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MINIREVIEWS

Biosimilars in inflammatory bowel disease: A review of post-marketing experience

Simona Deiana, Tommaso Gabbani, Vito Annese

Simona Deiana, Tommaso Gabbani, Vito Annese, Division of Gastroenterology, AOU Careggi University Hospital, 50139 Firenze, Italy

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Correspondence to: Vito Annese, MD, Emergency Department, Division of Gastroenterology, AOU Careggi University Hospital, Largo Brambilla 3, 50139 Firenze, Italy. annesev@aou-careggi.toscana.it
Telephone: +39-55-7946035

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Abstract

Biologic compounds are obtained from living organisms or cell cultures by means of biotechnology methods. A similar biologic drug, commonly called biosimilar, is a product copied by a native approved biologic drug whose license has expired. Biosimilar drugs usually are marketed at a lower price and provide important financial savings for public healthcare systems. Some differences between biosimilars and original biologic drugs might exist but they are acceptable if they fall within defined "boundaries of tolerance": differences in some features between the two molecules are considered important only if clinical relevant. Considering that the efficacy of the innovator biologic drug has already been established, the clinical studies required for approval of a biosimilar could be reduced compared with those required for the approval of the originator. In this review, real life data available in inflammatory bowel disease patients treated with biosimilars are reported, documenting in general satisfactory outcomes, sustained efficacy and no sign of increased immunogenicity, although, further controlled data are awaited.

Key words: Adalimumab biosimilar; CTP-13; ZRC-3197; Infliximab biosimilars; Biologic drugs

Core tip: Some differences between biosimilars and original biologic drugs exist but they are acceptable if they fall within defined "boundaries of tolerance": variations in some features of the two molecules are considered important only if clinical relevant. Several real-life clinical data are already available in inflammatory bowel disease patients treated with biosimilars with satisfactory outcomes, but further controlled trials are awaited.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic immune-mediated inflammatory gastrointestinal disorders that lead to impaired quality of life, disease complications and frequent need of surgery and hospitalization[1,2]. They represent a global public health problem; more than 3.5 millions of people are affected in Europe alone with a direct healthcare cost of 4.6-5.6 billions of Euros/year[3]. The prevalence of inflammatory bowel disease (IBD) is expected to increase further due to the early age of onset, the lifelong course and no increased mortality, therefore an appropriate long-term control of the disease is mandatory considering its social and economic burden. The introduction of targeted biological therapies has significantly improved the outcomes of IBD patients.

Infliximab was the first biological therapy approved in IBD followed by other anti-TNFα drugs (Adalimumab, Certolizumab, Golimumab) and by anti-integrin antibodies (Natalizumab, Vedolizumab). Other agents are under investigations in IBD, as Ustekinumab and Tofacitinib[4].

In the therapeutic paradigm, biological therapy was generally considered as separated from "conventional" treatment strategy, which includes mesalazine, glucocorticoids and oral immunosuppressants. The reasons are mostly related to the unknown safety profile of the biologics when they were first approved and their high cost. However, this distinction is not justified yet, especially by considering the progress made in the field of biological therapy and the advent of biosimilar drugs.

In response to the high cost of reference biological drugs and with the recent or imminent patent expiry, interest in biosimilars has grown. Because of their lower cost, they lead to a significant cost savings for the health community, increased earlier access to biological therapy and may facilitate the efficient allocation of the always limited financial resources[5]; more patients in the world could access biological agents earlier with also the possibility to switch from costly originator versions to biosimilar alternatives[6]. Biosimilars are expected to save 11.8-33.4 billion Euros between 2007 and 2020 in the EU and 44.2 billion US dollars over the 10-year period between 2014 and 2024[7].

BIOLOGICAL THERAPIES AND BIOSIMILARS

Biological products (or biologics) are defined as active substances derived from living cells or organisms with the aid of biotechnology methods (recombinant DNA, controlled gene expression, antibody technologies)[8]. The relatively high price of biologic agents and their recent or impending patent expiration has led to development of similar versions of these drugs, called "biosimilar agents". The World Health Organization defines a biosimilar as a "biotherapeutic product" which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product[9]. Indeed, post-translational modifications, in particular glycosilation, are specific to the individual production process; no two batches of a single biologic [either a reference product (RP) or a biosimilar] will ever be identical[10]. Those differences are acceptable if molecule falls within defined "boundaries of tolerance": variations in some features of the two molecules are only considered important if they are clinical relevant[11,12]. This principle applies also to biosimilars and their differences from RP are not significant if there are no clinically meaningful differences between the two drugs in terms of safety, purity and potency[13]. Comprehensive comparability testing is required to prove biosimilarity and to show that any differences found are not clinically meaningful: biosimilars undergo a strict regulatory process that involves proving structural, functional and biological biosimilarity to the RP.

