Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2017 August ; 65(2): 134–136. doi:10.1097/MPG.0000000000001572.

The Path of Interchangeability of Biosimilars in Pediatric Inflammatory Bowel Disease: Quality Before Cost-Savings

Dimple Patel, BS¹ and KT Park, MD, MS²

¹Saint Louis University School of Medicine, Saint Louis, MO

²Department of Pediatrics, Division of Gastroenterology, Stanford University Medical Center, Palo Alto, CA

Abstract

The advent of biosimilars in inflammatory bowel disease (IBD) represents an opportunity for cost-savings and increased patient access to effective disease-modifying therapies. While preliminary data in adult IBD and rheumatology patients suggest comparable effectiveness and pharmacokinetics between original biologics and biosimilars, long-term immunogenicity data are unknown. Without this data, conclusions about interchangeability should not be made for pediatric patients with IBD. Children affected by IBD, in particular, are a vulnerable group if automatic substitution and non-medical switching are allowed based on limited data in adult patients. Robust, long term immunogenicity data of biosimilars are needed in pediatric cohorts before policies allow interchangeability in children.

Keywords

Biosimilar; Biologic; interchangeability; inflammatory bowel disease; children

Introduction

In today's "Era of Biologics," traditional biological agents such as infliximab and adalimumab and newer agents such as vedolizumab and ustekinumab represent the most effective and expensive class of pharmacotherapy options for the treatment of inflammatory bowel diseases (IBD), namely Crohn's disease and ulcerative colitis. More recent studies show that pharmacy utilization costs, driven mainly by biologics use, are primary drivers of IBD economics, outpacing acute care costs, including hospitalizations (1, 2). Consequently, the anticipated advent of biosimilars represents the potential to generate cost savings and increase patient access to necessary treatment.

The Food and Drug Administration (FDA) defines a biosimilar as an officially approved biologic that is highly similar, but not identical, to an originator biopharmaceutical product.

Correspondence: KT Park, MD, MS, 750 Welch Road, Suite 116, Palo Alto, CA 94304, Phone: (650) 723-5070, Fax: (650) 498-5608, ktpark@stanford.edu.

Conflict of Interests

Authors have no relevant conflict of interest to report pertaining to this article and have not received any benefits in conceiving and writing this manuscript.

It has no clinically meaningful difference in terms of safety and effectiveness from the original biologic (3). Infliximab biosimilars have been approved by the European Medicines Agency for the treatment of IBD since 2013. Multiple budget impact models based on data from European countries have demonstrated considerable savings from switching a patient with IBD to a biosimilar (4, 5, 6). In the United States (US), the passage of the Affordable Care Act came with the Biologics Price and Competition and Innovation Act (BPCI Act), which created an abbreviated approval pathway to save time and money due to a less than full set of preclinical and clinical data (3, 7). In April 2016, the FDA approved Inflectra, the biosimilar for infliximab, for multiple indications, including the treatment of adult and pediatric patients with Crohn's disease and adult patients with ulcerative colitis (8).

The purpose of this contribution is to discuss the importance and current real-world use of biosimilars with a focus on the potential impact of interchangeability on children affected by IBD.

Why the Topic of Interchangeability is Important

CT-P13 (Inflectra; Pfizer Inc.) is approved as a biosimilar, not as an interchangeable product. An interchangeable product is a biosimilar to an already FDA-approved product that meets additional standards for it to be classified as such. An interchangeable drug produces the same clinical result when compared to the reference product, and does not increase the safety risk or diminish efficacy when switching from the originator drug. As a result, pharmacists or commercial or government payers can substitute the original reference product without intervention of the prescribing health care provider (3). A generic drug is considered to be interchangeable (Table 1).

The US, through the FDA, is the only nation that has formally addressed the interchangeability of biologics, under the BPCI Act. There are two different levels of approval, the first being "highly similar" and the second being "highly similar and interchangeable" (7, 9). However, the FDA has not released any specific regulatory guidance regarding what is necessary in order for a biosimilar to be approved as an interchangeable biologic.

Why Children Affected by IBD Are Most Vulnerable

Children with IBD are at potential risk by the concept of interchangeability between biosimilars and original biologics. If interchangeability is established, it will be possible for non-prescribing third-parties (i.e., pharmacists or payers) to intervene via automatic substitution or non-medical switching. "Automatic substitution" is an action whereby a pharmacist automatically substitutes a prescribed drug with another equivalent drug without consulting the provider. "Non-medical switching" is an action often performed by payers whereby the prescribed drug is switched to another equivalent drug because of economic needs often introduced in stable patients (10).

