

Switching from infliximab to biosimilar in inflammatory bowel disease: overview of the literature and perspective

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Abstract

Background: Biological therapy has revolutionized the treatment of inflammatory bowel disease (IBD). After the expiration of patents for biological innovator products, development of biosimilars increased. CT-P13 was the first biosimilar approved for the same indications as the reference product; however, the approval was based on extrapolated data from rheumatoid arthritis and ankylosing spondylitis. Our aim was to review clinical studies about switching from originator infliximab (IFX-O) to biosimilar infliximab (IFX-B) in IBD, focusing on recently published data and the future of biosimilars.

Methods: The PubMed database was searched for original articles published up to 1 December 2018 reporting data on IFX-B in IBD.

Results: A total of 29 studies assessing switching from IFX-O to IFX-B, 14 assessing induction therapy with IFX-B were found. Efficacy, safety and immunogenicity were discussed. Studies confirm that CT-P13 is safe and equally efficient as the reference product for both induction and maintenance therapy; and that switching from the reference product to biosimilar is non-inferior to continuous biosimilar use. However, efficacy and safety data on Flixabi (SB2) in IBD patients is lacking.

Conclusion: Switching from the originator to a biosimilar in patients with IBD is acceptable, although scientific and clinical evidence is lacking regarding reverse switching, multiple switching and cross-switching among biosimilars in IBD patients.

Keywords: biosimilar, inflammatory bowel disease, infliximab, switching

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Introduction

Infliximab (IFX) is a chimeric human–murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor alpha (TNF- α). TNF- α receptor activation is prevented by IFX through binding to TNF- α , thereby neutralizing its biological activity. This monoclonal antibody was first authorized in the European Union (EU) in August 1999 under the invented name of Remicade.^{1,2} Previously, IFX biological therapy was effective in inducing and maintaining remission in Crohn's disease (CD) and ulcerative colitis (UC) in large clinical trials^{3–5} and can change disease outcome by decreasing the rate of hospitalizations and surgery.^{6,7}

Expiration of patents for biological innovative products, including monoclonal antibodies (mAbs), has facilitated the development of similar versions of the original biopharmaceutical products, termed biosimilars. According to the World Health Organization definition, biosimilars are biotechnological products that are comparable with an already approved reference product in quality, nonclinical and clinical evaluation.

Extrapolation is the extension of efficacy and safety data originated from an already approved therapeutic indication for which the biosimilar has been clinically tested, to other indications for which the innovator product has been previously authorized. Importantly, we can take extrapolation into

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consideration only on a 'case by case' scientifically justified approach, based on overall comparability evidence.⁸ In the EU, when 'biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification'.⁹ Similarly, in the USA, the US Food and Drug Administration (FDA) requires sufficient scientific justification for extrapolating clinical data to support determination of biosimilarity for each condition, of use for which licensure is sought.¹⁰

In June 2013, the European Medicines Agency's Committee for Medicinal Products (CHMP) recommended the authorization of Inflectra and Remsima as biosimilar medicinal products containing IFX. Therapeutic indications as well as dosing regimen are the same as those of Remicade; the pharmaceutical form (concentrated powder for solution for infusion) and strength (100 mg IFX per vial) is also the same. Biosimilars were approved for all treatment indications of the reference product (RP), including rheumatoid arthritis (RA), adult and paediatric CD, adult and paediatric UC, ankylosing spondylitis (AS), psoriatic arthritis and psoriasis.^{1,2}

