The Role of Biosimilars in Inflammatory Bowel Disease

Sudarshan Paramsothy, MD, Noa Krugliak Cleveland, MD, Nada Zmeter, MD, and David T. Rubin, MD

Dr Paramsothy is an advanced IBD fellow, Dr Krugliak Cleveland is an internal medicine resident, Dr Zmeter is a clinical research coordinator, and Dr Rubin is a professor of medicine at the Inflammatory Bowel Disease Center at the University of Chicago Medicine in Chicago, Illinois.

Address correspondence to:
Dr David T. Rubin
Inflammatory Bowel Disease Center
University of Chicago Medicine
5841 South Maryland Avenue,
MC 4076
Chicago, IL 60637
Tel: 773-702-2950
Fax: 773-702-2182
E-mail: drubin@medicine.bsd.uchicago.edu

Keywords
Biosimilar, biologic, inflammatory bowel disease, Crohn's disease, ulcerative colitis

Abstract: Monoclonal antibody biologic therapies, introduced nearly 20 years ago, revolutionized the treatment of inflammatory bowel disease (IBD) and are now well established as the most effective agents available. As the first of these biologic agents starts to come off patent, biosimilar agents have emerged as alternatives to originator drugs. The unique drug development and manufacturing processes involved in the creation of biologic agents pose distinct regulatory challenges compared to generic formulations of conventional medications. Reductions in medication costs have been proposed to be a major benefit of biosimilar therapies; however, there are concerns regarding the adequacy of the existing regulatory process and data requirements for biosimilar therapy approval, as well as the true bioequivalence of these agents. Infliximab biosimilars for the treatment of IBD have been available in Europe and Asia for a few years and are expected to become available in the United States within the next 1 to 2 years. This article reviews biosimilar therapies and the current data with respect to IBD.

Since infliximab (Remicade, Janssen) was approved for the treatment of Crohn's disease in 1998,[1] monoclonal antibody biologic therapies have proven to be the most potent therapeutic agents available to treat inflammatory bowel disease (IBD). The first biologic agents targeted the tumor necrosis factor-alpha (TNFα) pathway (infliximab, adalimumab [Humira, AbbVie], and certolizumab pegol [Cimzia, UCB]).[2-9] More recently, biologic agents targeting different pathways have either been approved (eg, anti-integrins, such as natalizumab [Tysabri, Biogen] and vedolizumab [Entyvio, Takeda], and the anti–interleukin-12/-23 agent ustekinumab [Stelara, Janssen])[10-13] or are pending imminent approval for IBD. Biologic agents were initially reserved for the most advanced and aggressive disease as a treatment of last resort. However, increasing data and comfort regarding their safety profile have led to a shift in practice toward early implementation of biologic agents in at-risk patients to arrest progression early in the disease course before irreversible tissue damage has occurred.[14]

Table 1. Originator Biologic Products and Their Corresponding Biosimilars

Originator Biologic Product	Biosimilar
Infliximab (Remicade, Janssen)	CT-P13 (Inflectra or Remsima, Celltrion Healthcare)
Adalimumab (Humira, AbbVie)	ABP 501 (Amgen)

Biologic agents are currently considered chronic, long-term therapy and are often continued indefinitely upon commencement unless there is either loss of response or side effects, with data showing an increased likelihood of relapse upon cessation even in patients with long-term remission.[15] Biologic agents are also expensive, and given the increasing prevalence of IBD,[16] the lower threshold to institute biologic agents, and their subsequent long-term use, they are now the major source of total IBD expenditure.[17,18]

As the biologic era approaches 20 years, the first biologic agents have either come off patent or are approaching patent expiration, resulting in the expected emergence of biosimilars (Table 1). Janssen's patent relating to its infliximab formulation has already expired in Europe, and its US patent expires in September 2018. AbbVie's adalimumab formulation is expected to expire on December 31, 2016 in the United States and in April 2018 in Europe.[19-22]

Biosimilars: What They Are and Are Not

A biologic agent is a medicinal product that is derived from a natural source and includes large, protein-based therapeutic agents that are typically obtained from living cell lines using recombinant DNA technology such as hormones and monoclonal antibodies (Table 2). Biologic agents differ from conventional medications and have a much greater degree of structural complexity, not only being larger in size but also subject to posttranslational modifications. A biosimilar is a biologic product that is highly similar to a reference product (originator biologic agent) with respect to quality characteristics, biologic activity, immunogenicity, efficacy, and safety, notwithstanding minor differences in clinically inactive components.

A biosimilar is not considered a generic medication (Table 3). A generic drug is identical or bioequivalent to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.[23] It is also important to distinguish biosimilars from next-generation biologic agents (eg, adalimumab, certolizumab pegol), which, while directed toward the same molecular target as first-generation agents (eg, infliximab), are chemically distinct, independently developed, and do not depend upon demonstration of biosimilarity with an originator product for abbreviated approval.[24,25]

To be designated as interchangeable (Table 2) requires a higher standard than simply being biosimilar, and implies that free exchange with the originator biologic agent can occur with no greater risk of adverse effects or diminished efficacy. An interchangeable product must produce the same clinical result as the originator product in a specific patient. In addition, in order to receive the designation of being interchangeable, the biosimilar must have similar effectiveness and safety when switched

Table 2. Terms and Definitions[27]

Term	Definition
Biologic	• A medicinal product derived from a variety of natural sources • Includes large, protein-based therapeutic agents derived from living cell lines using recombinant DNA technology such as hormones and monoclonal antibodies
Biosimilar	• A biologic product that is approved based on showing that it is highly similar to an FDA-approved biologic product (originator product) and has no clinically meaningful differences in terms of safety and effectiveness from the originator product. Only minor differences in clinically inactive components are allowable.
Interchangeable	• A biosimilar to an FDA-approved originator product that meets additional standards for interchangeability. An interchangeable biosimilar may be substituted for the originator product by a pharmacist without the intervention of the health care provider who prescribed the originator product. • An interchangeable biosimilar is expected to produce the same clinical result as the originator biologic agent in any given patient.
Extrapolation	• Clinical studies of biosimilars can be performed in a disease state or sensitive population group and then inferred to work in other disease settings or indications for which the originator biologic product is approved and licensed, with sufficient scientific justification.

