

A SPECIAL MEETING REVIEW EDITION

Highlights in Biosimilars From the World Congress of Gastroenterology at ACG 2017

A Review of Selected Presentations From the World Congress of Gastroenterology at ACG 2017 • October 13-18, 2017

• Orlando, Florida

Special Reporting on:

- Biosimilars: What Are They and How Will They Change the Way We Practice?
- Infliximab Assay Used in Clinical Practice Validated for Measuring SB2 Infliximab Biosimilar's Serum Drug and Anti-Drug Antibody Levels
- Efficacy of Infliximab Biosimilar for Induction and Maintenance Therapy in Inflammatory Bowel Disease After Switch From Drug Originator: A Meta-Analysis
- Long-Term Efficacy, Safety, and Immunogenicity Data From a Phase III Confirmatory Study Comparing GP2017, a Proposed Biosimilar, With Reference Adalimumab
- Patient Perceptions Regarding the Use of Biosimilars in Inflammatory Bowel Disease
- FDA Public Forum on Biosimilars

With an Introduction and Expert Commentary by:

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WHAT ARE **BIOSIMILARS?**

Let's Clarify Biosimilars

Biosimilars are a new step in biologic medicines and are highly similar to originator (or "reference") biological products.¹

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Reference:

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Highlights in Biosimilars From the World Congress of Gastroenterology at ACG 2017: Introduction

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Biosimilars were developed in an effort to lower the costs of biologic drugs. The development of a biologic drug costs an estimated \$1.2 billion,¹ although the manufacturing costs are not publicly disclosed. Treatment costs can be unclear, as insurance discounts and rebates are often confidential. The perception is that a switch to a biosimilar will lead to an estimated cost savings of 10% to 50% for the purchaser.²

According to the US Food and Drug Administration (FDA), a biosimilar product is highly similar to a reference product, notwithstanding minor differences in clinically inactive components.³ There are no clinically meaningful differences in terms of safety, purity, and potency. However, a biosimilar is not a generic version of a drug. A biosimilar differs from a generic in many ways. The biosimilar is a protein, and the generic consists of organic chemical compounds. A biosimilar has a variable 3-dimensional structure, whereas the generic has a well-defined structure that is less complex. The route of administration may also differ; for example, it can be oral for a generic or parenteral for a biosimilar. The degradation process may also be different. For a biosimilar agent, the mechanism of action typically involves blocking or depletion, whereas generics generally rely on enzyme inhibition. The manufacturing costs of generic drugs are lower than

those for biosimilars. The biosimilar requires more labor to control and regulate the manufacturing process, more extensive quality control and testing for stability, and a higher level of record keeping for quality assurance, lengthening the time to batch availability.

Rigorous pathways are available to develop biosimilars, but they differ from those used in the originator drug. The preclinical analytic studies undertaken for the originator drug are emphasized in the development of biosimilars. Studies of pharmacokinetics and pharmacodynamics are important for both. Clinical trials are de-emphasized in the development of biosimilars, whereas they provide the foundation for the development of the originator agent. Large, adequately powered, randomized, controlled trials are needed for registration of an originator biologic, but they are not used in the approval of biosimilars. An equivalent study is needed to demonstrate biosimilarity; this study must show that the proposed product is neither inferior nor superior to the reference product. In contrast, a superiority study aims to show that a biosimilar agent is better than the originator agent. If a study shows that a biosimilar is better than the originator therapy, then the new drug must go through a separate FDA approval process. Evaluation of a biosimilar agent incorporates in vitro studies, structural

analyses, studies of glycosylation, functional assays, pharmacokinetics, pharmacodynamics, immunogenicity, toxicity studies, and functional assays. The FDA incorporates a step-wise approach to demonstrate similarity between a biosimilar and the originator biologic.

Questions have been raised regarding the feasibility of extrapolating efficacy and safety data from the originator agent to the biosimilar. Clinical trials in one indication are used as a rationale for clinical use in other indications. It is possible to extrapolate if the totality of the evidence demonstrates overall similarity with the originator biologic and if clinical similarity is demonstrated in a key indication. The FDA considers this extrapolation on a case-by-case basis. When the mechanism of action for a condition is not understood, separate clinical trials may be required. It is necessary to have patient population data and a clinical endpoint that is sensitive enough to detect clinically meaningful differences. Comorbidities, concomitant medications, and intersubject variability must be taken into account. Superimposable biologic data must address every functional aspect of the agent in question.

Types of Studies: Switching vs Substitution

There are 3 different types of studies comparing originator biologics vs

biosimilars: transition studies, substitution studies, and interchangeability studies. In a transition study, patients first receive treatment with either an originator biologic or the biosimilar. Patients are then switched over to another product, whether it be the biosimilar or the originator drug. They receive the therapy for a certain period, and then undergo evaluation for treatment endpoints.

In a substitution study (also known as a single-switch study), the patients switch from the originator agent to the biosimilar, or vice versa. Patients are followed for a period of time to evaluate immunogenicity and other clinical endpoints.

In an interchangeability study (also known as a multiple-switch study), patients switch several times between an originator biologic and the biosimilar. The field of inflammatory bowel disease (IBD) thus far lacks data from interchangeability studies.

Biosimilar Approvals

The first approval of a biosimilar agent occurred in Europe in 2006 and was for the hormone somatotropin. The European Medicines Agency has approved more than 30 polysaccharide and protein biosimilars, which include monoclonal antibodies, growth factors, and other hormones.⁴

In the United States, the first

biosimilar was approved in 2015.⁵ There are now several approved biosimilars, although not all are available for clinical practice. Filgrastim-sndz (Zarxio, Sandoz) was approved in March 2015. (After the FDA approves a biosimilar, the generic nomenclature is based on the name of the originator biologic followed by 4 random letters.) Three biosimilars were approved in 2016: infliximab-dyyb (Inflectra, Pfizer) in April, etanercept-szszs (Erelzi, Sandoz) in August, and adalimumab-atto (Amjevita, Amgen) in September (this later agent is not available). Several biosimilars were approved in 2017. Infliximab-abda (Renflexis, Merck) was approved in July. Adalimumab-adbm (Cyltezo, Boehringer Ingelheim) was approved in August, but it is not available. Bevacizumab-awwb (Mvasi, Amgen) was approved in September. Many more biosimilars for therapies used in IBD are expected in the future.⁶

Disclosure

Dr Lichtenstein has consulted for Abbott Corporation/AbbVie, Actavis, Alaven, Celgene, Ferring, Hospira, Janssen Ortho Biotech, Luitpold/American Regent, Pfizer Pharmaceuticals, Prometheus Laboratories, Romark, Salix Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, Takeda, and UCB; conducted research for Celgene, Janssen Ortho Biotech, Salix

Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, and UCB; received honoraria (CME program) from Ironwood, Luitpold/American Regent, Merck, and Romark; and received funding to the University of Pennsylvania (IBD Fellow Education) from Janssen Ortho Biotech, Pfizer Pharmaceuticals, and Takeda.

