

Biosimilars: Review of current applications, obstacles, and their future in medicine

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Abstract

Biosimilars are a growing drug class designed to be used interchangeably with biologics. Biologics are created in living cells and are typically large, complex proteins that may have a variety of uses. Within the field of gastroenterology alone, biologics are used to treat inflammatory bowel diseases, cancers, and endocrine disorders. While biologics have proven to be effective in treating or managing many diseases, patient access is often limited by high costs. The development of biosimilars is an attempt to reduce treatment costs. Biosimilars must be nearly identical to their reference biologics in terms of efficacy, side effect risk profile, and immunogenicity. Although the manufacturing process still involves production within living cells, biosimilars undergo fewer clinical trials than do their reference biologics. This ultimately reduces the cost of production and the cost of the biosimilar drug compared to its reference biologic. Currently, seven biosimilars have been approved by the United States Food and Drug Administration (FDA) for use in Crohn's disease, ulcerative colitis, and colorectal cancer. There are other biologics involved in treating gastroenterologic diseases for which there are no FDA approved biosimilars. Although biosimilars have the potential to reduce healthcare costs in chronic disease management, they face challenges in establishing a significant market share. Physician comfort in prescribing reference biologics instead of biosimilars and patient reluctance to switch from a biologic to a biosimilar are two common contributing factors to biosimilars' slow increase in use. More time will be needed for biosimilars to establish a larger and more consistent market share compared to their reference biologics. Additional da-

ta confirming the safety and efficacy of biosimilars, increased number of available biosimilars, and further cost reduction of biosimilars will all be necessary to improve physician confidence in biosimilars and patient comfort with biosimilars.

Key words: Biosimilars; Inflammatory bowel disease; Biologics; Inflammation; Drug class

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Core tip: This study elucidates the unique properties of biosimilars as a drug class and their effectiveness for inflammatory bowel conditions in lieu of first line biologics.

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INTRODUCTION

Therapeutic proteins, also known as biologics, are pharmaceutical agents created in a laboratory setting to mimic the structure of naturally produced proteins in the body. They may either mimic the natural protein's function or antagonize the function of the natural protein. These drugs are produced in living cellular systems, and they have proven to be effective treatment for many diseases including rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel diseases^[1]. Unfortunately, the high costs of therapeutic protein place a heavy financial burden on the healthcare system and limit the number of patients that are able to be covered. For example, monoclonal antibody therapy - one type of therapeutic protein - is projected to reach \$125 billion in global sales by 2020^[2]. As patents on biologic drugs expired, biosimilar drugs were developed and are helping to address this growing issue. The United States Food and Drug Administration (FDA) defines a biosimilar as "a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." These drugs are still created using living cells, but the synthesis pathway of the reference biologic is proprietary. Biosimilar developers instead analyze the final biologic and attempt to reverse engineer a feasible synthesis pathway.

The Affordable Care Act created a more efficient licensing pathway for these biosimilar drugs provided it can be proven that the biosimilar drug is not significantly different from its reference product in terms of effectiveness or safety. The process for biosimilar approval in Europe was established prior to that of the United

States. The European Medicine Agency (EMA) and the associated Committee for Medicinal Products for Human Use (CHMP) evaluate data gathered by pharmaceutical companies seeking approval for prospective biosimilars^[3]. In both the United States and in Europe, biosimilar drugs must undergo structural analyses, functional assays, animal studies, and finally clinical studies. Throughout each step of the abbreviated approval process the biosimilar drug is compared to its reference biologic and assessed for similarity^[4]. In contrast, a standard biological product undergoes a more traditional set of trials involving laboratory and animal testing to determine safety in humans followed by clinical trials.

A study in Europe examining the acceptance of biosimilars found that very few patients were willing to switch to a biosimilar if they were already taking a biologic. Increases in prevalence of biosimilar treatment are driven primarily by new patients that start on a biosimilar first. Even in a new patient population, significant price reductions, sometimes 50% or more, must be in place for physicians to consider prescribing a biosimilar^[5]. Market shares for biosimilars are increasing slowly. For example, the filgrastim biosimilar Zarxio held 15% of the United States filgrastim market in 2016 and the infliximab biosimilar Inflectra held less than 10% of the infliximab market (United States biosimilar market). Gastroenterology has many potential benefits from biosimilars in terms of increasing treatment access while reducing treatment costs. Inflammatory bowel diseases and gastrointestinal cancers utilize biologics regularly. Within the endocrinological function of gastroenterology, biosimilar insulin is also an area of active investigation as insulin costs and prevalence of diabetes both continue to increase.