FDA, US Food and Drug Administration.

Table 3. Biologic Agents and Biosimilars Vs Conventional and Generic Medications[28]

Biologic Agents and Biosimilars	Conventional and Generic Medications
Large molecular weight	Small molecular weight
Manufactured in unique cell line; similar but not identical copies can be made	Predictable chemical process; identical copies can be made
Complex structure with potential for posttranslational modifications	Simple, well-defined structure
Difficult to characterize	Easy to fully characterize
Higher potential for immunogenicity	Lower potential for immunogenicity

multiple times with the originator product, and such switches must not cause more risk than remaining on the originator product for the same amount of time.[26]

Regulatory and Developmental Processes

The manufacture of biologic agents is distinct from that of other pharmacologic agents in that biologic agents are derived from a natural source, often a unique cell line, and are sensitive to manufacturing conditions with the potential for posttranslational modifications.

The regulatory process for biosimilars is substantially more rigorous than for traditional generic medications, although it is abbreviated relative to originator biologic agents.[27,29-32] For originator biologic agents, approval by the US Food and Drug Administration (FDA) is dependent upon multiple preclinical and clinical phases of trials demonstrating the safety and effectiveness of the product.[26]

The European Medicines Agency first outlined its biosimilar regulatory pathway in 2005 and the FDA developed a framework in 2012.[27,33] FDA approval of biosimilars is based on evidence that the product is highly similar and has no clinically meaningful differences from the originator product in the parameters of safety, purity, and effectiveness.[26]

The developmental process for biosimilars is inverted compared with originator biologic agents, with an emphasis on proving biosimilarity with the originator product, or lack of clinically meaningful difference, rather than independently re-establishing efficacy and safety. Biosimilars are reverse-engineered based on the originator product, and, thus, the main developmental stage is the comprehensive analytical characterization of structure and function relative to the originator biologic product.[27,29-32] Clinical trials are permitted after demonstration of structural and functional biosimilarity to the originator product; thus, no clinically meaningful difference in outcomes would be expected to exist.[34]

Clinical Testing and Extrapolation

After passing regulations based on analytical characterization and pharmacodynamics and pharmacokinetic studies of the biosimilarity, proposed biosimilars are then required to complete adequately powered, comparative, randomized, controlled trials (RCTs) in a select sensitive patient population. The purpose of these clinical trials is to establish equivalence and detect clinically meaningful differences in efficacy, safety, and immunogenicity between the biosimilar and the originator product.

A controversial area within the biosimilar regulatory and approval processes is the concept of extrapolation. Extrapolation is the philosophy that clinical studies of biosimilars can be performed in one disease state or sensitive population group and then inferred to work in other disease settings or indications for which the reference biologic is approved and licensed (Table 2). Extrapolation is dependent on sufficient scientific justification, including (but not limited to) mechanism of action.[27] As such, there is no requirement to independently perform trials in each of the originator biologic indications in order to obtain approval of the biosimilar across all of the same indications. Rather, such approval can be granted based on the principle of clinical experience with the originator biologic and presumed identical mechanism of action due to the totality of evidence of biosimilarity.[27]

Approval is of particular importance for IBD, as the anti-TNFα biosimilars currently utilized for IBD across the world were approved without independent trials in IBD patients and were instead accepted as effective for these patients based on trials in rheumatologic conditions. Some IBD clinicians and researchers have argued that differences between IBD and other conditions in terms of immunogenicity and other factors mean that equivalence studies may not translate across conditions[35] and that comparative, noninferiority RCTs should be conducted specifically in IBD patients. Conversely, others, including biosimilar manufacturers, argue that the principle of extrapolation is already in place for changes in manufacturing protocols for originator biologic agents and that the requirements for biosimilars are more stringent in that they require clinical trials.

Due to the abbreviated phase 3 clinical testing and extrapolation, structured, prospective, phase 4, postmarketing surveillance takes on greater significance, and in essence becomes mandatory, as often this is the first time that disease-specific data for a biosimilar become available.

Proposed Advantages and Disadvantages

The main proposed advantage of biosimilars is that increased competition will lead to decreased costs and increased availability and accessibility of biologic therapies. It is partly upon this premise that regulatory authorities permit extrapolation to minimize drug development and regulatory approval costs. Five-year savings from adoption of CT-P13 (an anti-TNFα antibody biosimilar to infliximab marketed as Remsima [Celltrion Healthcare] in Europe and as Inflectra [Celltrion Healthcare] in the United States) for Crohn's disease in the United Kingdom, Italy, and France have been predicted at 76 to 336 million euros.[36] However, it has been argued that the cost savings will not be impressive relative to conventional and generic medications, as the regulatory process for biosimilars is rigorous. It is estimated that introducing a novel biologic therapy to market may cost as much as $800 million and that the cost for biosimilars may be less but still substantial, despite an abbreviated pathway for biosimilars.[37] Although biosimilars are predicted to be less expensive and to drive down costs, it is unclear to what degree these savings will affect patients in terms of decreased insurance costs or improved biologic accessibility.[38]

Disadvantages of biosimilars include the possibility of inferior clinical outcomes in the absence of a sufficient clinical evidence base prior to approval and concerns regarding nonmedical switching by insurance providers or governmental funding sources for health economic reasons. In turn, there is a theoretical concern that switching may result in the potential for increased immunogenicity and development of antidrug antibodies. It is also important to acknowledge that biosimilars should not be considered an additional or new therapeutic strategy and are unlikely to be effective in circumstances in which the originator biologic product failed or antidrug antibodies have developed. The clinical settings in which biosimilars will likely be of greatest value is in the de novo commencement of biologic therapy and potentially in the stabilized responder once interchangeability has been established.

