Clinical Gastroenterology and Hepatology 2019;17:818–823

CLINICAL PRACTICE UPDATE: COMMENTARY

Switching Between Biologics and Biosimilars in Inflammatory Bowel Disease

Laura E. Raffals,[*] Geoffrey C. Nguyen,[‡] and David T. Rubin[§]

[*]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [‡]Mount Sinai Hospital Centre for Inflammatory Bowel Disease, University of Toronto, Toronto, Canada; and [§]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, Illinois

Nearly 20 years ago, biologic therapy was introduced for the treatment of Crohn's disease (CD) and has since revolutionized the treatment of inflammatory bowel disease (IBD). The first biologic therapy approved by the Food and Drug Administration (FDA) for the treatment of CD was infliximab (Remicade, Janssen Pharmaceuticals). Since its approval in 1998, other biologics have become available for the treatment of IBD, including other anti–tumor necrosis factors (adalimumab, certolizumab pegol, golimumab), anti-integrins (natalizumab, vedolizumab), and anti-interleukin-12/23 therapies (ustekinumab). However, biologic therapy is costly and one of the largest contributors to direct medical costs in IBD. The biosimilars have been introduced in hopes of lowering the cost of biologic therapy through increased competition and treatment options. As the initial biologic therapies near the end of their patents, biosimilars are emerging and are becoming increasingly common for the treatment of IBD, particularly in Europe. There has been great skepticism about the safety and efficacy of biosimilars and as demonstrated in a recent study, many gastroenterologists are not informed about biosimilars and their approval process.[1] There is a need to disseminate information about biosimilars and their approval process to increase the comfort levels of gastroenterologists as these become a larger part of our practice. Here, we provide an overview of biosimilars, their manufacturing process, the FDA approval process, and the data available describing their safety and efficacy.

Biosimilars

Biosimilars are not simply generic versions of biologic therapies. Generic drugs are identical to their reference product (often a small-molecule drug) whereas biosimilars are highly similar but not identical to their reference product (often a large, complex protein-based drug). To understand biosimilars and the approval process for these therapies, it is important to understand what constitutes a biologic therapy and the process by which a biosimilar is developed. Biologic treatments are derived from a living source, such as humans, animals, or microorganisms; and in contrast to small-molecule drugs, the precise structure of a biologic therapy is difficult to fully characterize.[2]

The number of steps required to produce a biologic introduces numerous opportunities for variation in the molecular structure of the drug (variation in primary amino acid sequence; in protein folding or protein-protein interactions; or modifications to amino acids such as glycosylation).[3–5] Differences in the manufacturing process can also result in changes in the biologic properties of the molecule and even affect an agent's potential for immunogenicity (Figure 1). Biosimilars, although highly similar, are not identical to their reference product, so the approval pathway for biosimilars is different from that for generics.

Food and Drug Administration

Biologic therapies are approved under the Public Health Service Act (PHSA), which was subsequently amended through the Biologics Price Competition and Innovation Act of 2009 (BPCI) passed as part of the Affordable Care Act. Biologic therapies require submission of clinical trials demonstrating safety and efficacy for FDA approval (351(a) pathway). Biosimilars are not required to follow this same pathway and are offered an abbreviated pathway for approval, although a more intensive process compared with the approval process for generic drugs. The BPCI allows this abbreviated licensure pathway for biologics demonstrated to be "biosimilar to or interchangeable with an FDA-licensed biological reference product" with the intent to save money and time for the approval of these products and eliminating the need for the full set of preclinical and

Abbreviations used in this paper: **BPCI, Biologics Price Competition and Innovation Act of 2009; CD, Crohn's disease; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; PD, pharmacodynamics; PHSA, Public Health Service Act; PK, pharmacokinetics; UC, ulcerative colitis.**

This update was produced by the AGA Institute.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.08.064