INFLAMMATORY BOWEL DISEASES

The anti-tumor necrosis factor alpha (TNF- α) biologic infliximab is an effective treatment for inflammatory bowel diseases. The PLANETAS study, a phase I study, established biosimilar infliximab, CT-P13, as having equivalent pharmacokinetics with comparable safety and efficacy profiles to its reference infliximab while the PLANETRA study, a phase III study, found that CT-P13 had equivalent efficacy to reference infliximab after 30 wk of treatment^[6,7]. The patient populations in these studies, however, were patients with ankylosing spondylitis and rheumatoid arthritis. The PROSIT-BIO cohort study specifically investigated the safety and efficacy of CT-P13 in patients with ulcerative colitis and Crohn's disease. The data showed comparable results to those of similar studies with reference infliximab, but the study did not directly compare the biosimilar with its reference biologic^[8]. A prospective study of 210 patients also found that CT-P13 is effective in inducing clinical remission in Crohn's disease and ulcerative colitis but noted decreased response to treatment and increased risk of allergic

reactions in those previously treated with reference infliximab^[9]. A study of 96 patients comparing the efficacy of infliximab compared to biosimilar CT-P13 in maintaining remission in inflammatory bowel diseases found similar long-term outcomes and safety between the two treatment groups^[10]. Additionally, a study on CT-P13 in pediatric Crohn's disease reported remission after three doses in 24 of 36 patients and clinical response in 31 of 36^[11]. CT-P13 is currently marketed as Remsima™ and Inflectra™.

A double-blind, parallel-group study comparing another infliximab biosimilar, SB2, with reference infliximab in 584 patients with rheumatoid arthritis demonstrated similar safety, efficacy, immunogenicity, and pharmacokinetics at weeks 30 and 54^[12,13]. SB2 is currently marketed as Flixabi® and approved for treatment of multiple chronic inflammatory diseases including the treatment of Crohn's disease and ulcerative colitis in patients between the ages of 6 and 17.

A 2016 study examined survey responses of inflammatory bowel disease specialists regarding biosimilars. Out of 118 responses, only 19.5% were not confident with using biosimilars, and 44.4% believed the biosimilar to be interchangeable with the reference biologic. The primary perceived benefit reported was cost reduction, and the main concern was immunogenicity. A prospective multicenter study done in 2015 similarly elucidates a positive response profile of biosimilars, and further illustrates safety regarding immunogenicity^[9]. The overall positive outcomes when comparing biosimilar infliximab to its reference biologic have improved physicians' attitudes towards biosimilars in the context of treating inflammatory bowel disease.

INTERCHANGEABILITY

In addition to biosimilars, there exist "interchangeable" products. In order for a biosimilar to be considered interchangeable, it must undergo additional testing. The biosimilar in question must have equal clinical efficacy as its reference product and there must be no changes in safety or efficacy when switching between the biosimilar and its reference product. The purpose of a biosimilar being proven to be interchangeable is that the biosimilar may then be substituted in place of its reference biologic without physician involvement^[14]. The risks and concerns involved with this substitution are that switching from a reference biologic to a biosimilar may have reduced efficacy or increased immunogenicity. Data that display similar efficacy, safety profiles, and immunogenicity between a biosimilar and its reference product are not sufficient to determine the effects of switching between the products. While the Canadian Agency for Drugs and Technologies in Health (CADTH) has reported equivalent safety and efficacy in switching from reference biologic to biosimilar in treatment of rheumatologic diseases, the one cohort study examining interchangeability in treatme-

nt of Crohn's disease and ulcerative colitis had a sample size of eight patients at week 48 following the change to biosimilar infliximab^[15]. Six of the eight patients continued in remission, but the small sample size causes difficulty in extrapolating the findings to the general population^[16]. The NOR-SWITCH trial examined the safety and efficacy of switching from reference infliximab to a biosimilar infliximab compared to keeping patients on the reference infliximab. The study was constructed as a non-inferiority study and included patients with six different chronic inflammatory diseases. The trial concluded that switching to biosimilar infliximab was not inferior to continuing reference infliximab^[17]. While the study provides a necessary foundation for interchangeability studies, it did not control for variables within the patient population and it did not study each disease individually. A prospective study of 133 patients with inflammatory bowel disease measured antibodies to infliximab as well as C-reactive protein and erythrocyte sedimentation rate in context of disease activity scores to obtain numerical measurements of interchangeability. It found no differences between reference infliximab and biosimilar infliximab, but it also did not directly compare to continuing patients on reference infliximab^[18]. A study investigating efficacy, pharmacokinetics, and immunogenicity when switching from reference infliximab to a biosimilar infliximab in pediatric patients with inflammatory bowel disease demonstrated no significant differences compared to continuing therapy with reference infliximab^[19]. Additional studies focused on specific diseases and patient populations in the future will continue to advance biosimilars to interchangeable products.

