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## Biosimilars in paediatric inflammatory bowel disease

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### Abstract

The introduction of biological treatments has changed disease outcomes for patients with inflammatory bowel disease. Biologicals have high efficacy, and can induce and maintain remission after failed responses to conventional immunosuppressive and/or steroid therapy. The increasing occurrence of severe disease at diagnosis has resulted in infliximab being more often introduced as the first-line treatment in a "top-down" approach. Besides their favourable efficacy and safety profile, biologicals have one significant disadvantage, which is their high cost. This results in many patients stopping therapy prematurely, with the maintenance phase being too short. This often leads to disease exacerbation shortly after treatment cessation. Every newly started course of biological therapy can induce production of anti-drug antibodies, which can result in treatment failure and possible allergic/anaphylactic reactions. The introduction of biological biosimilars was intended to greatly reduce therapy costs thus increasing the availability of these agents to more patients. It was also anticipated that biosimilars would prevent premature termination of therapy. Analyses of paediatric data suggest that biosimilar infliximabs are equally effective as the reference infliximab. Safety patterns also seem to be similar. Paediatric experience places cost-therapy reductions at around 10%-30%.

**Key words:** Biosimilars; Paediatric inflammatory bowel disease; Infliximab; Biological treatment; Crohn's disease; Ulcerative colitis

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**Core tip:** Data on the use of biosimilars among paediatric patients are limited. Nevertheless, several original papers support adult findings that biosimilars are as effective and safe as the reference infliximab in this population.

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## INTRODUCTION

Inflammatory bowel disease (IBD) includes Crohn's disease (CD), ulcerative colitis (UC), and unclassified colitis. These diseases are characterised mainly by gastrointestinal symptoms, although extra-intestinal symptoms including general complications like mature or pubertal relapse and malnutrition can also occur. Therefore, it is very important to initiate effective treatment promptly. The introduction of biological therapies has dramatically changed treatment approaches and outcomes for patients with IBD. Biologics are medicinal products derived from living cell lines using recombinant DNA technology. At the beginning, biologics were reserved only for the most severe disease. However, the good safety profile of these agents has increasingly resulted in introduction shortly after diagnosis, especially in patients with poor prognostic factors. Early-onset IBD can have a more aggressive disease course<sup>[1,2]</sup>. Moreover, an increase in the incidence of paediatric IBD is being observed<sup>[3]</sup>. The first biologics introduced to treat IBD patients were anti-tumour necrosis factor (TNF) inhibitors. TNF $\alpha$  is an inflammatory cytokine produced by immune cells. The anti-TNF-reference molecules available to treat children with IBD are adalimumab (Humira, AbbVie) and infliximab (Remicade, Janssen). Infliximab was introduced for adult patients with IBD in 1998, and was the first biological molecule used to treat this disease. In 2007, Hyams *et al*<sup>[4]</sup> reported high efficacy and safety for infliximab among paediatric CD patients. In 2012, this was also documented in children with UC<sup>[5]</sup>. The safety and efficacy of adalimumab for children was also proven prospectively by Hyams *et al*<sup>[6]</sup>. Similar results have been presented in other retrospective analyses<sup>[7]</sup>.

## BIOSIMILARS: SIMILAR BUT NOT IDENTICAL

Biosimilars are biological products that are highly similar to the reference drugs. Their similarity needs to be proven in terms of their characteristics, biological activity, immunogenicity, efficacy and safety. Biosimilars cannot be viewed as generics because generics must be identical to the reference products. In 2013, after the licences for infliximab had expired, the first biosimilar for IBD approved by the European Medicinal Agency (EMA) was biosimilar infliximab under the brand names Remsima (Celltrion, Inc, Incheon, South Korea) and Inflectra (Pfizer, New York, NY, United States). In April 2016, the Food and Drug Administration (FDA) also approved the use of biosimilars. To be approved, all new biologics require physicochemical analyses, animal studies, clinical evaluations and clinical trials for each proposed