Perceptions of Patients and Gastroenterologists and Position Statements of Inflammatory Bowel Disease Associations

IBD patient perspectives of biosimilars were assessed in an online survey completed by 1181 patients.[39] Thirty-eight percent of patients had previously heard of biosimilars. Respondents' primary concerns were regarding safety (47%), efficacy (40%), and molecular basis (35%), with 25% of respondents expressing no concerns. The majority felt that the lower cost of biosimilars should not come at the expense of safety and efficacy, and only 12.5% of respondents felt that extrapolation was rational. Twenty-one percent of respondents were against the idea of interchangeability if not informed of the change. Overall, most patients were not familiar with biosimilars, had concerns, and wished to be involved in therapeutic decisions. A Canadian study suggested that patients were better informed but found similar reservations.[40]

Studies have been performed assessing the perceptions of gastroenterologists toward biosimilar therapy. The results reveal a degree of skepticism, particularly in regard to the abbreviated regulatory process, concept of extrapolation, and consequences of switching in terms of immunogenicity in the context of a limited evidence base. A survey of 307 European Crohn's and Colitis Organisation (ECCO) members in 2014 showed that IBD specialists were reasonably informed on biologic agents, regarded cost sparing (89%) as the main advantage, and listed immunogenicity (67%) as their main concern.[41] Most respondents felt that postmarketing surveillance and well-designed RCTs should be required. Interestingly, 64% disagreed with automatic replacement of originator biologic agents with a biosimilar by a pharmacist, although 18% supported substitution for new prescriptions, and only 6% felt that biosimilars were interchangeable. The majority of respondents were not confident about the use of biosimilars in clinical practice.[41]

These findings are reflected in the position statements of professional IBD associations, including the Crohn's and Colitis Foundation of America (CCFA) and ECCO.[42-47] The ECCO expressed concern regarding extrapolation and specified direct testing in IBD populations with a request that evidence specific to IBD patients be required to confirm efficacy and safety in this patient group, as prior experience with originator biologic agents suggests differences in effectiveness across different indications or disease states.[43] Key points of the CCFA statement include the need for (1) thorough human testing of the highest safety standards; (2) product information clearly defining and stating the risk of immunogenicity; (3) proof stating that switching (ie, interchangeability) would not lead to immunogenicity; (4) prescriber notification of substitution, with the ability to prevent substitution if deemed necessary; and (5) a unique name or identification number to minimize confusion.[42] Interestingly, a follow-up survey on biosimilars in 2016 suggested that IBD specialists have remained well informed and had fewer concerns and more confidence about their clinical use; 44% of IBD specialists now consider biosimilars and originator products interchangeable and only one-third were against extrapolation across indications.[48]

Currently Available Anti–Tumor Necrosis Factor-Alpha Biosimilars

Biosimilar growth factors have been utilized in Europe since 2006. CT-P13, the first biosimilar for IBD, was approved by the European Medicines Agency in mid-2013 across all originator infliximab (Remicade) indications based on a pharmacokinetics biosimilarity study in ankylosing spondylitis[49] and a single phase 3 clinical trial in rheumatoid arthritis.[50] CT-P13 has been utilized in several countries throughout Europe and Asia for the last 2 years and is now approved in over 60 countries. Although CT-P13 was approved in the United States in April 2016, it is not yet available for clinical use due to ongoing patent and legal issues. The infliximab biosimilar is indicated for treatment-naive patients or for a one-time switch or single transition from the originator infliximab and, importantly, is not considered interchangeable with the originator infliximab.[51] In July 2016, the FDA recommended licensure of the adalimumab biosimilar ABP 501 (Amgen) based on a pharmacokinetics study and 2 RCTs in rheumatoid arthritis and psoriasis.[52] The policy of extrapolation has meant that there have not been any RCTs of the new anti-TNFα biosimilar agents in IBD to date, as they are not a requirement for regulatory approval.

A recent systematic review of anti-TNFα biosimilar agents identified 19 studies, of which only five were phase 3 RCTs in rheumatoid arthritis (0 in IBD), with eight phase 1 studies (7 in healthy individuals) and 6 observational studies.[53] The researchers found that the pharmacokinetics, clinical efficacy, and adverse event data supported the comparability of biosimilar and originator products. Only 4 small cohort studies were identified that switched from originator biologic agent to biosimilar, although these studies suggested similar remission maintenance rates.[54-57]

