Biosimilars in Inflammatory Bowel Disease

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Over the past 2 decades, biological therapy with monoclonal antibodies targeting tumor necrosis factor-α has become a cornerstone of treatment of patients with inflammatory bowel disease. Although clinically effective, the biological therapies remain expensive, and their availability and utilization have been at times limited due to their high costs. Biosimilars are biological products similar to but not identical to the original biological agent or "reference biologic," also called "originator biologic." It is hoped that the use of biosimilars might enable these agents to become more available and, thus, decrease further expenditures related to the use of the original reference agents such as infliximab and adalimumab. In this study, we review the currently available evidence and shortcomings of these data supporting the use of biosimilars for the treatment of patients with inflammatory bowel disease, including their efficacy and safety as related to initiating therapy with biosimilar agents or switching between reference and biosimilar biologic agents.

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INTRODUCTION

Within the past 20 years, biological therapies such as monoclonal antibodies targeting tumor necrosis factor (anti-TNF)-α have become a cornerstone of the treatment of immune-mediated diseases including inflammatory bowel disease (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) and have been determined to be effective and safe therapies to induce disease remission and mucosal healing and, ultimately, improve the quality of life of patients with IBD (1,2).

Infliximab was the first U.S. Food and Drug Administration (FDA)–approved monoclonal antibody directed against TNF-α, a key component of the inflammatory pathway in IBD (3,4). Since its initial regulatory approval in 1998, infliximab has been used in more than 2.6 million individuals, and its efficacy and safety are well noted (4). After infliximab introduction, an additional 3 anti-TNF agents (adalimumab, certolizumab pegol, and golimumab) have been studied and approved for the treatment of patients with CD and UC (1).

These anti-TNF medications have altered the course of the disease and the paradigm for disease management, and thus, the ability to help patients with IBD achieve and maintain remission has been revolutionized (1,2). Their utilization has increased remarkably over the past decade, driving an increase of the share of costs (5,6). A recent study by Yu et al. has demonstrated a consistent rise in the market share biologics during the 9-year study period with the proportion of patients using biologics increasing from 21.8%–43.8% for CD and 5.1%–16.2% for UC in the United States (5). Furthermore, most costs allocated to outpatient IBD medications in the United States have been attributed to the increasing use of biologic therapies despite the relative minority of biologic-taking patients (5). The recent expiration of patents of the most common biologics for the treatment of IBD (infliximab and adalimumab) has led to the expansion of the market and introduction of biosimilar agents potentially resulting in a reduction of costs and better accessibility to most patients (7). In this study, we present an overview of emerging evidence for the use of biosimilars in IBD including their efficacy and a review of the safety of switching between reference biologic agents and biosimilar biologic agents and future directives.

WHAT ARE BIOSIMILARS: DEFINITIONS

Biosimilars are biologic agents that are highly similar to an existing FDA-approved reference biologic agent for purity, chemical activity, and bioactivity, with no clinically meaningful difference (8). The amino acid sequence of the active agent should be identical to the reference agent; however, a subtle difference in glycosylation might exist as a result of the production in various cell lines (7,9). These differences can theoretically influence the pharmacology of the biosimilar and their potential immunogenicity. According to the FDA (10), a biosimilar is "highly similar to the reference product notwithstanding minor differences in clinically inactive components."

It is essential to point out that biosimilars are biologic agents and not generics. Generics represent the term given to agents that contain the same chemical substance as the original brand drug and are typically classified as small molecules (e.g., 6-mercaptopurine, azathioprine, and methotrexate). Biologics differ from small molecules in several ways, including their composition, structure, route of administration, degradation, mechanism of action, and manufacturing costs (11,12) (Table 1).

To be approved by the FDA for use in patients, the biosimilar must demonstrate several features, including functional and structural similarities to the reference agent, similar pharmacokinetics, the development of antidrug antibodies, and the

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overall safety and efficacy of the reference agent (13) (Figure 1). Regulatory approval of biosimilar agents became possible through extrapolation (14). The term extrapolation is defined by the ability of a biosimilar to be approved for other indications based on the FDA-approved uses for a reference biologic agent, even if this indication was not specifically studied with the biosimilar in that disease state. This methodology (extrapolation) has allowed the approval of anti-TNF biosimilars in the treatment of CD and UC because the currently approved biosimilars were primarily investigated in other autoimmune-mediated diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS) (15,16). This process can be illustrated by reviewing the steps that occurred with biosimilar infliximab to receive marketing authorization. The course of events termed extrapolation evaluated the efficacy and safety results of the following studies in patients without IBD: these studies demonstrated efficacy and safety similar to originator infliximab, and as a consequence of obtaining results similar to originator, infliximab approval was given to biosimilar infliximab to use in patients with IBD. First, a phase 1, randomized, double-blind study (PLANETAS; Programme evaLuating the Autoimmune disease iNvesTigational drug CT-P13 in patients with AS) was conducted comparing pharmacokinetics, safety, and efficacy of CT-P13 (biosimilar) and innovator infliximab (Remicade) in patients with AS (15). The encouraging results of this study demonstrating equivalent pharmacokinetics profile and comparable tolerability, safety, and efficacy led to a phase 3, randomized, double-blind study (PLANETRA; Programmed evaLuating the Autoimmune disease iNvEstigational drug CT-P13 in patients with RA). The subsequent study demonstrated equivalence in efficacy and safety of CT-P13 compared with Remicade when given with methotrexate in patients with RA (16). Comparable immunogenicity was also confirmed in patients with RA or AS who switched from Remicade to CT-P13 (17,18). Thus, reaching these steps in all these studies provided the basis for regulatory approval of CT-P13 by the FDA in April 2016 (19).

Even though the biosimilar can be approved for the same indication as the reference biologic, it might not be interchangeable with the original biologic. When the term interchangeable is used, this is to indicate that the same clinical result is expected whether a biosimilar to the reference biologic agent is used and that these can be substituted without prescriber involvement (13).

Our current FDA-approved, anti-TNF biosimilars are not deemed to be interchangeable. To be classified as interchangeable, dedicated switching studies (with at least 3 switches between products for at least 2 exposure periods) before approving a biosimilar to be interchangeable are required by the FDA (13,20). Currently, there are no biosimilars to infliximab or adalimumab, which are designated to be interchangeable. Switching from one biosimilar to another of the same reference biologic agent and numerous switches among various molecules are not recommended, given the insufficient evidence of efficacy and safety of such switches (21–23) (Figure 2).

