



# The use of biosimilars in paediatric inflammatory bowel disease

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## Purpose of review

After expiry of the patent of originator anti-tumor necrosis factor drug infliximab (Remicade), CT-P13 was in 2013 the first infliximab biosimilar to be approved by the European Medicine Agency (EMA) for the same indications as the reference drug, including paediatric inflammatory bowel disease (IBD). The approval was based on extrapolation, after extensive in-vitro studies and clinical experience in patients with ankylosing spondylitis and rheumatoid arthritis. The extrapolation of CT-P13 to IBD and to paediatric patients raised concerns among paediatric IBD specialists.

## Recent findings

Now, almost 4 years later, we can conclude that those concerns have been resolved. There are a growing number of postmarketing studies and real-life data, so far mostly in adults and some in children with IBD. These studies show reassuring comparable efficacy, safety and immunogenicity between CT-P13 and the reference Infliximab.

## Conclusion

In Europe, biosimilars are increasingly regularly prescribed drugs in paediatric IBD. Due to their lower cost, treatment expenses have gone down considerably (up to 30% or more in some countries) and patient access has improved. However, additional well designed studies to investigate long term follow-up of biosimilars in children are still needed. In addition, clinical studies addressing pharmacokinetics, pharmacodynamics and optimal use of infliximab (originator as well as biosimilar) are still desirable.

## Keywords

adolescent, biosimilar, child, Crohn's disease, CT-P13, inflammatory bowel disease, infliximab, ulcerative colitis

## INTRODUCTION

In the past 20 years, the treatment and the management of paediatric inflammatory bowel disease (IBD) has radically changed after the introduction of mAbs. Currently, the mAb infliximab (IFX) is mostly used in paediatric IBD [1]. IFX was also the first anti-tumor necrosis factor (TNF) drug with patent expiry. Consequently, the biosimilar, CT-P13 [Remsima (Celltrion Inc, Yeonsu-gu, Incheon, Republic of Korea), Inflectra (Celltrion Inc, Yeonsu-gu, Incheon, Republic of Korea)] has been developed and approved. According to the European Medicine Agency (EMA), the definition of a biosimilar is a copy version of an already authorized biological medicinal product (the reference medicine) with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise [2]. So, in the opinion of the EMA, a biosimilar and the reference medicine are different versions of the same active substance.

Both the EMA and Food and Drug Administration (FDA) approved the use of CT-P13 in September 2013 and April 2016, respectively. After approval, CT-P13 was the first registered alternative for the original authorized IFX, Remicade. SB2 (Flixabi; Biogen, Hillerød, Denmark) followed CT-P13 and was the second biosimilar of IFX, approved in May 2016 [3]. The introduction and clinical experience of CT-P13 since EMA approval for the use in paediatric IBD will be evaluated.

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## KEY POINTS

- At approval, the biosimilar and the reference medicine are considered comparable if the differences between the biosimilar and the reference medicine are equal to or smaller than the differences between two batches of the reference medicine (or equal to or smaller than differences within the reference medicine after manufacturing changes).
- The quantity of published data is not comparable with the real-life experience with CT-P13 in PIBD.
- The number of countries using CT-P13 for PIBD as a regular treatment is growing rapidly.
- Postmarketing studies are still needed to be certain about long-term safety as for any new biopharmaceutical.
- Clinical studies investigating the infliximab treatment addressing pharmacokinetics, pharmacodynamics and optimal use in PIBD are desirable.

## CONCEPT OF THE BIOSIMILAR

The aim of biosimilar developers is not to establish an exact copy of the reference medicine but to engineer a similar version of the reference medicine that has the same efficacy and safety as the reference product [2<sup>•</sup>]. All biopharmaceuticals are medicines derived from a biological source. This makes micro heterogeneity inherent to variability of the biological expression inevitable. Apart from micro heterogeneity, over the years, small changes in the manufacturing process are made in the reference medicine [4]. All manufacturing changes are subject to EMA evaluation and are only approved in case no differences within efficacy and safety are to be expected [2<sup>•</sup>,5]. After almost 20 years of producing biological medicine, more than 400 changes in the manufacturing process have been carried through successfully [6]. To secure all these changes, the EMA has established a scientifically based regulatory framework ensuring that new versions are fully comparable to the original product [4].

The engineering process of a biosimilar starts with an analysis of the reference medicine. The aim is to reproduce the same molecular structure, receptor binding and biological activity [7]. This goes beyond molecular and pharmacokinetic equivalence to exclude any significant difference. Next, the compounds are tested *in vitro* and *ex vivo* followed by pharmacokinetics and pharmacodynamics, to proof comparability to the reference medicine [7,8].