At the 2016 ECCO and Digestive Disease Week conferences, a number of abstracts reporting the preliminary clinical experiences of IBD specialty centers with infliximab biosimilars were presented.[58,59] The observational data to date appear to be encouraging overall, although they are only short term (Tables 4-6). In general, infliximab biosimilars appeared to have equivalent efficacy and safety to the originator infliximab in the de novo induction setting for anti-TNFα–naive IBD patients. As expected, some studies suggested lower remission and response rates and higher infusion reaction rates in patients with prior anti-TNFα exposure. While the data appear to justify the policy of extrapolation, there is still insufficient evidence regarding interchangeability and the immunogenic consequences of switching, especially in otherwise stable patients who switch for financial rather than medical reasons. Available data for switching involve limited follow-up duration and almost exclusively involve a single switch. The largest cohort to date by Fiorino and colleagues[60] suggested that although biosimilar therapy is safe and effective, there was a 5-fold increase in loss of response (12.2% vs 2.3%; P=.001) in patients who were switched. Subtle posttranslational modifications unique to the biosimilars relative to the originator biologic product may be sufficient to lead to antidrug antibody formation with associated loss of response and drug reactions upon switching, especially if multiple switches back and forth between agents occur.[61] Longer-term observational and investigator-initiated biosimilar trial data specific to IBD are still required, with a particular emphasis on the immunogenic sequelae of switching to establish the validity of interchangeability, such as the recently completed NOR-SWITCH study.[62] NOR-SWITCH was a phase 4, multi-indication (Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis), multicenter, prospective, double-blind, noninferiority, RCT of nonmedical biosimilar-switching conducted by the Norwegian government, presented in abstract form at the United European Gastroenterology Week 2016 meeting.[63] A total of 481 patients were recruited across 40 centers; all patients had been on stable treatment with the originator infliximab for at least 6 months. The primary outcome was disease worsening at 12 months, which was noted in 53 of 202 (26.2%) originator infliximab–treated patients compared with 61 of 206 (29.6%) of the CT-P13–switched patients, with no significant difference between the 2 arms. When looking specifically at IBD patients, disease worsening was noted in 21.2% of originator infliximab–treated patients and 36.5% of CT-P13–treated Crohn's disease patients (n=155), while the respective values for ulcerative colitis were 9.1% and 11.9% (n=93), with the adjusted treatment differences within the prespecified noninferiority margin. No difference was identified in the detection of antidrug antibodies (originator infliximab, 7.1% vs CT-P13, 7.9%), trough drug levels, and frequency of adverse events, including infusion reactions.

With regard to therapeutic monitoring, good correlation of CT-P13 serum levels with various commercially available infliximab assays has been reported.[64] Furthermore, a recent study assessed sera of IBD patients both with and without measurable anti–originator infliximab antibodies to infliximab for cross-reactivity with CT-P13.[65] Results of the study showed that anti–originator infliximab antibodies similarly recognized and inhibited CT-P13, suggesting similar immunogenicity and shared epitopes. This study did not identify cross-reactivity with anti-adalimumab antibodies.

Table 4. Induction and Maintenance/Switch Studies of CT-P13 in IBD

Study	Population	Follow-Up	Efficacy	Safety
Park et al[66]	• **95 CD** (51 treatment-naive, 44 switched) • **78 UC** (62 treatment-naive, 16 switched)	Week 30	Clinical remission: • Moderate-to-severe CD: 59.0% treatment-naive; 80.6% switched • Fistulizing CD: 50% treatment-naive; 50% switched • UC: 37.0% treatment-naive; 45.5% switched Mucosal healing: • 69% treatment-naive; 67% switched	No unexpected adverse events (5 severe adverse events)
Kang et al[54]	• **8 CD** (3 treatment-naive, 5 switched) • **9 UC** (5 treatment-naive, 4 switched)	Week 8 (induction)	Clinical remission: • CD: 2/3 treatment-naive; 4/5 switched • UC: 5/5 treatment-naive; 4/4 switched	1 adverse event
Jung et al[55]	• **59 CD** (32 treatment-naive, 27 switched) • **51 UC** (42 treatment-naive, 9 switched)	Week 54	Clinical remission: • CD: 75% treatment-naive; 93% switched • UC: 50% treatment-naive; 67% switched Mucosal healing: • UC: 67% treatment-naive	5 adverse events in treatment-naive
Gecse et al[67,68]	• **184 CD** (25% non–treatment-naive) • **107 UC** (14% non–treatment-naive)	Week 54	Clinical remission: • CD: 47% • UC: 53% Decreased remission rates when associated with prior anti-TNFα exposure Decreased CRP	7.2% infusion reactions overall
Fiorino et al[60]	• **223 CD** (105 treatment-naive, 67 prior biologic agents, 51 switched) • **174 UC** (112 treatment-naive, 20 prior biologic agents, 42 switched)	6 months	Clinical response (CD+UC): • 92% treatment-naive • 84% prior biologic agents • 94% switched Loss of response in 12% of switched patients (5-fold greater than overall cohort)	8.3% severe adverse events 5.3% infusion reactions
Guerra Veloz et al[69,70]	• **75 CD** (71 switched) • **40 UC** (31 switched)	6 months	No difference between group in remission and group not in remission at start of study	Mild adverse events: 6.6% in CD; 5.0% in UC
Carvalho Lourenço et al[71]	• **19 CD** (CT-P13) • **41 CD** (IFX-R)	Week 24	Significant decrease in HBI and CRP compared with baseline in both groups	No infusion reactions with CT-P13
Hlavaty et al[57]	• **19 CD** • **6 UC**	Week 14 (induction); every 8 weeks for maintenance	Clinical remission (CD+UC): 84%	4 adverse events overall
Hamanaka et al[72]	• **8 CD** • **12 UC** (14 treatment-naive)	Week 22	Clinical remission: • CD: 100% • UC: 80%	1 infusion reaction
Murphy et al[73]	• **14 IBD** (CT-P13) • **22 IBD** (IFX-R)	Not reported	Higher surgery rate and hospital readmission rate, higher likelihood of corticosteroid augmentation, and no decrease in CRP with CT-P13	Not reported

CD, Crohn's disease; CRP, C-reactive protein; CT-P13, infliximab biosimilar; HBI, Harvey-Bradshaw index; IBD, inflammatory bowel disease; IFX-R, originator infliximab–Remicade; TNFα, tumor necrosis factor-alpha; UC, ulcerative colitis.