CURRENT BIOSIMILARS AVAILABLE FOR USE IN PATIENTS WITH IBD IN THE UNITED STATES

There are currently 3 FDA-approved biosimilars of infliximab and 5 FDA-approved biosimilars of adalimumab (24) (Table 2). These agents are FDA approved for the management of autoimmune-mediated diseases including IBD, while numerous additional biosimilar agents are being tested. To date, the United States has lagged behind the European expansion of biosimilars, which currently has a total of 9 European Medicines Agency (EMA)–approved adalimumab biosimilars and 4 EMA-approved infliximab biosimilars (25). Tables 2 and 3 list the US FDA-approved biosimilars of anti-TNF agents and current EMA=-approved biosimilars of anti-TNF agents, respectively, with the dates of approval listed.

In an effort to facilitate biosimilar nomenclature, the US FDA proposed a rule for naming biosimilars in August 2015. The names include distinguishing suffixes (devoid of meaning), composed of 4 random lowercase letters. The purposeful intention of this nomenclature system is to avoid an inaccurate perception of biosimilars efficacy, which in turn might influence practitioners prescribing practice of biosimilars (26).

EVIDENCE OF BIOSIMILARS IN AUTOIMMUNE-MEDIATED DISEASES

The initial agent, known as CT-P13, infliximab dyyb (Inflectra), has been the first biosimilar for infliximab approved in Europe in 2013 and in the United States in 2016 after 2 double-blinded randomized controlled trials (PLANETAS and PLANETRA) demonstrated its bioequivalence with infliximab regarding its pharmacokinetics, safety, and efficacy (15,16). Specifically, PLANETRA study was a 54-week, randomized, multicenter study that demonstrated the similar safety and efficacy of CT-P13 with originator infliximab in 606 patients with RA (16). Both products were shown to have similar antidrug antibody rates (48.4 vs 48.2%) and similar rates of adverse events (35.2% vs 35.9%). Similarly, the PLANETAS study was a 54-week randomized, parallel-group multicenter study that demonstrated the safety and efficacy of CT-P13 with reference to infliximab in patients with AS (15). The incidence of treatment-emergent adverse events was noted to be lower in the maintenance group vs in the switch group (48.9% vs 71.4%) although no statistical comparison was performed. In the subsequent phase 3 study, a total of 584 patients with severe to moderate RA on methotrexate were randomized to BOW015 or reference infliximab (Remicade) for 16 weeks (23,27). In an open-label extension trial, all patients were switched to BOW015 until week 54 (27–29). At week 54, primary and secondary outcomes were all comparable between the 2 treatment groups, and additional measures of disease activity and disability were similar between

Table 1. Distinction between biologics and small molecules[a] (13,14)

	Biologics (11,12)	Small molecules (11,12)
Composition	Protein	Organic chemical
Administration	Parenteral	Oral
Structure	Variable 3D structure	Well-defined structure
Degradation	Catabolism	Metabolism
Mechanism of action	Blocking or depletion	Enzyme inhibition
Manufacturing cost	High	Low/variable

[a]Small molecules are more inclusive, and generics represent a subset of the small molecules.

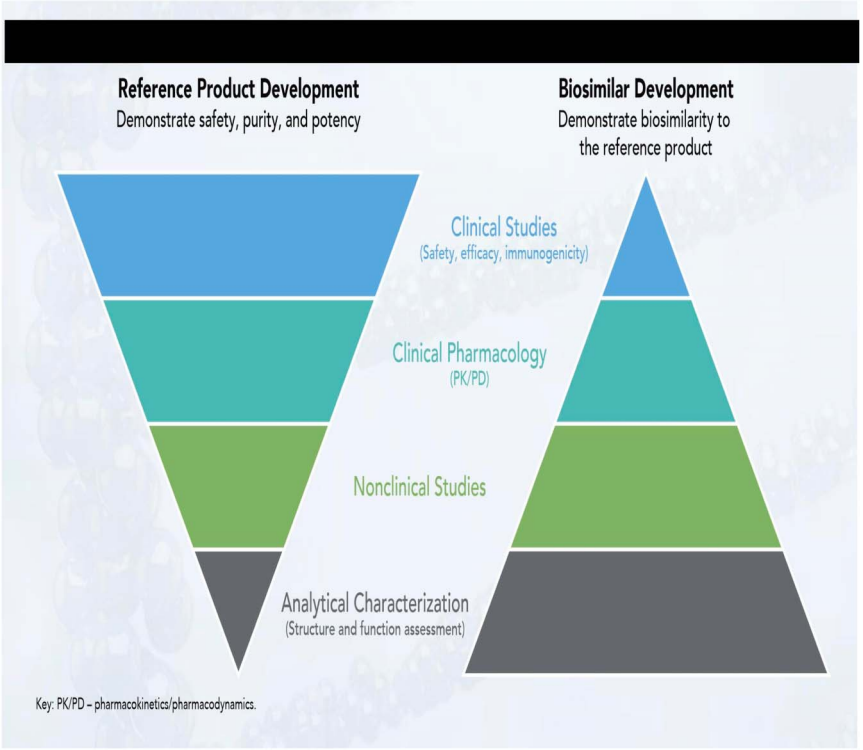

Figure 1. Reference product *vs* biosimilar development.

groups (27,29). However, there were no safety and immunogenicity data available.

In a prospective multicenter observational cohort study from Hungary, CT-P13 (infliximab dyyb (Inflectra) was found to be safe and effective to induce clinical remission in patients with CD or UC, but notably, those with previous infliximab exposure had decreased response rates and increased rates of allergic reactions (30). In addition, the most recent PROSIT-BIO cohort study (PRospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab BIOsimilar) evaluated the use of CT-P13 in consecutive 313 patients with CD and 234 with UC including 311 patients naive to previous use of biologics, 139 patients with previous exposure to biologics, and 97 patients switched to biosimilar after a mean 18 infusions of infliximab (31). The study demonstrated that after 8, 16, and 24 weeks, the efficacy estimations were 95.7%, 86.4%, and 73.7% for biologic naive patients, 97.2%, 85.2%, and 62.2% for biologic preexposed patients, and 94.5%, 90.8%, and 78.9% for switch groups, respectively (log-rank $P = 0.64$). Although there was no direct comparison between the biosimilar and infliximab, the efficacy and safety data were similar to what one would expect with infliximab (31).