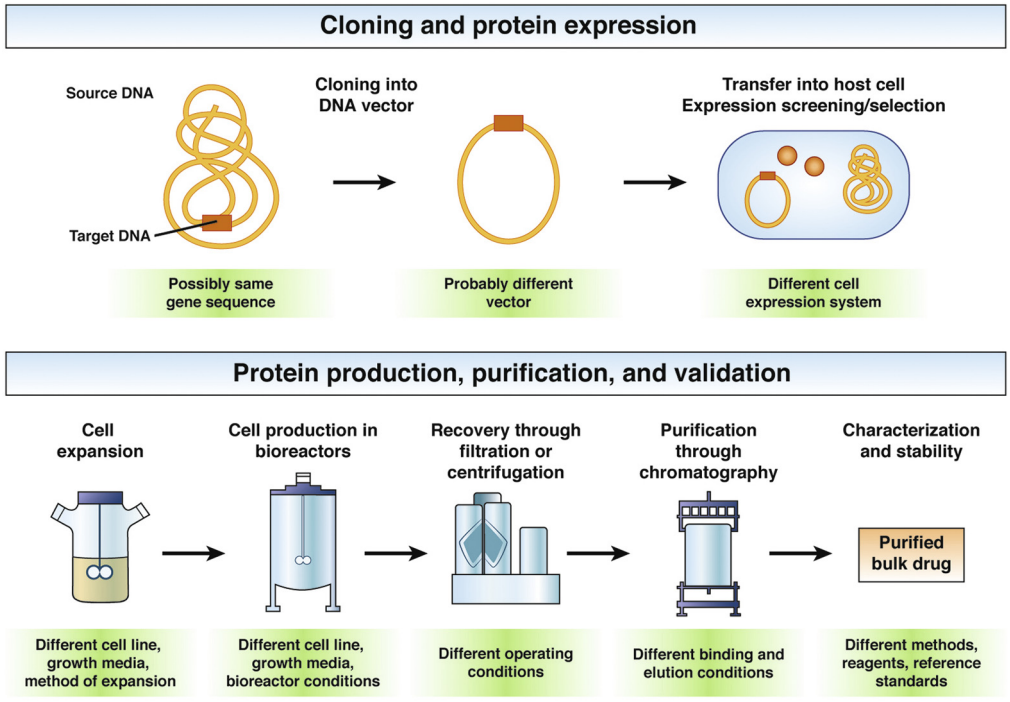

Figure 1. Manufacturing of biologic products is complex involving multiple steps that may vary between manufacturers, which may lead to differences between a biosimilar and reference product that cannot be fully characterized using available analytical techniques.

clinical studies.[6] The PHSA defines biosimilarity as "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" (Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHSA).

The FDA's recommended stepwise approach requires demonstration that a biosimilar is similar to the originator biologic in structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), immunogenicity, and clinical safety and efficacy.[7] However, this approach is not intended to re-establish the safety and effectiveness of a product, but rather to assess the biosimilarity between the proposed product and the reference product. The approach includes a comparison of the structural and functional properties. Initial assessments help determine what additional studies should be considered to better understand how structural or functional differences are clinically relevant. Animal studies are required to assess toxicity and further support biosimilarity. After the initial analytic and animal studies are completed, the FDA recommends an FDA review of data to help address remaining uncertainties regarding biosimilarity before carrying out human clinical trials. The final steps for a sponsor to demonstrate biosimilarity involves comparative human PK and PD (as appropriate) studies, studies examining clinical immunogenicity, and comparative clinical studies of safety and efficacy.

The FDA looks at the totality of the evidence provided by a sponsor when considering biosimilarity (Figure 2). For example, even in the presence of minor differences between the proposed biologic and the originator biologic, if there is sufficient evidence that identified differences are not clinically meaningful and there are no significant concerns related to the safety and purity of the proposed agent, the product may meet the FDA's criteria for biosimilarity.

The FDA Center for Drug Evaluation and Research has approved 7 biosimilars in the United States. The first biosimilar for IBD approved in the United States was CT-P13 (FDA nonproprietary name: infliximab-dyyb; trade name: Inflectra), a biosimilar of infliximab that was approved in April 2016 for several indications including the treatment of CD and ulcerative colitis

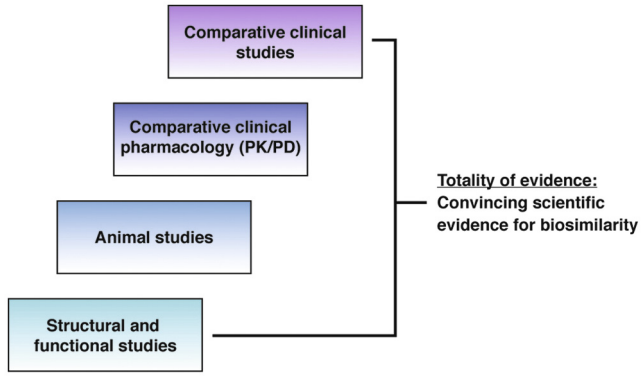

Figure 2. The Food and Drug Administration suggests a stepwise approach to demonstrate biosimilarity of a proposed biosimilar to an originator biologic. This process includes studies demonstrating similarity in structure and function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), and immunogenicity, as well as clinical safety and efficacy. The Food and Drug Administration considers the totality of evidence to determine biosimilarity.

