.

STATEMENTS

EMA approved the use of biosimilars for infliximab for all indications, including adult and paediatric IBD. The ESPGHAN 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

Post-marketing 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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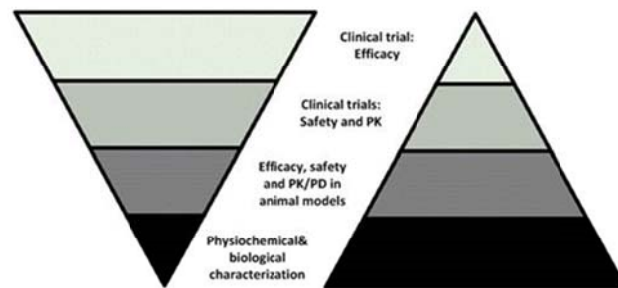
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Figure 1. The biosimilar principle

1a. Process development of new drug (original)

1b. Process development of biosimilar: reversed engineering and body of evidence

While 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, where the emphasis is on the proof of similarity (physiochemical and biological characterization). Revision of figure, derived from McCamish et al. [5]



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