

Biosimilars in Pediatric IBD: Updated Considerations for Disease Management

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Abstract: Biologic drugs have significantly modified the pharmacological management of several chronic conditions, including inflammatory bowel diseases (IBD). By contrast, in the last two decades, biologics have been associated with increased direct medical costs. As patents for the reference drugs have expired, the development and commercialization of biosimilars through abbreviated licensing pathways represented an affordable alternative in patients fulfilling the indication for biologics. A growing body of evidence, first in adults and then in the pediatric age group too, has provided reassuring data in terms of efficacy and safety of biosimilars both in naïve patients and in those previously on reference drugs who had to switch to the biosimilar. This review summarizes the currently available evidence for biosimilar use in IBD, with a focus on pediatric IBD. The most common practical approaches to biosimilar use in the pediatric clinical settings are also discussed.

Keywords: anti-TNF, CT-P13, Crohn's disease, ulcerative colitis, inflammatory bowel disease, children

Introduction

Inflammatory bowel diseases (IBDs), which include Crohn's disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unclassified (IBD-U), are chronic, life-long diseases that affect the gastrointestinal tract and have relapsing-remitting behavior.^{1,2} Traditionally, broad-spectrum anti-inflammatory medications such as amino-salicylates and steroids, as well as immunosuppressive agents including thiopurines or methotrexate, have been used in treatment.^{3,4} Over the last few decades, the prevalence of IBD has risen exponentially in developed nations, both in children and adults, creating the opportunity for novel therapeutic approaches.^{5,6} The introduction of monoclonal antibodies directed against tumor necrosis factor- α (TNF- α), an inflammatory cytokine produced by activated macrophages, T lymphocytes, and natural killer cells, has significantly changed the management and outcome of IBDs and has become a core component of the pharmacological treatment for these diseases.^{3,4} However, these drugs are expensive and constitute a major source of healthcare spending for IBD patients.⁷ The patent on the reference anti-TNF- α infliximab (IFX) expired in 2013, allowing companies to commercialize its biosimilar. Biosimilars are a major topic of interest in terms of lowering the financial burden of certain chronic diseases, including IBD.⁸ The present study aims to provide an in-depth overview of the key aspects of biosimilar use in IBD, with an updated focus on their use in pediatric IBD.

Biologic Therapies in IBD

Biologic drugs are monoclonal antibodies that target specific cytokines implicated in the inflammatory cascade, such as TNF- α or small molecules like integrins or interleukin 12 and 23, which can be produced by living cells, blood, or plasma, or produced using recombinant DNA and controlled gene expression technologies.⁹ The binding and neutralization of TNF- α , both soluble and transmembrane, is the most recognized mechanism of action of these drugs, but other possible mechanisms of action have emerged as having a potential role in IBD (Figure 1). The majority of them have