The second biosimilar to IFX gain marketing authorization in Europe (as Flixabi) in April 2016 was SB2. It received authorization for the treatment of RA, adult and paediatric CD, adult and paediatric UC, AS, psoriatic arthritis and psoriasis.¹¹ Clinical data derived from two studies were the basis of the regulatory approval. One of the studies was a randomized, phase I pharmacokinetic study, which compared SB2 and Remicade in 159 healthy individuals.¹² The other study was a randomized, double-blind, multinational, parallel-group, phase III study, which compared SB2 with the IFX RP in 584 patients with moderate-to-severe RA despite methotrexate therapy.^{13,14} SB2 maintained similar efficacy, safety and immunogenicity with IFX for up to 54 weeks in patients with moderate to severe RA. Radiographic progression was comparable at 1 year.¹⁴ There are no real-life data available in the field of IBD yet. Open-label extension of this study was also published by Smolen *et al.*¹⁵ At week 54, 94 patients on Remicade were transitioned to SB2 (Remicade/SB2), 101 patients on the originator continued to receive originator (Remicade/Remicade), while the 201 patients on SB2 continued to receive SB2 (SB2/SB2). The safety, immunogenicity and efficacy profiles remained comparable between the groups to week 78, revealing that there were no emergent

treatment issues or clinically relevant immunogenicity after switching from Remicade to SB2.

According to economic studies, IFX biosimilars (IFX-Bs) result in substantial cost reductions for IBD-related healthcare. It is assumed that biosimilars may cost 15–75% less than the originator product. If the achieved budget savings were used to cover more biological therapy, several additional IBD patients could be treated. To be noted, only 13% and 15% of clinically eligible CD and UC patients had access to biological therapy in the United Kingdom in 2012.^{16–20}

At the beginning of the biosimilar story in IBD, many physicians who treated patients with IBD opposed extrapolation from other indications. For example, according to the European Crohn's and Colitis Organization (ECCO) position statement, a biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication in which the reference biological was safe and effective.²¹ ECCO advocates the need for specific evidence in patients with IBD to establish efficacy and safety for this condition.

The PubMed database was searched for original articles published up to 1 December 2018 reporting data on IFX biosimilar (IFX-B) in IBD. The key words were: (infliximab and biosimilar) and (inflammatory bowel disease). A total of 29 studies (Table 1) assessing switching from IFX originator to biosimilar CT-P13^{22–50} and 14 assessing induction therapy with IFX-B CT-P13 were found.^{32,39,43,46,51–60}

In this article, we provide an updated review of switching from IFX originator (IFX-O) to IFX-B in patients with IBD, with discussion focusing on recently published data.

Are the originator and the biosimilar infliximab similar concerning immunogenicity and efficacy?

According to the European Medicines Agency (EMA)'s workshop in 2009 on biosimilar mAbs, the question 'Should the biosimilar framework be expanded to include products with differences in the amino-acid sequence?' was discussed. The general consensus was that the biosimilar and RP 'have to be the same, and avoidable changes such as amino-acid substitutions should not be allowed'.⁶¹ During the authorization process of a biosimilar

Table 1. Observational studies: switching from originator infliximab to CT-P13 biosimilar.