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Biosimilars: What Are They and How Will They Change the Way We Practice?

Dr Peter Laszlo Lakatos presented an overview of biosimilar drugs and experience with infliximab biosimilars.¹ Biosimilar drugs are created to mimic existing drugs (which are referred to as reference or originator molecules).² Owing to the complexity of manufacturing biological molecules, a biosimilar drug is not identical to the originator molecule. As described by the US Food and Drug Administration (FDA), a biosimilar is a biological product that is highly similar to the reference product, notwithstanding minor differences in clinically active components.³ There must be no clinically meaningful differences between the reference product and the biosimilar product in terms of safety, purity, and potency. The most important difference between the 2 types of drugs involves the way they are evaluated. The evaluation of biosimilar molecules is based on laboratory analyses of factors such as primary structure, impurities, higher order structure, biological activities, and posttranslational modifications. In contrast, clinical trials are essential for evaluating originator molecules and represent the majority of the effort put toward evaluating the molecule prior to approval. In a disease area such as inflammatory bowel disease (IBD), it would be very difficult to assess actual clinical differences between an originator molecule and a biosimilar, owing to variability in disease presentation, response to treatment, very high response rates with placebo, and other factors. As a result, analytical techniques provide the majority of evidence to determine if a biosimilar will have any clinically meaningful differences in a patient population.

Infliximab Biosimilars

CT-P13 is a biosimilar of infliximab, which is an inhibitor of tumor necrosis

factor α (TNF- α) that is approved for the treatment of Crohn's disease (CD) and ulcerative colitis (UC).⁴ A systematic review with a meta-analysis evaluated studies of CT-P13 as induction therapy in patients with CD or UC. The study showed that clinical efficacy was similar to that achieved in prior studies of infliximab and other anti-TNF molecules (Figure 1).⁵ Adverse events were rare, occurring in 8% of patients with CD or UC. CT-P13 was evaluated in a prospective, uncontrolled, observational study conducted in Hungary.^{6,7} The study was initiated in May 2014 after the European Medicines Agency approved CT-P13 for the treatment of all infliximab indications, including rheumatoid arthritis, ankylosing spondylitis, CD, UC, psoriatic arthritis, and psoriasis. The patient population consisted of newly diagnosed patients with CD or

UC who had no prior exposure to an anti-TNF- α agent, and patients who had previously responded to infliximab and had a drug holiday of at least 1 year. Evaluations occurred at weeks 2, 6, and 14, and then every 3 months, with a planned investigation period exceeding 54 weeks. The study included 209 patients with CD and 144 patients with UC. In the CD cohort, 47% of patients were male, and the median age at disease onset was 24 years (interquartile range [IQR], 19-34 years). The median disease duration was 5 years (IQR, 2-11 years), and 24.3% of patients had received prior anti-TNF therapy. In the UC cohort, 51% were men, and the median age at disease onset was 28 years (IQR, 22-39 years). The median disease duration was 5 years (IQR, 2-11 years), and 19.4% of patients had received prior anti-TNF therapy. Concomitant use of corticosteroids or azathioprine

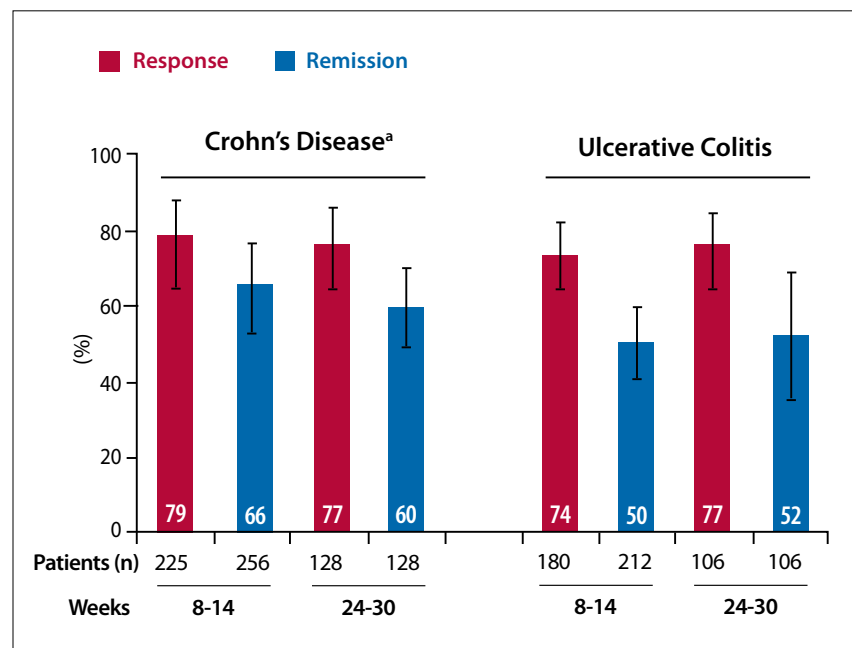


Figure 1. Pooled clinical response and remission rates after induction therapy with the infliximab biosimilar CT-P13. The error bars show the mean upper and lower limits.

^aLuminal Crohn's disease. Adapted from Komaki Y et al. *Aliment Pharmacol Ther.* 2017;45(8):1043-1057.⁵

was reported in 42.6% and 60.3% of patients in the CD cohort, respectively, and in 64.6% and 51.4% of patients in the UC cohort.

Response rates with CT-P13 were similar to those observed previously with approved anti-TNF- α agents. At week 14, 86% of patients with CD had achieved a response and 49% were in remission, whereas 74% of patients with UC had achieved a response and 56% were in remission. At week 30, 81% of patients with CD had achieved a response and 53% were in remission, whereas 66% of patients with UC had achieved a response and 43% were in remission. Response and remission rates were lower in patients who had received prior treatment with an anti-TNF- α agent. Among 136 patients with CD, the 54-week response rate was 65%, and the 54-week remission rate was 48%. Among 99 patients with UC, the 54-week response rate was 50%, and the 54-week remission rate was 43%. The mean level of C-reactive protein decreased significantly by week 14 in both patient groups and was maintained throughout the study ($P < .001$). Infusion reactions were observed in 8.8% of patients, and 9% of patients developed infections.

An ongoing study is investigating CT-P13 vs infliximab as induction with crossover after week 14.^{8,9} The randomized, double-blind, parallel group, phase 3 study enrolled 214 patients with active CD and a CD activity index (CDAI) score between 220 and 450 points. The study's primary objective is to demonstrate that CT-P13 is noninferior to infliximab at week 6 of induction treatment based on the CDAI-70 response rate. The study met its primary endpoint, demonstrating similar outcomes at week 6 based on CDAI-70 response ($P = .561$), CDAI-100 response ($P = .774$), and rates of clinical remission ($P = .832$). Week 30 results also showed similar outcomes with infliximab or the biosimilar drug, and drug trough levels and rates of anti-drug antibodies were comparable to results observed with infliximab in prior studies (Figure 2).