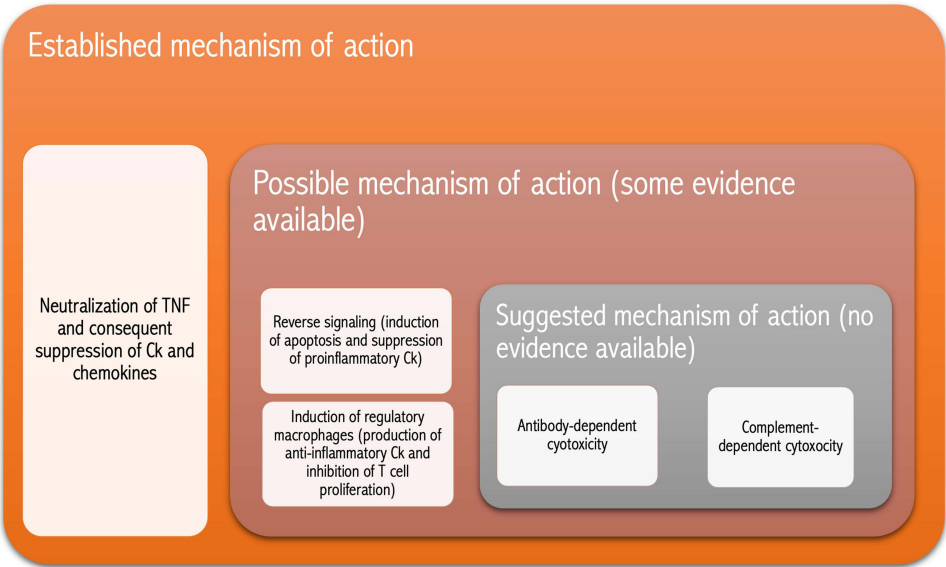


Figure 1 Key mechanisms of action of anti-TNF agents in inflammatory bowel diseases. TNF, tumor necrosis factor; Ck, cytokine.

been demonstrated to be comparable between the reference anti-TNF- α drugs (infliximab, IFX; adalimumab, ADA) and their respective first biosimilars (CT-P13 and ABP 501, respectively).¹⁰

The medical management of IBD was significantly changed by the introduction of these molecules, with the first being the anti-TNF- α IFX, which received the Food and Drug Administration (FDA) approval for CD in 1998. Since that time, other anti-TNF- α molecules, including adalimumab and golimumab, have been licensed for use in both adults and children (Table 1). In children, the anti-TNF- α reference drugs currently available to treat IBD are represented by IFX (Remicade, Janssen) and ADA (Humira, AbbVie).^{3,4} Biologic treatment is increasingly considered as a key component of the medical management of both adult and pediatric IBDs. In various clinical trials and real-world studies, its efficacy has been proven in terms of induction and maintenance of remission, steroid-sparing effects, mucosal healing, higher quality of life, and lower rates of admissions and surgery.^{11–14} In pediatric CD patients, anti-TNF- α therapy is indicated for induction and maintenance of remission in cases of severe active disease despite immunomodulator treatment (step-up therapy). In pediatric UC patients, IFX should be considered in chronically active or steroid-dependent disease, uncontrolled by mesalamine and thiopurines, for both induction and maintenance of remission.⁴ ADA could be considered for those who initially respond but then lose response or are intolerant to IFX.⁴ In new-onset patients with

Table 1 Mechanisms of Actions and Indications of EMA Approved Biologics for IBD

Name	Mechanism of Action	Adult Indications	Pediatric Indications
Infliximab	Anti-TNF- α inhibitor	UC and CD	UC and CD
Adalimumab	Anti-TNF- α inhibitor	UC and CD	UC and CD
Certolizumab	Anti-TNF- α inhibitor	CD	None
Golimumab	Anti-TNF- α inhibitor	UC	None
Vedolizumab	$\alpha 4\beta 7$ integrin inhibitor	UC and CD	None
Natalizumab	CAM $\alpha 4$ inhibitor	CD	None
Ustekinumab	IL-12 and IL-23 inhibitor	CD and UC	None

Abbreviations: CAM, cell adhesion molecule; CD, Crohn's disease; EMA, European Medicines Agency; IBD, inflammatory bowel disease; IL, interleukin; TNF- α , tumor necrosis factor- α ; UC, ulcerative colitis.

a high risk of a complicated disease course, as well as extraintestinal manifestations and/or fistulizing perianal CD, anti-TNF- α therapy is recommended as first-line treatment (top-down strategy).^{3,4,15,16} The good efficacy and safety profile of biologic drugs, along with growing confidence in their utilization, have progressively supported the top-down strategy and/or longer duration of treatment.^{3,4}

Biosimilars in the Management of Pediatric IBD

The relatively high costs of anti-TNF- α agents, combined with the impending or actual expiration of patents for several biologic drugs, has resulted in the development of “highly similar” versions of the reference product known as “biosimilars,” which are viewed as important tools for controlling costs and increasing access to biologic drugs.^{17,18} In pediatric IBD clinical practice, biosimilars may be used in some situations (Table 2).

What are Biosimilars Made of?