Study	Country, year	CD	UC	Switch CD/UC	Follow-up week	Stop, %	AEs, %	ADA, %
Jung <i>et al.</i> ³⁵	Korea, 2015	59	51	27/9	54	7.4/33.3	2.7	n.a.
Sieczkowska <i>et al.</i> ²⁵	Poland, 2016	32	7	32/7	32	6.25/ 43	2.5	n.a.
Smits <i>et al.</i> ²⁶	The Netherlands, 2017	57	24	57/24	52	7	6	8
Guerrero Puente <i>et al.</i> ²⁸	Spain, 2017	23	13	23/13	33.6	2.7	8.3	n.a.
Eberl <i>et al.</i> ²⁷	Finland, 2017	32	30	32/30	16	0	4.8	3.2
Fiorino <i>et al.</i> ²⁹	Italy, 2017	313	234	97	24	5.2	12.1	n.a.
Argüelles-Arias <i>et al.</i> ²³	Spain, 2017	67	31	67/31	52	12.2	11.2	n.a.
Buer <i>et al.</i> ³⁰	Norway, 2017	99	44	99/44	26	0.7	14.1/2.2	3.5
Razanskaite <i>et al.</i> ³⁸	United Kingdom, 2017	118	23	118/23	n.a.	28.7	n.a.	40
Schmitz <i>et al.</i> ²²	The Netherlands, 2017	86	47	86/47	52	26	9.8	6
Jahnsen and Kaasen Jørgensen ³²	Norway, 2017	37	19	37/19	26	0	0	n.a.
Kolar <i>et al.</i> ³⁴	Czech Republic, 2017	56	18	56/18	56	3.6/11.1	n.a.	6
Tursi <i>et al.</i> ³⁹	Italy, 2017	0	29	0/11	52	n.a.	0	n.a.
Avouac <i>et al.</i> ⁴⁰	France, 2018	41	23	41/23	34	4.7	4.7	n.a.
Binkhorst <i>et al.</i> ⁴⁴	The Netherlands, 2018	135	62	135/62	16	10	6.1	3
Kang <i>et al.</i> ⁴¹	Korea, 2018	32	6	32/6	52	7.8	60.5	2.6
Strik <i>et al.</i> ⁴²	The Netherlands, 2018	61	59	60/58	16	0	80	4
Ratnakumaran <i>et al.</i> ⁴³	United Kingdom, 2018	173	14	173/14	52	2.1	4.7	n.a.
Bergqvist <i>et al.</i> ⁴⁵	Sweden, 2018	195	118	195/118	52	n.a.	2.2	2.7
Armuzzi <i>et al.</i> ⁴⁶	Italy, 2018	87	68	87/68	52	3.9	11.6	n.a.
Smits <i>et al.</i> ⁴⁸	The Netherlands, 2018	57	24	57/24	104	12.1	9.6	8.4
Høivik <i>et al.</i> ⁴⁹	Norway, 2018	99	44	99/43	72	8.4	2.8	1.4

ADA, antidrug antibody; AEs, adverse events; CD, Crohn's disease; n.a., not applicable; UC, ulcerative colitis.

drug, extensive comparability exercises, including physicochemical characteristics and *in vitro* and *ex vivo* biological analyses are made.

Based on physicochemical characterization studies, IFX-B is identical to RP in terms of primary structure, while it is highly similar in higher-order

structure, monomer and aggregate contents, overall glycan type and distribution, potency and binding affinity.⁶²

Based on comparability exercises, Remsima and Inflectra were similar to Remicade in all major physicochemical parameters and biological activities. A minor difference in the amount of afucosylated IFX was remarked upon by the CHMP, translating into a lower binding affinity towards specific fragment-crystallizable (Fc) receptors and a lower *ex vivo* antibody-dependent cellular cytotoxicity activity. However, this difference was not considered clinically meaningful, as it did not influence the activities of Remsima or Inflectra in experimental models regarded as more relevant to the pathophysiological conditions in patients.^{1,2}

The cornerstone of the approval of CT-P13 was based on data from two randomized, controlled, double-blind clinical trials in RA and AS, which showed equivalent outcomes between IFX-O and CT-P13.^{63,64} The EMA license for the use of CT-P13 in IBD was granted on the basis of extrapolation from rheumatology data. In 2017, the extension study of PLANETRA and PLANETAS showed that switching from RP to its biosimilar CT-P13 is possible without negative effects on safety or efficacy in patients with AS.^{65,66} Furthermore, switching from the IFX RP to CT-P13 after 1 year of IFX RP treatment showed continued comparable efficacy, immunogenicity and safety, to maintenance of CT-P13 treatment during the second year of the treatment.⁶⁶ In PLANETRA, similar results were demonstrated in RA patients.⁶⁵

As both reference IFX and its biosimilar were comparable, cross-immunogenicity can develop. Ben-Horin and colleagues have demonstrated ($n = 125$) that anti-Remicade antibodies in patients with IBD recognize and functionally inhibit Remsima to a similar degree, suggesting similar immunogenicity and shared immunodominant epitopes on these two IFX agents.⁶⁷ Ruiz-Arguello and colleagues revealed that anti-IFX antibodies of patients with rheumatic diseases treated with Remicade, cross-react with either Inflectra or Remsima.⁶⁸ A study revealed that despite additional epitopes possibly found in the biosimilar, epitopes influencing the immune response to IFX are also present. This suggests that Remicade-treated antidrug antibody (ADA)-positive patients should not switch to

the biosimilar, since antibodies can interact with biosimilar and loss of response may occur.⁶⁷ These findings support the use of therapeutic drug monitoring before switching.⁶⁷ Another study found that in UC early trough levels (TLs) were predictive for short- and medium-term clinical efficacy whereas in CD, week 2 TLs were associated only with short-term clinical outcomes.⁶⁹