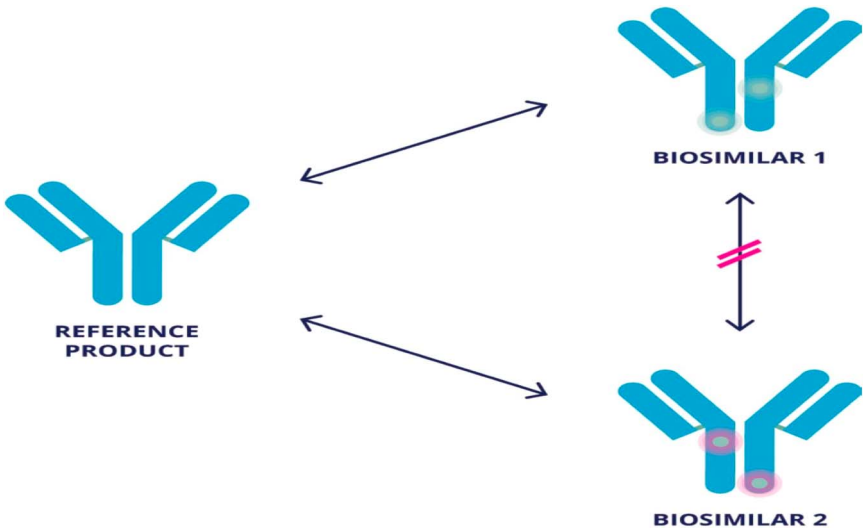

Figure 2. Switching from originator to biosimilars 1 and 2 is supported by evidence with no data supporting switches from biosimilar 1 to biosimilar 2.

Table 2. Biosimilars of tumor necrosis factor-α antagonists approved in the United States (23)

Reference product	Biosimilar (brand name)	Date of FDA approval
Infliximab	Infliximab-dyyb (Inflectra)	April 5, 2016
	Infliximab-abda (Renflexis)	April 21, 2017
	Infliximab-qbtx (Ixifi)	December 13, 2017
Adalimumab	Adalimumab-atto (Amjevita)	September 23, 2016
	Adalimumab-adbm (Cyltezo)	August 25, 2017
	Adalimumab-adaz (Hyrimoz)	October 30, 2018
	Adalimumab-bwwd (Hadlima)	July 23, 2019
	Adalimumab-afzd (Abrilada)	November 18, 2019

FDA, U.S. Food and Drug Administration.

Similarly, another infliximab biosimilar, SB2 (Infliximab-abda (Renflexis), was studied in randomized, double blind studies comparing it with infliximab originator in patients with RA, and it was found to have similar pharmacokinetics, efficacy, and safety (26). Additional infliximab biosimilars have since been approved in both the United States and other countries throughout the world (13,25).

We recently performed a systematic review, identifying 70 published studies and abstracts evaluating data on switching between the infliximab biosimilar and the reference agent, most of which were observational studies (7). For clinical data analysis, 6 randomized controlled trials were identified, and 5 of these studies were performed in patients with rheumatologic conditions (16,32–34). By contrast, the NOR-SWITCH trial (34) (Switch trial from Norway), a randomized, double-blind noninferiority study evaluating patients on infliximab who were randomized to continue infliximab or switched to CT-P13 (currently called infliximab dyyb; Inflectra) for 52 weeks, also included patients with IBD. The study demonstrated noninferiority of switching to biosimilar CT-P13 compared with originator infliximab for indications such as CD (155 patients, 32%), UC (93 patients, 19%), RA (78 patients, 16%), spondyloarthritis (91 patients, 19%), and psoriatic arthritis (30 patients, 6%). The primary endpoint was disease worsening at 12 months, based on predefined, condition-specific criteria (30% vs 26%, adjusted treatment difference −4.4%, 95% CI −12.7 to 3.9) (34). Overall, disease worsening was not significantly different between the 2 groups, nor was adverse events. The NOR-SWITCH study, however, was not powered to estimate differences in outcomes separately for each indication. The development of antidrug antibodies was also similar between the 2 groups. Notably, in all 6 trials evaluated by our group, the participants only underwent a single transition switch (7) (Table 4) Large sample sizes would be needed to detect a clinically meaningful difference, and we did not feel that this was met because many switches occurred in an open-label extension, and those were not powered to detect either noninferiority or equivalence. Currently, there is still not enough high-quality evidence to suggest interchangeability between biosimilars or the reference agent although recent studies add additional arguments for the continuous use of biosimilars in patients with IBD (7,35,36) The NOR-SWITCH extension trial in 380 of 438 patients who completed the main study, throughout the 78-week study period, demonstrated no difference in safety and efficacy between patients who maintained CT-P13 and patients who were switched from originator infliximab to CT-P13, thus providing evidence that switching from originator infliximab to CT-P13 is efficacious and safe (37).

EVIDENCE FOR CLINICAL USE OF BIOSIMILARS IN IBD

There are 2 main clinical scenarios in which a biosimilar can be initiated in our daily IBD practice. The first clinical scenario involves nonmedical switching of patients in remission from an originator biologic to biosimilar, whereas a second scenario involves a switch occurring during the active phase of the disease. In this scenario, the patient is naive to anti-TNF therapy and initiates their initial anti-TNF therapy with a biosimilar.

