Biosimilars are biologic products that are highly similar to a previously approved reference (or originator) biologic drug in terms of safety, purity, and potency (efficacy). These medications are increasingly being approved by global regulatory agencies in the hopes of reducing treatment costs. To date, six biosimilars in the United States have been approved for the treatment of inflammatory bowel disease (IBD). Despite their approval by regulatory bodies and several years-worth of ‘real world’ evidence supporting their use, this class of medications remain somewhat unfamiliar to many clinicians and patients. This review aims to answer common questions regarding biosimilars and their use for IBD. It is written in a question/answer format for easy reference and guides the reader from the basics of biosimilars, to clinically relevant questions encountered in the clinic, to their policy implications, among other topics.

INTRODUCTION

This review addresses the use of biosimilars in patients with inflammatory bowel disease (IBD). Here we aim to guide the reader from the basics of biosimilars, to clinically relevant questions encountered in the clinic, to their policy implications, among other topics. The goal is to provide an evidence-based review of the topic that answers common questions and can be applied easily to the clinic, for both counseling IBD patients on the use of biosimilars and taking care of patients who are on biosimilars or considering a switch from an originator product.

What are biosimilars?

Biosimilars are biologic products that are highly similar to a previously approved reference (or originator) biologic drug in terms of safety, purity, and potency (efficacy). In the United States (US), biosimilar products first entered regulatory pathways following the passage of the Affordable Care Act, which included the Biologics Price Competition and Innovation Act of 2009. This
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Is it possible to distinguish an originator from a biosimilar prescription?

In the US, six biosimilars have been approved by the Food and Drug Administration (FDA) as of December 2018 (Table 2). Three are infliximab biosimilars – Inflectra™ (infliximab-dyyb), Renflexis™ (infliximab-abda), and Ixifi™ (infliximab-qbtx) – and three are adalimumab biosimilars – Amjevita™ (adalimumab-atto), Cyltezo™ (adalimumab-adbm), and Hyrimoz™ (adalimumab-adaz). Each biosimilar has a unique, non-proprietary name designed to identify the base compound (i.e. infliximab) and distinguish it from the originator and from other biosimilars with the use of a four-letter suffix (that has no inherent meaning). Thus, when prescribing a biosimilar, the trade name or non-proprietary name with a four-letter suffix should be specified. Of the FDA approved biosimilars, only Inflectra™ (infliximab-dyyb) and Renflexis™ (infliximab-abda) have been marketed in the US. The adalimumab biosimilars appear to be in patent litigation with the likely possibility of no market competition until 2023.

How are biosimilars approved?

Recognizing the above differences in complexity and cost, global regulatory bodies such as the FDA and European Medicines Agency have outlined pathways to efficiently approve any new product shown to be sufficiently similar to a reference product that is no longer under patent protection. In
order to achieve a balance between rapid approval and confidence in the new agent, the FDA’s current guidance relies on two principles: 1) explicit demonstration of substantial similarity between the proposed product and the reference, and 2) implicit reliance on the existing safety and efficacy evidence in support of the reference product across treatment indications.

The abbreviated pathway for biosimilar approval acknowledges that the goals of biosimilar development are fundamentally different from that of novel agents; while new biologics must be demonstrated to be safe and efficacious for each proposed indication, the burden of proof for biosimilars primarily lies in demonstration of substantial similarity to the reference product (Figure 1). To demonstrate biosimilarity, the FDA has outlined a step-wise approach with a heavy emphasis on analytical assays and clinical pharmacology. The objectives of biochemical assays are to comprehensively characterize the attributes of the molecule, including any post-translational modifications (e.g. folding, subunit interactions, glycosylation) that might affect the immunogenicity of the product. Because biosimilars must be delivered using the same administration route, dose, and frequency as the reference product, they must be shown to have essentially equivalent pharmacokinetics.

How were biosimilars approved for IBD?

A key distinction between applications for novel biologic therapies and biosimilars is that the latter can potentially be approved for all of the indications of the reference product without explicit safety and efficacy testing for each indication. This process, called extrapolation (Table 1), is contingent on a case-by-case assessment of the known mechanisms of action, pharmacokinetics, immunogenicity, and other factors. Take for instance the first biosimilar to be FDA-approved for IBD: infliximab-dyyb (i.e. CT-P13, Inflectra™). Although this agent was approved for all the indications of originator infliximab (including Crohn’s disease and ulcerative colitis), the only controlled testing of the drug at the time of approval included a phase 1 study for ankylosing spondylitis (PLANETAS1) and a phase 3 study for rheumatoid arthritis (PLANETRA2).

The rationale in the approval process given by the FDA and other regulatory bodies is that the pre-clinical data as well as the clinical trial data for which infliximab-dyyb was formally tested (i.e. the totality of the data) supported its mechanism of action, pharmacokinetics, immunogenicity, and toxicity as being sufficiently similar to infliximab as used for IBD. While extrapolation for each indication is performed on a case-by-case basis based on the totality of the data, this process serves to accelerate the delivery of biosimilar products and to reduce costs by avoiding replicative clinical trials for each clinical indication for which the originator is approved.
Is there controlled trial evidence for the use of biosimilars in IBD?