Clinical trial data and observational studies concerning immunogenicity and efficacy

Data available about the safety and efficacy of switching from IFX-O to IFX-B are increasing. One of the largest studies was the PROSIT-BIO, and the prolonged follow up was the PROSIT cohort, which enrolled 810 patients with IBD (452 CD, 358 UC): A total of 459 patients were naïve to anti-TNF- α therapy, 196 had a previous exposure to biologics and 155 were switched to CT-P13 (Inflectra or Remsima because of different local regulations) after a mean of 17 infusions of IFX. Infusion reactions occurred in 17%, 29% and 11.6% of each group, respectively. Infusion reactions and drug discontinuation for infusion reactions were two- and threefold more frequent in patients pre-exposed to IFX, respectively. Therapy failure rate was 7.4% in TNF-naïve patients, 7.6% in the previous biologic therapy group and 2% in the switched group. Efficacy after 1 year was 71% for the naïve, 64% for the pre-exposed and 82% for the switched groups. The limitation of this study was that no data of TLs or ADAs were available.^{29,46}

The first randomized, non-inferiority, double-blind, phase IV trial with 52 weeks of follow up, the NOR-SWITCH, was recently published.²⁴ Patients with informed consent were randomized in a 1:1 ratio to either continue IFX-O or to switch to CT-P13 treatment, with unchanged dosing regimen. A total of 482 patients were enrolled and randomized (241 to IFX-O, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the IFX-O group and 206 in the CT-P13 group). Patients were diagnosed with CD (31%), UC (19%), spondyloarthritis (19%), RA (16%), psoriatic arthritis (6%) and chronic plaque psoriasis (7%). Disease worsening occurred in 26% of patients in the IFX-O group and 30% of patients in the CT-P13 group. The frequency of adverse events was similar between groups (for serious

adverse events, 10% for IFX-O to 9% for CT-P13; for overall adverse events, 70% *versus* 68%; and for adverse events leading to discontinuation, 4% *versus* 3%, respectively).²⁴

A study, sponsored by Celltrion, has been designed to assess non-inferiority in efficacy and to assess the overall safety of CT-P13 compared with IFX in patients with active CD up to week 54 [ClinicalTrials.gov identifier: NCT02096861]. This study will also provide information about switching from IFX-O to CT-P13 and from CT-P13 back to IFX; the enrolment is closed with 214 patients included but no data are available yet. The SIMILAR trial [ClinicalTrials.gov identifier: NCT02452151] is a randomized, double-blind, parallel study performed in The Netherlands. The trial will compare the efficacy of IFX-B with IFX-O to demonstrate its non-inferiority in patients with IBD in remission under treatment with IFX up to 3 months.²⁹

The largest study with a 1-year follow-up period was published by Bergqvist and colleagues.⁴⁵ In this prospective, observational study, 313 IBD patients were switched from IFX-O to CT-P13. At 12 months, 68.2% of CD and 78.9% of UC patients were in remission, respectively. TLs did not change significantly during follow up, furthermore, they found no significant difference between patients with or without an immunomodulator.

The longest, prospective, observational study results were published by Smits and colleagues.⁴⁸ A total of 83 IBD patients were enrolled in the study. In their cohort, 66% of IBD patients continued CT-P13 beyond 2 years after switching from Remicade. Main reasons for discontinuation was loss of response, adverse events and stable disease remission. They found that TL remained unaffected and disease activity did not change significantly during the 2-year follow-up period.⁴⁸ A study conducted in the Czech Republic included 74 IBD patients who switched to IFX-B (prospectively followed patients) and 119 naïve patients with newly initiated therapy (retrospectively assessed). They found no difference in C-reactive protein and faecal calprotectin at week 56 compared with week 0. No increase in immunogenicity was found in switched patients, and the type and frequency of adverse events were comparable with the original preparation in both cohorts.³⁴ Schmitz and colleagues published a multicentre observational prospective cohort study including 133 IBD patients with a