NONMEDICAL SWITCH FROM REFERENCE AGENT TO BIOSIMILAR ANTI-TNF THERAPY IN PATIENTS WITH IBD

This approach was explored and recently analyzed based on 2 recent randomized controlled studies involving 448 patients in remission on infliximab for at least 3 months–6 months, who were randomized to either continuation of originator or switch to the biosimilar CT-P13 (34,38,39). Both studies (34,38) followed up patients for 1 year. Overall, the intention-to-treat remission rates were similar between the 2 groups with a relative risk of not being in remission at 1 year with infliximab originator of 0.89 (95% CI 0.58 to 1.38) (39). The intention-to-treat loss of response or worsening disease rate was decreased with the originator of infliximab compared with the biosimilar (relative risk of loss of response of worsening disease of 0.64; 95% CI 0.44 to 0.94) (39). The German trial presented in

Table 3. Biosimilars of tumor necrosis factor-α antagonists approved in Europe (24)

Reference product	Biosimilar (brand names)	Date of EMA approval
Adalimumab	IMRALDI	August 24, 2017
Adalimumab	KROMEYA	April 21, 2019
	IDACIA	April 21, 2019
Adalimumab	AMGEVITA	March 22, 2017
	SOLYMBIC	March 22, 2017
Adalimumab	CYLTEZO	Authorized November 2017, withdrawn January 2019
Adalimumab	HALIMATOZ	July 26, 2018
	HEFIYA	July 26, 2018
	HYRIMOZ	July 26, 2018
Adalimumab	HULIO	September 19, 2018
Infliximab	INFLECTRA	September 10, 2013
Infliximab	FLIXABI	May 26, 2016
Infliximab	REMSIMA	September 10, 2013
Infliximab	ZESSLY	September 19, 2018

EMA, European Medicines Agency.

abstract form reported data for CD and UC and indicated that worsening of disease was seen more often in CD (per-protocol worsening = −14.3 difference [95% CI −29.3% to 0.7% in favor of infliximab originator]) than with UC (per-protocol worsening = −2.6% difference [95% CI −15.2% to 10.0% in favor of infliximab originator]) (38,39). In comparison, a trial by Jorgensen et al. (34) analyzed all the diseases separately. No detailed safety data were available in these trials other than general adverse events reported in all diseases based on the trial by Jorgensen et al. (34).

An additional scenario that might require further investigation is switching back to reference infliximab in patients who are on maintenance therapy with biosimilar infliximab therapy. Ilias et al. (40) also evaluated the effects of a reverse switch from biosimilar to originator infliximab due to reimbursement policies. Their prospective observational cohort

Table 4. Summary of the main randomized trials of biosimilars in autoimmune-mediated diseases

Name of the study	Drugs assessed	Study design	Study population	Primary clinical outcomes	Results
SB2 transition trial (31,32)	SB2 (INF)	78-wk randomized phase 3 single-transition study	Patients with RA; randomized; at wk 54 randomized to INF/SB2 (94 patients), INF/INF (101 patients) and SB2/SB2 (201 patients)	Efficacy, safety, and immunogenicity with a switch from INF to SB2, INF/INF, and SB2/SB2 groups at 78 wk	Efficacy was sustained and comparable across treatment groups INF/SB2, INF/INF, and SB2/SB2. American College of Rheumatology 20 responses rates between wk 54 and 78 were: INF/SB2, 63.5%–72.3%; INF/INF, 66.3%–69.4%; SB2/SB2, 65.6%–68.3%. Treatment-emergent adverse events (AEs) of the INF/SB2, INF/INF, and SB2/SB2 were 36.2%, 35.6%, and 40.3% and infusion-related reactions were in 3.2%, 2.0% and 3.5%, respectively. Among patients who were negative for antidrug antibodies (ADAs) up to wk 54, newly developed ADAs were reported in 14.6%, 14.9%, and 14.1% of the INF/SB2, INF/INF, and SB2/SB2, respectively.
Japanese RA study (33)	CT-P13	Single-arm OLE, a phase ½ study up to 134 wk	Patients with RA	Efficacy and safety of CT-P13, switched to CT-P13 at wk 54 from CT-P13 (38 patients) and INF (33 patients)	At wk 134, AE, efficacy, and safety comparable in 2 groups
PLANETRA OLE (21)	CT-P13	54-wk randomized parallel-group multicenter, phase 3 study, assesses at wk 102	Patients with RA	Efficacy and safety of CT-P13	At wk 102, efficacy and safety were similar in both groups
PLANETAS OLE (18)	CT-P13	54-wk randomized parallel-group multicenter study, assesses at wk 102	Patients with AS	Efficacy and safety	At wk 102, efficacy and safety were similar
BOW015 phase 3 OLE (27–29)	BOW015	Open-label extension up to 54 wk	Patients with RA	Efficacy	At wk 54, disease activity similar among both groups
NOR-Switch (34)	CT-P13	Randomized, double-blind, noninferiority, phase 4 transition study with 52-wk follow-up	Patients with RA, SA, UC, CD, and PsO; in 2 groups: INF (202 patients and CT-P13 (206 patients)	Disease worsening at wk 52	At wk 54, disease worsening occurred in 26.2% and 29.6% in the reference INF and CT-P13 groups, respectively.

CD, Crohn's disease; INF, infliximab; PsO, psoriatic arthritis; RA, rheumatoid arthritis; SA, spondyloarthitis; UC, ulcerative colitis.

study from Hungary included 174 unselected and consecutive patients with IBD who were switched from maintenance therapy with an infliximab biosimilar to originator infliximab. They observed no significant changes in clinical remission, trough levels, and antidrug antibodies levels in this patient population (40). Specifically, there was no significant difference in the proportion of patients in clinical remission at week 8 before the switch (82.5% with CD and 82.9% with UC), at baseline (80.6% with CD and 81.6% with UC), at week 16 (77.5% with CD and 83.7% with UC), or at week 24 (CD 76.3% with CD and 84.9% with UC) ($P = 0.60$ among groups for patients with CD and $P = 0.98$ among groups for patients with UC).

A recent systemic review that evaluated nonmedical switching of originator infliximab to an infliximab biosimilar in patients with IBD (41) included 49 study reports (3 randomized clinical controlled trials, 40 observational trials, and 1 case series). The conclusion of this systematic review, based on all the studies, suggested that nonmedical switching of originator infliximab to infliximab biosimilar is safe with no efficacy, safety, or immunogenicity concerns. However, the limitations of these supporting data include that there were a small number of randomized controlled studies included in this analysis with a predominance of observational cohort studies. Thus, clinical and regulatory organizations should be aware of these limitations of study designs before implementing any new policy. For example, in May 2019, the government of British Columbia launched the Biosimilar Initiative through its Pharmcare program. The primary goal of this program was to switch patients who were using originator biologics, including originator infliximab, to a biosimilar with a requisite that this occur by March 2020 (42). Even though the key argument for nonmedical switching is cost savings, the danger remains that biosimilar switching might not be as cost-effective, mainly when originator therapies are being offered at the same price as biosimilars (43). This brings further arguments against the universal implementation of such policies of a nonmedical biosimilar switching until more randomized controlled studies are available.