Table 5. Induction Studies of CT-P13 in IBD

Study	Population	Follow-Up	Efficacy	Safety
Jahnsen et al[74]	• **46 CD** (33 treatment-naive, 13 prior biologic agents [IFX-R, ADA, GOL]) • **32 UC** (27 treatment-naive, 5 prior biologic agents [IFX-R, ADA, GOL])	Week 14	Clinical remission: • CD: 79% • UC: 56% Significant reduction in CRP and calprotectin	No unexpected adverse events
Keil et al[75]	• **30 CD** • **22 UC** (all anti-TNFα treatment–naive)	Week 14	Clinical remission: • CD: 50% • UC: 41% Decreased CRP	4 adverse events overall
Farkas et al[76,77]	• **63 UC** • **18 CD**	Week 14 (UC); Week 8 (CD)	Clinical remission: • UC: 47.6% • CD: 50.0% Mucosal healing: • UC: 47.6%	New antidrug antibodies in 7 UC treatment–naive patients
Malickova et al[78]	• **60 IBD** (CT-P13; all anti-TNFα treatment–naive) • **71 IBD** (IFX-R)	Week 14	Not assessed	No difference in antidrug antibodies or other autoantibodies
Sieczkowska et al[79]	• **36 CD (**17 treatment-naive) Pediatric	Week 14	• Clinical remission: 72% • Decrease in mean PCDAI	1 allergic reaction
Muhammed et al[80]	• **32 CD** (18 CT-P13, 14 IFX-R) • **9 UC** (6 CT-P13, 3 IFX-R) Pediatric	Not specified	No significant difference in clinical efficacy	No significant difference in infusion reactions
Bortlik et al[81]	• **79 CD** • **25 UC**	Week 22	Complete or partial response: • CD: 89.6% • UC: 78.3% Mucosal healing: • UC: 50.0%	20 adverse events New antidrug antibodies in 10% of patients
Kaniewska and Rydzewska[82]	• **77 CD** (IFX-R) • **52 CD** (CT-P13) • **47 CD** (ADA)	12 months, then 6 months postcessation	No difference in clinical response, CDAI, calprotectin, or relapse rate	No difference in allergic reaction rates among IFX-R and CT-P13
Kaniewska and Rydzewska[83]	• **32 UC** (IFX-R) • **35 UC** (CT-P13)	Induction therapy (3 doses) and 6 months follow-up	No significant difference in clinical response or endoscopic remission	No difference in adverse events
Turk et al[84]	• **25 UC** • **19 CD** • **2 unclassified**	8 months	• Clinical and laboratory remission: 79% • Mucosal healing: 32% of patients in remission	No severe adverse events

ADA, adalimumab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; CT-P13, infliximab biosimilar; GOL, golimumab; IBD, inflammatory bowel disease; IFX-R, originator infliximab–Remicade; PCDAI, Pediatric Crohn's Disease Activity Index; TNFα, tumor necrosis factor-alpha; UC, ulcerative colitis.

Table 6. Maintenance/Switch Studies of CT-P13 in IBD

Study	Population	Follow-Up	Efficacy	Safety
Smits et al[85,86]	• **57 CD** • **24 UC** • **2 unclassified** (all switched from IFX-R to CT-P13)	Week 16	No change in median disease score, fecal calprotectin, or CRP Increased median infliximab trough levels	No severe adverse events New antidrug antibodies in 2 patients
Sieczkowska et al[87,88]	• **32 CD** • **7 UC** (Pediatric; all switched from IFX-R to CT-P13)	8 months (CD); 5 months (UC)	Clinical remission: • CD: 88% • UC: 57%	No significant difference in adverse events Antidrug antibodies in 4 patients
Bettey et al[89]	• **134 IBD** (all switched from IFX-R to CT-P13)	Week 16	No change in drug persistence	No difference in incidence rate of side effects
Kolar et al[90]	• **56 CD** • **18 UC** (all switched from IFX-R to CT-P13)	Week 24	No difference in CRP, calprotectin, disease activity, or infliximab trough levels	No infusion reactions No difference in antidrug antibodies
Díaz Hernández et al[91]	• **62 CD** • **10 UC** (all switched from IFX-R to CT-P13)	6 months	Clinical remission: 86%	No unexpected adverse events
Jørgensen et al[63]	**481 patients** • **155 CD** • **93 UC** • **91 SpA** • **77 RA** • **30 PsA** • **35 Ps** (all switched from IFX-R to CT-P13)	Week 52	Noninferiority in disease worsening: • Among all patients: 26.2% (IFX-R) vs 29.6% (CT-P13) • CD: 21.2% (IFX-R) vs 36.5% (CT-P13) • UC: 9.1% (IFX-R) vs 11.9% (CT-P13)	No difference in detection of antidrug antibodies, trough drug levels, and frequency of adverse events

CD, Crohn's disease; CRP, C-reactive protein; CT-P13, infliximab biosimilar; IBD, inflammatory bowel disease; IFX-R, originator infliximab–Remicade; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; UC, ulcerative colitis.

Conclusion

The emergence of biosimilar agents poses unique challenges and opportunities in the care of IBD patients, for whom biologic agents are often the most effective therapies available. There is concern regarding the abbreviated regulatory process and extrapolation of biosimilar formulations and risks involved with nonmedical switching. However, the data currently available are positive in regard to the bioequivalence of these agents in the de novo setting, although interchangeability has not been adequately established. An important new risk for clinicians to understand is the cross-reactivity of biosimilar and originator antidrug antibodies. Ongoing postmarketing studies are essential to clearly define the safety, efficacy, and immunogenicity profiles of biosimilar agents in IBD and inform future regulatory processes.