follow-up period of 52 weeks. They found no differences in drug levels and disease activity between IFX innovator and biosimilar. The high proportions of discontinuers were mostly due to elective withdrawal or subjective disease worsening.²² A total of 143 IBD patients were switched from Remicade to Remsima in a study from Oslo, published by Buer and colleagues. The follow-up period lasted 6 months; 97% of patients remained on the medication throughout the follow up. They found switching from Remicade to Remsima was feasible and with few adverse events, including very limited antidrug antibody formation and loss of response.³⁰ Other, previously published studies detected similar results, as switching from Remicade to CT-P13 biosimilar is well tolerated with comparable efficacy, safety and interchangeability with its originator.^{30,31,35,38,51} Studies conducted in the paediatric population found that IFX-B seems to be as effective and safe as its originator.^{25,41,47}

A large study from Denmark including 802 patients diagnosed with RA, AS and psoriatic arthritis revealed that the nationwide nonmedical switch to CT-P13 had no negative impact on disease activity. Adjusted 1-year CT-P13 retention rate was slightly lower than for IFX in a historic cohort.³⁶ In a study conducted in biosimilar-naïve paediatric patients, efficacy and occurrence of adverse events were similar in original and biosimilar groups, only the cost reduction was significantly higher in the biosimilar group.⁵⁴

According to a recently published Spanish observational study, the factors associated with relapse were similar to those expected in patients continuing with Remicade. They found that longer clinical remission time before switching and detectable IFX levels at the time of switching were associated with a lower risk of relapse.²⁸ In another study where maintenance IFX therapy was switched to IFX-B, no changes were detected in disease activity after switching. In UC patients TLs before and after switching differed significantly, but clinical significance for this difference is doubtful.²⁷ In a Norwegian study, none of the patients had to discontinue IFX treatment due to loss of response, which was explained by a higher number of therapy escalations based on plasma IFX level alone.

Controversial data are coming from studies according to ADA formation and infusion reactions after switching to CT-P13. A prospective, multicentre, nationwide cohort from Hungary reported on 210

consecutive patients (126 CD and 84 UC).⁶⁰ Clinical remission rates at week 14 were significantly higher in IFX-naïve CD and UC patients, compared with those with previous exposure.⁶⁰ CT-P13 drug TLs and ADAs in IBD patients at weeks 0, 2, 14 and 30 were in line with results reported for the originator. Early TLs were slightly lower in UC compared with CD. Patients with previous exposure to anti-TNFs had lower early TL coupled with ADA positivity and were more likely to develop infusion reactions.⁶⁰ However, Fiorino and colleagues reported in a single-centre cohort study on 100 IBD patients (59 CD, 41 UC; 52 naïve to CT-P13, 18 switched from IFX-O to CT-P13 and 30 controls continuing the originator) that those receiving CT-P13 had no increased risk of secondary loss of response, infusion reactions or development of ADAs.⁷⁰ In the SECURE trial, serum concentrations of IFX 16 weeks after switching to CT-P13 were non-inferior to those at baseline in patients with stable UC and CD.⁴²

Switching from infliximab to biosimilar: does any debate remain?

Development of biosimilars is challenging, because any slight changes in the drug structure (e.g. changes in the protein by altering the amino-acid sequencing as well as the protein folding) have the potential to modify the efficacy, safety and quality of the drug in development. Even without changes to the reference drug by the manufacturer, slight modifications in the molecule's construction may occur as a result of changes in the production site, or in the method of production (e.g. new technologies used in an effort to increase production).⁷¹ The originator product will have varied over its lifetime. Pre- and postchange products have already been used in patients and both can be on the market at the same time; therefore, several switches can and do occur between these products during the course of a treatment regimen.⁷²