indication. The approval pathway is concerned mostly about clinical trials to confirm safety and efficacy. For approval of biosimilars, structural, analytical and *in vitro* similarity must be shown. A clinical trial is sufficient to prove conformity for only one indication. If equivalence is revealed, this indication can be extrapolated for all indications involving the reference drug<sup>[8]</sup>. Indeed, approval to use the biosimilar infliximab in IBD patients has been based on extrapolation. The clinical testing of biosimilar infliximab has been performed in rheumatologic diseases. A multicentre, double-blind, randomised phase I study (PLANETAS) compared the pharmacokinetics, safety and efficacy of the reference infliximab and the biosimilar infliximab (CT-P13) in 250 anti-TNF-naïve ankylosing-spondylitis patients<sup>[9]</sup>. The pharmacokinetics of both infliximab molecules were equivalent. Further, the efficacy and safety profiles were both highly similar. "PLANETRA" was a multicentre, double-blind, randomised phase III study conducted among patients with rheumatoid arthritis<sup>[10]</sup>. The patients had concomitant therapy with methotrexate. The authors ascertained that the efficacy, safety and immunogenicity of both molecules were similar. Approval by extrapolation met with deep concern among gastroenterologists, and with reluctance to initiate use. This was reflected in the first European Crohn's and Colitis Organisation (ECCO) recommendations<sup>[11]</sup>. Similar results for rheumatology were not considered sufficiently conclusive to ensure the safety and effectiveness of biosimilars in IBD patients. There was a suspicion that the different mechanisms of anti-TNF action, and especially the concomitant therapy used for rheumatic disease, might change the appearance of antibodies. Thus, the work undertaken in rheumatological conditions would not be suitable for proving the safety and efficacy of new biosimilars in IBD, especially for children. Non-clinical *in vitro* studies on CT-P13 highlighted the differences in Fc $\gamma$ RIIIa-receptor binding, and in antibody-dependent cell-mediated cytotoxicity from the reference infliximab molecule<sup>[12]</sup>. Although the differences were considered to be clinically insignificant in IBD patients, the problem was widely discussed in the context of patient safety and treatment efficacy<sup>[13,14]</sup>. An interesting study describing biological activities of CT-P13 and the reference infliximab has been published recently. Lim *et al*<sup>[15]</sup> used especially produced intestinal cells stimulated by a mixture of cytokines to start the inflammatory process to determine whether both drugs had similar functions *in vitro*. The research design included varying evaluations of the supposed anti-TNF action. Firstly, the suppression of pro-inflammatory cytokine secretion was detected. TNF $\alpha$  mobilised immune cells to the inflammatory site, which induced the extrication of inflammatory cytokines and mediators from epithelial and immune cells. Infliximab neutralised and inhibited soluble-TNF $\alpha$ , which had the effect of diminishing the expression of mediators<sup>[16]</sup>. Lim *et al*<sup>[15]</sup> detected that inhibition of the secretion of the pro-inflammatory cytokines, interleukin (IL)-6 and IL-8,

**Table 1 Treatment of Crohn's disease paediatric patients with biosimilar infliximab**

Study	Number of patients	PCDAI before treatment	Time of assessment after induction	Remission (%)
Richmond <i>et al</i> <sup>[21]</sup>	29	27.5 (7.5-55)	12 wk	67
Chanchlani <i>et al</i> <sup>[19]</sup>	29	28 (20, 40)	3 mo	79
Sieczkowska-Golub <i>et al</i> <sup>[20]</sup>	36	52.5	14 wk	67

PCDAI: Paediatric Crohn's Disease Activity Index.

was similar with both infliximab forms. This research group also evaluated how neutralisation of soluble TNF $\alpha$  induced apoptosis of intestinal epithelial cells. The induction of apoptosis in monocytes and lymphocytes by infliximab is a significant action because of the diminished cytokine release, which leads to blockade of the inflammatory response<sup>[17]</sup>. The action of infliximab in neutralising soluble TNF $\alpha$  suppresses intestinal epithelial apoptosis. For this, both infliximab forms were shown to work similarly. Another comparison aim was examination of apoptosis and cytokine suppression, which is induced by reverse signalling when infliximab molecules bind to transmembrane TNF $\alpha$ . The authors detected that the infliximabs had similar ability to induce apoptosis, and both molecules demonstrated congruous dose-dependent cytokine suppression. Other tests revealed similar results for both infliximab molecules in the case of the promotion of regulatory macrophages. Based on their analyses, the authors verified an insignificant difference in antibody-dependent cell-mediated cytotoxicity<sup>[15]</sup>.

## A STATEMENT OF BIOSIMILAR USE IN PAEDIATRICS

Shortly after biosimilars became available on the market, a statement was released about their use by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the Paediatric IBD Porto Group. The paper was an expert opinion directed at paediatric gastroenterologists taking care of children with IBD. Because of the lack of clinical trials among IBD patients, the paper could not be regarded as containing strict recommendations, and was summarised in three propositions. Firstly, the authors advocated giving high priority to conducting paediatric trials with long-term follow-up, to support EMA decisions on biosimilar approvals for paediatric IBD. Secondly, the experts did not recommend switching patients to a biosimilar during sustained remission until clinical trials verifying the safety and efficacy of biosimilars in IBD were available. Thirdly, all participants agreed that post-marketing surveillance programmes measuring the efficacy, safety and immunogenicity in children with IBD, should be a mandatory requirement for the marketing of biologics and biosimilars for specific indications<sup>[18]</sup>.