Dr Rubin is a consultant for and has received grant support from AbbVie, Janssen, Takeda Pharmaceuticals, Pfizer, Amgen, and Samsung Bioepis, and is chair of the Government and Industry Affairs Committee with the Crohn's & Colitis Foundation of America. The other authors have no relevant conflicts of interest to disclose.

References

1. Kornbluth A. Infliximab approved for use in Crohn's disease: a report on the FDA GI Advisory Committee conference. *Inflamm Bowel Dis*. 1998;4(4):328-329.
2. Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol*. 2008;6(6):644-653.
3. Huang X, Lv B, Jin HF, Zhang S. A meta-analysis of the therapeutic effects of tumor necrosis factor-α blockers on ulcerative colitis. *Eur J Clin Pharmacol*. 2011;67(8):759-766.
4. Hanauer SB, Feagan BG, Lichtenstein GR, et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549.
5. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353(23):2462-2476.
6. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130(2):323-333.
7. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65.
8. Schreiber S, Rutgeerts P, Fedorak RN, et al; CDP870 Crohn's Disease Study Group. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology*. 2005;129(3):807-818.
9. Sandborn WJ, Feagan BG, Stoinov S, et al; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357(3):228-238.
10. Sandborn WJ, Colombel JF, Enns R, et al; International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2) Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2005;353(18):1912-1925.
11. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711-721.
12. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.
13. Sandborn WJ, Gasink C, Gao L-L, et al; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med*. 2012;367(16):1519-1528.
14. Hommes D, Baert F, van Assche G, et al. Management of recent onset Crohn's disease: a controlled, randomized trial comparing step-up and top-down therapy. *Gastroenterology*. 2005;129(1):371.
15. Louis E, Mary JY, Vernier-Massouille G, et al; Groupe D'etudes Thérapeutiques Des Affections Inflammatoires Digestives. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology*. 2012;142(1):63-70.e5.
16. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol*. 2015;12(4):205-217.
17. Park KT, Colletti RB, Rubin DT, Sharma BK, Thompson A, Krueger A. Health insurance paid costs and drivers of costs for patients with Crohn's disease in the United States. *Am J Gastroenterol*. 2016;111(1):15-23.
18. van der Valk ME, Mangen M-JJ, Severs M, et al; COIN study group and the Dutch Initiative on Crohn and Colitis. Evolution of costs of inflammatory bowel disease over two years of follow-up. *PLoS One*. 2016;11(4):e0142481.
19. Global uptake of biosimilars. Generics and Biosimilars Initiative. http://gabionline.net/Reports/Global-uptake-of-biosimilars. Published March 8, 2012. Accessed November 15, 2016.
20. Biosimilars: barriers to entry and profitability in the EU and US. Generics and Biosimilars Initiative. http://gabionline.net/layout/set/print/content/view/full/1451. Published September 16, 2011. Accessed November 15, 2016.
21. US$67 billion worth of biosimilar patents expiring before 2020. Generics and Biosimilars Initiative. http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020. Published June 29, 2012. Updated January 20, 2014. Accessed November 15, 2016.
22. Fleck A, Smith-Parker JC. Janssen and Celltrion likely to be in litigation over Remicade biosimilar until patent expiration—legal experts. Biopharm Insight. http://www.biopharminsight.com/janssen-and-celltrion-likely-be-litigation-over-remicade-biosimilar-until-patent-expiration-legal. Published May 29, 2015. Accessed November 15, 2016.
23. What are generic drugs? US Food and Drug Administration. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm144456.htm. Updated June 19, 2015. Accessed November 15, 2016.
24. Gecse KB, Khanna R, van den Brink GR, et al. Biosimilars in IBD: hope or expectation? *Gut*. 2013;62(6):803-807.
25. Beck A. Biosimilar, biobetter and next generation therapeutic antibodies. *MAbs*. 2011;3(2):107-110.
26. Graham LR, Scudder L, Christi L. The brave new world of biosimilars. Medscape. http://www.medscape.com/viewarticle/863411. Published May 25, 2016. Accessed November 15, 2016.
27. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. US Food and Drug Administration. www.fda.gov/Downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Published April 2015. Accessed November 15, 2016.
28. Genazzani AA, Biggio G, Caputi AP, et al. Biosimilar drugs: concerns and opportunities. *BioDrugs*. 2007;21(6):351-356.
29. Kozlowski S. US FDA perspectives on biosimilar biological products. Presented at: 2014 Biotechnology Technology Summit; June 13, 2014; Rockville, MD.
30. Electronic code of federal regulations. US Government Publishing Office. http://www.ecfr.gov/cgi-bin/text-idx?SID=d71ee99b08756e59793eff05d6c0e9fd&mc=true&node=pt21.5.320&rgn=div5#se21.5.320_121. Updated November 10, 2016. Accessed November 15, 2016.
31. Guidance for industry: S6 preclinical safety evaluation of biotechnology-derived pharmaceuticals. US Food and Drug Administration. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074957.pdf. Published July 1997. Accessed November 15, 2016.
32. Abbreviated new drug application (ANDA): generics. US Food and Drug Administration. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/. Updated August 4, 2016. Accessed November 15, 2016.
33. Guideline on similar biological medicinal products. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Published October 30, 2005. Accessed November 15, 2016.
34. Gomollón F. Biosimilars in inflammatory bowel disease: ready for prime time? *Curr Opin Gastroenterol*. 2015;31(4):290-295.
35. Feagan BG, Choquette D, Ghosh S, et al. The challenge of indication extrapolation for infliximab biosimilars. *Biologicals*. 2014;42(4):177-183.
36. Kim J, Hong JA, Kudrin A. 5 year budget impact analysis of CT-P13 (infliximab) for the treatment of Crohn's disease in UK, Italy and France. In: Proceedings from the European Crohn's and Colitis Organisation; February 18-21, 2015; Barcelona, Spain. Abstract P137.
37. Edelman B. Explaining the cost of biotech therapies. *Biotechnol Healthc*. 2004;1(2):37-41.
38. Gray N. What's so scary about biosimilars? BioPharmaDIVE. http://www.biopharmadive.com/news/whats-so-scary-about-biosimilars/422974/. Published July 20, 2016. Accessed November 15, 2016.
39. Peyrin-Biroulet L, Lönnfors S, Roblin X, Danese S, Avedano L. Patient perspectives on biosimilars: a survey by the European Federation of Crohn's and Ulcerative Colitis Associations [published online July 31, 2016]. *J Crohns Colitis*. doi:10.1093/ecco-jcc/jjw138.
40. Attara G, Bailey R, Bressler B, et al. Canadian patient and caregiver perspectives on subsequent entry biologics/biosimilars for inflammatory bowel disease. *Gastroenterology*. 2016;150(4)(suppl 1):S443-S444.
41. Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. *J Crohns Colitis*. 2014;8(11):1548-1550.
42. Crohn's and Colitis Foundation of America position statement: biosimilars. Crohn's & Colitis Foundation of America. http://www.ccfa.org/assets/pdfs/advocacy/biosim-position.pdf. Accessed November 15, 2016.
43. Danese S, Gomollon F; Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis*. 2013;7(7):586-589.
44. Devlin SM, Bressler B, Bernstein CN, et al. Overview of subsequent entry biologics for the management of inflammatory bowel disease and Canadian Association of Gastroenterology position statement on subsequent entry biologics. *Can J Gastroenterol*. 2013;27(10):567-571.

