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REVIEW

Insights on the use of biosimilars in the treatment of inflammatory bowel disease

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Abstract

Biologic therapy, such as those that target tumor necrosis factor (TNF) signaling, has proven to be an efficacious method of treatment for patients with inflammatory bowel disease (IBD) with regards to symptom management and mucosal healing. However, the rising prevalence of IBD worldwide and the ever-increasing burden of biologic pharmaceuticals in the health care industry is alarming for insurance companies, clinicians, and patients. The impending patent expiry and the relatively high costs of biologics, particularly anti-TNF agents, have paved the way for biosimilar development for IBD. The United States Food and Drug Administration defines a biosimilar as a biological product that is highly similar to its reference medicinal product, with no clinically meaningful differences in terms of safety, purity, and potency. The hope with biosimilars is that their entry into the market will be able to drive competition between pharmaceutical companies to reduce prices like that of the generic market, and that access to appropriate biologic treatments for IBD patients is increased in the long-term. Yet, there are challenging issues such as indication extrapolation and interchangeability that are still being debated in the field of IBD and must be addressed in future issued guidance. This review will discuss the issues and implications concerning the use of biosimilar therapy for IBD.

Key words: Biosimilar; Biologic; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Indication extrapolation; Interchangeability

Core tip: The expiration of patent protection for various biologics and increasing health care expenses has paved the way for biosimilars to enter the market. The introduction of biosimilars is expected to produce cost savings in the health care industry as well as provide patients with inflammatory bowel disease with wider access to treatment.

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INTRODUCTION

There are two conditions that mainly characterize inflammatory bowel disease (IBD): ulcerative colitis (UC) and Crohn's disease (CD). These are chronic, relapsing, immune-mediated inflammatory diseases of the gastrointestinal tract. Whereas UC is an inflammatory condition that only affect the colon, CD is a chronic inflammatory condition with pathological features such as patchy transmural inflammation and fibrostenosis[1]. Urbanization, industrialization, and lifestyle are all factors that contribute to the rising incidence of IBD worldwide[2]. It has been estimated that approximately 1.4 million Americans are affected by IBD and afflicted with recurrent symptoms of bloody diarrhea, abdominal pain, bowel obstruction, and other co-morbid conditions[3,4].

The introduction of biologic therapy for IBD proved to be a breakthrough for patients with the disease[5]. Biologic products are highly complex molecules that are manufactured using living organisms[6]. In the pharmaceutical industry, biologics that are classified as monoclonal antibodies (mABs), particularly those that serve to antagonize tumor necrosis factor (TNF) signaling, have provided specialists and IBD patients with a proven and efficacious method of symptom management, mucosal healing, and prevention of long-term complications[7,8]. TNFα is a cytokine responsible for causing an inflammatory response towards tissue damage, and it was discovered to play an important role in the pathophysiology of chronic immunological diseases, including IBD and rheumatoid arthritis (RA)[9]. In addition, mABs that antagonize the α4β7 integrin have been developed to treat IBD. The α4β7 integrin was found to be involved in interactions that facilitate T-cell extravasation into the GI tract[10]. Patients who fail to respond or demonstrate hypersensitivity to anti-TNF therapy may also be treated with biologics that target the interleukin (IL)-12 and IL-23 pathways. IL-12 and IL-23 are proinflammatory cytokines that play a role in the differentiation of T-helper cells into type 1 T-helper cells as well as T-helper cell proliferation[11]. Currently, four anti-TNF biologics (infliximab, adalimumab, golimumab, and certolizumab) and two anti-integrin biologics (natalizumab and vedolizumab) have been approved for use in IBD treatment, while one anti-IL biologic that targets IL-12 and IL-23 (ustekinumab) has been approved for CD treatment[12,13].

Despite the effectiveness of biologics in treating IBD, the approaching patent expiry of certain anti-TNF agents has triggered the development of highly similar versions of these drugs known as "biosimilars" (Table 1). The approval of these biosimilar therapies is expected to generate competition in the pharmaceutical market that will reduce the financial burden of patient care and allow more patients to access treatment. However, the effectiveness of biosimilars is being debated due to several factors including an expedited regulatory approval process for biosimilar therapy and the notion that once approved, a biosimilar may be approved for all other indications for which the reference medicinal product (RMP) has been approved, without the need for clinical trials for the latter indications[14,15]. The purpose of this review is to discuss the emergence and implications of biosimilar market entry and to evaluate the progress of biosimilar therapy for IBD.