Table 1. Biosimilars Approved by the Food and Drug Administration for Inflammatory Bowel Disease

Biosimilar nonproprietary	Trade name	Reference product	Manufacturer	Date approved
Infliximab-dyyb	Inflectra	Remicade	Celltrion	April 2016
Adalimumab-atta	Amjevita	Humira	Amgen	September 2016
Infliximab-abda	Renflexis	Remicade	Samsung Bioepsis	May 2017
Adalimumab-adbm	Cyltezo	Humira	Boehringer Ingelheim	August 2017
Infliximab-qbtx	Ixifi	Remicade	Pfizer	December 2017

(UC).[8] A full list of biologic therapies, related biosimilar and interchangeable products, and the dates a biological product was licensed can be found in the Purple Book.[9] Biosimilars that have been approved by the FDA for IBD are shown in Table 1. Of note, among the 5 approved biosimilars, only 2 have been licensed, reflecting the significant impediments between approval and licensing.

Extrapolation

The FDA allows for extrapolation of comparative clinical data across indications.[7] If the sponsor fulfills the PHSA requirements for their product, the sponsor may apply for licensure of their product for more than 1 condition for which the reference product is approved. In this situation, the FDA may extrapolate findings from one indication to another indication that was not formally studied with the proposed biosimilar if the reference product is approved for that indication. The applicant must justify extrapolation by demonstrating that their product's mechanism of action, PK and PD properties, immunogenicity, and expected toxicities of the product do not differ across patient groups. As an example, pharmacokinetic studies for Inflectra versus Remicade were carried out in ankylosing spondylitis,[10] and comparative clinical effectiveness trials for Inflectra and Remicade were carried out in rheumatoid arthritis.[11] Data from these trials were extrapolated to other indications such as CD and UC.

Interchangeability

An interchangeable product is one that meets additional requirements set by the BPCI. The standards for interchangeability are higher than the standards for biosimilarity. The requirements needed to be designated an interchangeable product include demonstration by the sponsor that their biosimilar can produce the same clinical result as the reference product and that there are no safety or efficacy differences if the interchangeable product and the originator are switched back and forth.[12] Moreover, in demonstrating interchangeability the FDA recommends that the comparator reference biologic be a U.S.-licensed product, which presents a challenge because most biologic switching studies were conducted in Europe.[13] An interchangeable product may be substituted for a reference product without the approval of the prescribing provider. Thus, there is great concern and controversy among providers about the practice of interchangeability. Pharmacy laws and practices vary across states, so even if a biosimilar meets the requirements for interchangeability, this practice may not be allowed across all states. Currently, there are no biologics for the treatment of IBD that have been designated by the FDA as interchangeable.

Review of CT-P13 Trials and IBD Studies

Although primary equivalence studies in the IBD population have not been performed, there are numerous postmarketing experiences of biosimilar infliximab in the CD and UC populations. The majority of these experiences and studies exist for biosimilar infliximab CT-P13. Most are descriptors of studies in which patients on stable dosing with reference infliximab (Remicade) are transitioned to CT-P13. There are a couple of notable studies that randomized patients for ongoing follow-up. As would be expected given the totality of evidence for biosimilar infliximab, the data in CD and UC support that this therapy is equivalent in its efficacy and safety in the IBD population. In addition, the majority of evidence demonstrates that there is neither an increased loss of response after transitioning to the biosimilar nor an increased immunogenicity.

Published studies exploring switching between CT-P13 and originator in IBD are from Europe and Asia and are summarized in Table 2.

The most prominent biosimilar study that included IBD patients was the NOR-SWITCH study funded by the Norwegian government.[14] This was a prospective, 52-week, randomized, double-blind, noninferiority trial of patients of all infliximab indications who received the originator infliximab. They were randomized to be switched to either the originator infliximab or biosimilar, CT-P13. The unique endpoint of this study was "disease worsening" in any of the diseases for which originator infliximab had approval (rheumatoid arthritis, CD, UC, spondyloarthritis, psoriatic arthritis, and plaque psoriasis). Although the endpoint is not validated, it is notable that there was no significant difference in loss of response, safety, or immunogenicity between those who remained on originator infliximab for the duration of the study compared with those who were switched to