As defined by the FDA, a biosimilar is highly similar to an existing FDA-approved reference product in terms of safety, purity, and potency (safety and effectiveness).¹⁹ According to the World Health Organization (WHO), a biosimilar consists of a “biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product”.²⁰ The regulatory process for a biosimilar worldwide is centered on showing biosimilarity between the biosimilar and the reference drug in terms of structural and functional characteristics, biological property (bioactivity), and immunogenicity. It is worth noting that the regulatory process is not intended to “independently establish the safety and efficacy of the proposed product,”¹⁹ because it has already been proven for the originator. A four-step approach is used to perform the similarity evaluation, which includes preclinical molecular, structural, and functional analytic studies, as well as clinical pharmacokinetic, pharmacodynamic, effectiveness, safety, and immunogenicity data in humans. Comparative efficacy trials in humans may not be required if there is strong evidence that pharmacokinetic or pharmacodynamic results well match the biosimilar and the originator drug.^{19,21,22} The final approval of biosimilars is then based on shortened licensing pathways in which data “extrapolation” across all indications of the reference product is accomplished without any need for clinical studies and even though the biosimilar has not been formally analyzed in all indications or populations of the originator.^{23–25} Extrapolation of molecules in the same class with the same mechanism of action from adults to children or across indications is prevalent in clinical practice when there is insufficient supporting evidence or when clinical studies are underway.^{23–25} Nonetheless, known mechanisms of action (for example, TNF- α inhibition) in different diseases may not result in the same clinical efficacy.²⁶ As previously mentioned, the anti-TNF- α reference drugs currently available to treat pediatric IBD patients are represented by IFX and ADA. The expiry of the patent on Remicade in 2013 allowed its biosimilars to be marketed. The first biosimilar of IFX to be approved by the regulatory agencies was CT-P13, in 2013 by the European Medicine Agency (EMA) and in 2016 by the FDA.^{27,28} The approval of CT-P13 in both adult and pediatric IBD patients was based on extrapolation. The clinical testing of biosimilar IFX in rheumatologic diseases revealed evidence of comparability in terms of pharmacokinetics, safety, and efficacy between the reference and biosimilar IFX.^{29,30} CT-P13 biosimilars are marketed under a variety of

Table 2 Clinical Settings for Biosimilar Use in Pediatric IBD

Setting	Start biosimilar	<ul style="list-style-type: none"> • Anti-TNF-α naïve patients fulfilling indications for biological treatment • Patients previously treated with reference drug and stopped treatment due to remission or for reasons not related to an adverse reaction, or primary/secondary loss of response • Contraindications: allergic reactions, primary treatment failure, or loss of response due to antibodies to reference product
	Switch from reference drug to biosimilar	<ul style="list-style-type: none"> • It may be driven by cost and/or local or regional directions • Suggested in patients in clinical remission, on stable dosing, and with therapeutic drug levels • Multiple switches from reference drug to a biosimilar or between biosimilars are currently not recommended

Abbreviations: IBD, inflammatory bowel disease; TNF- α , tumor necrosis factor- α .

brand names, including Remsima (Celltrion, Incheon, South Korea) and Inflectra (Hospira, Lake Forest, IL, USA). Other biosimilars of IFX were marketed, such as SB2, also known as Flixabi (Samsung Bioepis, Incheon, Republic of Korea) and Renflexis (Merck, Kenilworth, NJ), and PF-06438179, also known as Zessly (Sandoz GmbH). There are currently seven authorized IFX biosimilars and ten approved ADA biosimilars (Table 3). To date, no biosimilars exist for the anti-integrins vedolizumab and natalizumab or the anti-interleukin 12/23 ustekinumab, while clinical trials for new biologics in the class and biosimilars to these reference drugs are ongoing.^{31,32}

Which Evidence Exists for Biosimilars in the Pediatric Setting?