Considering that the efficacy of the original biologic drug has already been confirmed, the clinical studies required for the approval of a biosimilar could be significantly less compared with clinical trials required for the approval of the reference product. Moreover, developing a biosimilar give the opportunity to pharmaceutical companies to get the authorization for all indications held by the native biologic drug, the so-called "extrapolation". Extrapolation of data from one indication to another is also a pivotal aspect of biosimilar development[14-16]. Food and drug administration (FDA), Health Canada and European medicines agency (EMA) in the past have usually allowed the medical companies to perform extrapolation for all indications, thanks to comparability exercises without real clinical data for all indications[15].

INFLIXIMAB AND INFLIXIMAB BIOSIMILAR

Several multicenter, randomized, double-blind clinical trials have established the efficacy and safety of the infliximab in the treatment of IBD[17-19]. The results of the ACCENT Ⅰ study[20] laid the foundations for the management and dosage of infliximab in CD patients in clinical practice. The major experience with infliximab in UC is based on the pivotal ACT trials; ACT Ⅰ and ACT Ⅱ demonstrated that Infliximab is able to induce clinical remission, mucosal healing and steroid sparing in UC patients[21].

The CT-P13 (Remsima-Celltrion, Incheon, South Korea and Inflectra-Hospira, Lake Forest, IL, United States), which is the first biosimilar agent of Infliximab,

has been approved for the therapy of IBD and other autoimmune diseases in India and South Korea during the year 2012[22]. Today more than 34000 patients in more than 40 countries worldwide have been treated with this drug[23]. Two pivotal trials conducted in rheumatologic diseases have demonstrated its efficacy and its safety. The first randomized, phase Ⅰ, double-blind study was performed in patients with ankylosing spondylitis. In this study the CT-P13 pharmacokinetic was demonstrated to be similar to that of the original drug. Moreover, the two biosimilar drugs showed good performance in terms of efficacy and safety[24].

Subsequently a phase Ⅲ, double-blind study was performed in 604 rheumatoid arthritis patients. Two groups of patients were randomized to receive CT-P13 or Infliximab, at the same dose of 3 mg/kg and both received also methotrexate. The two patient groups showed similar response rate, drug-related adverse events and development rate of anti-drug antibodies at the end of the study[25].

Regarding immunogenicity, it is well-known that is common to most biologics including Infliximab. It is associated with the loss of response, an increased rate of infusion reactions and other adverse events[26]. The degree of immunogenicity is not the same for all biologics and only minor differences in the formulation, purity or packaging of a biological drug can affects its immunogenicity profile. In both PLANETAS and PLANETRA[24,25] study, anti-drug antibodies (ADAs) against CT-P13 and Infliximab were measured with similar findings for the two agents. During the extension phase, ADA incidence was comparable between maintenance and switches groups and did not increase significantly.

All these data further support the extrapolation of CT-P13 to all the indications for which IFX is approved. Although clinical efficacy has only been demonstrated in rheumatologic diseases, in September 2013 EMA approved the biosimilar of infliximab not only for treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, but also for IBD in adults and children. Even if the number of IBD patients treated with CT-P13 is limited, clinical experience is growing and initial data are now available: some studies have been published as full articles and some additional studies have also been presented only in abstract form (Table 1).

CT-P13 POST-MARKETING STUDIES IN ADULT IBD

No randomized controlled trials are available on the use of CT-P13 in IBD. A randomized, double-blind, parallel group study, the NOR-SWITCH study (ClinicalTrials.gov identifier: NCT02148640) is currently being pursued in Norway. The purpose of this study is to assess the safety and efficacy of switching from infliximab to the biosimilar treatment Remsima in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, CD and chronic plaque psoriasis. It was estimated to be completed in May 2016, but fully published data are not available yet. Another study, sponsored by Celltrion, has been designed to assess non-inferiority in efficacy and to assess overall safety of CT-P13 compared to infliximab in patients with active CD up to week 54 (ClinicalTrials.gov Identifier: NCT02096861). This study will also provide information about switching from infliximab to CT-P13 and from CT-P13 back to infliximab; the enrolment is closed with 214 patients included but no data are available yet.