BIOSIMILAR VS REFERENCE AGENT TREATMENT IN PATIENTS WITH IBD NAIVE TO ANTI-TNF THERAPY

This scenario involves mandating the use of a biosimilar prescription over the reference agent when the patient has active disease and is biologic naive. This particular clinical scenario was addressed in the recent randomized controlled trial, which was performed by Ye et al. (36), comparing the efficacy of CT-P13 (infliximab dyyb; Inflectra) with originator infliximab in patients with active CD. All patients enrolled in this trial were previously naive to biologic therapy. In this multicenter, double-blind, phase 3 study, 220 patients were randomly assigned to CT-P13, followed by CT-P13; CT-P13, followed by infliximab; infliximab, followed by infliximab; or infliximab, followed by CT-P13, with the switches taking place at week 30. The trial was a noninferiority study with a sample size that had 85% power for a noninferiority margin of −20%.

The primary response assessed was the proportion of patients with a decrease of 70 or more points in the Crohn's Disease Activity Index from baseline to week 6 (non-inferiority margin 20%). The study concluded that Crohn's Disease Activity Index-70 response rates at week 6 were similar for CT-P13 (77 [69.4%, 95% CI 59.9 to 77.8] of 111) and infliximab (81 [74.3%, 95% CI 65.1 to 82.2] of 109; difference −4.9% [95% CI −16.9 to 7.3]), thereby establishing noninferiority. Over the total study period, 147 (67%) of patients experienced at least 1 treatment-emergent adverse event (36 [64%] in the CT-P13–CT-P13 group, 34 [62%] in the CT-P13–infliximab group, 37 [69%] in the infliximab–infliximab group, and 40 [73%] in the infliximab–CT-P13 group). In conclusion, the study showed noninferiority of CT-P13 to infliximab in patients with active CD, suggesting that the biosimilar CT-P13 could be a new option for the treatment of active CD. The 4 groups were similar after week 30, but this randomized controlled trial was not powered to show the statistical difference, and the study showed noninferiority of CT-P13 to infliximab in patients with active CD, suggesting CT-P13 as a new option of the treatment of active disease.

This clinical scenario of using biosimilar vs originator treatment in patients with IBD with active disease naive to anti-TNF therapy was also further evaluated by the recent French multicenter equivalence cohort study by Meyer et al. (35), which compared the effectiveness and safety of CT-P13 (infliximab dyyb, Inflectra) and reference product in patients with CD, naive to infliximab. This study used the French nationwide health administrative database with the primary outcome being a composite endpoint comprised of death, CD-related surgery, all-cause hospitalization, and switch to another biologic therapy (35). Among study patients, there were 2,499 patients in the CT-P13 group compared with 2,551 in the originator infliximab group evaluated between 2015 and mid-2017. No differences between the groups were found for the primary outcome (the hazard ratio [HR] was in favor of CT-P13 = 0.92; 95% CI 0.85 to 0.99). There were also no differences for CD hospitalizations (HR 1.00; 95% CI 0.9 to 1.11), surgery (HR 1.09; 95% CI 0.92 to 1.28), or switch to different biologics (HR 0.93; 95% CI 0.79 to 1.08). The groups were similar for demographic characteristics such as age, sex, disease duration, and previous medications. The main difference was that the treatment duration was longer for the originator when compared with CT-P13, which could have influenced the results in favor of the biosimilar.

There was an additional study by the same group, which additionally addressed the effectiveness and safety of originator infliximab compared with biosimilar CT-P13 in 3,112 patients with UC (44). The primary outcome of this study was a composite endpoint (death, UC-related surgery, all-cause hospitalization, and reimbursement for other biologics) evaluated in patients with UC. A total of 710 patients in the reference product group and 743 patients in the CT-P13 group met the composite endpoint. In a multivariable analysis of the primary outcome, CT-P13 was equivalent to the reference product (HR 1.04; 95% CI 0.94–1.15). The number of serious infections was lower in the CT-P13 group (HR 0.65; 95% CI 0.48–0.88). In addition, there was no difference in the incidence of solid or hematologic malignancy (HR 0.81; 95% CI 0.41–1.60). This study demonstrated the bioequivalence of CT-P13 compared with the reference infliximab product with a large sample size. In addition, it also highlighted that combination therapy with thiopurines has been more efficacious than monotherapy. However, there are limitations of this study that should be acknowledged, such as not including all-related clinical activity, the lack of endoscopic

Table 5. Summary of published recently clinical trials of biosimilars in inflammatory bowel disease