Studies evaluating the efficacy and safety of biosimilars in IBD have primarily been conducted among adult patients.^{33–37} The European Crohn's and Colitis Organization (ECCO) guidelines stated that the efficacy and safety of CT-P13 are comparable with its reference product, both in patients who are naïve to IFX or have been switched to CT-P13.¹⁷ A recent randomized, multicenter, double-blind trial showed non-inferiority of CT-P13 to IFX in 220 adult patients with active CD.³³ Data on the effectiveness and safety of biosimilars in pediatric IBD is steadily increasing.³⁸ The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Pediatric IBD Porto Group stated that CT-P13 can be considered as a reliable alternative to the reference drug for remission induction and maintenance in children with IBD who are candidates for IFX treatment.²⁶ Available pediatric studies have suggested that biosimilar IFX and the reference drug have comparable efficacy, safety, and immunogenicity, even after switching (Table 4).^{39–47} However,

Table 3 Currently Approved Biosimilars for IBD in Europe and US

Reference Product	Biosimilar Product	Location and Approval Date	
		EU	US
Infliximab (Remicade)	Infliximab-dyyb (Inflectra)	October 2013	April 2016
	Infliximab (Remsima)	October 2013	-
	Infliximab (Flixabi)	May 2016	-
	Infliximab-abda (Renflexis)	-	May 2017
	Infliximab-qbtx (Ixifi)	-	December 2017
	Infliximab (Zessly)	May 2018	-
	Infliximab-axxq (Avsola)	-	December 2019
Adalimumab (Humira)	Adalimumab-atto (Amgevita in EU/ Amgevita in US)	March 2017	September 2016
	Adalimumab (Imraldi)	August 2017	-
	Adalimumab-adbm (Cyltezo)	-	August 2017
	Adalimumab (Hyrimoz)	July 2018	October 2018
	Adalimumab-flkjp (Hulio)	September 2018	July 2020
	Adalimumab (Idacio)	April 2019	-
	Adalimumab-bwwd (Hadlima)	-	July 2019
	Adalimumab-afzb (Abrilada)	-	November 2019
	Adalimumab (Amsparity)	February 2020	-
	Adalimumab-aqvh (Yusimry)	-	December 2021

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Abbreviations: EU, European Union; IBD, inflammatory bowel disease; US, United States.

Table 4 Studies Investigating the Use of CT-P13 in Pediatric IBD

Year of Publication	Design	Patients on Anti-TNF- α	Main Findings	Other Endpoints Included
2016 ⁴³	Prospective	N=39 (elected to switch)	88–57% clinical remission rate at the last follow-up assessment for CD and UC patients, respectively	Inflammatory biomarkers, adverse reactions
2017 ⁴⁰	Prospective	N=36	86% clinical response rate and 67% remission rate at the end of induction	Inflammatory biomarkers, adverse reactions
2018 ⁴¹	Prospective	N=40	67% remission rate at the end of induction	Inflammatory biomarkers, adverse reactions
2018 ⁴²	Prospective	N=257 (N=82 on biosimilar)	No significant difference in remission rates between reference and biosimilar at the end of induction	Adverse reactions, costs
2018 ⁴³	Prospective	N=74 (N=38 elected to switch)	No significant difference in remission rates between reference and biosimilar	Inflammatory biomarkers, trough levels, adverse reactions
2018 ⁴⁴	Prospective	N=33 (elected to switch)	No significant difference in remission rates within 12 months after the switch	Inflammatory biomarkers, trough levels, adverse reactions, costs
2019 ⁴⁵	Prospective	N=42 (elected to switch)	No significant difference in remission rates in comparison to baseline or at the last infusion before the switch	Inflammatory biomarkers, trough levels, adverse reactions
2020 ⁴⁶	Retrospective	N=51 (N=28 on biosimilar)	No significant difference in clinical response rates between reference and biosimilar IFX at the end of induction	Inflammatory biomarker (fecal calprotectin), trough levels, adverse reactions
2021 ⁴⁷	Prospective	N=56 (N=15 elected to switch)	Reduced PCDAI score at month 6 compared with baseline	Adverse reactions

Abbreviations: IBD, inflammatory bowel disease; TNF- α , tumor necrosis factor- α .

these studies are observational and limited by their small sample size and the varying lengths of follow-up in individual patients.