Although the approval of biosimilars for IBD has been based on extrapolated data, controlled trial data have emerged examining the use of biosimilars in IBD (Table 3). The NOR-SWITCH trial was a double-blind, non-inferiority study of patients receiving originator infliximab who were randomly assigned to either continue this treatment or switch to infliximab-dyyb. Of the 482 enrolled subjects who underwent randomization and treatment assignment, 155 had Crohn’s disease and 93 had ulcerative colitis. The primary endpoint was a composite endpoint disease worsening by non-invasive scores (including the Harvey-Bradshaw Index and partial Mayo score for the IBD subgroups, respectively). Subgroup analysis of the IBD patient population, analyzed by per-protocol analysis and adjusted for the duration of reference Infliximab use demonstrated non-inferiority both globally as well as within both IBD subgroups. Moreover, there were no systematic differences seen between groups for inflammatory markers (e.g. fecal calprotectin, c-reactive protein), anti-drug antibodies, pharmacokinetics, safety, or number of patients in clinical remission at one year.

A second randomized controlled trial of infliximab-dyyb in biologic-naïve patients with active Crohn’s has recently been published. The study randomized patients to infliximab vs infliximab-dyyb for 30 weeks, and subsequently re-randomized patients to continue versus crossover and continue through 54 total weeks of observation. The investigators assessed a primary endpoint of clinical response by Crohn’s Disease Activity Index-70 (CR-70) criteria at week 6; secondary endpoints included CR-70 at weeks 30 and 54. The investigators found that infliximab-dyyb met the non-inferiority margin of 20% and showed no concerning differences in safety compared to the originator infliximab.

What has been the real-world experience with IBD biosimilars from a safety and efficacy standpoint?

A sizeable number of publications reporting real-world experience of switching IBD patients to biosimilars have already been published (Table 3). Most of this data has come from Europe, where national healthcare payors exercise greater control over treatment options.

The overall consensus from these studies, which range from studies of both new starts on infliximab products vs switching from the reference to the biosimilar in adults and children, is that biosimilars appear to have similar safety, efficacy, and immunogenicity as the reference. These findings have for the most part been consistent with the experience for rheumatological disease. Of note, all of these referenced studies are of infliximab products; very limited data of
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adalimumab biosimilars in IBD has been published thus far.

The largest of these studies to date was an administrative database study of infliximab-naïve Crohn’s patients initiated on reference infliximab vs infliximab-dyyb. Time-to-event analysis for a primary composite endpoint of Crohn’s related surgery, all-cause hospitalization, and reimbursement for another biologic demonstrated non-inferiority of the biosimilar within a prespecified margin of 10% – an even tighter margin than that of the NOR-SWITCH trial. They additionally showed no signal for differences in safety between the biosimilar and reference product.

Some open-label studies have suggested higher discontinuation rates upon switching to a biosimilar, especially in the setting of rheumatologic disease. These findings have raised the possibility of a significant nocebo effect – a diminished or negative effect of medical treatment resulting from adverse patient expectations. As such, increased patient education on biosimilars has been recommended as a means of mitigating this effect.

Are biosimilars considered interchangeable with the reference product? Who determines what version of the drug my patient will get?

Although biosimilars are considered highly similar to the reference product, they are not considered interchangeable. Interchangeability as defined by the FDA is a more stringent standard, implying that 1) it would be expected to produce the same clinical result in any given patient as the reference, and 2) that the risks of safety or diminished efficacy resulting from alternating or switching between products is no greater than that of using the originator without switching. The consequences of interchangeability are that such biosimilars may be substituted for the reference without the intervention of the prescriber, subject to state pharmacy laws. Meeting this higher standard requires additional data and studies from the manufacturer of a proposed interchangeable product.

To date, no biologics for any indication have been approved by the FDA as interchangeable. This does not imply that patients should not be switched or newly initiated on biosimilar products, but rather that patients in the US will receive the specific version of a biologic prescribed by their provider, and switches between biologic cannot be done without the provider’s knowledge or approval.

What is the position of gastroenterology societies and patient advocacy societies on switching from the originator to a biosimilar product for IBD?

While there are many high-quality patient and physician resources on the use of biologics from the American College of Gastroenterology and American Gastroenterology Association, formal position statements have been published by the Crohn’s and Colitis Foundation and the European Crohn’s and Colitis Organization on switching.

The Crohn’s and Colitis Foundation does not oppose single transitions of stable patients from an originator to a biosimilar (or vice versa) by third parties (payers or pharmacies), but is opposed to multiple switches if the agents involved have not been designated as interchangeable by the FDA. They also endorse, when switches occur, that patients and providers are informed of the exact agent the patient is receiving and whether it has received an interchangeable designation.