During the nonclinical investigations of the biosimilar CT-P13, there were differences found

*in vitro*. The amount of afucosylation level differed from the reference medicine, Remicade, leading to a minimal difference in FcγRIIIa receptor binding. Apart from this, further studies showed a difference in antibody-dependent cell-mediated cytotoxicity (ADCC) from Remicade. Extended investigations followed, including demonstration of differences in binding affinities to natural killer cells but not to neutrophils, where after these differences were considered not clinically relevant both on efficacy and safety [4,5,9].

After extensive nonclinical investigation, clinical investigations are required for approval of a biosimilar [2<sup>•</sup>,5,7]. The approval of CT-P13 was based on two clinical trials [5].

The first was the PLANETAS study; this was a phase I randomized, double-blind, multicentre study comparing the pharmacokinetics, safety and efficacy of authorized IFX and CT-P13 without methotrexate in 250 anti-TNF-naïve ankylosing spondylitis (AS) patients. The primary outcome was to demonstrate comparable pharmacokinetics at a steady state in terms of area under the concentration-time curve (AUC<sub>τ</sub>), maximum steady-state serum concentration (C<sub>max, ss</sub>) between CT-P13 and Remicade. Secondary outcomes were efficacy endpoints including 20 and 40% improvement responses according to Assessment in AS international working group criteria (ASAS 20 and ASAS40) and safety. Total follow-up was 30 weeks. Pharmacokinetics profiles of CT-P13 and Remicade were equivalent. CT-P13 was well tolerated with an efficacy and safety profile highly similar to Remicade [5,10].

The last step before a biosimilar will get approval, a clinical phase III trial in the most sensitive indication of the reference medicine, is required proving the similarity [2<sup>•</sup>,11]. This was done in the PLANETRA study. The PLANETRA trial is a phase III randomized, double-blind, multicentre study combining IFX with methotrexate in patients with rheumatoid arthritis (RA). The primary goal of this study is to demonstrate equivalence of CT-P13 to Remicade, in a very sensitive study population. Therefore, adult RA patients were chosen with the American College of Rheumatology 20% (ACR20) as an endpoint to assess clinical response. After 30 weeks, CT-P13 showed a comparable ACR 20, pharmacokinetics profile and immunogenicity. It should be noted there were some serious adverse events observed in patients who received CT-P13. There was a higher incidence of serious infections, including active tuberculosis. The authors concluded that this observed difference between CT-P13 and the reference medicine Remicade was most likely based on chance finding and concluded that

efficacy, safety and immunogenicity in patients was similar in both groups [5,12].

At approval, the biosimilar and the reference medicine are considered comparable at the same level as two different batches of the reference medicine or after a manufacture change in the reference medicine itself [2<sup>°</sup>]. The aim of the Phase III was to prove similarity between the biosimilar and the reference medicine and was not designed to establish efficacy in patients, as this was already known from the reference product.

## **BENEFIT OF THE INTRODUCTION OF BIOSIMILARS: COST REDUCTION AND ACCESSIBILITY**

Probably, the most important benefit of the introduction of biosimilars is the start of competition in the market. An interesting result of this competition is a decrease of price for anti-TNF medication in general with 10% [13]. It must be noted that there may be impressive differences between official price lists and prices after negotiations. As a result, different cost reductions have been reported so far. In 2015, the Orion Pharma, in Norway, offers a discount of 72% to LIS for CT-P13 (Remsima), the national procurement organization [14]. In 2016, this led to a cost reduction of adalimumab, IFX, etanercept, certolizumab pegol and golimumab together of more than 30% compared with costs before the biosimilar introduction in Norway [13].

It is likely that the substantially lower costs will lead to a wider availability for paediatric IBD patients, a patient group in high need of effective and well tolerated treatment. Although anti-TNF has already proven very effective in the treatment of paediatric IBD, it is even more well tolerated than previously thought, as the Develop registry (industry-sponsored prospective, long-term observational registry of paediatric IBD patients) has shown that the use of IFX is not associated with an increased malignancy risk [15<sup>°</sup>]. Next to this, competition between pharmaceutical companies is an incentive to further improve clinical care for paediatric IBD and stimulate research such as the investigator initiated TISKids study [16].