Considering the growing evidence that pediatric-onset IBD is phenotypically more aggressive than adult-onset IBD, children with IBD are disproportionately more vulnerable to substitution and non-medical switching if long-term, robust interchangeability data in

pediatrics are not established (11, 12). Furthermore, sustainability of treatment (particularly the first-line biologic) is arguably more important in children with IBD given their lengthier duration of drug exposure. To date, small induction and single-switch (i.e., originator to biosimilar) studies in pediatric IBD patients have been published (13, 14). No long-term, multiple-switch (e.g., originator to biosimilar to originator) studies in pediatric or adult patients have been performed.

Weak Strength of Evidence for Interchangeability

The FDA approved CT-P13 for all indications of infliximab on the basis of “extrapolation,” the extension of the approval for one indication to other indications without additional clinical studies (15). The data comparing biosimilars to biologics is based on 2 published randomized, double blind, multicenter, parallel-group, prospective studies in adult patients with rheumatoid arthritis (PLANETRA) and ankylosing spondylitis (PLANETAS). Both studies demonstrated that the safety and efficacy between CT-P13 and infliximab are comparable in those populations (16). Nevertheless, the assumption that biosimilars are efficacious and well tolerated in patients with IBD, especially children, and are interchangeable (based only on evidence from rheumatology trials) is highly debatable (17). The data obtained from the PLANETRA and PLANETAS trials may not be applicable for IBD, particularly pediatric IBD, given the inherent differences in disease pathophysiology (16).

Within the IBD population, there are only a handful of European observational studies published demonstrating that biosimilars are comparable to the original biologics, with a majority of them performed in adults. There is currently one prospective study of children with Crohn’s disease and ulcerative colitis who were switched to an infliximab biosimilar. The study concluded that the biosimilar produced similar results and seemed to be as effective as the infliximab originator (13). Extrapolated biologic drug dosing from adult phase 3 trials may not result in comparable drug exposure in children with IBD, as supported by pediatric pharmacokinetic (PK) data from the REACH infliximab trial (18). Though the PK properties are similar between adults and children, dosing needs can be different between children and adults, possibly leading to differential treatment failure rates (19).

Immunogenicity Is a Concern in Pediatric IBD

All biologics can form antidrug antibodies, particularly early on in the treatment (20), diminishing their efficacy or increasing risk of adverse reactions. Immunogenicity of biologics or biosimilars dramatically alters the therapeutic sustainability. Original biologics went through all required phases of clinical trials for each indication, testing the immunogenicity for each patient population. Although there is new evidence in the adult population demonstrating that the immunogenicity of biosimilars is similar to the original biologics (21), it is premature and possibly risky to assume that interchangeability will not cause differences in immunogenicity without long-term evidence in the pediatric population (19). Pediatric physiology is not the same as that in adults. Notably, for example, children

with IBD have increased clearance of infliximab, leading to lower drug troughs and potentially a higher probability of developing auto-antibodies with standard dosing (18, 22).

Conclusion

Numerous biosimilars are under development given the expiration of originator biologic patents. Multiple groups have released position statements regarding the use of biosimilars. The American College of Rheumatology stated studies for one indication does not prove the same for other indications and that safety in adults is not guaranteed in children (23). The ESPGHAN Paediatric IBD Porto Group has also indicated the need for pediatric trials with long-term follow-up to support the safety and efficacy of biosimilars (16).

In conclusion, the FDA should require independent data in the pediatric IBD population to support the promising efficacy and safety of biosimilars. Once established, the topic of interchangeability needs clear, evidence-based guidance from medical societies advocating for children affected by IBD, including NASPGHAN, ESPGHAN, CCFA, and ECCO. In particular, longer term data need to show safety and efficacy when patients are switched between biologic and biosimilar – possibly multiple times if automatic substitution and non-medical switching are allowed under interchangeability. Although biosimilars have the potential to decrease the economic burden and increase patient access to expensive therapies, strength of evidence is necessary to ensure quality.

Acknowledgments

Source of Funding

KP is supported by National Institutes of Health (DK094868), and has received research support from AbbVie, Janssen, and Takeda not related to this article.

