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Commentary

Biosimilar Interchangeability and Emerging Treatment Strategies for Inflammatory Bowel Diseases: A Commentary

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Abstract: This commentary summarizes a collection of key references published within the last ten years, and identifies pharmacologic research directions to improve treatment access and success through greater biosimilar or "follow-on" biologic utilization combined with other targeted small molecule agents that possess unique pathophysiologic mechanisms for inflammatory bowel diseases (IBD) in adult and pediatric patients. Since they are not identical to the originator or reference biologic agent, all biosimilars are not generically equivalent. However, in the US and other countries, they are considered therapeutically interchangeable if the manufacturer has demonstrated no clinically meaningful differences from the reference product. Comparisons of different clinical initiation and switching scenarios are discussed with reference to interchangeability, immunogenicity, nocebo effect, cost effectiveness, and time courses for discontinuation rates.

Keywords: antibody; biologic; biosimilar; Crohn disease; guideline; inflammatory bowel disease; molecule; small; monitoring; monoclonal; nocebo; pediatric; switching; drug; ulcerative colitis

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1. Introduction

The most commonly used reference anti-TNF-α biologic products for moderate to severe Crohn Disease (CD) and ulcerative colitis (UC) include adalimumab and infliximab with several biosimilars on the market or in development including adalimumab-adaz, -adbm, -afzb, -atto, -bwwd, and -fkjp; and infliximab-dyyb, -abda, -axxq, and -qbtx, respectively. Three biosimilars for infliximab have been marketed in the US in the past five years. Six biosimilars for adalimumab have been approved for marketing since 2016, and are expected to be marketed somewhere in the world in 2023 [1]. No biosimilar products currently exist for the anti-integrins, vedolizumab and natalizumab, or for the anti-interleukin 12/23, ustekinumab, although clinical trials are underway both for other biologics within the class and biosimilars to these reference products [2,3].

While guidelines have been developed for the treatment of CD and UC populations, questions remain regarding the appropriate selection, monitoring, and switching rules for both biologic and biosimilar use in individual patients [4–7]. Based on disease severity at initial presentation, patients are started often on a biologic or combinations of biologics (i.e., agents with different mechanisms of action, such as combining an anti-TNF-α and an anti-integrin or anti-IL 12/23) instead of steroids and immunomodulators, especially in children [8–11]. In fact, higher rates of morbidity and mortality have been observed in patients treated with prolonged steroids compared to biologics [12]. Because of the expense of biologics and their negative cost-benefit calculations compared to surgical intervention, biosimilars have been touted to improve patient access through a reduction in the clinical, economic, and humanistic costs of treatment [13–15]. Moreover, because treatment success with anti-TNF-α-based ranges from 33 to 50% in the long term, research to increase the array of pharmacotherapy choices, including re-purposing existing anti-inflammatory agents, is ongoing. This commentary reviews key citations published within the last ten years, and identifies pharmacologic research directions for the improved utilization of biosimilars and other potential combination targeted non-biologic therapies.

2. Switching to Biosimilars

While there is ample evidence to assert that biosimilars for infliximab and adalimumab are comparable to the reference product in moderate to severe IBD [8,16–39], there are no head-to-head comparisons between them. This lack of scientific evidence has caused some to question whether it is appropriate to extrapolate the indications for the reference product to the biosimilar, and concerns related to reverse signaling, induction of regulatory macrophages, and antibody-dependent cellular cytotoxicity have been raised in addition to pharmacokinetic differences, especially with respect to systemic clearance [40–43]. While clinical response rates in the short and long-term have been shown to be comparable, switching patients to biosimilars needs to be individualized and programmatic [7]. In the case of infliximab-dyyb, two efficacy trials and three clinical trials were conducted in rheumatoid patients and summarized in a recent report. The efficacy trials showed no significant differences in the relevant functional characteristics or in the adverse event profiles. The clinical trials displayed no differences in Cmax or the area under the curve (AUC). These results allowed US regulators to extrapolate data to support indications expanded into IBD [44]. Efforts to optimize therapy for preserving colonic integrity using combinations of agents, many of which will act topically within the bowel lumen, will drive future research programs.

There are three scenarios where switching medications occur: (1) biosimilar instead of biologic in treatment-naïve patients; (2) biologic to biosimilar switch; and (3) biosimilar to biologic in the same class [8,34–39,45]. There is evidence of a slow uptake of biosimilar use due to lack of third-party insurance coverage for multiple reasons (including contractual reference product rebates to pharmacy benefit managers), patent disputes in court related to approved indications, and reference product manufacturer market strategies which limit use [46,47]. According to the Biosimilars Council, a division of the Association for Accessible Medicines, the use of biosimilars could result in $54B USD savings over the next 10 years, and improve access to biosimilars for an additional 1.2 M patients in the US alone [48]. Table 1 summarizes biosimilars that have been approved for use in the US by the Food and Drug Administration.