45. Mularczyk A, Gonciarz M, Bartnik W, et al. Biosimilar medicines—their use in the treatment of inflammatory bowel diseases. Position statement of the Working Group of the Polish National Consultant in Gastroenterology. *Prz Gastroenterol*. 2014;9(1):1-3.
46. Annese V, Vecchi M; Italian Group for the Study of IBD (IG-IBD). Use of biosimilars in inflammatory bowel disease: statements of the Italian Group for Inflammatory Bowel Disease. *Dig Liver Dis*. 2014;46(11):963-968.
47. Argüelles-Arias F, Barreiro-de-Acosta M, Carballo F, Hinojosa J, Tejerina T. Joint position statement by "Sociedad Española de Patología Digestiva" (Spanish Society of Gastroenterology) and "Sociedad Española de Farmacología" (Spanish Society of Pharmacology) on biosimilar therapy for inflammatory bowel disease. *Rev Esp Enferm Dig*. 2013;105(1):37-43.
48. Danese S, Fiorino G, Michetti P. Changes in biosimilar knowledge among European Crohn's Colitis Organization (ECCO) members: an updated survey. *J Crohns Colitis*. 2016;10(11):1362-1365.
49. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis*. 2013;72(10):1605-1612.
50. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis*. 2013;72(10):1613-1620.
51. Ault A. FDA advisers back infliximab biosimilar CT-P13. Medscape. http://www.medscape.com/viewarticle/858749. Published February 10, 2016. Accessed November 15, 2016.
52. ABP 501, a proposed biosimilar to Humira (adalimumab). US Food and Drug Administration. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM510293.pdf. Published July 12, 2016. Accessed November 15, 2016.
53. Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of biosimilar tumor necrosis factor-α inhibitors compared with their reference biologics: a systematic review. *Ann Intern Med*. 2016;165(8):565-574.
54. Kang YS, Moon HH, Lee SE, Lim YJ, Kang HW. Clinical experience of the use of CT-P13, a biosimilar to infliximab in patients with inflammatory bowel disease: a case series. *Dig Dis Sci*. 2015;60(4):951-956.
55. Jung YS, Park DI, Kim YH, et al. Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: a retrospective multicenter study. *J Gastroenterol Hepatol*. 2015;30(12):1705-1712.
56. Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert Opin Biol Ther*. 2015;15(12):1677-1683.
57. Hlavaty T, Krajcovicova A, Sturdik I, et al. Biosimilar infliximab CT-P13 treatment in patients with inflammatory bowel diseases: a 1-year, single centre retrospective study. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P655.
58. Armuzzi A, Dotan I. Digital oral presentation session 4—IFX & IFX biosimilars. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands.
59. *Gastroenterology*. 2016;150(4)(suppl 1):S1-S1271.
60. Fiorino G, Manetti N, Variola A, et al. Prospective observational study on inflammatory bowel disease patients treated with infliximab biosimilars: preliminary results of the PROSIT-BIO cohort of the IG-IBD. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P544.
61. Rubin DT. Conclusions about interchangeability of anti-TNF biosimilars are premature. Letter to *Annals of Internal Medicine*. http://annals.org/article.aspx?articleid=2540851. Accessed November 15, 2016.
62. ClinicalTrials.gov. The NOR-SWITCH study (NOR-SWITCH). https://clinicaltrials.gov/ct2/show/NCT02148640?term=NCT02148640. Identifier: NCT02148640. Accessed November 15, 2016.
63. Jørgensen K, Olsen I, Goll G, et al. Biosimilar infliximab (CT-P13) is not inferior to originator infliximab: results from the 52-week randomized NOR-SWITCH trial. In: Proceedings from the United European Gastroenterology Week; October 15-19, 2016; Vienna, Austria. Abstract LB15.
64. Malíčková K, Ďuricová D, Bortlík M, et al. Serum trough infliximab levels: a comparison of three different immunoassays for the monitoring of CT-P13 (infliximab) treatment in patients with inflammatory bowel disease. *Biologicals*. 2016;44(1):33-36.
65. Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut*. 2016;65(7):1132-1138.
66. Park SH, Kim YH, Lee JH, et al. Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea. *Expert Rev Gastroenterol Hepatol*. 2015;9(suppl 1):35-44.
67. Gecse KB, Lovász BD, Farkas K, et al. Efficacy and safety of the biosimilar infliximab CT-P13 treatment in inflammatory bowel diseases: a prospective, multicentre, nationwide cohort. *J Crohns Colitis*. 2016;10(2):133-140.
68. Gecse K, Vegh Z, Kurti Z, et al. Efficacy and safety of biosimilar infliximab after one year: results from a prospective nationwide cohort. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract DOP028.
69. Guerra Veloz MF, Arias FA, Amarillo RP, et al. Safety and efficacy of infliximab biosimilar (Remsima©) in Crohn's disease patients in clinical practice: results after 6 months of treatment. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P452.
70. Guerra Veloz MF, Argüelles Arias F, Perea Amarillo R, et al. Safety and efficacy of infliximab biosimilar (Remsima©) in ulcerative colitis disease patients in clinical practice: results after 6-months treatment. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P600.
71. Carvalho Lourenço L, Anapaz V, Oliveira AM, et al. Biosimilar infliximab in real-life Crohn's disease's anti-TNFalfa naïve patients: a comparative observational cohort study (SIMRECRO study). In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P327.
72. Hamanaka S, Nakagawa T, Koseki H, et al. Infliximab biosimilar in the treatment of inflammatory bowel disease: a Japanese single-cohort observational study. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P329.
73. Murphy C, Sugrue K, Mohamad G, et al. Biosimilar but not the same. In: Proceedings from the European Crohn's and Colitis Organisation; February 18-21, 2015; Barcelona, Spain. Abstract P505.
74. Jahnsen J, Detlie TE, Vatn S, Ricanek P. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: a Norwegian observational study. *Expert Rev Gastroenterol Hepatol*. 2015;9(suppl 1):45-52.
75. Keil R, Wasserbauer M, Zádorová Z, et al. Clinical monitoring: infliximab biosimilar CT-P13 in the treatment of Crohn's disease and ulcerative colitis. *Scand J Gastroenterol*. 2016;51(9):1062-1068.
76. Farkas K, Rutka M, Golovics PA, et al. Efficacy of infliximab biosimilar CT-P13 induction therapy on mucosal healing in ulcerative colitis. *J Crohns Colitis*. 2016;10(11):1273-1278.
77. Farkas K, Rutka M, Bálint A, et al. Efficacy of the new infliximab biosimilar CT-P13 induction therapy in Crohn's disease and ulcerative colitis—experiences from a single center. *Expert Opin Biol Ther*. 2015;15(9):1257-1262.
78. Malickova K, Duricova D, Kolar M, et al. No difference in immunogenicity of the original and biosimilar infliximab in patients with inflammatory bowel disease: short-term results. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P311.
79. Sieczkowska J, Plocek A, Banaszkiewicz A, et al. Efficacy of biosimilar infliximab induction therapy in paediatric patients with Crohn's disease: 1.5 years of experience. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P530.
80. Muhammed R, Whyte L, Protheroe S, et al. Comparison of efficacy and safety of biosimilar infliximab to originator infliximab in children with inflammatory bowel disease. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P382.
81. Bortlik M, Kolar M, Duricova D, et al. Biosimilar infliximab is effective and safe in inflammatory bowel disease patients naïve to anti-TNF therapy: a tertiary centre experience. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P495.
82. Kaniewska M, Rydzewska G. Efficacy and safety of biosimilar of infliximab (Inflectra) in adult patients with Crohn's disease during 1 year of treatment, followed 6 months of observation: a one-centre retrospective study. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P519.
83. Kaniewska M, Rydzewska G. Efficacy and safety of biosimilar of infliximab in rescue therapy in adult patients with severe ulcerative colitis. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P645.