To date, no study has been done to evaluate the efficacy and safety of an ADA biosimilar in pediatric IBD. There is also no pediatric data on the use of biosimilars in children who have had a secondary loss of response or adverse event to the originator. A secondary loss of response to a biologic is a common situation in which a patient has a sufficient response when the medication is commenced but then has either a subsequent declining response (symptoms reappear before the next dose) or a full flare at any moment before the next dose.⁴⁸ An adult study investigated the cross-reactivity of antibodies to IFX (ATI) to IFX biosimilar (infliximab-dyyb) in 125 IBD patients and found that serum samples from all the patients with positive ATI to the originator cross-reacted to the biosimilar, whereas none of the patients with negative ATI showed cross-reactivity.⁴⁹ The ATI titers for the reference drug and infliximab-dyyb were thoroughly correlated and demonstrated similar functional competition for and suppression of drug binding to TNF- α .⁴⁹ It does not appear to be advisable to use a biosimilar to a reference drug in patients who have experienced a secondary loss of response or adverse reaction to the originator, as it appears unlikely that patients with non-response to the originator drug benefit from a biosimilar trial, and an increased risk of complications mediated by ATI may occur. On the other hand, biosimilars can be subjected to the same established tests for therapeutic drug monitoring and ATI as the reference drug.

Which are the Main Concerns Regarding the Use of Biosimilars for Pediatric IBD?

The major concern in the pediatric population is the issue of interchangeability and automatic or non-medical switching. “Automatic therapeutic substitution” refers to the automatic substitution of a prescribed medicine for an equivalent one, usually without prior communication with the prescriber.⁵⁰ “Non-medical switching” refers to the practice of switching a prescribed drug to a comparable drug, which is typically done by insurance companies and is often motivated by financial benefit.⁵¹ A recent systematic review looked at the non-medical switching of originator IFX to an IFX biosimilar in adult

IBD patients. They were included 44 different studies in total, including three randomized controlled trials, 40 observational trials, and one case series.⁵² The authors concluded that non-medical switching from originator to biosimilar was safe and had no negative impact on efficacy, safety, or immunogenicity. However, only three small randomized controlled trials were included in this analysis, with observational cohort studies predominating. The American College of Rheumatology's position statement on biosimilars stated that safety in adults does not guarantee safety in children.⁵³ A recent research study expressed worry about the absence of long-term data on the immunogenicity of biosimilars in pediatric IBD.⁵⁴ The authors urge that the FDA not presume interchangeability is achievable in this cohort until long-term trial evidence is available. The ESPGHAN Pediatric IBD Porto Group issued its first position statement on the use of biosimilars in pediatric IBD in 2015.⁵⁵ The authors cautioned against extrapolating clinical results from adult studies to children with IBD.⁵⁶ The following were the key points from this statement: (i) physicians' willingness to accept FDA approval of biosimilars based on extrapolation; (ii) physicians' concerns about immunogenicity and loss of response when switching from a reference biologic to a biosimilar and inversely; (iii) the need for the FDA to collaborate with interested parties (insurance and patients) to try to educate physicians and patients about biosimilars; and (iv) shared decision-making and transparency between the FDA and interested parties (insurance and patients). Following the release of new safety data, an updated ESPGHAN position statement in 2019 claimed that switching from the originator IFX to CT-P13 was safe and well-tolerated in children, better if in clinical remission and after at least three induction infusions.²⁶ Importantly, multiple switches between the originator and biosimilars or between different biosimilars are not yet recommended in pediatric patients with IBD due to a lack of sufficient interchangeability data.²⁶ IBD experts also recommended additional studies in this population of patients, including long-term follow-up and post-marketing surveillance of the efficacy, safety, and immunogenicity of biosimilars if delivered to young patients.²⁶