Table 1. Biosimilars approved and launched in the US for CD and UC.

Reference Biologic	Biosimilar	Approved	Launched
Enbrel (etanercept)	Erelzi (etanercept-szzs)	August 2016	
	Eticovo (etanercept-ykro)	April 2019	
Humira (adalimumab)	Amjevita (adalimumab-atto)	September 2016	
	Cyltezo (adalimumab-adbm)	September 2016	
	Hyrimoz (adalimumab-adaz)	October 2018	
	Hadlima (adalimumab-bwwd)	July 2019	
	Abrilada (adalimumab-afzb)	November 2019	
	Hulio (adalimumab-fkjp)	July 2020	
Remicade (infliximab)	Inflectra (infliximab-dyyb)	April 2016	November 2016
	Renflexis (infliximab-abda)	April 2017	July 2017
	Ixifi (infliximab-qbtx)	December 2017	
	Avsola (infliximab-axxq)	December 2019	

3. Combining Biosimilars with Non-Biologic Small Molecules

Combinations of anti-TNF-α biosimilars with anti-adhesion, anti-integrin, and interleukin 12/23 antagonists (more common in children than in adults) as well as Janus kinase inhibitors (tofacitinib, peficitinib, upadacitinib, filgotinib), sphingosine-1-phosphate [S1P] receptor modulators (ozanimod, etrasimod), phosphodiesterase-4 inhibitors (apremilast), selective histone deacetylase 3 inhibitors (givinostat, vorinostat) and/or substitutions of phosphatidylcholine (LT-02) (i.e., agents with different mechanisms of action) are on research agendas in various phases and treatment horizons [49–56]. Brief research reports on the use of small molecules and combinations with either the reference product or the

biosimilar for potential treatment are nascent and based only on clinical experience. Therapy may be optimized through personalized approaches based on disease severity, lesion location, and phenotypes in addition to the use of therapeutic and clinical targets [57–59]. Future research should quantify the relative contribution of each of these choices to overall treatment success, as a recent economic study suggests that tofacitinib may be more cost-effective than any injectable biologic [60]. Table 2 summarizes the non-biological small molecules under current investigation for CD and UC.

Table 2. Non-biological agents with potential for therapeutic use in CD and UC.

Therapeutic Class or Mechanism of Action	Investigational Agent
Janus kinase (JAK) inhibitors	Tofacitinib Peficitinib Upadacitinib
Sphingosine-1-phosphate (S1P) receptor modulators	Ozanimod Etrasimod
Phosphodiesterase 4 (PDE-4) inhibitors	Apremilast
Histone deacetylase (HDAC) inhibitors	Ginvinostat Vorinostat
Mucoprotective substitutions of phosphatidylcholine	Phosphotidylcholine (modified release form)

Many of these newer non-biologic therapies are under investigation, primarily in adults with IBD, and several (tofacitinib, upadacitinib, ozanimod, apremilast, vorinostat) have been approved for other indications for them. While approved recently in the European Union and Japan, the US FDA has rejected filgotinib's application for use in adult rheumatoid arthritis, citing concerns about the overall risk-to-benefit profile at the 200 mg dose. However, with the increasing prevalence of CD and UC in children, coupled with the up to 50% durability of remission, studies which validate safety and effectiveness of non-biologics in pediatric IBD populations are needed. In addition to solid oral dosage forms, oral liquid formulations appropriate for pediatrics are in development or are on the market. For example, tofacitinib is available in a mass-produced 1 mg/mL oral liquid, and is indicated in children two years and older for juvenile rheumatoid arthritis [61]. Givinostat received rare pediatric disease designation for Duchenne muscular dystrophy, and the manufacturer has included a 10 mg/mL oral suspension formulation into the clinical protocol. A vorinostat 50 mg/mL compounded oral suspension has been reported in the literature based on a Children's Oncology Group report for use in refractory solid tumors [62]. While none of these non-biologics have a labeled pediatric indication for either CD or UC currently, manufacturers would be prudent to include pediatric-friendly dosage forms, such as oral liquids, minitablets, and orally-disintegrating tablets, in future product submissions.