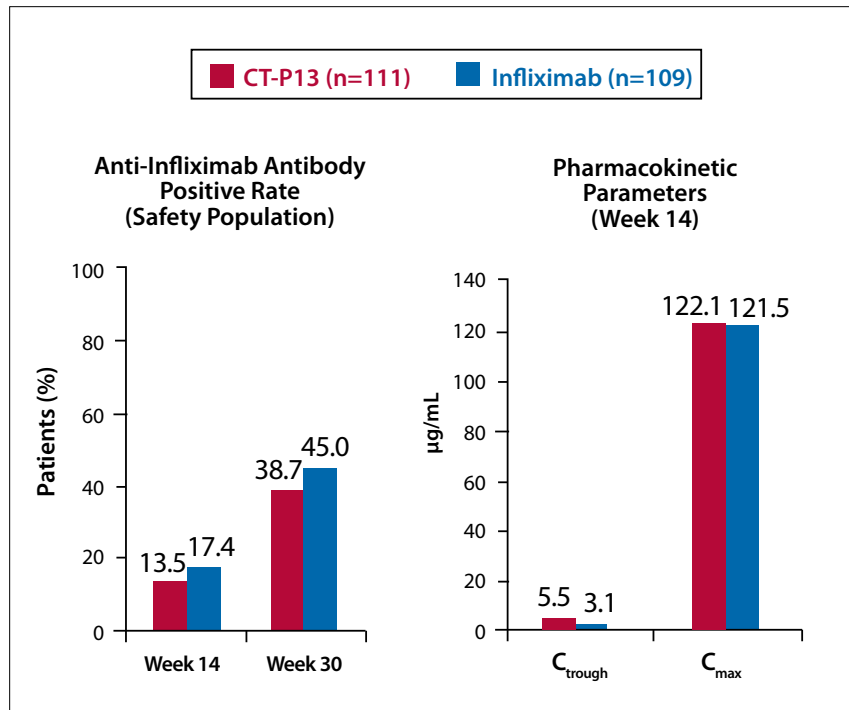


Figure 2. Anti-infliximab antibodies and pharmacokinetics in a study of CT-P13. Adapted from Kim YH et al. DDW abstract 248. *Gastroenterology*. 2017;152(5 suppl 1):S65.⁹

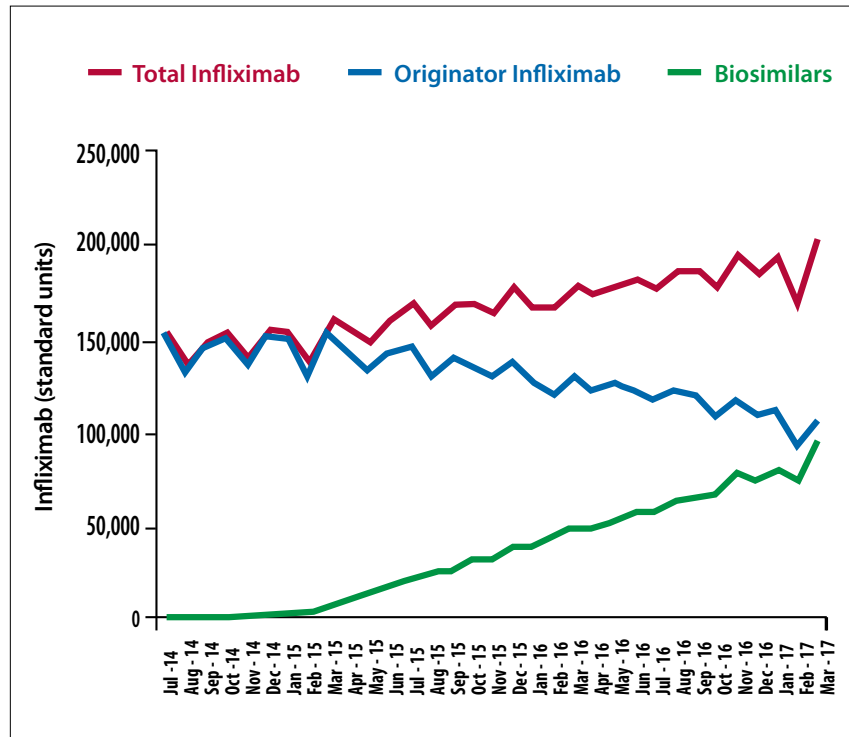


Figure 3. Use of infliximab biosimilars in Europe. Based on data from IMS MIDAS Unit sales. Adapted from Lakatos PL. Biosimilars: what are they and how will they change the way we practice? Presented at: the World Congress of Gastroenterology at ACG 2017; October 13-18, 2017; Orlando, Florida.¹

Safety and Efficacy of Switching

Results from a meta-analysis suggest that patients with CD or UC who switched from infliximab to CT-P13 experienced acceptable rates of response and remission.⁵ In addition, the NOR-SWITCH study investigated the safety and efficacy of switching from infliximab to CT-P13 among patients with CD or UC, as well as in patients with chronic plaque psoriasis, psoriatic arthritis, spondyloarthritis, or rheumatoid arthritis.¹⁰ The noninferiority, double-blind, phase 4 trial enrolled patients who had received at least 6 months of infliximab prior to enrollment. The study randomly assigned 482 patients to continue on infliximab or switch to CT-P13. The primary endpoint, disease worsening during 52-week follow-up, was similar for both arms (adjusted treatment difference: -4.4 ; 95% CI, -12.7 to 3.9).

Uptake of the infliximab biosimilar has been highest in Europe, where it has reached approximately 50%

(Figure 3). In Norway, the uptake of biosimilars is close to 100%. In contrast, uptake of the infliximab biosimilar has been miniscule in Canada, despite the fact that increasing use of biosimilar drugs can decrease drug spending. The European Crohn's and Colitis Organisation recommends that patients switch from infliximab to the biosimilar infliximab.¹¹

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Infliximab Assay Used in Clinical Practice Validated for Measuring SB2 Infliximab Biosimilar's Serum Drug and Anti-Drug Antibody Levels

Therapeutic drug monitoring of infliximab has proven useful for guiding dose adjustments and therapeutic strategies.¹ An infliximab detection kit is commercially available for therapeutic drug monitoring of circulating TNF- α , prescribed anti-TNF- α drugs, and anti-drug antibodies. A study was conducted to validate the kit for measuring serum levels of SB2, an infliximab biosimilar, and anti-SB2 antibodies.² For spiking experiments, 2 batches of SB2 were compared with infliximab originator as a control. Serum matrices included 2 from individual healthy donors and 1 from a pool of healthy donors. There were 58 clinical samples collected from

patients with IBD who were receiving treatment with the infliximab originator. Of these, 30 samples showed detectable levels of infliximab, and 28 samples showed detectable levels of anti-infliximab antibodies.