Knowledge on Biosimilar Use

The state of knowledge on biosimilar experiences in IBD is limited. In 2013, a survey by ECCO showed that a minority of IBD experts were aware and confident about the benefits and issues of biosimilars. In a later survey promoted by ECCO, they were reported fewer concerns and more confidence about biosimilar use in clinical practice.^{57,58} A more recent web survey revealed that pediatric IBD experts in Italy have a good level of knowledge on biosimilar use advantages, disadvantages, costs, and traceability.⁵⁹ The increasing confidence in biosimilar use may be linked to the growing post-marketing studies and the dissemination of real-world data. Patient education is also an important aspect of the acceptance of biosimilar treatment. Morris et al⁶⁰ have recently demonstrated the successful application of a quality improvement approach to boost biosimilar use from 1% to 96% in intravenous anti-TNF- α naïve pediatric patients. This was achieved through substantial provider and patient education and expediting the prior authorization process for all inpatient and outpatient biosimilar starters.⁶⁰ Patient and provider education is even more essential when considering a switch from the originator to its biosimilar because of the existence of the so-called "nocebo effect".⁶¹ The "nocebo effect" arises when the expectation of side effects leads to the occurrence of those symptoms, which can occur when patients move from brand-name to generic medications.⁶¹ As a result, generic drugs are frequently associated with significantly higher patient reporting of side effects and treatment non-adherence. This "nocebo effect" may also occur in patients who switch from biologic drugs to biosimilars.⁶² Physicians can help to reduce the "nocebo effect" with biosimilars through (i) clear communication and positive framing (for instance, "the great majority of patients have a good tolerance to this treatment"), (ii) an authorized concealment approach (for instance, for milder side effects, or asking whether they would prefer to be informed about these side effects or not), and (iii) involvement of (older) patients in the decision-making process.⁶¹ The effects of positive framing have been seen in a study enrolling patients receiving the opioid painkiller remifentanyl, where positive treatment expectations significantly boosted remifentanyl's analgesic effectiveness.⁶³ However, the insurance demand to switch a patient from the originator to its biosimilar often comes with insufficient notification to allow for information and reassurance.⁶¹

Impact of Biosimilars on Costs

The basic principle underlying the development of biosimilars is healthcare systems' expectation that these molecules will reduce the financial burden of biologic therapy, hence boosting access to these treatments and allowing for more

intensive treatment regimens when clinically indicated.⁶⁴ Although biosimilar prices vary across Europe,⁶⁵ they are at least 15–45% less expensive than the originator biologics.⁶⁶ The potential for cost reductions varies between biologic classes depending on sales, competition, and the timing of biosimilar launches. Together with monoclonal antibody antineoplastics and insulin, they account for more than 60% of the expected savings (Figure 2).⁶⁷ The price evolution of off-patent biologics and biosimilars is rapid across Europe, with reductions on certain biosimilars reaching up to 80%.⁶⁵ In Europe, most biologics are off-patent and biosimilars are available for clinical use. The extrapolation process, which minimizes the number of clinical studies required for biosimilar approval and hence lowers costs, is primarily responsible for the cost savings associated with the usage of biosimilars. A study by Jha et al⁶⁸ estimated a 1-year cumulative cost savings for the usage of Remsima in six autoimmune indications (including CD and UC) for five countries (Belgium, Germany, Italy, Netherlands, UK), projecting an annual cost saving of €2.89 million in Belgium (10% discount scenario) to €33.80 million in Germany (30% discount scenario). Some pediatric studies reported a comparison of costs between reference IFX and CT-P13.^{41,42,44} Overall, considerable cost reductions from using biosimilar IFX based on estimated and averaged local procurement rates were reported. Richmond et al⁴¹ reported an average 38% cost reduction per vial from the originator to the biosimilar Remsima over 12 weeks and around £47,800 (€57,000) of savings for the total number of infusions. In another study, the cost-saving for the total number of infusions was around £875 000 (€998 526) over a year.⁴² Cost savings from biosimilars can be used to increase patient access to biologic therapy. The hypothetical budget impact study by Jha et al⁶⁸ has computed that 250 to 2602 additional patients can be treated with the money saved from biosimilars.