A meta-analysis of 11 observational studies reporting outcome in 829 patients treated with IFX-B found that pooled rates of clinical response among CD and UC at weeks 8–14 were 0.79 and 0.74, respectively, and at weeks 24–30 were 0.77 and 0.77, respectively. The pooled rates of sustained clinical response among CD and UC after switching from IFX-O to CT-P13 at weeks 30–32 were 0.85 and 0.96, respectively, and at weeks 48–63 were 0.75–0.83, respectively. Adverse events were rare in CD and UC as well (0.1 and 0.22).⁷³

Although more studies are published on the efficacy and safety of CT-P13 in IBD, an evidence-based statement about the use of biosimilars is still not available. Published studies have reported no significant difference from IFX-O, so far.^{73,74} IFX-B tolerability and safety in IBD was extrapolated from RA and AS trials,^{63,64} while real-life data were congruent with it^{35,51,55,56,58–60,75} and also contributed to significant cost savings in the health budget.^{32,38} Studies also confirmed the long-term efficacy and safety of CT-P13 therapy.⁵⁷

Second biosimilars: are they interchangeable?

The effect of multiple switches from the original biologic to a biosimilar, then to a different biosimilar is not well known. The recently published EGALITY study conducted in patients with plaque-type psoriasis was a phase III confirmatory efficacy and safety study. The objective of the study was to evaluate effects of repeated switching (three consecutive switches until week 30) between GP2015 and etanercept. None of the treatment groups were positive for binding ADAs in the treatment period. These results suggested that multiple switches between the abovementioned two biologics had no effects on clinical data.⁷⁶

In the field of IBD, CT-P13 was the first biosimilar to IFX to obtain approval by the EMA in September 2013. In May 2016, a second biosimilar to IFX called SB2 received marketing authorization in Europe. In years to come, more and more biosimilars for IFX will be available; therefore, it is crucial to standardize the regulatory legislation, clarification of interchangeability and substitution of IFX. Currently, clinicians often need to decide about switching from the reference biologic agent to a biosimilar. In future, switching to a new biosimilar, 'reverse switching' back to the RP, or 'cross-switching' from one biosimilar to another might also have to be considered.⁷⁷

Conclusion

The availability of biosimilars on the market is considered a breakthrough due to the pharmacoeconomic implications. One of the most crucial drivers of biosimilar use is cost saving and therefore higher patient access. The cost saving will probably allow earlier access of patients to biological therapy, which can affect IBD's natural course. Early in the story of biosimilars, issues

surrounding indication extrapolation were focused upon; whether IFX-B can really be equally effective and well tolerated in IBD patients. In 2014, after approving the two IFX-B mAbs, a 15-question multiple choice anonymous web survey was supported by ECCO.⁷⁸ They found that only 6% of responders thought that the originator and biosimilar mAb were interchangeable. Based on available, long-term, follow-up studies, CT-P13 can be administered safely in daily clinical practice for induction and for maintenance of clinical remission. Switching from reference IFX to IFX-B had no detrimental effect on efficacy, safety, or immunogenicity compared with continuous IFX-B therapy, according to the extensions of PLANETAS, PLANETRA and available real-world data in IBD, based on clinical retrospective and prospective studies. Now it seems that in the case of CT-P13, the previous 6% reaches 100%; switching from originator to IFX-B is safe, without the risk of loss of response. In switching to the SB2 biosimilar, we do not have safety and efficacy data from the IBD population; therefore, long-term duration of follow-up studies with measurement of TLs and antibody levels, as well as observation for divergence of similarity over time are awaited.

In the future, even after EMA approves biosimilars, postmarketing surveillance and prospective follow-up studies are needed to ensure interchangeability of different biosimilars and to demonstrate the lack of switch-related changes in safety and efficacy or immunogenicity. It is important that every newly registered biosimilar has to follow these rigorous standards. Only one question remains: the forced, nonmedical switch; usually, to save money. Based on the available data published so far, insurance companies may initiate the nonmedical switch, which must be accepted by physicians and patients, as well.

Switching from the originator to a biosimilar in patients with IBD is acceptable; however, with regards reverse switching, multiple switching and cross-switching, scientific and clinical data are still lacking.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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