THE RISE OF BIOSIMILARS

What are biologics?

Biologic medicines are considerably more complex than small-molecule chemical generics. Compared with small-molecule medicines, which can be synthesized relatively easily and replicated chemically, biologics are large and complex three-dimensional structures produced using living cell lines and are difficult to replicate[16].

Whereas chemical generics only require about 50 critical tests during the manufacturing process, biologics demand a highly regulated manufacturing process consisting of 250 or more tests and a sophisticated quality control protocol[17]. In order to produce biologic agents, the gene for the protein of interest is inserted into a cell that produces and secretes the biologic agent in culture. After harvesting, the biologic undergoes protein purification before product formulation and packaging for clinical use[16]. Biologics are typically made in living cells that are highly sensitive to environmental changes and external conditions (such as temperature, light, and shear forces). As a result, different batches of the same biologic will vary in structural properties such as size, post-translational modifications, and folding pattern[17,18].

For patients with IBD, biologic treatment is an effective therapy. Infliximab (IFX) is a human-murine chimeric mAB that blocks the action of TNFα (anti-TNF) and is used to treat various immune-mediated inflammatory diseases[19]. Remicade, an IFX biologic used in the treatment of various auto-immune and inflammatory diseases, has been approved as therapy for induction and maintenance of moderate-to-severe CD and UC in both adult and pediatric IBD patients[20]. Subsequent to the approval of IFX, three other anti-TNF drugs (adalimumab, certolizumab pegol, and golimumab) and two anti-integrin biologics (natalizumab and vedolizumab) are approved therapies to treat IBD, while one anti-IL biologic that targets IL-12 and IL-23 (ustekinumab) has been approved for CD treatment[12,13].

Table 1 Comparison of biologics and biosimilars

	Biologics	Biosimilars
Development costs[26,103]	Approximately $2 billion	Approximately $100-250 million
Characterization	Exhibits heterogeneity	Exhibits heterogeneity
Patent duration	20 yr; up to 12-yr exclusivity period	No patent licensing
Approval process	Submission of a BLA	Submission of an aBLA
Immunogenicity	Possible risk	Possible risk
Indication extrapolation	Not permitted	Case-by-case basis

aBLA: Abbreviated biologics license application; BLA: Biologics license application.

What are biosimilars?

The regulatory pathway of a biologic drug is a time-consuming process that requires successful clinical trials that demonstrate clinical efficacy as well as approval from regulatory agencies such as the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA)[14,21,22]. However, in the context of biosimilars, regulatory agencies only need to ensure that high similarity or comparability is demonstrated between the biosimilar and its RMP before a biosimilar candidate can be approved and marketed, resulting in a simpler approval pathway[15].

According to the FDA, a biosimilar is a biological product that is highly similar to a RMP, with no clinically meaningful differences in terms of safety, purity, and potency[22]. Biosimilars and generic drugs both represent competition towards brand-name drugs. Although a manufactured generic is an exact copy of the original small-molecule medicine, it is not possible to generate identical copies of a biologic[23]. Since biologics are difficult to replicate, biosimilars are manufactured using alternate methods such that the final product is almost identical to the RMP with respect to the primary amino acid sequence[24]. Due to the inherent variability of the living bacteria-based systems used to make biosimilar drugs, there is micro-heterogeneity between biosimilar and RMP[25].

The emergence of biosimilar therapies is an inevitable outcome of patent expiration. From the date of filing, a drug's patent lasts up to 20 years, with exclusivity lasting up to 12 years, according to the Biologics Price and Competition Innovation Act of 2009[26]. Pharmaceutical companies rely on patent exclusivity and protection to benefit from investment return. Once a patent expires, companies are immediately able to market generics, which usually have lower prices driven by competition[27]. The anticipation with biosimilars is that their entry into the market will be able to drive competition between pharmaceutical companies, to reduce prices comparably to how the generic market has, and to increase overall patient access to appropriate biologic treatments in the long-term. Currently, only two biosimilars have been approved for use in IBD in the United States: infliximab-dyyb and adalimumab-atto[28,29]. However, multiple anti-TNF biosimilars have either been proposed, are being tested in late stage clinical trials, or are awaiting approval from regulatory agencies (Table 2).