Table 2. Switch Studies of Originator Infliximab to Biosimilar CT-P13 in IBD

Study	Population	Follow-Up	Efficacy Endpoints	Safety
Jørgensen et al[14]	482 patients: 155 CD 93 UC (subjects on IFX-R randomized to continue IFX-R or switch to CTP-13)	Week 52	Noninferiority study Primary endpoint: Worsening disease activity during 52-week follow-up. - Among all patients: 26.2% (IFX-R) vs 29.6% (CT-P13) - Among CD: 21.2% (IFX-R) vs 36.5% (CT-P13)[a] - Among UC: 9.1% (IFX-R) vs 11.9% (CT-P13)[a]	No difference in detection of antidrug antibodies, trough drug levels, and frequency of adverse events
Smits et al[17,18]	57 CD 24 UC 2 IBD unclassified (all switched from IFX-R to CT-P13)	Weeks 16 and 52	• No change in median disease score, fecal calprotectin, or CRP at weeks 16 and 52 • Increased median infliximab trough levels at week 16	• Serious adverse events in 4% of patients with 1-year follow-up • Detectable antidrug antibodies in 8% of patients at week 52
Sieczkowska et al[19,20]	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
Razanskaite et al[21]	143 IBD (all switched from IFX-R to CT-P13)	Week 16	• No change in mean CRP, albumin, Hb, platelet, WBC, drug persistence • Improvement of IBD-control-8 score	• No difference in incidence rate of side effects • No increase in immunogenicity
Kolar et al[22]	56 CD 18 UC (all switched from IFX-R to CT-P13)	Week 56	No difference in CRP, calprotectin or disease activity	• No difference in type and frequency of adverse events • No increase in immunogenicity
Díaz Hernández et al[23]	62 CD 10 UC (all switched from IFX-R to CT-P13)	6 months	Clinical remission: 86%	No unexpected adverse events
Jacobs et al[16] & Strik et al[24]	61 CD 59 UC (all switched from IFX-R to CT-P13)	Week 16	Noninferiority of infliximab trough levels before and 16 weeks after switch	One adverse event (perianal abscess)

CD, Crohn's disease; CRP, C-reactive protein; CT-P13, infliximab biosimilar; Hb: hemoglobin; IBD, inflammatory bowel disease; IFX-R, infliximab–Remicade; UC, ulcerative colitis; WBC, white blood count.
[a]Sample size calculations were not powered to demonstrated noninferiority within CD and UC subgroups.

CT-P13. The study was not powered to look at the different disease indications, but the authors reported a breakdown of results nonetheless. There was not a significant difference in loss of response noted in the CD and UC patients, but the CD risk difference slightly favored remaining on originator drug (risk difference, –14.3%; 95% confidence interval, –29.3 to 0.7) while the UC patients were noted to have a more balanced result (risk difference, –2.6%; 95% confidence interval, –15.2 to 10.0). The recently published SECURE trial suggests that infliximab levels 16 weeks after switching from originator to biosimilar infliximab were noninferior to baseline levels in both CD and UC.

As would be expected with the structure of the biosimilar antibodies, antidrug antibodies to the biosimilar do cross-react to the originator antibodies of infliximab. This cross-reactivity was nicely demonstrated in a study of 125 IBD patients in Israel.[15] The authors concluded that antioriginator infliximab (Remicade) antibodies in IBD patients both recognize and functionally inhibit CT-P13 biosimilar infliximab to a similar degree. The critically important point of this finding is that patients who develop antidrug antibodies to originator infliximab or to the biosimilar should not be switched to the biosimilar or the originator, respectively. Otherwise, they would likely experience the same reaction, which may result in an immediate hypersensitivity reaction such as anaphylaxis and could be life-threatening. It is further noteworthy that the commercially available therapeutic drug assays can be used with the biosimilar as effectively as they are with the originator drugs.

Considerations for use of Biosimilars

In considering the different scenarios in which patients may be treated with biosimilar agents, the available data support use of biosimilars in new starts of infliximab. However, when given a choice, the decision to transition a patient who is in remission on an originator biologic to a biosimilar or vice versa should be made by the IBD physician provider and individualized, and patients should be informed and involved in the decision-making process. Special consideration should be taken for transitioning to biosimilars in children and pregnant women who are in stable remission as there is limited pharmacokinetic, immunogenicity, efficacy, and safety data in these vulnerable populations. Because maintenance of remission during pregnancy is critical for achieving healthy outcomes for mother and fetus, nonmedical switching should be avoided during the antenatal period until there is more safety data on switching in this population. As noted previously, none of the biosimilars currently have received the unique FDA designation of "interchangeability." This means that these therapies have not demonstrated safety in multiple switches, and therefore still require notification determined on a state-by-state basis from the pharmacist, infusion center, or payer. Nonetheless, the experience with the biosimilars in the real world of IBD patients and treatments supports their efficacy and safety. Systematic reviews suggest potentially substantial cost savings depending on the pricing of the biosimilar relative to the originator and physician-prescribing practices.[16] Whether cost savings to payers, infusion centers, hospitals, and health services will, in any way, be passed on to patients with reduced insurance premiums, copays, or increased access remains to be seen.