## **EXTRAPOLATION OF CT-P13**

When CT-P13 was approved for the European market, the approval included all indications of the reference IFX (Remicade). Therefore, this also applied to paediatric IBD (in children >6 years old). This was based on the concept of extrapolation [5]. Extrapolation in the context of biosimilars means that efficacy and safety data are extrapolated from

one indication to another, based on evidence for the same mechanism of action [4,7]. The EMA decided on extrapolation of CT-P13 to IBD patients based on literature data, comprehensive mechanistic in-vitro tests and preliminary observational data in 23 patients with ulcerative colitis and Crohn's disease [5,10,17,18<sup>°°</sup>].

Extrapolation based on experience in adults to treatment in children is common, awaiting trials in children being performed [19]. The question is whether this is justified in case of anti-TNF biosimilars for the use in paediatric IBD. IBD is a complex disease caused by a combination of interaction between genetic determinants, disruption of mucosal barriers, aberrant inflammatory signals, loss of tolerance and environmental triggers. There are clear predominantly phenotypical differences between paediatric-onset IBD and adult-onset IBD, for example a more severe clinical presentation and a higher risk of familial disease. However, the pathogenesis, mechanisms of symptom development and histopathological features are still presumed to be comparable [20,21].

Despite this hesitation, the EMA decided to extrapolate the indications of CT-P13 also to this specific patient group. This may well be justified, as pharmacokinetics data for the reference IFX have been studied in paediatric Crohn's disease patients. The clearance of IFX is plausibly influenced by different patient factors such as albumin, body weight and the presence of antibodies against IFX [22,23]. A recent study investigated 692 patients including 112 children (mean age 13 years; mean weight 42 kg) and 580 adults (age range of total group 6–76 years) and compared pharmacokinetics and pharmacodynamics in two trials. No age-related differences in pharmacokinetics were found, but unfortunately, children of different weight and age groups were not compared separately [24]. According to recent studies, pharmacokinetics and pharmacodynamics are probably multifactorial processes also influenced by severity and extensiveness of disease, growth and maturity [21]. Further studies investigating these influences on IFX treatment in both children and adults are desirable.

## **THE USE OF BIOSIMILARS IN INFLAMMATORY BOWEL DISEASE**

After approval of biosimilars, the ECCO wrote a position statement expressing doubts about the decision of the EMA to include IBD in the approved indications on the basis of extrapolation. In their statement, they insisted on more clinical studies in IBD patients [25]. These doubts after approval have been drastically changed over the last years. In 2013

and 2015, the ECCO performed surveys asking 118 IBD specialists about their opinions and knowledge on biosimilars. The 2013 survey showed that 63% of the specialists did not have confidence in the use of biosimilars, in 2015, so in 2 years' time, this was reduced to only 19.5% [26,27]. Published data of multiple clinical trials support this changed confidence. In April 2017, Komaki *et al.* performed a systematic review including 11 observational studies (total number of patients  $n = 829$ ), including one study in children ( $n = 39$ ) [29<sup>¶</sup>]. All received CT-P13 or the reference IFX, Remicade, and during treatment, there was a switch between both drugs. They concluded that efficacy and safety of CT-P13 and Remicade had an excellent clinical comparability [29<sup>¶</sup>].

### THE USE OF BIOSIMILARS IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE

In 2015, the European PORTO group produced the first position paper on the use of biosimilars in paediatric IBD, with the following three statements:

- (1) Giving high priority to performing paediatric trials with long-term follow-up to support the decision of the EMA to approve CT-P13 for indications including paediatric IBD is advocated.
- (2) 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.
- (3) 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 [30].

Despite this priority to perform more trials since then, only a small amount of prospective, observational studies have been published, all in Poland. In that country, the reference IFX was not available resulting from administrative restrictions in most of the hospitals. This was a clear reason to switch to the biosimilar CT-P13 of Remicade. Sieczkowska *et al.* [28<sup>¶</sup>] included 39 children in the first study (32 with Crohn's disease and seven with ulcerative colitis). All Crohn's disease patients first received induction therapy with Remicade and were switched while on IFX maintenance therapy. At the moment of switching, 22 out of 32 (69%) patients were in clinical remission, defined by a Pediatric Crohn's Disease Activity Index (PCDAI) less than 10 or less than 7.5 without the 'height' item. At the end of the follow-up period of 11 months, even more patients had achieved clinical remission (28/32; 88%). Three out