COMPARING BIOLOGICS AND BIOSIMILARS

Mechanism of action

IBD is characterized by immune dysregulation in a genetically predisposed individual, resulting in overproduction of TNFα by macrophages, monocytes, and T cells[30,31]. Anti-TNF therapy is an efficacious method that can treat IBD by blocking proinflammatory mediator TNF. Anti-TNF mAbs can also induce the formation of regulatory immunosuppressive macrophages and anti-inflammatory cytokines to further treat IBD[31]. Certain mAbs such as IFX and adalimumab (ADA), but not certolizumab, have the ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC), an immune response characterized by the lysis of target cells by activated effector cells, including natural killer cells, monocytes, macrophages, neutrophils, and eosinophils[32]. The crystallizable fragment of the IgG1 antibodies of these mAbs is necessary to exhibit ADCC[33].

Molecules in the same class, such as TNF inhibitors, may be extrapolated across all indications because they share the same mechanism of action. Extrapolation across indications is a process that may be considered when there are changes in manufacturing from an originator biologic or route of administration[18]. Typically, clinical data that corresponds to one indication may be extrapolated to additional indications based on information on comparability. Because clinical efficacy of the RMP is already established, the number of preclinical and clinical studies required for approval may be less for biosimilars, and studies may only be required for a subset of indications[34]. Clinical studies and analytical tests that observed comparability in physiochemical features and mechanism of action between RMP and biosimilar supported the approval of infliximab-dyyb across all indications of IFX by the FDA and EMA[18,28,35].

Pharmacokinetic profile

Pharmacokinetics (PK) refers to various factors (absorption, bioavailability, distribution, metabolism, and excretion) involved with the movement of a drug into,

Table 2 Proposed anti-tumor necrosis factor biosimilars[1]

Reference medicinal product	Biosimilar name
Infliximab	Infliximab-dyyb (Celltrion)[2]
	SB2 (Samsung Bioepis)
	PF-06438179 (Sandoz)
	BOW015 (Epirus)
Adalimumab	Adalimumab-atto (Amgen)[2]
	SB5 (Samsung Bioepis)
	ZRC-3197 (Zydus Cadila)
	MSB11022 (Merck KGaA)
Certolizumab pegol	PF688 (PFEnex)
Golimumab	BOW100 (Epirus)

[1]Information for each biosimilar was derived from the website of its respective drug company; [2]Approved by the United States Food and Drug Administration.

through, and out of the body. In addition to patient-related factors (*e.g.*, genetic makeup, sex, body mass index, age, and disease severity), chemical properties can also influence PK parameters[36]. Compared with small-molecule medicines, biologics and biosimilars will have a slower rate of absorption, smaller volume of distribution, different mechanisms of paracellular and transcellular movement, and different routes of clearance[37]. A biosimilar must display a comparable PK profile to the RMP. Results from a randomized study indicated that three formulations of IFX [infliximab-dyyb, United States RMP, and European Union (EU) RMP] had highly similar PK and safety profiles[38]. In addition, an understanding of PK is necessary to optimize therapeutic development and dosing in patients[37].

Immunogenicity

Biologics have been shown to elicit an immunogenic response in some patients, characterized by a release of antibodies by antibody-secreting B cells[39]. When present, anti-drug antibodies can neutralize the clinical efficacy of a biologic as well as cause unpredictable side effects and loss of response[40]. Immunogenicity is a major health concern with all biologics as well as biosimilars. Manufacturing, post-translational modifications, route of administration, and patient characteristics are several factors known to influence immunogenicity[41].