84. Turk N, Brinar M, Grgic D, et al. Croatian database from 5 centres: efficacy and safety of infliximab biosimilar in treatment of inflammatory bowel disease score patients. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P577.
85. Smits LJ, Derikx LA, de Jong DJ, et al. Clinical outcomes following a switch from Remicade(R) to the biosimilar CT-P13 in inflammatory bowel disease patients: a prospective observational cohort study. *J Crohns Colitis*. 2016;10(11):1287-1293.
86. Smits L, Derikx L, Drenth J, et al. Elective switching from Remicade® to biosimilar CT-P13 in inflammatory bowel disease patients: a prospective observational cohort study. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract DOP030.
87. Sieczkowska J, Jarzębicka D, Banaszkiewicz A, et al. Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease. Preliminary observations. *J Crohns Colitis*. 2016;10(2):127-132.
88. Sieczkowska J, Jarzebicka D, Oracz G, et al. Immunogenicity after switching from reference infliximab to biosimilar in children with Crohn's disease. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P617.
89. Bettey M, Downey L, Underhill C, et al. Outcomes of a managed switching programme changing IBD patients established on originator infliximab to biosimilar infliximab. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract DOP029.
90. Kolar M, Duricová D, Brotlik M, et al. Switching of patients with inflammatory bowel disease from original infliximab (Remicade®) to biosimilar infliximab (Remsima™) is effective and safe. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract DOP032.
91. Díaz Hernández L, Rodríguez González GE, Vela González M, et al. Efficacy and safety of switching between originator and biosimilar infliximab in patients with inflammatory bowel disease in practical clinic: results to 6 months. In: Proceedings from the European Crohn's and Colitis Organisation; March 16-19, 2016; Amsterdam, The Netherlands. Abstract P449.