of 32 Crohn's disease patients required surgery because of a complicated disease course. According to the authors, this was caused by the severity of the Crohn's disease. These patients already had high PCDAI scores while switching to CT-P13. Concerning safety, only one adverse event happened. This patient needed to stop after developing an allergic reaction to CT-P13. In 22% of the patients, mild infections were reported during treatment. Of the patients with ulcerative colitis, only four out of seven were still receiving biosimilar treatment at the moment the author wrote the article. All of them were in remission defined by a Pediatric Ulcerative Colitis Activity Index (PUCAI) less than 10 at the end of follow-up ( $5 \pm 3.6$  months). The treatment with CT-P13 was discontinued in three out of seven patients. One of those patients got a varicella zoster infection, the second an allergic reaction and the last patient was switched to adalimumab after a loss of therapeutic response following the seventh dose of CT-P13. In the latter patient, unfortunately, no IFX levels or antibodies to IFX (antibodies to infliximabs) were measured.

Sieczkowska *et al.* [28<sup>¶</sup>] also recently published a second study containing data of 36 IBD children, treated in three different academic Polish centres. Thirty of the 36 were anti-TNF naive when starting CT-P13 treatment. After a follow-up of 14 weeks, 86 and 67% of patients, respectively, had clinical response or were in clinical remission. One patient developed an allergic reaction [31<sup>¶</sup>].

The results found in both studies were comparable in response and safety to the reference IFX. Assessment of response to CT-P13 in both studies was limited to clinical and laboratory parameters, and no endoscopic procedures were performed. Therefore, unfortunately, it was not possible to compare mucosal healing between patients treated with CT-P13 and the reference IFX.

The quantity of published data is not in proportion to the real-life experience with CT-P13 in PIBD. Just like the use of CT-P13 in adults with IBD, the number of countries using CT-P13 for PIBD as regular treatment is growing rapidly. Countries that switched fully to CT-P13 are the United Kingdom, Poland, Norway and Hungary. So, more research data coming from these countries may be expected in the near future.

### BIOSIMILARS IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE; THE FUTURE

In this study, mainly the experiences with the biosimilar CT-P13 have been discussed. However, a second biosimilar of IFX, SB2 (Flixabi), has already



received approval in May 2016 [3]. Currently, there are many more biosimilars in the pipeline. Six more IFX biosimilars, and even 17 adalimumab biosimilars, are in different phases of development. The patent of adalimumab (Humira) has been expired in June 2017 within Europe and will expire in November 2017 within the USA [32].

Following approval for all biosimilars, a risk management plan (RMP) is made and published as part of the European Public Assessment Report (EPAR). In the RMP, the safety concerns and a pharmacovigilance plan for each biosimilar are described. The pharmacovigilance plan includes multiple postmarketing studies. For CT-P13, concerns about long-term safety of children in general and children with Crohn's disease and ulcerative colitis in particular were mentioned [5]. For instance, Pfizer/Hospira supports the collection of data for CT-P13 in paediatric IBD [16,33,34]. The objective of these trials is to collect real-life data regarding pharmacokinetics, pharmacodynamics, treatment strategies and long-term follow-up for these specific indications.

## INTERCHANGEABILITY

In the Europe (EU), the definition of interchangeability is changing one drug for another where the second drug is expected to achieve the same clinical effect in a given clinical setting and in any patient. The interchangeability between two biosimilars is controversial [35]. The concern is that switching between different biosimilars will lead to an increase of the risk of immunogenicity. Increased immunogenicity may lead to more adverse reactions and may limit the use of a very valuable anti-TNF medication in a vulnerable population with little alternative treatment strategies. However, previous investigations of safety signals related to interchangeability did not find any related events. According to EMA, biosimilars can be used interchangeably after approval [36,37]. However, at the moment, automatic drug substitution is not recommended by the EMA or even allowed according to the EU law [35].

## CONCLUSION

CT-P13 was the first biosimilar considered similar to Remicade. After approval by the EMA, there have been concerns by the (paediatric IBD) specialists about the similarity, safety, efficacy and immunogenicity of CT-P13 as compared with the reference IFX (Remicade).

Four years after approval, the concerns about biosimilar IFX have drastically changed. Fear of the

use of CT-P13, for PIBD, was not justified and provides reassurance for the robustness of the approval process by EMA. The first real-life data experience of CT-P13 in (paediatric) IBD confirmed similarity. However, additional well designed studies to investigate long-term follow-up of biosimilars in children are still needed. In addition, clinical studies addressing pharmacokinetics, pharmacodynamics and optimal use of both IFX originator and biosimilar are still desirable.

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