4. Psychosocial Aspects and the Nocebo Effect

Most guidelines agree that it is important to assess mental health disorders and stress, not as contributors to IBD etiology, but as influencers of its course [63]. The gut–brain connection between enhanced intestinal autophagy and psychosocial stress has been posited to modulate gut microbiota and inflammation [64]. Although psychosocial factors such as anxiety, depression, and perceived stress appear to play a significant role in IBD pain [65], mental illness often precedes the development of IBD [66–68]. Moreover, non-psychiatric morbidities, as well as significant physical trauma experienced early in life, can increase the risk of behavioral comorbidities in IBD. The early recognition and treatment of depression and other psychosocial burdens through enhancing self-efficacy and locus of control within integrated multidisciplinary care pathways is essential, and is likely to improve the overall health and wellbeing of patients in the general course of IBD [69]. While a number of pharmacologic agents, such as selective serotonin reuptake inhibitors, tricyclic anti-depressants, and neuromodulators, have been employed to reduce

psychological stress, studies of these agents in IBD are lacking. Multidisciplinary care teams which address the biopsychosocial impacts of IBD on patients' lives seem to provide better results to improve patient care and quality of life [70].

One prominent non-pharmacological effect seen in patients that are candidates for a switch from a reference product to a biosimilar is the so-called "nocebo effect" [71–74]. This effect has been observed in adult and pediatric patients and their parents/caregivers, and the response may be more pronounced in patients who do not want to switch to the biosimilar. To minimize this effect, healthcare provider–patient communication should be based mainly on the clarification of what biosimilarity means, and should stress the data on efficacy and safety of biosimilar drugs rather than expense reduction.

The nocebo effect may have an important impact on an increased discontinuation rate after switching in the absence of patient symptomatology [73,75]. Real-world studies of anti-TNF-α agents show higher discontinuation rates in patients switched to biosimilars for non-medical reasons than in historical cohorts maintained on innovators [8,71,76]. In addition, there is evidence that the naming convention for biosimilars affects patients' perception of interchangeability. The four-letter suffix attached to the reference product name, unique to the US market, differentiates the biosimilar. Now, this practice has been applied to all new biologics [77] which may further confuse the issue for providers and patients alike.

5. Additional Considerations for Pediatric Patients

The prevalence of pediatric-onset IBD has risen in the past two decades, and most patients with moderate to severe IBD will require dose escalation within the first year of treatment [78]. Consensus-based guidelines suggest that in children previously naïve to anti-TNF-α agents, either infliximab or adalimumab can be initiated as a "top-down" strategy in CD and for steroid-dependency or chronic disease activity in UC. Infliximab dose escalation (i.e., to 10 mg/kg or interval shortening to every 6 weeks) and switching to adalimumab or golimumab have been suggested in those with a loss of response or intolerance. Several recent observational studies in pediatric patients confirmed the results of randomized trials conducted in adult populations (that is, there were no differences in the pharmacokinetic, immunogenic, safety, or effectiveness when switching children with IBD) [23,79,80]. Combination with immunomodulators and/or other biologics may lower the risk of antibody formation [81]. As mentioned earlier, oral liquid formulations containing child-appropriate excipients and vehicles need to be a part of the research and development for small molecule non-biologic agents.

Developmental delays in the attainment of age-appropriate weight and height affects between 40–60% of children with IBD, with weight loss, reduced bone mineral density, and delayed onset of puberty as the most important concerns [82]. Vitamin D3 deficiency and osteoporosis may occur in over 75% and 25% of patients, respectively, and decreased levels of insulin-like growth factor and testosterone are seen as disease severity progresses [83]. Used for many years to reduce bone turnover in childhood cancer, trials of zoledronic acid infusions and, to some degree, denosumab, are ongoing to validate their effectiveness in addressing secondary osteoporosis precipitated by chronic steroid use and malnutrition in these children [84,85].

6. Summary

Biosimilar development and utilization, as well as non-biologic oral agents with unique pathological targets, will continue to dominate efforts to improve patient access and reduce the overall cost of care as non-surgical treatments for CD and UC in adults and children. Therapeutic drug monitoring, combined with inflammatory biomarkers, have become the standard of care to assess effectiveness. New combinations of agents with different mechanisms of action, in addition to immunomodulators, will drive regimen optimization (especially those acting locally within the bowel lumen). Future research should quantify the relative contribution of each of these choices to overall treatment

success. Patient and provider education and positive framing of non-medical switching strategies needs to be incorporated into organized programs for both adult and pediatric populations, including parents and caregivers, so that the negative attribution towards biosimilar initiation or switching is minimized. Psychosocial issues often impact the development and progress of IBD, and are best approached through a multidisciplinary approach. Early attention to growth and development in children is paramount to optimal physical and psychological well-being. Research to elucidate pharmacotherapies of choice for anxiety, depression, and pain is needed in children and adults. The development of non-biologic small molecules that can be absorbed orally or affect the colonic lumen topically will be vital for the achievement of sustained clinical remission in adults and children. Oral liquid formulations for children and those that cannot swallow oral solids is important for continued success in treating vulnerable patient populations.

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