Conclusion

Available pediatric studies confirm that the IFX biosimilar is as effective and safe as the reference drug, whilst simultaneously reducing the cost of treating IBD versus the originator. Cost reduction is considered the most important advantage of biosimilars. By lowering overall treatment costs while maintaining a high level of patient care, the use of biosimilars represents a chance to drastically cut healthcare costs and enhance patient access to biologic therapies. In recent years, biosimilars of anti-TNF- α have been increasingly used, even in pediatrics. Most IBD experts have reported

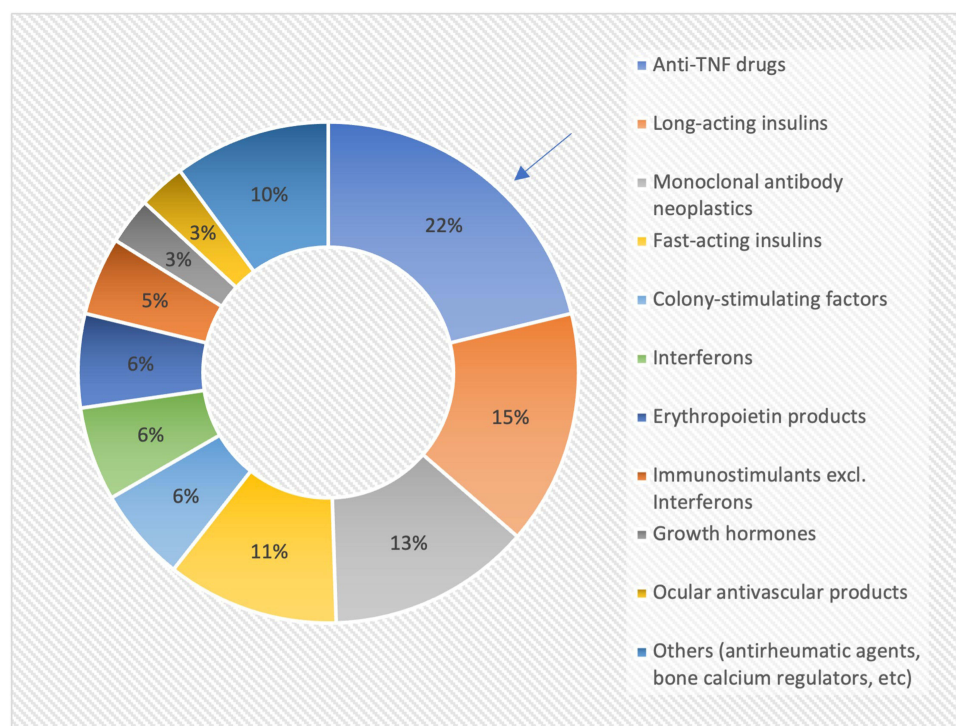


Figure 2 Potential cost reductions across biologic classes.

increasing awareness of the advantages, efficacy, and safety of biosimilars in pediatric IBD. Clear communication, proper education, and patient reassurance appear to be associated with a reduced “nocebo effect” and are therefore needed to overcome the remaining barriers to effective switching in both pediatric and adult IBD patients. Additionally, currently available studies do not report any major issues with the immunogenicity of biosimilars. Further prospective, randomized-controlled trials are needed to support the validity of these studies, including the biosimilars of ADA for which data are currently lacking.

Abbreviations

ADA, adalimumab; ATI, antibodies to infliximab; CD, Crohn’s disease; ECCO, European Crohn’s and Colitis Organization; EMA, European Medicine Agency; FDA, Food and Drug Administration; IBD-U, inflammatory bowel disease unclassified; IBD, inflammatory bowel disease; IFX, infliximab; SIGENP, Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition; TNF- α , tumor necrosis factor- α ; UC, ulcerative colitis; WHO, World Health Organization.

Disclosure

The authors report no conflicts of interest in this work.

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