## INFLIXIMAB BIOSIMILAR EXPERIENCES

### Induction and maintenance therapy with biosimilar infliximab

Regardless of the above-mentioned statement, in some

centres biosimilars were used in paediatric IBD patients, mainly due to the unavailability of the originator molecule. Nevertheless, there are only a few studies reporting the use of biosimilars in children. A recently published multi-centre study involved 278 paediatric patients, who started infliximab-reference therapy ( $n = 175$ ), infliximab biosimilars ( $n = 82$ ) or adalimumab ( $n = 21$ ). Unfortunately, in assessing infliximab efficacy with the Paediatric Crohn's Disease Activity Index (PCDAI) score, only 24% (42/175) of the reference infliximab patients were assessed at baseline along with 35% (29/82) of the biosimilar infliximab group. At the 3-mo follow-up, the PCDAI scores were known only for 11% (19/175) and 18% (15/82) of the reference and biosimilar groups, respectively. Most of the reference infliximab (28/33 *i.e.*, 85%) and biosimilar (19/22 *i.e.*, 86%) groups presented with a response. Remission was achieved in 25/37 (68%) and 19/24 (79%), respectively. Some of the patients had their disease severity assessed by Physician's Global Assessment (PGA), with an improvement also observed. Among this cohort no unexpected adverse events occurred, but six of the 121 (5%) patients assessed at the 3-mo follow-up experienced various conditions including a rash (2 patients), fever (2 patients), blood abnormality (1 patient) and difficulty in breathing (1 patient)<sup>[19]</sup> (Table 1). A study conducted among Polish paediatric patients assessed the induction efficacy of the biosimilar infliximab. The assessment involved 36 patients from three hospitals. Three induction doses were administered to 34/36 (94.4%) patients. Fourteen weeks after the first biosimilar dose was given, a clinical response was achieved in 31/36 (86%) patients, and remission in 24/36 (67%). Only one allergic reaction was reported during the drug infusion. Mild adverse events occurred, mainly upper-respiratory tract infections. No serious adverse events were observed<sup>[20]</sup> (Table 1). Two of the above-mentioned studies compared their results to historical work in similar patient cohorts treated with the reference infliximab, with similar findings. The authors reported a similar efficacy and safety profile among both cohorts, treated with biosimilar and reference infliximabs. A study from the United Kingdom used 40 paediatric patients, most of whom were naïve for anti-TNF treatment. The cohort consisted of 29 CD and 11 UC patients, with almost all (95%) receiving concomitant therapy. The biosimilar infliximab induced remission in 14/21 (67%) patients. Significant decreases in PCDAI were observed. One patient presented with an infusion-associated allergic reaction<sup>[21]</sup> (Table 1). As with the Polish cohort patients with allergic reactions, their reactions had been affected by prior exposure to originator infliximab.

**Table 2 Switching experiences among paediatric inflammatory bowel disease patients**

Study	Number of patients	Time of follow up	Remission (%)
Kang <i>et al</i> <sup>[25]</sup>	32 CD and 6 UC	1 yr	78.9
Sieczkowska <i>et al</i> <sup>[24]</sup>	32 CD and 7 UC	8 ± 2.6 mo (range 2-11) for CD 5 ± 3.6 mo (range 0-9) for UC	88 57

CD: Crohn's disease; UC: Ulcerative colitis.

**Table 3 Biosimilars approved by the European Medicinal Agency in use among inflammatory bowel disease patients<sup>[38-40]</sup>**

Name of biosimilar	Manufacturer	Date of approval
Infliximab		
Flixabi	Samsung Bioepis	May-16
Inflextra	Hospira	Sep-13
Remsima	Celtrion	Sep-13
Adalimumab		
Amgevita	Amgen	Jan-17
Cyltezo	Boehringer Ingelheim	Sep-17
Hyrimoz	Sandoz	Jun-18
Imraldi	Samsung Bioepis	June 20016
Solymbic	Amgen	Jan-17

The paediatric data are supported by studies in adults. To date, studies assessing the efficacy and safety of biosimilars have primarily been conducted among adult patients. Komaki *et al*<sup>[22]</sup> presented a systematic review of 829 IBD patients from 11 observational studies. The patients either received biosimilar therapy from the beginning or were switched from the reference infliximab. The authors concluded that both infliximab molecules were highly similar in terms of safety and efficacy. Another systematic review, which aggregated data from 11 observational studies, was carried out by Radin *et al*<sup>[23]</sup>. A total of 1007 patients were included. The authors did not observe any significant difference in efficacy or safety between the reference infliximab and the biosimilar CT-P13. There are no data on use of the new biosimilar infliximab Flixabi (Samsung Bioepis, United Kingdom) among children.