References

1. 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. [PubMed: 26195179]
2. van der Valk ME, Mangen MJ, Severs M, et al. Evolution of Costs of Inflammatory Bowel Disease over Two Years of Follow-Up. *PLoS One*. 2016 Apr 21;11(4):e0142481. [PubMed: 27099937]
3. Information on Biosimilars. U.S. Food & Drug Administration; May 10. 2016 Web [Accessed 13 Sept. 2016]
4. Severs M, Oldenburg B, van Bodegraven AA, et al. The Economic Impact of the Introduction of Biosimilars in Inflammatory Bowel Disease. *J Crohns Colitis*. 2016 Aug 29. pii: jjw153 Epub ahead of print.
5. Gulácsi L, Brodszky V, Baji P, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. *Expert Rev Clin Immunol*. 2015; 11(Suppl 1):S43–52. [PubMed: 26395836]
6. Brodszky V, Rencz F, Péntek M, et al. A budget impact model for biosimilar infliximab in Crohn's disease in Bulgaria, the Czech Republic, Hungary, Poland, Romania, and Slovakia. *Expert Rev Pharmacoecon Outcomes Res*. 2016; 16(1):119–25. [PubMed: 26162458]
7. Wolf DC. Biosimilars in Crohn's Disease and Ulcerative Colitis. *Inflamm Bowel Dis*. 2016 Apr; 22(4):994–7. [PubMed: 26933749]
8. FDA Approves Inflectra, a Biosimilar to Remicade. U.S. Food & Drug Administration; Apr 5. 2016 Web. 13 Sept. 2016

9. Gascón P, Tesch H, Verpoort K, et al. Clinical experience with Zarzio® in Europe: what have we learned? *Support Care Cancer*. 2013 Oct; 21(10):2925–32. [PubMed: 23903799]
10. Nguyen E, Weeda ER, Sobieraj DM, et al. Impact of non-medical switching on clinical and economic outcomes, resource utilization and medication-taking behavior: a systematic literature review. *Curr Med Res Opin*. 2016 Jul; 32(7):1281–90. [PubMed: 27033747]
11. Cuffari C. Diagnostic considerations in pediatric inflammatory bowel disease management. *Gastroenterology & hepatology*. 2009; 5(11):775.
12. Vernier-Massouille G1, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, Merle V, Salomez JL, Branche J, Marti R, Lerebours E, Cortot A, Gower-Rousseau C, Colombel JF. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology*. 2008 Oct; 135(4): 1106–13. [PubMed: 18692056]
13. Sieczkowska J, Jarz bicka D, Banaszkiewicz A, et al. Switching Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease. Preliminary Observations. *J Crohns Colitis*. 2016 Feb; 10(2):127–32. [PubMed: 26721942]
14. Sieczkowska J, Jarz bicka D, Meglicka M, et al. Experience with biosimilar infliximab (CT-P13) in paediatric patients with inflammatory bowel diseases. *Therap Adv Gastroenterol*. 2016 Sep; 9(5):729–35.
15. Gomollón F. Biosimilars in inflammatory bowel disease: ready for prime time? *Curr Opin Gastroenterol*. 2015 Jul; 31(4):290–5. [PubMed: 26039720]
16. de Ridder L, Waterman M, Turner D, et al. Use of Biosimilars in Paediatric Inflammatory Bowel Disease: A Position Statement of the ESPGHAN Paediatric IBD Porto Group. *J Pediatr Gastroenterol Nutr*. 2015 Oct; 61(4):503–8. [PubMed: 26154031]
17. Chingcuano F1, Segal JB1, Kim SC1, et al. Bioequivalence of Biosimilar Tumor Necrosis Factor- α Inhibitors Compared With Their Reference Biologics: A Systematic Review. *Ann Intern Med*. 2016 Oct 18; 165(8):565–574. [PubMed: 27479870]
18. Fasanmade AA, Adedokun OJ, Blank M, et al. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther*. 2011; 33:946–64. [PubMed: 21741088]
19. Frymoyer A, Piester TL, Park KT. Infliximab Dosing Strategies and Predicted Trough Exposure in Children With Crohn Disease. *Journal of Pediatric Gastroenterology and Nutrition*. 2016; 62(5): 723–727. [PubMed: 26890885]
20. Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut*. 2014 Aug; 63(8):1258–64. [PubMed: 24041539]
21. Ben-Horin S, Yavzori M1, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut*. 2016 Jul; 65(7):1132–8. [PubMed: 25897019]
22. Singh N, Rosenthal CJ, Melmed GY, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2014 Oct; 20(10):1708–13. [PubMed: 25153505]
23. American College of Rheumatology Position Statement: Biosimilars. Web [Accessed 13 Sept. 2016]

Table 1

Differences Between Generic Drugs and Biosimilars

	Generic Drugs (A=A)	Biosimilars (A A)
Production	Chemical synthesis	Complex biological process in cell lines in specialized production facilities
Sensitivity to production process change⁷	Less sensitive	Sensitive
Reproducibility⁷	Easy to establish	Difficult to establish
Interchangeability	Regulatory agencies generally designate the two as interchangeable	Due to their complexity and impurity profiles, interchangeability of biologics or biosimilars could have clinical consequences and repeated switches may increase immunogenicity
Substitution	Depending on local rules, pharmacists may be authorized or even required to substitute a generic for the original without informing the prescribing physician (automatic substitution)	Biosimilar status by regulator does not imply interchangeability