Concomitant use of immunomodulators such as azathioprine (AZA) and methotrexate (MTX) can prevent immunogenicity by decreasing the formation of anti-drug antibodies and reducing systemic inflammation[42]. The SONIC study evaluated the safety of efficacy of treating CD patients with IFX or AZA alone or in combination therapy. At week 26, there was a greater occurrence of corticosteroid-free remission and mucosal healing in those treated with combination therapy than with monotherapy. Additionally, there were fewer patients that developed serious infections in the combination therapy group, compared with both the IFX and AZA groups[43]. A similar study, UC SUCCESS, was performed to evaluate combination therapy in UC patients. At week 16, greater occurrence of mucosal healing and corticosteroid-free remission was observed those treated with combination therapy than with IFX or AZA alone[44]. The COMMIT study evaluated the safety and efficacy of IFX alone or in combination with MTX in CD patients. Although combination therapy was well tolerated, the number of patients who achieved corticosteroid-free remission at week 14 and maintained remission at week 50 was similar in both groups. However, only 4% of patients who received MTX developed antibodies to IFX, compared with 20% who received IFX alone. Furthermore, trough serum concentrations of IFX was also higher, albeit not statistically significant, in patients who received MTX[45].

The use of immunomodulatory agents on biosimilar treatment has shown to be feasible. In an extension of the PLANETRA study, all enrolled patients received intravenous infliximab-dyyb and concomitant methotrexate. Both the maintenance and switch groups displayed a similar proportion of patients with anti-drug antibodies[46]. Notably, the EMA also mentions the concomitant use of methotrexate in the European public assessment report for infliximab-dyyb[35].

THE BENEFITS OF BIOSIMILARS

Potential cost savings with biosimilars

The high prices of biologic pharmaceuticals have placed a burden on the healthcare industry, accounting for a continually increasing share of drug spending in the United States and limiting patient access to appropriate treatment. The Office of the Assistant Secretary for Planning and Evaluation estimates that United States drug spending totaled about $457 billion in 2015, making up 16.7% of overall health care spending. Notably, prescription drug expenditures are rising at a faster rate than overall spending, due to factors such as population growth, inflation, and a higher number of prescriptions per patient[47].

The estimated total costs of IBD in the United States range from $14.6B to $31.6B[48]. The growing prevalence of the disease worldwide, in conjunction with the high costs, is concerning for the economy and may lead to unsustainable healthcare costs in the future. Compared to patients without the disease, direct medical expenditures have been found to be around $13663 to $17434 higher for patients with CD and $10039 to $12615 higher for patients with UC[49].

Biosimilars are expected to produce savings across the board in the health care industry as a result of various factors, such as reduced research and development costs, competition driven by patent expiry, and a simpler approval pathway. An Excel-based model of Remsima for the treatment of various inflammatory autoimmune diseases was created to estimate the budget impact of Remsima. The model, which covers

five countries (Germany, the United Kingdom, Italy, the Netherlands, and Belgium) projects the biosimilar to induce cost savings over one year of $63 million (pounds converted to dollars) and the treatment of 3900 additional patients[50]. Furthermore, another budget impact model of Remsima in six different countries (Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia) was developed while taking into two scenarios: BSc1 (interchangeability disallowed) and BSc2 (interchangeability allowed, 80% of patients taking IFX are interchanged to biosimilar). In this model, which estimates budget impact of Remsima in the treatment of RA only, savings of $21M (BSc1) and $29M (BSc2) are projected over 3 years, as well as the treatment of an additional 1200 to 1800 patients[51].

The EU has provided the healthcare industry with a preliminary impression of biosimilar market entry. Biosimilars have been available in the EU since 2006, and the observed average list prices are 30% lower than the RMP, compared to the 70% to 80% savings that generics induce[26,52]. Because biosimilars are more difficult to manufacture, the cost reduction is not expected to be as drastic as seen with generics.

Currently, filgrastim-sndz (Zarxio), an anti-cancer drug, infliximab-dyyb, and adalimumab-atto are the only biosimilars approved in the United States[28,29,53]. The entry of biosimilars into the United States market is important for the overall development and financial success of the pharmaceutical industry, bearing in mind that a majority of world biologics sales come from the United States[54]. From 2014-2024, it is anticipated that the entry of the 11 most likely biosimilars into the market will lead to $250 billion in savings for the American healthcare industry, with the possibility of greater disease control and reduced inpatient stays and outpatient visits[55].