### Switching

Only two studies in paediatric patients reported their experiments involving changing the infliximab molecule during the same course of therapy (Table 2). The first study, conducted in Poland, concerned 39 patients, 32 of whom had CD while 7 had UC. All the patients who were over 16 years of age, and all parents needed to consent to continuation of therapy with biosimilars, due to the unavailability of the reference molecule. The young people had the drug change at different times in the maintenance phase, with none presenting during follow-up with disease exacerbation after biosimilar introduction. No serious adverse events occurred, and the incidence of mild adverse events did not differ before and after drug change<sup>[24]</sup> (Table 2). The second study, conducted in Korea, was a comparison of patients after the switch

to biosimilars with those remaining on the reference infliximab therapy. The 74 patients were divided into two groups (the reference and biosimilar groups) who were followed-up for one year after therapy. Decisions on the treatment types were made by the patients and their guardians. The reference infliximab group comprised 36 patients (28 with CD and 8 with UC), while 38 (32 with CD and 6 with UC) elected to switch to CT-P13. Maintenance therapy of one-year duration was continued by 86.1% of the patients with the reference infliximab, and 92.1% with the biosimilar. Sustained remission was attained in 28/36 (77.8%) of the patients on the reference infliximab and 30/38 (78.9%) of the patients in the CT-P13-switch group. Eight of the patients taking part in the study did not finish the year of follow-up. Three achieved total remission and did not wish to continue with further therapy, three needed to change to adalimumab due to loss of response, and two were lost to follow-up. No serious adverse events or infusion-related reactions were observed<sup>[25]</sup> (Table 2). Several studies of adults assessed patients around the time of switching. Most of them aimed at assessing disease activity, safety and immunogenicity. None of the adult studies reported worsening disease after switching<sup>[26-31]</sup>.

### BIOSIMILAR ADALIMUMAB

The first biosimilar adalimumab appeared in India and was named ZRC-3197 (Exemptia - Zydus Cadila Healthcare Ltd.). A prospective, randomised, double-blind, multi-centre, parallel-group, active, controlled study among rheumatoid arthritis patients confirmed that the biosimilar adalimumab was similarly effective and tolerated as the reference molecule<sup>[32]</sup>. The licence for adalimumab in Europe expired. The currently available biosimilar substances approved by the EMA and FDA are presented in Tables 3 and 4. Many new biosimilars are in the pipeline<sup>[33]</sup>. To date, there appears to be no paper published on the use of the biosimilar adalimumab for IBD.

### CHANGES IN KNOWLEDGE OF BIOSIMILARS

One year after the biosimilar infliximab became available clinically, Danese *et al*<sup>[34]</sup> conducted an anonymous survey of gastroenterologists to assess their knowledge and perception about the biosimilars that were emer-



**Table 4 Biosimilars approved by the Food and Drug Administration in use among inflammatory bowel disease patients<sup>[41]</sup>**

Name	Brand name	Date of licensure
Infliximab		
Infliximab-abda	Renflexis	Apr-17
Infliximab-dyyb	Inflectra	Apr-16
Infliximab-qbtx	Ixifi	Dec-17
Adalimumab		
Adalimumab-adbm	Cyltezo	Aug-17
Adalimumab-atto	Amjevita	Sep-16

ging. Within the time frame from the appearance of the biosimilars to the analysis, there was a change in opinion as ascertained by observational studies and personal experience. Among all the participants, 83% had access to biosimilars. One year after the introduction of biosimilars, only 19.5% of the respondents felt no confidence in them. This reflected a substantial drop compared with the 63% reported in 2013. There were no significant changes in the granting of permission for automatic substitution (89.8% vs 84.8% in 2013). The change of mind was about interchangeability. Only 5.9% of respondents in 2013 thought that the two infliximab forms were interchangeable compared with 44.4% in the survey. In 2013, 72.3% would not switch during maintenance therapy. Currently, 39.9% would not switch, due to concerns about insufficient safety data<sup>[34]</sup>. Apprehension about interchangeability is still high, especially as more new biosimilar molecules might soon be available.

## COST SAVINGS

The high efficacy and safety of biologics makes them the preferred therapy type. The main limitation of their use is high cost. Because of the expense of therapy, biologics are usually used in the most severe disease forms. Furthermore, therapy is often discontinued too early due to cost limitations. The introduction of biosimilars raised great expectations regarding reductions in therapy costs<sup>[35-37]</sup>. Cost reductions bring enormous benefits through making treatment available to a greater number of patients, and increasing the possibility of a long maintenance phase. In two paediatric studies, calculations of cost reductions were done. In a Scottish paediatric study, the average cost reduction was around 38%<sup>[21]</sup>. A recently published United Kingdom study confirmed savings during one-year of therapy of around 10%-30%<sup>[19]</sup>.

## CONCLUSION

To date, published data on paediatric IBD remain limited. Nevertheless, the above-mentioned studies show that the efficacy and safety of biosimilars and the originator infliximab are similar. The results are comparable to data on adults.

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