LIMITATIONS

The main concerns raised regarding biosimilars are immunogenicity, efficacy, adverse effects when switching from a biologic to a biosimilar, and possible long-term effects^[20]. This issue has been well documented in two recent 2017 trials, comparing the implications of switching from an infliximab innovator to biosimilar, over the span of 1 year in IBD patients. With its results showing enhanced clinical effectiveness and an appropriated side effect profile^[16,18]. FDA approval addresses questions regarding immunogenicity and efficacy. Although the approval process for biosimilars is expedited, potential biosimilars must prove equivalent efficacy without additional immunogenicity or side effects^[21,22]. In terms of switching between products, studies have shown that switching between two structurally different proteins that have a similar intended effect is not associated with increased risk for adverse events^[23]. Thus, switching between proteins that share a nearly identical structure should also present no additional risk. The concern that has yet to be addressed is the potential long-term effects. As all other characteristics of biosimilars are comparable to biologics, it seems unlikely that long term ris-

Table 1 Biologics approved for the management of gastrointestinal inflammatory and oncological conditions

Condition/disease	Biologic	FDA approved biosimilar
Crohn's disease	Infliximab (anti-TNF α)	Remsima, Inflectra, Renflexis, Flixabi
	Adalimumab (anti-TNF α)	Amjevita, Cyltezo
	Certolizumab (anti-TNF α)	NA
	Vedolizumab (anti- α 4-integrin)	NA
	Natalizumab (anti- α 4-integrin)	NA
	Ustekinumab (anti-IL-antibody)	NA
Ulcerative colitis	Infliximab (anti-TNF α)	Remsima, Inflectra, Renflexis, Flixabi
	Adalimumab (anti-TNF α)	Amjevita, Cyltezo
	Golimumab (anti-TNF α)	NA
Colorectal cancer	Bevacizumab (anti-VEGF)	Mvasi
	Ramucirumab (anti-VEGF)	NA
	Cetuximab (anti-EGFR)	NA
	Pantimumab (anti-EGFR)	NA
	Trastuzumab (anti-HER2/neu)	Ogivri

VEGF: Vascular endothelial growth factor; IL: Interleukin; EGFR: Epidermal growth factor receptor; NA: An FDA approved biosimilar is not available.

ks would be substantially different. However, only more time and more data will be able to answer with certainty. The main limitation of biosimilars is patient and physician acceptance with many patients preferring to stay on biologics and physicians preferring to prescribe biologics.

FUTURE DIRECTIONS

Continuing to manufacture new biosimilars as patents on biologics expire will be the primary means of increasing biosimilar prevalence. Many biologics used to treat inflammatory bowel disease or gastrointestinal cancers do not have corresponding biosimilars at this time (Table 1). Overall acceptance of biosimilars of patients will depend on comfort of physicians educating patients and prescribing biosimilars. Physician comfort will depend on additional clinical trials and increasing the amount of available data. Improving insurance coverage of new biosimilars will also increase patient access to biosimilars. Insurance companies are more comfortable covering biosimilars that have been on the market longer, but as more biosimilars become available it is possible that they will provide coverage even for new biosimilars.

DISCUSSION

Currently there are seven biosimilars approved in the United States. The most recent, biosimilar bevacizumab, was approved in September, 2017. In the case of infliximab and its biosimilar, it is likely that greater price differences will have to be seen before physicians will be convinced to switch away from the reference product. The average cost per year for infliximab treatment as of 2012 was \$24000^[22]. As of 2016, there was only a 15% price difference between infliximab and its biosimilar. The reluctance of both patients and physicians to switch to a biosimilar may imply that increases in market shares for biosimilars will be a matter of time as more biologic-naïve patients are placed on biosimilars to begin their tr-

eatment regimen. The reluctance of physicians also may affect clinical trials and even patient outcomes through the nocebo effect, which has been documented as causing generalized side effects despite a lack of plausible pharmacological mechanism based on the drug itself or side effects more severe than observed when medication use is blinded^[24,25]. The way in which a physician discusses the effects of a drug with a patient influence the possibility of a nocebo effect. As such, patients receiving biosimilars from physicians who are reluctant to prescribe them may experience more adverse events or decreased treatment efficacy.

Additional studies will also be needed to further examine interchangeability of biologics and biosimilars. The case of switching from a biosimilar to a biologic if the biosimilar does not produce significant clinical improvement should also be explored, especially considering the number of biologic-naïve patients who may be started on a biosimilar rather than biologic therapy. However, as illustrated above, numerous studies have shown to carry similar efficacy when switching from an original biologic agent to a biosimilar. Biosimilars have great potential to improve access to disease modifying therapies over a wide range of chronic illnesses, extending even to some cancers. The more cost-efficient manufacturing process of biosimilars may also open the way to greater experimentation with pharmacological therapies.

CONCLUSION

Biosimilars have the potential to improve patient access to high level drug therapies as well as alleviate the financial strain that chronic illnesses place upon healthcare systems worldwide. To accomplish this, however, physicians will need to be more comfortable prescribing biosimilars instead of their reference products and the prices of biosimilars will need to be significantly lower than their biological counterparts.

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