An open-label, retrospective, multicenter study has evaluated the safety and the efficacy of CT-P13 (Remsima®) in patients with IBD in South Korea[27]. One hundred and seventy-three patients were included: 95 patients with moderate-to-severe CD and 78 patients with moderate-to-severe UC. Treatment-related adverse events occurred in 10% of patients and were mostly mild-moderate in severity. There were five serious treatment-related adverse events (two infusion-related reactions, two infections, one abdominal pain) and no cases of malignancy, pneumonia, or death. No significant differences were observed in treatment-emergent antibody response (TEAR) incidence between naïve patients and the switch group. No unexpected treatment-emergent adverse events were observed during the study. Although the study was not powered for efficacy, positive outcomes for response and remission were also reported in patients with CD, and UC. All data confirm that CT-P13 was well tolerated and efficacious in patients with IBD.

Another retrospective multicenter study from South Korea has evaluated CD and UC patients treated with IFX biosimilar (both infliximab-naïve patients and patients who switched to CT-P13 from its originator) by using Crohn's disease activity index (CDAI) and partial Mayo score[28]. The efficacy of CT-P13 was maintained in 92.6% of patients with CD and in 66.7% of patients with UC after the switch from infliximab to biosimilar drug. Only 2 CD patients and 1 UC patient stopped therapy after switch because of lack of efficacy. Regarding safety, no CD patients reported adverse event during CT-P13 therapy, while 6 UC patients (11.8%) experienced adverse events.

Moreover, an open-label case series has evaluated 17 IBD patients (8 CD and 9 UC) at a tertiary center in South Korea[29]. Nine patients (four UC and five CD) switched from IFX to CT-P13 during the remission period and among these, one patient lost effect and another discontinued CT-P13 due to arthralgia. No serious or unexpected ADRs were evident.

Unlike previous studies, which only evaluated the efficacy and safety of CT-P13, an Hungarian prospective, multicenter, observational study also examined the immunogenicity of treatment with CT-P13 in IBD[30]. 210 patients (126 CD and 84 UC) patients

Table 1 Major real-world studies of CT-P13 in inflammatory bowel disease[32,34,35]

Study	Design	Follow-up	Effect parameters	IBD	Nr	TNF-naive	Efficacy (%, *n*/*n*)		Safety (%, *n*/*n*)	
							Clinical response	Remission rate	Adverse event	IRR
Park *et al*[27], 2015 South Korea	Open-label, retrospective, multicenter	30 wk	CDAI	CD[4]	95	51	77.8[3] (35/45)	57.8[3] (26/45)	17.9 (17/95)	2.1 (2/95)
			Mayo score	UC	78	62	72.2[5] (39/54)	37[5] (20/54)	26.9 (21/78)	1.3 (1/78)
Jung *et al*[28], 2015 South Korea	Open-label, retrospective, multicenter	54 wk	CDAI	CD	59	32	87.5[3] (7/8)	75.0[3] (6/8)	0 (0/59)	0
			Mayo score CRP	UC	51	42	100[3] (12/12)	50[3] (6/12)	11.8 (6/51)	NR
Kang *et al*[29], 2015 South Korea	Open-label, case-series, tertiary center	8 wk	CDAI	CD	8	3	66.7[3] (2/3)	66.7[3] (2/3)	0	NR
			Mayo score	UC	9	5	100[3] (5/5)	100[3] (5/5)	0	NR
Gecse *et al*[30], 2015 Hungary	Open-label, prospective, observationalmulticenter	14 wk	CDAI	CD	126	93	81.4 (79/97)	53.6 (52/97)	17.1[2] (36/210)	6.6[2] (14/210)
			FDA Mayo score CRP PLT count	UC	84	68	77.6 (45/58)	58.6 (34/58)		
Farkas *et al*[31], 2015 Hungary	Open-label, prospective, observational tertiary center	8 wk	CDAI	CD	18	16	37.5[1] (6/16)	50 (8/16)[1]	NR	NR
			Mayo score	UC	21	19	20[1] (3/15)	66.7[1] (10/15)		
Jahnsen *et al*[32], 2015 Norway	Open-label, prospective, observational single-center	14 wk	HBI	CD	46	33	NR	79 (34/43)	NR	2.2 (1/46)
			Mayo score CRP Calprotectin	UC	32	27	NR	56 (18/32)	NR	3.1 (1/32)
Sieczkowska *et al*[35], 2015 Poland	Open-label, prospective, observationalswitching, pediatric	8 mo 5 mo	PCDAI PUCAI CRP	pCD pUC	32[5] 7[5]	26 6	NR NR	87.5 (28/32) 57.1 (4/7)	NR NR	3.1 (1/32) 28.6 (2/7)