Study	Design/intervention	Population	Primary outcome	Results
Jorgensen et al. (34)	Randomized maintenance on INF; switch to T-P13 (randomized)	N (all) = 484; N (CD) =155; N (UC) = 93	Disease worsening—CD: 21.2% in infliximab, 36.5% CT-P13; UC: 9.1% infliximab, 11.9% CT-P13. Risk difference—CD: 14.3 (−29.2 to 0.7); UC: −2.6% (−15.2 to 10.0)	At wk 54, disease worsening occurred in 26.2% and 29.6% in the reference infliximab and CT-P13 groups, respectively.
Ye et al. (36)	International, randomized, double-blind, phase 3 noninferiority study	N (CD) = 220; 111 patients randomly assigned to initiate CT-P13 (56 to the CT-P13–CT-P13 group and 55 to the CT-P13–infliximab group) and 109 patients to initiate infliximab (54 to the infliximab–infliximab group and 55 to the infliximab–CT-P13 group).	Proportion of patients with a decrease of 70 points or more in Crohn's Disease Activity Index (CDAI) from baseline to wk 6	CDAI-70 response rates at wk 6 were similar for CT-P13 (77 [69.4%, 95% CI 59.9 to 77.8] of 111) and infliximab (81 [74.3%, 95% CI 65.1 to 82.2] of 109; difference −4.9% [95% CI −16.9 to 7.3]), thereby establishing noninferiority. Over the total study period, 147 (67%) patients experienced at least 1 treatment-emergent adverse event (36 [64%] in the CT-P13–CT-P13 group, 34 [62%] in the CT-P13–infliximab group, 37 [69%] in the infliximab–infliximab group, and 40 [73%] in the infliximab–CT-P13 group).
Meyer et al. (35)	Cohort: comparative real-life equivalence cohort study (the French nationwide health administrative database).	5,050 patients with CD (infliximab-naive patients): treatment with RP (n = 2,551) or CT-P13 (n = 2,499)	A composite endpoint of death, CD-related surgery, all-cause hospitalization, and reimbursement of another biologic therapy	1,147 patients in the RP group and 952 patients in the CT-P13 group met the composite endpoint (including 838 and 719 hospitalizations, respectively). In the multivariable analysis of the primary outcome, CT-P13 was equivalent to RP (HR 0.92; 95% CI 0.85 to 0.99). No differences in safety outcomes were observed between the 2 groups: Serious infections (HR 0.82; 95% CI 0.61 to 1.11), tuberculosis (HR 1.10; 95% CI 0.36 to 3.34), and solid or hematologic cancer (HR 0.66; 95% CI 0.33 to 1.32)
Meyer et al. (44)	Cohort: comparative real-life equivalence cohort study (the French nationwide health administrative database).	Patients with UC (n = 3,112)	A composite endpoint (death, ulcerative colitis-related surgery, all-cause hospitalization, and reimbursement for other biologics)	710 patients in the RP group and 743 patients in the CT-P13 group met the composite endpoint. In the multivariable analysis of the primary outcome, CT-P13 was equivalent to the RP (HR 1.04; 95% CI 0.94–1.15). The number of serious infections was lower in the CT-P13 group (HR 0.65; 95% CI 0.48–0.88). There was no difference in the incidence of solid or hematologic malignancy.

CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; RP, reference product; UC, ulcerative colitis.

data, and a lack of trough levels and antidrug antibodies; moreover, there was some heterogeneity between centers with the lack of a central randomization process.

The results of the most recently published studies in patients with IBD (Table 5) support the switch between the reference infliximab agent to CT-P13 and point out that the reverse switch

can be considered equivalent (35,36,40,44). However, the overall quality of available evidence that supports starting a patient with active IBD on a biosimilar in a patient who is infliximab naive rather than using originator infliximab to induce and maintain remissions is considered low according to the established GRADE criteria (39). New studies are still encouraged, including further randomized trials and international registries, which could collect and compare all safety and efficacy data of biosimilar.

WHY CONSIDER USING BIOSIMILARS

Factors leading to the development, use, and access of biosimilars

There are several factors that have driven the development and subsequent use of biosimilars. These include the expiration of patents of several biologic agents. Furthermore, technological innovation in biomanufacturing can play a role, including an improved selection on high producing cell lines and less costly bioreactors, all together leading to improved production yields and lower costs. In addition, global socioeconomics with mounting cost pressures on government budgets and the need to increase access to patients and curb rising healthcare costs. In addition, specific regulatory initiatives have been introduced including the Biologics Price Competition and Innovation Act in the United States in 2009 and the EMA regulations in Europe in 2006 (45,46). These regulatory initiatives have led to the establishment of an abbreviated pathway for the approval of biosimilars by allowing the introduction of an extrapolation process once a drug has demonstrated efficacy in a single approved indication (47). It was believed that this could help to reduce the cost of biologic agents (by creating competition to drive down prices), incentivize innovation, and increase patient access to biologic treatment.

Current costs of biosimilars

A recent review has highlighted that the cost to develop a generic medication is USD 1–4 million; the cost to develop a new biologic agent is approximately USD 1.9 billion with recognition that less than 10% of agents make it to market (48). The cost to develop a biosimilar is, on average, substantially less than an originator agent in the range of USD 100–250 million.

Given the magnitude of the expenditure for biologics in the United States (and similarly in the world), opportunities to save costs have been assessed, and as a consequence, biosimilars have been looked at very favorably in this context. Recent estimates from a study from the Rand Corporation (49) have suggested that the introduction of biosimilars in the United States has the potential to reduce biologic spending of more than USD 54 billion over 10 years (range of sensitivity analyses suggest a range of USD 25 to 150 billion, based on varying biosimilar penetration (5%–60%; mean 28%), with most coming from biosimilar anti-TNF inhibitors.

In 2018, 2 of the top-selling biologic agents were adalimumab and infliximab, with an estimated revenue of USD 19.9 billion (US sales of $13.7 billion and the remainder of the world of $6.2 billion) and almost USD 5.9 billion ($5.3 billion of Johnson and Johnson and $0.58 billion of Merck), respectively (50). Based on the recent analysis of Medicare, average sales price payments over the nearly 4-year period the availability of infliximab biosimilar has resulted in lower net costs of the reference agent to health plans and insurers by 11% from a peak of $85.81 per 10 mg in January 2018 to $76.65 per 10 mg in January 2019 (51). When there is no biosimilar competition, the costs of the reference agent will be steadily increasing each year by approximately 11% and, thus, might result in a higher price in 2023 when finally biosimilar adalimumab becomes available (51).

It is estimated that monoclonal antibodies will reach USD 125 billion in sales by the end of the year 2020. By introducing biosimilars, increased competition in the marketplace can lead to reduced costs and can help curb rising healthcare costs, whereas also increasing patient access to these medications. Increased access has been demonstrated with other non-IBD biosimilars in the past (52).