Wider accessibility for patients

The entry of biosimilars to market is expected to give patients more choices and greater access to treatment. Prior to the development of biosimilars, those who required biologic therapy were either restricted to a limited number of costly treatment options or placed on a waiting list. A cross-sectional study, performed in 49 European countries, revealed that RA patients in lower income countries struggle with affordability and have less access to biologic and synthetic disease-modifying drugs[56]. Fortunately, due to projected cost reductions associated with biosimilars, a large number of patients are expected to have a larger complement of options available to them earlier in the course of the disease.

Furthermore, if switching between a particular RMP and its biosimilar are observed to be clinically noninferior to continued treatment of the RMP, then concerns about biologic shortages and waiting lists would potentially be alleviated. In 2014, there were 1000 additional patients in the Czech Republic who were able to initiate treatment than in the previous year, due to the cost savings of biosimilars[57].

CHALLENGES WITH BIOSIMILARS

Indication extrapolation

There is uncertainty as to the level of efficacy of certain biologic molecules in different indications. While IFX and etanercept (ETN) are effective in treating RA, ETN was determined to be futile in treating CD[58]. Studies show that in patients with CD, both IFX and ETN are successful in TNF blocking, but only IFX is capable of inducing apoptosis in order to reduce the number of inflammatory cells[59]. Notably, IFX provides clinical improvement in RA, but not by the induction of apoptosis[60].

The extrapolation of indications for infliximab-dyyb for the indications of IFX has also prompted questioning. IFX is effective in multiple tissues and organ systems (joints, axial skeleton, GI tract, and skin). However, even though the approval of infliximab-dyyb in the EU was mainly supported by studies in ankylosing spondylitis (AS), a chronic inflammatory disease that affects the spinal vertebrae and sacroiliac joints, and RA, the specific distribution and effectiveness of IFX and infliximab-dyyb to affected tissues is not known, presenting a potential problem in indication extrapolation[34,61-63]. In 2014, Health Canada approved infliximab-dyyb for all indications except for UC and CD due to a lack of clinical data demonstrating proper mechanism of action in all indications of IFX, and residual uncertainty regarding the role and impact of small differences in ADCC[34,64,65]. Because anti-TNF agents may also depend on ADCC in addition to TNFα neutralization, changes in ADCC tests pose a challenge for extrapolation[33].

Immunogenicity

As with biologics, it is important to take into consideration the unpredictable risk of immunogenicity when introducing a biosimilar to the market. While effective for treating inflammatory diseases such as IBD, some patients either fail to respond or develop a loss of response. Because indication extrapolation for a biosimilar requires less clinical data than the initial approval of a biologic would, information regarding immunogenicity of the biosimilar in patients for indications without substantial data becomes difficult to support without performing extensive clinical trials[34]. The FDA and World Health Organization have advised that immunogenicity be investigated in populations that are at the highest risk of an immune response and immune-related adverse events[15,66]. Furthermore, performing *in vivo* and *in vitro* assays (*e.g.*, size exclusion, western blots, and enzyme-linked immunosorbent assays) throughout development can lessen the probability of an immunogenic response[39].

Recent data suggests that it may not be appropriate to extrapolate immunogenicity data from the RMP to the biosimilar. Following results of a study which revealed cross-reactivity between anti-IFX antibodies and infliximab-dyyb, the European League Against Rheumatism stated that switching from IFX to infliximab-dybb may not be appropriate for all patients[67]. Given the unpredictability of anti-drug antibody formation, diagnostic tests have been developed in order to better estimate the efficacy of biologics and biosimilars in patients with IBD. The Anser IFX and Anser ADA, developed by Prometheus Laboratories, were designed to measure the serum levels and antibodies of patients being treated with IFX or ADA, respectively. In a cohort study of patients with acute UC (n = 115), detectable trough serum concentrations of IFX were shown to predict improved outcomes[68]. Recently, the Anser IFX was validated for use in patients who are treated with infliximab-dyyb[69].