For samples spiked with SB2, recovery ranged from 81% to 105%. For the infliximab originator, the recovered amount ranged from 100% to 108%. Quantification with the commercially available kit showed similar behavior for SB2 and the infliximab originator ($R^2=0.91$). Specificity was demonstrated by adding polyclonal antibodies directed against the infliximab originator to the clinical samples spiked with SB2; assay results

were below the lower limit of quantification. Coefficients of variation ranged from 2.2% to 10.3% for between-run precision and from 4.4% to 12.7% for within-run precision. The results for precision within and between runs met the acceptance criteria of having a coefficient of variation of less than 20%. The kit was stressed by storage at 37°C for 7 days prior to use and yielded results within $\pm 20\%$ of the nonstressed kit, thus meeting the acceptance criteria.

Storage of SB2-spiked serum samples for 7 days at 4°C, 3 days at room temperature, or exposure to 5 freeze-thaw cycles yielded results that were within $\pm 20\%$ of values obtained

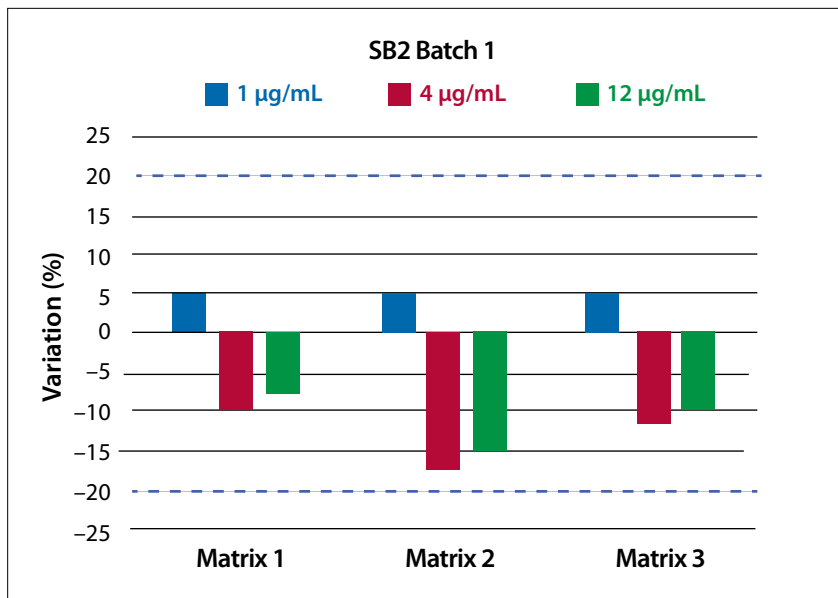


Figure 4. Accuracy of an assay measuring levels of serum drug and anti-drug antibodies among patients treated with the infliximab biosimilar SB2. Data for batch 1 are shown. Adapted from Noguier G et al. Abstract P2137. Presented at: the World Congress of Gastroenterology at ACG 2017; October 13-18, 2017; Orlando, Florida.²

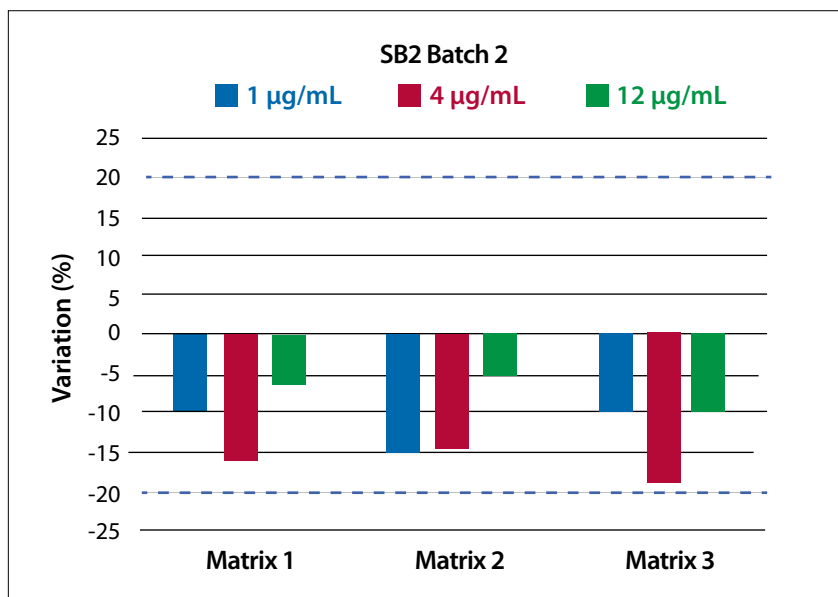


Figure 5. Accuracy of an assay measuring levels of serum drug and anti-drug antibodies among patients treated with the infliximab biosimilar SB2. Data for batch 2 are shown. Adapted from Noguier G et al. Abstract P2137. Presented at: the World Congress of Gastroenterology at ACG 2017; October 13-18, 2017; Orlando, Florida.²

with control samples that had been stored at -20°C . To demonstrate the ability to detect anti-SB2 antibodies with the kit, 28 clinical samples with detectable anti-infliximab antibodies were evaluated after the addition of the infliximab originator or SB2, and all 28 samples yielded residual levels of anti-infliximab antibodies below the lower limit of quantification (Figures 4 and 5).

SB2 was added to the detection reagent, which contained biotinylated

infliximab. Although the 28 clinical samples were initially shown to contain anti-infliximab antibodies, the addition of SB2 to the detection reagent yielded results below the lower limit of quantification for all 28 samples. The 28 clinical samples with detectable levels of anti-infliximab antibodies were used to detect the infliximab originator, SB2–batch 1, or SB2–batch 2 coated on microplates, and the results were compared. SB2 vs the infliximab originator yielded

an R^2 of 0.98, and SB2–batch 1 vs SB2–batch 2 yielded a correlation of $R^2=0.97$ (Figure 6).