Conclusions

It is anticipated that biosimilars for IBD are here to stay. Additional biosimilars to infliximab and to adalimumab, as well as other monoclonal antibodies used in the treatment of IBD, are under development. Provided that the regulatory pathway remains rigorous and postmarketing surveillance is performed adequately, clinicians and patients can be reassured that these agents will provide the same well-described effectiveness for moderate-to-severe CD and UC without new safety concerns. Future work will require additional understanding of the real-world challenges of transitioning and potential delays due to communications or appropriate supply lines. In addition, there remains an educational gap to be filled regarding how clinicians understand these agents and making sure that, while involved in their recertification and administration, recognize the cross-reactivity of antidrug antibodies.

References

1. Cohen H, Beydoun D, Chien D, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. Adv Ther 2017;33:2160–2172.
2. Christl L. FDA's overview of the regulatory guidance for the development and approval of biosimilar products in the US. 2016. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevHowDrugsareDevelo/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM428732.pdf. Accessed December 7, 2017.
3. Epstein AA, Kremer JM, Siegel E. Applying biologic therapies to the management of patients with rheumatoid arthritis. Semin Arthritis Rheum 2014;43:577.
4. Camacho LH, Frost CP, Abella E, Morrow PK, Whittaker S. Biosimilars 101: considerations for U.S. oncologists in clinical practice. Cancer Med 2014;3:889–899.
5. Kuhlmann M, Covic A. The protein science of biosimilars. Nephrol Dial Transplant 2006;21(Suppl 5):4–8.
6. U.S. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. 2015. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed December 7, 2017.
7. U.S. Food and Drug Administration. Biosimilar development, review, and approval. 2017. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580429.htm. Accessed December 7, 2017.

8. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm. Accessed December 7, 2017.
9. U.S. Food and Drug Administration. Purple book: Lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Available at: https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm. Accessed December 7, 2017.
10. 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;72:1605–1612.
11. 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;72:1613–1620.
12. U.S. Food and Drug Administration. Biosimilar and interchangeable products. 2017. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm. Accessed December 7, 2017.
13. U.S. Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product guidance for industry. 2017. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Accessed July 22, 2018.
14. Jørgensen KK, Olsen IC, Goll GL, et al; NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017;389:2304–2316.
15. 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;65:1132–1138.
16. Jacobs I, Petersel D, Isakov L, Lula S, Lea Sewell K. Biosimilars for the treatment of chronic inflammatory diseases: a systematic review of published evidence. BioDrugs 2016;30:525–570.
17. 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;10:1287–1293.
18. Smits LJT, Grelack A, Derikx LAAP, et al. Long-term clinical outcomes after switching from Remicade® to biosimilar CT-P13 in inflammatory bowel disease. Dig Dis Sci 2017;62:3117–3122.
19. Sieczkowska J, Jarzebicka D, Banaszkiewicz A, et al. Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease. Preliminary Observations. J Crohns Colitis 2016;10:127–132.
20. 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.
21. Razanskaite V, Bettey M, Downey L, et al. Biosimilar infliximab in inflammatory bowel disease: outcomes of a managed switching programme. J Crohns Colitis 2017;11:690–696.
22. Kolar M, Duricova D, Bortlik M, et al. Infliximab biosimilar (Remsima™) in therapy of inflammatory bowel diseases patients: experience from one tertiary inflammatory bowel diseases centre. Dig Dis 2017;35:91–100.
23. 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 (Abstract P449). Presented at: European Crohn's and Colitis Organisation; March 16–19, 2016; Amsterdam, the Netherlands.
24. Strik AS, van de Vrie W, Bloemsaat-Minekus JPJ, et al; SECURE study group. Serum concentrations after switching from originator infliximab to the biosimilar CT-P13 in patients with quiescent inflammatory bowel disease (SECURE): an open-label, multicentre, phase 4 non-inferiority trial. Lancet Gastroenterol Hepatol 2018;3:404–412.

Reprint requests
Address requests for reprints to: Geoffrey C. Nguyen, MD, PhD, University of Toronto, Faculty of Medicine, Division of Gastroenterology, Mount Sinai Hospital, 600 University Avenue, Room 437, Toronto, Ontario M5G 1X5, Canada. e-mail: geoff.nguyen@utoronto.ca; fax: (416) 586-5971.

Conflicts of interest
This author discloses the following: Geoffrey C. Nguyen. Abbvie, Janssen Pharmaceuticals, Pfizer, Merck & Co, Inc, Samsung Bioepis, and Amgen. The remaining authors disclose no conflicts.