[1]The patients who completed induction treatment; [2]At week 30; [3]In TNF-naïve patients only; [4]Including fistulizing active CD (n = 12); [5]Patients had switched from infliximab to CT-P13. NR: Not reported; CDAI: Crohn's disease activity index; CRP: C-Reactive protein; FDA: Food and drug administration; HBI: Harvey-bradshaw index; PLT count: Platelet count; PCDAI: Pediatric Crohn's disease activity index; PUCAI: Pediatric ulcerative colitis activity index; CD: Crohn's disease; UC: Ulcerative colitis.

were included. Adverse events were reported in 17.1% of all patients. Infusion reactions occurred in 6.6% of patients and were significantly more common in those with previous IFX exposure; serious infectious adverse events occurred in 5.7% of all patients, resulting in one death. Therapeutic drug levels were monitored and anti-drug antibodies ADAs were measured. Patients exposed to previous infliximab treatment had significantly higher baseline ADA positivity as compared with naïve patients (CD patients P = 0.006, UC patients P = 0.02), while there was no significant difference in ADA positivity at Week 14 between patient groups when stratified according to previous infliximab exposure. Moreover, this study showed that patients with previous infliximab exposure had a tendency towards lower early mean trough levels of the drug, decreased response rates and were more likely to develop allergic reactions.

Another Hungarian observational, prospective study enrolled 39 IBD (18 CD and 21 UC) patients to evaluate efficacy, safety and immunogenicity of CT-P13[31]. At week 8 clinical response and remission was achieved in 37.5% and 50% of the patients with luminal CD, and in 20% and 66.7% of UC patients. The study reported a mild arthralgia and an anaphylactic reaction after the second infusion of CT-P13 in a patient with high ADA levels and previously treated with the originator IFX. One UC patient developed toxic megacolon and underwent to colectomy.

A prospective observational study performed in a single center in Norway has evaluated the efficacy, tolerability, and safety of CT-P13 in 78 patients with moderate to severe disease (46 CD, 32 UC)[32]. About 79% of CD patients and 56% of UC patients achieved remission at week 14. There were no unexpected adverse events reported during the study. Immunogenicity was seen in 8 patients (4 CD and 4 UC) and lead to discontinuation of treatment in seven patients.

A German single-center study has evaluated 33 IBD patients treated with CT-P13 biosimilar and 86 IBD patients who received the infliximab[33]. CT-P13 serum levels, IFX serum levels and anti-drug antibody serum levels were measured in both groups to uncover significant differences in anti-drug immunogenicity. In total the analysis revealed no significant differences in anti-drug immunogenicity in patients receiving CT-P13 and Infliximab, demonstrating the feasibility of drug monitoring in IBD patients treated with the biosimilar.

A recent study[34] demonstrated that anti-Infliximab antibodies in IBD patients recognize and functionally inhibit CT-P13 to a similar degree, suggesting similar immunogenicity profile. All 69 positive anti-Infliximab patients were cross-reactive to CT-P13. Titers of antibodies to infliximab and CT-P13 were strongly correlated (r values between 0.92 and 0.99, P < 0.001). Anti-Infliximab antibodies of IBD patients exerted similar functional inhibition on CT-P13 or Infliximab TNF-α binding capacity.

In conclusion, all published studies show no

apparent differences between biosimilar infliximab and the originator. However, contrasting data have been reported in a study reported in abstract by Murphy *et al*[35] They showed a higher rate of surgery and inadequate disease control in patients treated with CT-P13 compared with those treated with infliximab. But, response and remission rates were not reported and no descriptions of baseline characteristics are available.