Current biosimilars' costs savings

The anticipated cost-saving and increased access to biosimilars seem to be far less than those expected in the United States. Even though the costs and risks of developing biosimilars are much lower when compared with the reference drugs, the recent report estimated only approximately 3% of biologic expenses ($3.2 billion) to be subject to competition from biosimilar agents according to the 1 report from 2018, and US healthcare systems and payers are still awaiting savings related to biosimilar use. In the most recent communication, Kim et al. assessed whether market entry of infliximab biosimilars was associated with changes in the utilization and cost of TNF inhibitors when using claims data from a large US commercial health plan (53). In a large commercial insurance database analyzed between January 2016 and March 2019, there was less than 1% uptake of biosimilar infliximab (53). After the market entry, biosimilar infliximab (infliximab-dyyb and infliximab-abda) had sparse uptake, accounting for just 0.1% of total TNF inhibitor use in 2017Q2 and 0.9% in 2019Q1. For biosimilar infliximab, the mean quarterly insurance paid per treated patient was similar to that for originator infliximab from 2017Q2 ($83,222 vs $8,656) to 2018Q2 ($10,112 vs $9,795) and decreased moderately in 2018Q3 (%8,111 vs $9,535), maintaining more than $1,000 difference thereafter. Median (interquartile range) patient out-of-pocket costs per dispensing during the study period was $37 ($5–$86) for adalimumab, $0 ($0–$350) for infliximab, and $0 ($0–$426) for biosimilar infliximab (53). These findings suggest that current cost savings from infliximab biosimilars in the United States remain inadequate.

Roadblocks to biosimilars

There are important obstacles that have to be overcome to increase the use of biosimilars. This includes several factors that remain unique to the United States, such as delayed regulatory policies, prolong patent litigation activities, various federal reimbursement rules, rebate contracting policies, and the overall limited competition. Mehr and Brook (51), in their recent review, discussed such limitations in the US system, pointing out that the rationale behind the limited access and uptake is linked with the drug regulatory systems, legislated drug approval pathways, and intellectual property protection between the US and EU markets. It is known that the EMA had introduced the regulatory pathway and market development for biosimilar agents, and since the approval of the first biosimilar in 2006 and as of the end of 2018, at least 53 biosimilars have been authorized by EMA for 15 difference reference products. In comparison, the

US FDA since its first product approval in 2014 and as of the end of 02/24/2020 has approved 26 biosimilars for 9 reference products (23).

Moreover, in the United States, the way in which pharmaceuticals are purchased by third-party payers has played a significant role. In view of these, the US Federal government has been making all efforts to address all these factors and to encourage the faster approval and utilization of biosimilars (51). As of July 2018, the Biosimilars Action Plan was published, pointing out to the lack of competition of biologics and outlining 4 key goals, including streamlining the approval process, improving regulatory clarity, enhancing educations efforts to improve understanding among stakeholders, and collaborating the Federal Trade Commission to address anticompetitive behaviors (54,55).

A survey of US payers (56) revealed that the expectations of saving above 20% might only occur after 2023 when adalimumab biosimilar is available as a prescription agent. The most recent survey of managed care and specialty pharmacy professionals (57) expressed a positive attitude toward the efficacy and safety biosimilars and achieving goals of the Biologics Price Competition and Innovation Act of 2009 by implementing many diverse strategies. These included the primary implementation role of biosimilar manufactures (4%–5%), the federal government (26%), and managed care organizations (15%) (57).

From the European experience, we can learn that the actual costs savings associated with biosimilars vary among member countries from relatively high utilization of biosimilars and greater discount as in Norway or Denmark to slower adoption as in the United Kingdom (51,58). The discounts offered in each country member are dependent on its system for bidding on pharmaceutical purchases (59). These differences could be related to whether healthcare financing of a country is based on a single-payer model. In the United States, manufactures are required to negotiate with various government and commercial payers for reimbursement of their products leading to further delays. Most of US states introduced legislation allowing a substitution by the pharmacy of an interchangeable biosimilar when one is available, whereas this concept of interchangeability is not required with the EMA and leaves the decision in the hands of providers. Currently, however, there are no biosimilar agents in the United States for patients with IBD, which have been deemed interchangeable. Recent policy changes introduced by the Centers for Medicare and Medicaid Services in which biosimilars are reimbursed might lower government expenditures. However, the market is still dependent on confidential rebates, and Pharmacy Benefits Managers might still maintain profit and makes competition limited (51).

Further important factors include physicians' and patients' concerns about effectiveness and safety and immunogenicity. In a survey of US physicians toward nonmedical switching, more than 80% of physicians did not want stable patients to switch, and more than 50% of physicians anticipated a nonmedical switch from originator to a biosimilar. The perception was that this action would have a negative impact on efficacy and safety (60,61). High-quality switch studies and registration quality clinical trials of a biosimilar in patients with IBD are still desired. Up to now, most of trials for FDA approval have been conducted in patients with rheumatologic disorders, and extrapolation was the key regulatory component in their approval for use in patients with IBD. Although the concerns of biosimilar safety and efficacy are addressed by the clinical trials performed before FDA approval, biosimilars have not been used for as long of a duration as the reference products. An additional issue to be addressed is how to use therapeutic drug monitoring in patients who have had their biologic therapy initiated on biosimilars or were switched to biosimilar therapies. So far, clinical evidence confirms similar antibody formation rates when comparing originator product with a biosimilar. Strik et al. demonstrated that the serum concentration of infliximab after switching to CT-P13 has not changed (62). These data were recently presented in the results of the 16-week SECURE trial, which also indicated that switching to infliximab-dyyb (Inflectra) was safe and well tolerated by patients with remitted IBD (62). However, it remains uncertain whether these antibodies to originator infliximab are directed against shared epitopes of CT-P13 and whether there is also cross-reactivity (16,26). In addition, pharmacovigilance should be applied for biosimilars and biologics, and all unforeseen adverse events and immunogenicity data need to be carefully collected.

Another concern is that nonmedical switching of biological medication might lead to a "nocebo" effect defined as an unexplained and unfavorable therapeutic effect after switching. Boone et al. (63) conducted a recent study on infliximab biosimilar implementation in 125 patients with immune-mediated inflammatory disease based on shared decision-making under effectiveness and safety monitoring. Overall, no significant longitudinal changes in disease activity assessment, safety, laboratory outcomes were demonstrated in any of the indications in 9 months. An overall nocebo response was confirmed in 16 of 125 patients (12.8%) during a minimal observation period of 6 months after transitioning to biosimilar infliximab (63).

Additional concern from a clinical perspective is avoiding at all costs, a scenario in which a patient determined to be primary nonresponder to a specific biologic agent is required to be switched to a biosimilar of that product just based on cost savings, which can potentially be mandated by the payer. This patient will similarly not respond to the biosimilar, and this practice should not occur. Based on the current data and studies that we have about biosimilars, clinical practitioners should be entirely responsible for the prescribing of biosimilars, and these agents should not be automatically switched by pharmacists. All inclusion and exclusion criteria applying to various switching scenarios should be clarified in new clinical guidelines.