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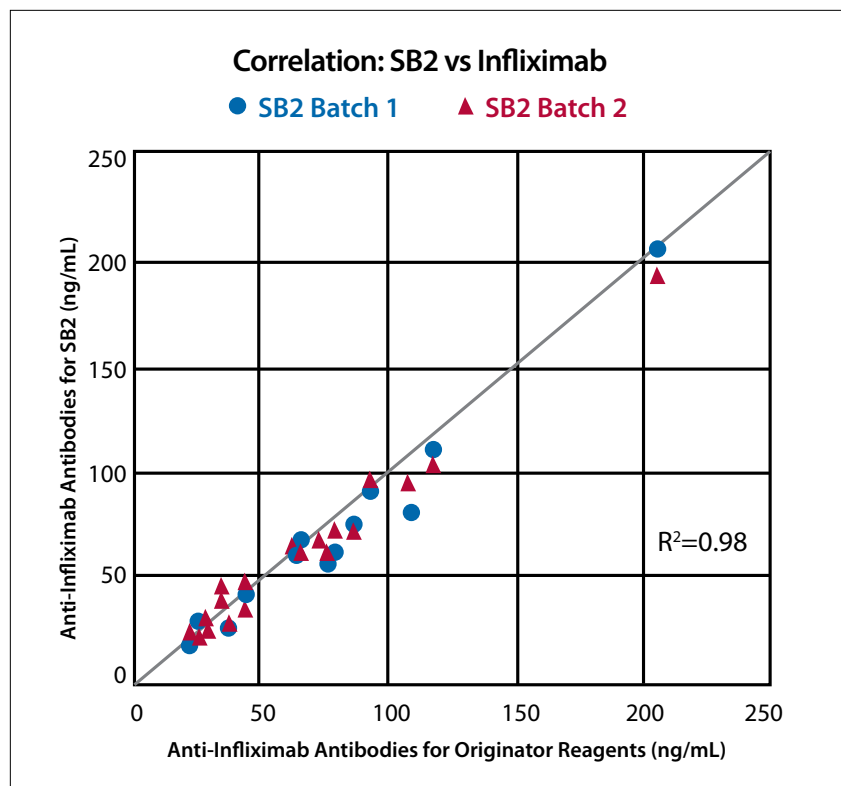


Figure 6. Correlation of anti-infliximab antibodies in the infliximab biosimilar SB2 vs the originator reagents. Adapted from Noguier G et al. Abstract P2137. Presented at: the World Congress of Gastroenterology at ACG 2017; October 13-18, 2017; Orlando, Florida.²

Efficacy of Infliximab Biosimilar for Induction and Maintenance Therapy in Inflammatory Bowel Disease After Switch From Drug Originator: A Meta-Analysis

A systematic literature search and meta-analysis was performed to evaluate the efficacy of CT-P13 in maintaining IBD remission after a switch from the infliximab originator.¹ Search terms included the following: “inflammatory bowel disease,” “Crohn’s disease,” “ulcerative colitis,” “CT-P13,” and “infliximab.” The study included publications listed on PubMed through May 2017. Both prospective and retrospective studies were included. Patients were receiving stable therapy with the infliximab originator at the time of the switch to CT-P13. Overall efficacy was defined as the proportion of patients who continued on CT-P13 with improvement or no change in disease activity after the switch. Maintenance efficacy was

defined as the proportion of patients who maintained remission from the time of the switch to the end of the study follow-up. The statistical analysis was performed using a random effect model with assessment of heterogeneity by the I^2 statistic.

Eight studies met the eligibility criteria, including 7 prospective cohort studies and 1 retrospective case series. The pooled patient population included 594 patients, with a follow-up of 8 to 24 weeks. Estimates of overall efficacy ranged from 65.1% to 100.0%, with a pooled estimate of overall efficacy of 83.5% (95% CI, 75.3%-91.7%; $P=.30$; I^2 , 16.64). Maintenance efficacy ranged from 80.8% to 100.0% across 5 studies with available data, and the pooled

estimate of maintenance efficacy was 82.6% (95% CI, 72.8%-92.5%; $P=.94$; I^2 , 0.00). The overall efficacy was 78.0% (95% CI, 68.3%-87.6%) for patients with CD, based on 6 studies, and 79.7% (95% CI, 63.4%-96.0%) for patients with UC, based on 5 studies. Maintenance efficacy was 82.4% (95% CI, 71.0%-93.9%) for patients with CD and 83.5% (95% CI, 64%-100%) for patients with UC, based on 5 and 4 studies, respectively (Table 1).

A comparison between patients with CD vs UC was made based on data from 5 studies. There was no difference in the pooled estimates of overall efficacy between patients with CD vs UC (odds ratio, 0.85; 95% CI, 0.39-1.85; $P=.19$; I^2 , 34.97). Three

Table 1. Pooled Estimate of Overall and Maintenance Efficacy of CT-P13 in Patients With Crohn's Disease and Ulcerative Colitis

	Overall Efficacy		Maintenance Efficacy	
	Number of Studies	Pooled Estimate (CI)	Number of Studies	Pooled Estimate (CI)
Crohn's Disease	6	78.0% (68.3%-87.6%)	5	82.4% (71.0%-93.9%)
Ulcerative Colitis	5	79.7% (63.4%-96.0%)	4	83.5% (64%-100%)

Adapted from Kashani A et al. Abstract 1308. Presented at: the World Congress of Gastroenterology at ACG 2017; October 13-18, 2017; Orlando, Florida.¹

studies provided data for maintenance efficacy in CD vs UC; again, no difference emerged for the 2 patient populations (odds ratio, 1.04; 95% CI, 0.53-2.07; $P=.83$; I^2 , 0.00).

In summary, the switch from the infliximab originator to CT-P13

appeared to be efficacious in the IBD setting and was equally effective in CD and UC. CT-P13 presents a cost-effective alternative to the infliximab originator. One limitation of the study was the relatively short duration of follow-up.

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Long-Term Efficacy, Safety, and Immunogenicity Data From a Phase III Confirmatory Study Comparing GP2017, a Proposed Biosimilar, With Reference Adalimumab

To demonstrate biosimilarity for a new agent and to gain approval for use in a given indication, testing must determine the physicochemical, biological, pre-clinical, and clinical properties of the new agent.¹ GP2017 is a proposed biosimilar to adalimumab that is

being investigated in a multicenter, double-blind, comparator-controlled, randomized phase 3 trial. Results from 17 weeks after randomization demonstrated similar efficacy, safety, and immunogenicity between GP2017 and the reference adalimumab.²

Dr Andrew Blauvelt presented

long-term efficacy, safety, and immunogenicity data for patients continuously treated with GP2017 or reference adalimumab from randomization to week 51.³ Eligible patients were adults with moderate-to-severe chronic plaque psoriasis that was active but clinically stable. Patients had previously received treatment with phototherapy or systemic therapy or were eligible for such therapies. Patients were required to have a baseline Psoriasis Area and Severity Index (PASI) score of at least 12, an Investigators Global Assessment score of at least 3, and a body surface area affected by plaque psoriasis of at least 10%. Patients were first randomly assigned to receive treatment with reference adalimumab or GP2017 at an initial dose of 80 mg, followed by 40 mg every other week up to week 17. Patients who experienced an improvement of at least 50% in their PASI score at week 16 were then randomized 2:1 at week 17 to either remain on the same treatment or to undergo