Interchangeability

One of the major obstacles for the entry of biosimilars into the market is interchangeability. The Abbreviated New Drug Application (ANDA) is an application that uses bioequivalence as a basis to demonstrate that a new generic is similar enough to the original branded drug. Most generics are considered interchangeable once the ANDA is approved, and pharmacists are allowed to switch branded drugs for generics at the point of purchase, subject to state law[70,71]. Conversely, interchangeability of biosimilars is not immediately granted upon ANDA approval, which poses a challenge for clinical use[72].

Manufacturers face concerns with both clinician and patient acceptance, as well as the reluctance to use the biosimilar in treatment, especially if such a change is to alter a long established prescribing practice[73]. The FDA states that an interchangeable product is "expected to produce the same clinical result as the RMP in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the RMP is not greater than the risk of using the RMP without such alternation or switch[74]". As a result, a biosimilar product may not necessarily be interchangeable. Because an application for interchangeability requires the fulfillment of additional criteria, manufacturers may decide not to pursue the "interchangeable" designation. Without investing in extra clinical trials, patient and clinician confidence in non-interchangeable biosimilars could potentially decrease, despite a more rapid market entry[70].

In the EU, a majority of biosimilars had relatively little market share because of a lack of interchangeability[75]. A majority of United States states and Puerto Rico have either considered, passed legislation, or enacted law regarding the automatic substitution of biologics for biosimilars at the pharmacy level[76]. Automatic substitution allows pharmacists to replace biologics with biosimilars without informing or obtaining approval from the prescribing physician[77]. There are currently no studies that demonstrate the implications of cross-switching (switching between two biosimilars), reverse-switching (switching from a biosimilar to its RMP), or switching between multiple biosimilars. However, it is possible that switching between multiple biosimilars may lead to an immunogenic reaction and reduced efficacy of the drug. Because antibodies can develop within 2 to 3 treatments, an updated statement from the European Crohn's and Colitis Organization advises against switching within six months of initiating treatment for non-medical reasons[78]. Ultimately, the FDA is expected to issue their official guidance on interchangeability by the end of 2017[79].

THE STATE OF BIOSIMILAR DEVELOPMENT

Infliximab-dyyb

The results of two randomized and double-blind clinical studies, PLANETRA and PLANETAS, contributed to the approval of infliximab-dyyb in the EU for all the indications of the RMP (infliximab): RA, CD, UC, AS, psoriatic arthritis (PsA), and psoriasis (PsO)[80]. Six hundred and six RA patients enrolled in PLANETRA were randomized to receive either IFX (n = 304) or infliximab-dyyb (n = 302) in combination with MTX and folic acid. In PLANETAS, 250 AS patients were randomized to receive either IFX (n = 125) or infliximab-dyyb (n = 125) alone. At weeks 14 and 30 of both studies, the biosimilar was shown to have demonstrated to have highly similar PK, efficacy, safety, and immunogenicity[61,62]. In 2016, results from a secondary analysis of PLANETAS were made available. Through week 54, the observed PK parameters and immunogenicity remained similar in the two treatment groups. Withdrawal rates were similar in both the biosimilar (n = 19) and RMP (n = 21) treatment groups, with the most common cause being the case of a treatment-emergent adverse event (TEAE). The most common TEAEs (occurring in over 10% of patients in each treatment group) were abnormal liver function test and infusion-related reaction[63].

Several studies have been performed to address infliximab-dyyb induction in IBD (Table 3). Mixed results suggest that infliximab-dyyb and IFX may not have similar clinical efficacy and safety in patients with the disease. In Ireland, a study was performed to compare 14 IBD patients taking an IFX biosimilar (Inflectra) from January to July 2014 to 22 IBD patients commenced on IFX from December 2011 to December 2013. Results indicated that Inflectra demonstrated a significant decrease in clinical efficacy, with a 29%

Table 3 Clinical studies on infliximab-dyyb induction in inflammatory bowel disease