Further concerns include the potential traceability of biosimilar whether safety issues arise, for example, in patients who undergo multiple switches without appropriate notifications to patients and their physicians if such switches occur.

It is currently believed by many individuals that biosimilars are as safe and effective long-term agents as their reference agents, but adequately powered, longer-term clinical trials are still encouraged to confirm these beliefs. The creation of international registry studies might help uncover the presence of uncommon adverse events. Furthermore, more robust switching studies are needed before biosimilars can be sanctioned to be classified as interchangeable with the reference agent, particularly with studies involving 2 or 3 switches. There have been "multiple switches" studies performed, including anti-TNF and other non–anti-TNF biosimilars (64,65). Gerdes et al. (65) evaluated efficacy, safety, and immunogenicity of GP2015 and the

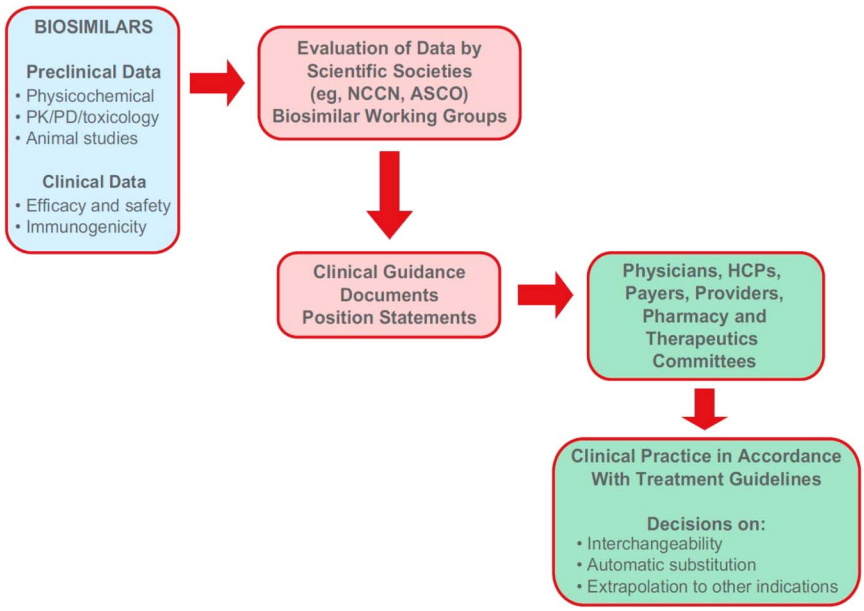

Figure 3. The role of scientific societies in evaluating biosimilars data and constructing guidelines and positions' statements.

etanercept originator product (ETN, Enbrel) and reported effects of repeated switching between GP2015 and ETN in 531 patients with psoriasis. Treatment efficacy, safety, and immunogenicity were similar between the pooled continued and pooled switched treatments during the treatment period, indicating that there are no effects in the short term on clinical data of multiple switches between GP2015 and ETN (65). Blauvelt et al. (64) evaluated the impact of multiple switches between GP2017 and reference adalimumab after the demonstration of equivalent efficacy and similar safety/immunogenicity in adult patients with active, clinically stable moderate to severe plaque psoriasis. Switching up to 4 times between GP2017 and reference adalimumab had no detectable impact on efficacy, safety, or immunogenicity (64).

Furthermore, the lack of practice guidelines for the use of biosimilars makes their adaptation challenging. Figure 3 illustrates the potential role of scientific societies such as the National Comprehensive Cancer Network or American Society of Clinical Oncology in evaluating data supporting biosimilar use followed by clinical guidelines and statements. Once clinical guidelines and positions statements are developed, providers will rely on such documents to establish their practice policy and to make key decisions about use of biosimilars, such as appropriateness of automatic substitution and extrapolation to other indications of the reference biologics. Although biosimilars have the potential to drive down costs through competition, overall pricing can be more complex, with complicated rebates and patient programs leading to confusion and increased cost to the patient.

CONCLUSIONS

Biosimilars have continued to be shown to be safe and effective medications and, thus, are able to compete with the reference agents. The potential benefits, to decrease cost and increase patient access, could have a significant impact on healthcare. Further studies are needed before interchangeability can be approved. Cross-switching or multiple switching among biosimilars should not be recommended until more clinical data become available. Physicians, advanced practice providers, and patient's comfort in accepting the use of biosimilars in lieu of originator biologics remain an obstacle that needs to be addressed through appropriate educational programs and new clinical guidelines and gastrointestinal societies' position statements. Long-term clinical trials and international registry databases, which evaluate the safety and efficacy of biosimilars, should be continued and encouraged. Importantly, the data from the registry studies could help to alleviate any patients' concerns about the use of biosimilars and improve physician's comfort in prescribing biosimilars. The era of biosimilar use in treating patients with IBD has been initiated although further research is still required.

CONFLICTS OF INTEREST

Guarantor of the article: Gary R. Lichtenstein, MD.
Specific author contributions: A.M.B.: preparation of the manuscript, review of the manuscript, and submission of the manuscript. Y.S.: preparation of the manuscript. G.R.L.: preparation and critical review of the manuscript.
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Study Highlights

WHAT IS KNOWN

- ✓ Biosimilar products have the potential to reduce spending on biologic therapies and increase access to patients with indicated conditions.
- ✓ Key strategies to expand Biosimilars include the following: providing evidence-based education; incentivizing prescribers; expanding formulary policies; continuing to advance U.S. FDA guidance; new clinical studies including international registries and randomized controlled studies.
- ✓ The successful implementation of these strategies depends on collaboration among managed care professionals, providers, patients, manufacturers, government agencies, and legislators.

WHAT IS NEW HERE

- ✓ The results of the most recently published studies support the switch between the reference infliximab and biosimilar infliximab.
- ✓ The quality of evidence supporting initiating therapy with a biosimilar in infliximab-naïve patients with active disease rather than originator infliximab to induce and maintain remissions is considered low according to the GRADE criteria. New studies are still encouraged, including further randomized trials, in addition to international registries to help collect and compare safety and efficacy data.

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