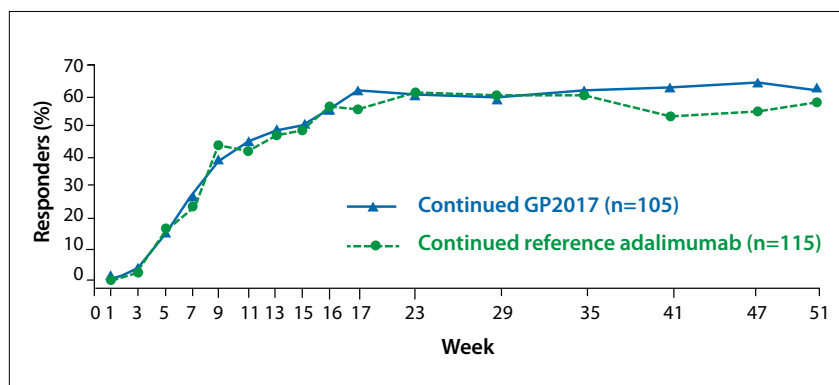


Figure 7. Response rates according to the investigator's global assessment over time in patients treated with the adalimumab biosimilar GP2017 or reference adalimumab. Blauvelt A et al. Abstract P2166. Presented at: the World Congress of Gastroenterology at ACG 2017; October 13-18, 2017; Orlando, Florida.³

a sequence of 3 treatment switches between GP2017 and reference adalimumab until week 35. For weeks 36 through 51, patients returned to their originally assigned treatment.

Results were available from 128 patients who received continuous treatment with GP2017 and 171 with reference adalimumab. Patient characteristics were well-balanced between the 2 arms. Patients had a mean age of approximately 46 years, and 63% were male. The PASI response rates and the mean percent change from baseline in the PASI score were similar for both arms throughout the entire 51 weeks of the study (Figure 7). The PASI 75 response rates were 75.2%

in the GP2017 arm vs 67.8% in the adalimumab reference arm at week 17. These rates rose to 84.5% vs 79.6%, respectively, at 51 weeks. Response rates according to the Investigators Global Assessment scale were also similar for both arms throughout the entire 51 weeks, with rates of 59.8% in the biosimilar arm vs 55.1% in the adalimumab reference arm.

No safety signals were raised. One death occurred in the GP2017 arm, but it was not considered related to the study drug. Anti-drug antibodies were detected during at least 1 evaluation during the 51-week study in 38.8% of GP2017 patients and in 45.3% of the reference adalimumab patients.

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Patient Perceptions Regarding the Use of Biosimilars in Inflammatory Bowel Disease

B iologic agents have been effective in treating IBD, but the high costs present a formidable barrier for some patients.^{1,2} Biosimilars may provide a cost-effective alternative to originator molecules, and numerous clinical studies have demonstrated similar efficacy between biosimilars and the reference molecule in patients with IBD.^{3,4} To assess patient perceptions and knowledge regarding biosimilar medications and to evaluate willingness to switch from an originator molecule to a biosimilar, adults with IBD in a single outpatient gastroenterology clinic were surveyed between March 2017 and May 2017.⁵

The 121 surveyed patients had a mean age of 37.8 ± 15.5 years, and 52% were male. There were 67 patients with CD (55.3%), and 53 patients with UC (43.8%). One patient was unsure of the diagnosis. The mean

time since diagnosis was 11.0 ± 10.3 years. Prior treatments included infliximab (57.9%), adalimumab (40.5%), vedolizumab (22.3%), ustekinumab (7.4%), certolizumab (6.6%), and golimumab (3.3%).

The term “biosimilar medications” was familiar to 27% of patients prior to the survey (Table 2). Most patients (76%) were either “somewhat uncomfortable” or “very uncomfortable” using a biosimilar medication that had not been tested in clinical trials specifically for UC or CD. Fifty-seven percent of study participants were either “somewhat uncomfortable” or “very uncomfortable” exchanging their current medication for the respective biosimilar, and 92% wanted to be informed prior to switching to a biosimilar medication. A significant correlation was observed between the number of

years since the diagnosis of IBD and the patient’s level of comfort with the idea of switching to a biosimilar therapy ($R = .203$; $P = .027$). The findings from this study may help physicians discuss biosimilar medications with their patients who have IBD.

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Table 2. Patient Perceptions Regarding Biosimilar Medications

Characteristic	All Participants (n=121)	Diagnosis ^a		P Value
		Ulcerative Colitis (n=53)	Crohn's Disease (n=67)	
Heard of "biosimilar medications," n (%)	33 (27.3)	18 (34.0)	15 (22.5)	.201
Concerns about biosimilar medications, n (%)^b				
Cost	56 (46.3)	26 (49.1)	29 (43.3)	.533
Safety	85 (70.2)	34 (64.2)	50 (74.6)	.223
Effectiveness	99 (81.8)	45 (84.9)	53 (79.1)	.412
Side effects	88 (72.7)	37 (69.8)	50 (74.6)	.564
How medication is made	33 (27.3)	11 (20.8)	21 (31.3)	.189
"The cost of a medication is important to me," n (%)				
Completely disagree	11 (9.1)	6 (11.3)	5 (7.5)	.941 ^c
Somewhat disagree	10 (8.3)	3 (5.7)	7 (10.4)	
Not sure	11 (9.1)	5 (9.4)	6 (9.0)	
Somewhat agree	40 (33.1)	17 (32.1)	23 (34.3)	
Completely agree	49 (40.5)	22 (41.5)	26 (38.8)	
How comfortable are you using a medication that has not been tested in clinical trials for ulcerative colitis or Crohn's disease? n (%)				
Very uncomfortable	32 (26.4)	9 (17.0)	22 (32.8)	0.501 ^c
Somewhat uncomfortable	60 (49.6)	28 (52.8)	32 (47.8)	
No opinion	6 (5.0)	4 (7.5)	2 (3.0)	
Somewhat comfortable	18 (14.9)	9 (17.0)	9 (13.4)	
Very comfortable	3 (2.5)	1 (1.9)	2 (3.0)	
Did not answer	2 (1.7)	2 (3.8)	0 (0.0)	
"Biosimilar medications should be tested in clinical trials specifically in ulcerative colitis or Crohn's disease before use in patients with these conditions," n (%)				
Completely disagree	3 (2.5)	2 (3.8)	1 (1.5)	0.795 ^c
Somewhat disagree	5 (4.1)	1 (1.9)	4 (6.0)	
Not sure	10 (8.3)	3 (5.7)	7 (10.4)	
Somewhat agree	32 (26.4)	17 (32.1)	15 (22.4)	
Completely agree	69 (57.0)	28 (52.8)	40 (59.7)	
Did not answer	2 (1.7)	2 (3.8)	0 (0.0)	
Comfort exchanging current medicine for biosimilar, n (%)				
Very uncomfortable	26 (21.5)	11 (20.8)	14 (20.9)	.795 ^c
Somewhat uncomfortable	43 (35.5)	16 (30.2)	27 (40.3)	
No opinion	20 (16.5)	11 (20.8)	9 (13.4)	
Somewhat comfortable	27 (22.3)	13 (24.5)	14 (20.9)	
Very comfortable	3 (2.5)	0 (0.0)	3 (4.5)	
Did not answer	2 (1.7)	2 (3.8)	0 (0.0)	

^aA patient responded "not sure."