Ref.	Study	Population	Results	Safety
Jahnsen *et al*[84]	Prospective observational	CD = 46; UC = 32	Clinical remission rate at week 14: 79% (CD), 56% (UC) Significant decrease in CRP, calprotectin	No adverse events reported
Jung *et al*[82]	Retrospective multicenter	CD = 32; UC = 42	Clinical response at week 54: 87.5% (CD), 100% (UC) Clinical remission rate at week 54: 75% (CD), 50% (UC)	Adverse events in 11% of UC patients
Gecse *et al*[85]	Prospective, multicenter, nationwide cohort	CD = 126; UC = 84	Clinical response at week 14: 81.4% (CD), 77.6% (UC) Clinical remission rate at week 14: 53.6% (CD), 58.6% (UC)	Adverse events in 17.1% of all patients
Murphy *et al*[81]	Descriptive	IBD = 36 (Remicade = 22; Inflectra = 14)	CRP levels: increase in 93% of Inflectra patients, decrease in 100% of Remicade patients	29% increase in hospital readmission and 75% increase in surgery rates with Inflectra patients
Sieczkowska *et al*[86,104]	Switch from RMP to Infliximab-dyyb	Pediatric CD = 32; Pediatric UC = 7	Clinical remission rate: 88% (CD), 57% (UC) Decrease in PCDAI, CRP, ESR	No adverse events reported
Smits *et al*[87]	Prospective, observational, cohort switch	CD = 57; UC = 26	No significant change in DAI, CRP, calprotectin at week 16	No adverse events reported

CD: Crohn's disease; CRP: C-reactive protein; DAI: Disease Activity Index; ESR: Erythrocyte sedimentation rate; HBI: Harvey-Bradshaw Index; IBD: Inflammatory bowel disease; PCDAI: Pediatric Crohn's Disease Activity Index; UC: Ulcerative colitis.

increase in surgery rate and 75% increase in hospital readmission[81]. Another retrospective multi-center study evaluated the efficacy and safety of infliximab-dyyb in anti-TNF naïve UC (n = 42) and CD (n = 32) patients. After switching, therapeutic efficacy was maintained in 93% (25/27) of CD patients and 67% (6/9) UC patients at 54 wk. There were adverse events reported in 11% of UC patients, but the results indicated comparable efficacy, safety, and interchangeability between RMP and biosimilar[82]. Clinical data from 46 CD and 32 UC patients in a infliximab-dyyb induction study demonstrated comparable efficacy and safety to the RMP. At week 14, 76% (32/42) of CD patients and 56% (18/32) of UC patients were in clinical remission, and decreases in the Harvey-Bradshaw Index (HBI), calprotectin levels, and C-reactive protein (CRP) levels were observed in both indications. In addition, no adverse events were reported[83,84]. A prospective, multi-center, nationwide cohort that examined infliximab-dyyb induction in CD (n = 126) and UC (n = 84) revealed clinical response in 81.4% (CD) and 77.6% (UC) of patients as well as remission rates of 53.6% (CD) and 58.6% (UC). Adverse events were reported in 17.1% of all patients[85].

Currently, there is limited data that addresses the switching to a biosimilar from its RMP in IBD. However, studies have suggested that switching between biosimilar and RMP in IBD patients is feasible[86,87]. NOR-SWITCH was a randomized, double-blind, parallel-group study in Norway that evaluated the safety and efficacy of a single switch from IFX to infliximab-dyyb in patients with various inflammatory diseases (RA, spondyloarthritis, PsA, UC, CD, and chronic PsO). The study began in October 2014 and is expected to be completed in January 2017[88]. Data presented at the United European Gastroenterology Week 2016 revealed that switching to infliximab-dyyb was not inferior to continued treatment with RMP IFX[89].

SB2

Samsung Bioepis's SB2 (Flixabi), an IFX biosimilar, was approved in the EU for all the indications of infliximab, as listed above. The approval of Flixabi was facilitated by a randomized, double-blind Phase 3 study which demonstrated comparable PK and immunogenicity to IFX, and equivalent values for ACR20 in both the SB2 and IFX treatment groups at week 30 and 54[90,91].

PF-06438179

Sandoz acquired the rights to Pfizer's IFX biosimilar, PF-06438179, in February 2016[92]. In September 2013, a Phase 1 study, REFLECTIONS (B537-02), comparing PF-06438179 to IFX in healthy volunteers (n = 146) indicated comparability in the PK and immunogenicity profiles of both treatment groups[93]. REFLECTIONS (B537-02) is an ongoing randomized, double-blind Phase 3 clinical study comparing PF-06438179 to IFX in combination with methotrexate in patients with acute RA. The study began in August 2014 and is expected to be completed in May 2017[94].