CT-P13 POST-MARKETING STUDY IN PEDIATRIC IBD

The effects of switching to CT-P13 from infliximab have been investigated in a small prospective observational study from Poland of 39 pediatric IBD patients (32 CD, 7 UC)[36]. In the CD subgroup, 22 (69%) patients were in clinical remission before switching. In the CD group 69% were in remission at the time of switching and 31% had mild to moderate disease activity. After two infusions with CT-P13 a significant reduction in pediatric CDAI (PCDAI) was seen. After a further mean follow-up of 8 mo after switching, 88% of the patients were in clinical remission. One infusion reaction to infliximab biosimilar was observed in a CD patient, which led to treatment discontinuation. In general, adverse event incidence did not differ significantly before and after the switch from infliximab RP to CT-P13. Despite several limitations of this study, as the small sample size, the heterogeneity of time of switching during therapy and the great variation in length of the individual follow-up period, it demonstrates that switching from infliximab RMP to CT-P13 seems to be well tolerated in children with CD.

ADALIMUMAB BIOSIMILARS

The originator biologic Adalimumab (Humira) is a human recombinant monoclonal antibody. This IgG1 antibody binds to TNF-alpha, avoiding it to join with its specific receptors. As is largely known, TNF-alpha is an important activator of the inflammatory cascade and a modulator of apoptosis mechanisms. The originator drug (AbbVie's Humira) adalimumab, was approved since 2002 in US and since 2003 in Europe. This drug has generated income for 12.5 billion of dollars worldwide in 2014, but at the end of 2016 the license will expire in the United States, while in Europe will expire in first half of 2018. Nowadays, Adalimumab is authorized for the therapy of Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Juvenile Idiopathic Arthritis, Psoriasis, CD, and Ulcerative Colitis.

At the end of 2014, the first Adalimumab biosimilar drug started to be commercialized in India. The Indian drug company Zydus Cadila Healtcare Ltd started to sell the adalimumab biosimilar drug, ZRC-3197, with the name of Exemptia, for the first time in the world[37]. Analytical techniques were behind demonstration of the biosimilarity of ZRC-3197 in comparison with the original adalimumab. Primary and secondary structures were showed to be identical to the originator product. Also, ZRC-3197 showed comparable level of heterogeneity and purity, when matched with originator adalimumab drug. Moreover, ZRC-3197 demonstrated similar key properties if compared with Humira, analyzed by with cell-based assay and plasma resonance techniques. ZRC-3197 showed a Tumor Necrosis Factor counteracting activity and a tie kinship for FcγRⅢa receptor comparable with Adalimumab originator[38]. Cadila Healthcare Ltd at the end of 2013, launched a randomized, parallel-group, active controller, phase Ⅲ trial to evaluate efficacy, tolerability and safety of ZRC-3197 in comparison with Humira in Rheumatoid Arthritis patients. In this study, 120 patients affected by Rheumatoid Arthritis for at least six months and seropositive active illness, were enrolled. All patients were in treatment with Methotrexate, 10-25 mg/wk for a minimum of twelve weeks at a fixed dose in the last four weeks. Patients were randomized to the administration of Humira (AbbVie) 40 mg or Exemptia (Zyndus) 40 mg every two weeks for three months by a subcutaneous route. The proportion of subjects with an ACR 20 response on day 84 was the primary endpoint. The secondary end-points were: modification of Disease Activity Score 28, proportion of subjects with an ACR 50 response, proportion of subjects with an ACR 70 response and comparison between the two groups of percentage of patients with antidrug antibodies[39]. By analyzing the data from this study, ZRC-3197 showed comparable degree of efficacy, safety, and tolerability if compared with the original drug Humira. However, complete data of this trial are not yet available. In any case, based on these data, Indian drugs authority gave the agreement for ZRC-3197 marketing. In European Union and United States this drug would not had the agreement for marketing because of a more strict regulatory process[40]. Post-marketing efficacy and safety data has not been showed[41].

CONCLUSION

Several clinical data are already available in IBD patients treated with IFX-biosimilar or who were switched from to CT-P13 with satisfactory outcomes, sustained efficacy and no sign of increased immunogenicity or any other safety concerns. However, further controlled data are needed, and additional studies that will support the validity of indication extrapolation to IBD are ongoing. No contraindication for switching from the originator to the relative biosimilar have been raised, however some gastroenterological and rheumatologic scientific associations have pointed out doubts about extrapolation technique of indication and its results. Realization of specific trials for each disease is desirable before biosimilar approval. Unfortunately, the increasingly number of treatment with biologics

and their high cost, necessarily require a reduction of the price of these compounds to allow their sustainability by healthcare systems. More long term data on loss of response rates in switched therapies of IBD, as well as more data on drug levels and antibodies are awaited to assist physicians' and patients' confidence.

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