^bPatients could select more than 1 response.

^cChi-square test.

Adapted from Pineles D et al. Abstract 2165. Presented at: the World Congress of Gastroenterology at ACG 2017; October 13-18, 2017; Orlando, Florida.⁵

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FDA Public Forum on Biosimilars

At the FDA Public Forum on Biosimilars, Dr Sue Lim of the Center for Drug Evaluation and Research provided a perspective from the FDA on the regulatory pathway and approval process for biosimilars in the United States.¹ Data showing analytical similarity provide the foundation of a biosimilar development program. Analyses should demonstrate the molecular structure, as well as known biological activities and any mechanisms of action identified for the reference product. In addition, there must be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. From a regulatory perspective, rather than directly demonstrating the safety and efficacy of the product, the biosimilar compound must be shown to be similar to the reference compound; the FDA then relies on comparative data with the reference product to evaluate whether the reference product is safe and effective. This approach avoids reproducing costly clinical trials, which is particularly important in the case of rare diseases. In addition to meeting the molecular and clinical criteria, if the product is administered on a long-term basis, the safety and efficacy must not be diminished by switching from the biosimilar product to the reference product. The indications proposed in the biosimilar labeling must be the same as those already approved for the reference product, and the biosimilar agent must have the same dosage and route of administration.

For a biosimilar to be considered interchangeable, information must be provided to show that the safety and efficacy are not diminished by switching from the reference molecule to the biosimilar. Moreover, a clinical study must demonstrate that switching multiple times between the reference product and the biosimilar product

does not have a negative impact on efficacy and safety, including immunogenicity and rates of specific adverse events. If molecular analyses show signs that biosimilar products differ in any way from the reference product, then clinical studies must be designed to address uncertainties relating to the clinical performance of the biosimilar molecule. Pharmacokinetic and pharmacodynamic studies provide the most sensitive clinical endpoints for assessing differences between the biosimilar and reference products. Assessing specific markers in the relevant cellular pathways or those involved in the mechanisms of action is particularly useful to provide evidence that the biosimilar is acting in a similar manner to the reference product. Finally, a comparative study may be designed to answer any remaining questions regarding biosimilarity, in addition to allowing direct assessment of safety and immunogenicity.

Dr Joachim Musaeus of the European Medicines Agency discussed the approval of biosimilars in the European Union (EU).¹ In the European system, a centralized regulatory procedure is mandatory for certain diseases and for biotech products, including biosimilars. The centralized review process yields a single product insert that is translated into all EU languages. The European Medicines Agency has issued Overarching Biosimilar Guidelines and product-specific biosimilar guidelines.² The agency defines a biosimilar product as a biological medicine or product that is similar to a reference biological product and does not meet the definition of a generic medicinal product. The Overarching Biosimilar Guidelines state that the biological medicine or product must contain a version of the active substance of an already authorized, original biological medicine or product. Biosimilarity is established by assessing the physical and chemical properties and

performing functional characterization, followed by pharmacokinetic and pharmacodynamic studies, and, finally, clinical studies.

Guidelines from the European Medicines Agency stipulate that, when biosimilar comparability has been demonstrated in one specific indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but must be scientifically justified. In cases where it is unclear whether the safety and efficacy confirmed in one indication would be relevant to another indication, additional data are required. Extrapolation should be considered in light of the totality of the available data. Reference information has been developed at the European Medicines Agency to foster the understanding of biological medicines and biosimilars developed and approved in the United States. The agency also provides a guide for healthcare professionals to help doctors and nurses explain biosimilars to their patients.³

The European Medicines Agency does not provide recommendations regarding interchangeability between biosimilar and reference products. Decisions pertaining to interchangeability are left to the individual EU members. However, several studies across the EU have evaluated clinical efficacy, safety, and immunogenicity in patients who switched from the originator infliximab to the biosimilar infliximab. For example, the NOR-SWITCH study compared switching from the originator infliximab to the biosimilar CT-P13 vs continuous treatment with the originator infliximab.⁴ The phase 4 trial demonstrated that switching to the biosimilar treatment was not inferior to continuous treatment with the reference molecule, based on a prespecified non-inferiority margin of 15%.

Dr Tara Altepetter of the FDA discussed biosimilars from the clinician's perspective.¹ Extrapolation can

be understood by reviewing CT-P13 as an example. CT-P13 was the first biosimilar TNF- α blocker approved by the FDA. The application included controlled clinical studies in rheumatoid arthritis and ankylosing spondylitis, and the drug ultimately received approval for all of the eligible indications of reference infliximab, including IBD. Demonstration of the mechanisms of action included antibody-directed cellular cytotoxicity, which raised some concerns. In response, the applicant performed more tests with additional product lots and showed consistent results within the acceptable quality range. Key pharmacokinetic and biodistribution parameters were examined, and immunogenicity was assessed, with particular emphasis on usage with concomitant methotrexate. Many years of experience with reference infliximab have shown that adverse events tend to be similar across indications. Rare but serious adverse events include serious opportunistic infections and risk of malignancies.

The FDA concluded that the scientific justification and the totality of the evidence were sufficient to extrapolate approval of the biosimilar across all eligible indications held by the reference product.

Small differences between products that are not apparent in the short-term could lead to meaningful clinical differences over time. Thus, demonstration of interchangeability requires evidence that switching several times between the reference product and the biosimilar will not lead to adverse events, such as increased rates of transfusion reactions or injection-site reactions; increased potential for anaphylaxis; or the development of anti-drug antibodies. The FDA has issued draft guidelines that describe how to design an appropriate switching study.⁵ To demonstrate interchangeability, studies will need to transition patients back and forth between the reference and biosimilar products while providing adequate exposure to both products. Although the infliximab biosimilar has

not been evaluated directly in a clinical study of IBD patients, providers should feel confident that the biosimilar drug has met the requirements of a strict scientific evaluation for similarity.

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Highlights in Biosimilars From the World Congress of Gastroenterology at ACG 2017: Commentary

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Several abstracts at the World Congress of Gastroenterology at the 2017 American College of Gastroenterology meeting provided data on the use of biosimilars. Research was presented that compared biosimilars with the originator agents, evaluated use of an assay for an originator biologic to measure serum levels of the biosimilar, and surveyed patient's perceptions on biosimilars.