BOW015

In September 2014, Epirus Biopharmaceutical's BOW015 became the first IFX biosimilar to be approved in India, facilitated by Phase 3 clinical data of BOW015 in RA patients[95]. Currently, Epirus has launched another Phase 3 study in Europe, the UNIFORM study, comparing BOW015 and IFX in patients with active RA. Data is expected after the study's primary completion

date in July 2017[96].

Adalimumab-atto

Amgen submitted an abbreviated Biologics License Application (aBLA) to the FDA in November 2015 for adalimumab-atto (Amjevita), a biosimilar candidate to its ADA biologic, Humira, following the completion of two phase 3 studies[97]. The FDA approved Amjevita across all eligible indications of Humira in September 2016. Amgen's first study was a randomized, double-blind, active-controlled phase 3 comparative study performed to demonstrate comparable safety, efficacy, and immunogenicity of ABP 501 and ADA with patients with moderate-to-severe RA. Amgen believes that the study met the primary endpoint of ACR20. Secondary endpoints, ACR50 and ACR70, as well as the incidence of TEAEs were also comparable between ADA and ABP 501[98]. Another randomized, double-blind phase 3 study of Amjevita was performed in patients with moderate-to-severe plaque PsO. Results achieved the primary endpoint for efficacy of the study with a percent improvement in Psoriasis Area and Severity Index from baseline to week 16 of treatment, and safety and immunogenicity were observed to be comparable between ADA and Amjevita[99].

ZRC-3197

In December 2014, the first ADA biosimilar, Zydus Cadila's ZRC-3197 (Exemptia) launched in India[100]. Approval of ZRC-3197 was facilitated by a randomized, double-blind study comparing Exemptia and ADA in patients with RA, yielding comparability data demonstrating high similarity between the biosimilar and the RMP in terms of efficacy, tolerability, and safety. The 12-wk study saw only 3 of 120 subjects drop out, all due to adverse events, and no deaths were reported[101].

MSB11022

In March 2016, Merck KGaA announced the initiation of AURIEL-PsO, a randomized double-blind study to evaluate the safety and efficacy of its ADA biosimilar candidate, MSB11022, compared with ADA in patients with moderate-to-severe plaque PsO. Data is expected in December 2016, with the study to be completed around September 2017[102].

CONCLUSION

Biologic therapy has greatly facilitated treatment for IBD, and the introduction of biosimilars has the potential to be a breakthrough development for IBD patients. Increasing prescription drug expenditures have limited patient access to the appropriate biologic treatment, contributing to a heightened interest in biosimilars, which are expected to trigger cost savings upon biologic patent expiry. Reflecting upon the biosimilar experience in the EU, savings of around 30% from the RMP were observed. Moreover, current studies and experience provide optimism with regards to future cost savings and interchangeability with their RMPs. The FDA's recent approval of Inflectra marks significant progress in the emergence of biosimilar therapy in the United States. Ultimately, as more biosimilars enter the market, competition is expected to drive prices down.

Perhaps the greatest hurdle that pharmaceutical companies face is clinician and patient acceptance. Issues such as immunogenicity and interchangeability cannot be avoided. It has been suggested that the development of anti-drug antibodies may have an inhibitive effect on clinical response and patient outcomes. Although diagnostic tests such as the Anser IFX are able to provide some clarification to patients, additional studies are necessary in order to clear up any uncertainty with regards to the influence of anti-drug antibodies. In addition, taking steps to improve manufacturing processes and production may contribute to avoid changes that influence an immunogenic response in patients. As more data becomes available, biosimilars have the opportunity to increase patient access to a more affordable form of appropriate treatment. Given the large number of studies in progress, it is conceivable that more promising results will expedite the transition towards biologic and biosimilar interchangeability as well as higher confidence in interchangeability and active switching between biosimilar and RMP.

Hopefully, when the appropriate guidance is finalized, the FDA will be able to answer many of the questions that manufacturers and companies have pertaining to biosimilar labeling and interchangeability. With the necessary data and guidance at their disposal, it will be feasible for clinicians to develop a treatment plan that is more personalized and tailored towards specific patients than before.

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