Biosimilars vs the Originator Biologic

Dr Amir Kashani and colleagues conducted a meta-analysis of studies evaluating the efficacy of the infliximab biosimilar known as CT-P13 for induction and maintenance therapy after a switch from the originator biologic.¹ The analysis included 8 studies, with data for 594 patients, published through May 2017. The analysis examined heterogeneity according to the I^2 statistic. It found that CT-P13 for induction and maintenance therapy was effective for patients with inflammatory bowel disease (IBD), whether Crohn's disease or ulcerative colitis. The pooled estimate for overall efficacy was 83.5%, with 78.0% for Crohn's disease and 79.7% for ulcerative colitis.

There were some important limitations to this meta-analysis. The number of studies and the number of patients were both exceptionally small.

In addition, the studies included were not necessarily randomized, placebo-controlled trials. They may have been noninferiority studies. Another drawback is that the duration of the studies ranged from 8 weeks to 24 weeks. A 24-week study is appropriate, but an 8-week study is too short to truly define maintenance. Approximately 20% of patients lost efficacy throughout the course of the study, which is a substantial proportion in a short duration. A key issue with induction therapy is safety, including immunogenicity. The analysis did not provide data on safety.

Dr Andrew Blauvelt presented data from a phase 3 study comparing long-term efficacy, safety, and immunogenicity of GP2017, a biosimilar for adalimumab, vs the originator biologic.² The patient population had moderate-to-severe chronic plaque psoriasis. The drug dosages were much lower than those used in IBD. The study found that the safety and immunogenicity were similar between the 2 therapies. The levels of binding anti-drug antibodies were high, at 39% for GP2017 and 45% for reference adalimumab. The rates of adverse events were also high, at 61% with GP2017 and 64% for reference adalimumab. In patients with IBD, adalimumab is relatively safe and well-tolerated.

This study has uncertain relevance to IBD, given the different dosing schedule and the high rates of

immunogenicity and adverse events. However, when assessing a biosimilar, an evaluation of noninferiority data for one disease state provides sufficient evidence for use in another disease state. To date, no studies have been performed in patients with IBD to gain FDA approval for registration of biosimilars. There have been many postapproval studies performed in patients with IBD to help assuage fears.³⁻¹³

An Assay for the Infliximab Biosimilar SB2

Dr Guillaume Noguier and coworkers studied whether an assay for the infliximab originator could be used to measure serum drug and antibody levels for the infliximab biosimilar known as SB2.¹⁴ It would be expected that an assay for an originator drug could also be used for the biosimilar. Previous data have shown that serum levels of a biosimilar are measurable by an assay for the originator biologic.^{15,16} A few studies have shown that individually derived assays cross-react with a similar percentage of positivity in patients who are antibody-positive. The analysis by Dr Noguier confirmed these findings, showing that the assay had high precision and accuracy when measuring levels associated with SB2. These data suggested that the assay for the infliximab originator can be used for the biosimilar in clinical practice.

The analysis by Dr Noguier used spiked samples; it did not use samples from patients directly. An analyst usually divides the unknown sample into 2 portions, so that a known amount of the analyte (a spike) can be added to one portion. These 2 samples—the original and the original plus spike—are then analyzed. The sample with the spike will show a larger analytical response than the original sample, owing to the additional amount of analyte added to it. The difference in analytical response between the spiked and unspiked samples is due to the amount of analyte in the spike. This provides a calibration point to determine the analyte concentration in the original sample. The analysis by Dr Noguier was therefore performed in an artificial environment. Ideally, a study would take serum samples from patients and send them to different laboratories. However, use of the spiked samples simulated the actual reality.

Patient Perceptions of Biosimilars in IBD

I serve as chair of the American Gastroenterological Association Biosimilars Committee. One of our main tasks is to educate patients and physicians about biosimilars. Patient perception of biosimilars is an important area. There is a question of whether patients will feel safe when switching between an originator drug and a biosimilar. I believe that the patient's reaction depends on the clinical scenario, which can include the following:

- A patient is initiating therapy and begins with a biosimilar as the first biologic agent. This patient may be more accepting of a biosimilar if it is the first treatment, rather than if he or she had started treatment with another drug, such as an originator agent, and was asked to switch later.
- A patient has been doing well on an originator drug for years, and then is asked to switch to a new biosimilar. (This is termed a nonmedi-

cal switch.) In this case, the patient may be less accepting of the switch to a biosimilar. He or she might have been very ill previously, and may fear that switching to a new biosimilar could lead to a loss of efficacy.

- A patient has been doing well for a good amount of time on an originator biologic and then is asked to switch to a biosimilar. Given that he or she is doing well, this patient may be reluctant to switch but does so. In the future, he or she may be asked to switch to another biosimilar (ie, biosimilar number 2). This may occur for a variety of reasons. For example, a patient may switch jobs and get new insurance that receives preferred rates with a different biosimilar.

When a physician or health care provider speaks with a patient about the potential of using a biosimilar, the presentation is very important. Before a change is contemplated, the patient should be educated about biosimilars and informed that a switch will likely occur. It is not good practice to inform the patient of a switch the day he or she arrives for treatment.

Dr David Pineles and colleagues presented results from a study on patient perceptions and knowledge of biosimilars.¹⁷ They examined issues such as the patient's level of comfort, preferences, and potential barriers to implementation. They found that most patients were uncomfortable using a biosimilar that had not been evaluated in a clinical trial for IBD. Patients with a longer time since diagnosis of Crohn's disease were more comfortable with the idea of switching from a biologic to a biosimilar.

Clinicians are concerned about how to best present the idea of biosimilars to their patients. There are questions about when the discussion should be made, and whether information should vary according to the patient's level of education. My perception is that patients will feel more comfortable if the treatment is perceived to be safe and has supportive data. However,

there will always be patients who prefer to remain on their original treatment. For example, some patients refuse to take the generic version of a drug, and some may decline a switch to a biosimilar. These patients have the option to continue the originator, but it may be at a higher premium (ie, cost to the patient).

Disclosure

Dr Lichtenstein has consulted for Abbott Corporation/AbbVie, Actavis, Alaven, Celgene, Ferring, Hospira, Janssen Ortho Biotech, Luitpold/American Regent, Pfizer Pharmaceuticals, Prometheus Laboratories, Romark, Salix Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, Takeda, and UCB; conducted research for Celgene, Janssen Ortho Biotech, Salix Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, and UCB; received honoraria (CME program) from Ironwood, Luitpold/American Regent, Merck, and Romark; and received funding to the University of Pennsylvania (IBD Fellow Education) from Janssen Ortho Biotech, Pfizer Pharmaceuticals, and Takeda.

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WHAT ARE **BIOSIMILARS?**

Let's Clarify Biosimilars

Biosimilars are a new step in biologic medicines and are highly similar to originator (or "reference") biological products.¹

Merck can help.

There is a great deal of complexity surrounding biosimilars. At Merck, we believe in providing clarity among the confusion. We want to deliver clear, concise answers and information that will help you understand biosimilars.

Get answers at
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Reference:

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