The European Crohn’s and Colitis Organization (ECCO) reports that switching from the originator to a biosimilar in patients with IBD is acceptable. They highlight that scientific and clinical evidence is lacking regarding reverse switching, multiple switching and cross-switching among biosimilars. They endorse that switches should be performed following appropriate discussions between patients and their physician and other team, members.

Can biosimilars be used in patients who have had a secondary loss of response or adverse reaction to an originator product? Can they be monitored using existing therapeutic drug monitoring assays?

A secondary loss of response to a biologic describes a common phenomenon whereby a patient experiences an adequate response when the therapy is started but then experiences either a subsequent waning response (symptoms recur before the next dose) or full flare at any point before the following dose. The most informative study related to this question was one that specifically

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tested the cross-reactivity of anti-infliximab antibodies to infliximab-dyyb in 125 IBD patients. The investigators found that sera from all of the patients with antibodies to the originator cross-reacted to infliximab-dyyb whereas none of the controls without anti-infliximab antibodies showed cross-reactivity. The anti-drug antibody titers against infliximab and infliximab-dyyb were almost perfectly correlated. Moreover, they showed that these antibodies showed similar functional competition for and inhibition of drug binding to tumor necrosis factor alpha (TNF-\(\alpha\)).

Overall, the results suggest two important points. First, biosimilar drugs are sufficiently similar to the originator as to result in meaningful results when subject to existing assays for therapeutic drug monitoring and anti-drug antibodies against the reference product. Second, patients with non-response to the originator drug are unlikely to benefit from a trial of a biosimilar and may even be at increased risk for complications mediated by anti-drug antibodies such as anaphylaxis. Thus, we typically do not recommend using the biosimilar to an originator biologic in the patient who experiences a secondary loss of response or adverse reaction to the originator with the expectation that the outcome will be different than using the originator.

Have biosimilars lowered the cost of treatment and/or increased access to treatment?

Early and preliminary data from Europe have been optimistic regarding the cost savings resulting from

Table 3. Selected Studies and Guidelines Pertinent to the use of Biosimilars in IBD

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Notes</th>
<th>References</th>
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<tr>
<td>Controlled Trials</td>
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<tr>
<td>NOR-SWITCH</td>
<td>Only published trial experience for biosimilars in IBD, showed non-inferiority of Infliximab-dyyb for maintenance of remission in subjects previously stable on the originator. No differences in adverse effects, inflammatory markers, antidrug antibodies, or clinical remission at 1 year.</td>
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<tr>
<td>CT-P13 vs Infliximab for Crohn’s disease</td>
<td>Phase 3 non-inferiority double blind clinical trial. Biologic-naïve subjects with Crohn’s randomized to initiate Infliximab or Infliximab-dyyb, and continue vs switch at week 30, and assessing efficacy at weeks 6, 30 and 54. No differences in efficacy (Clinical Response – 70 at weeks 6, 30, 54), safety, or immunogenicity were identified.</td>
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<tr>
<td>Observational Studies (Selected)</td>
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<tr>
<td>PROSIT-BIO</td>
<td>One of the early observational cohort studies of IBD biosimilars comprising of biologic-naïve and originator infliximab-experienced patients – over 500 total. Suggested no significant safety or efficacy differences.</td>
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<tr>
<td>Komaki et al. 2017 Systematic Review and Meta-analysis</td>
<td>The only meta-analysis of IBD biosimilars (specifically Infliximab-dyyb) published to date, comprised of 11 published observational studies. Suggested excellent efficacy and safety of Infliximab-dyyb.</td>
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<tr>
<td>Meyer et al. 2019 French Equivalence Study</td>
<td>The largest observational cohort of biosimilars in IBD to date; used a national payor database to demonstrate non-inferiority for composite outcome of Crohn’s-related surgery, all-cause hospitalization, and reimbursement for another biologic. No differences in safety were seen.</td>
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<tr>
<td>Society Position Statements</td>
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<tr>
<td>European Crohn’s and Colitis Organization</td>
<td>Based on a consensus meeting held in 2016, suggests that “Switching from the originator to a biosimilar in patients with IBD is acceptable.” Provides guidance regarding practical aspects of patient communication on this topic.</td>
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</tr>
<tr>
<td>Crohn’s and Colitis Foundation</td>
<td>Does not oppose single transitions of stable patients from an originator to a biosimilar (or vice versa) but opposes multiple switches for drugs not designated as interchangeable by the FDA. Supports transparency so that patients and providers be explicitly aware what agent a patient is receiving.</td>
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the introduction of biosimilars into the market. At the 2018 Interdisciplinary Autoimmune Summit, Jonathan Kay reported that the Norwegian government was able to secure a 40% cost savings on infliximab as a result of a competitive bidding process. Cost projections published by authors from the RAND corporation proposed a potential windfall of $44.2 billion as in the US over a ten-year window. However, data supporting increased access to care because of widespread biosimilar entry into the marketplace is not yet available.

CONCLUSION

In summary, biosimilars are biologic products that are highly similar to, and lacking in, clinically meaningful differences from the off-patent reference product. Six anti-TNF biosimilars have been approved in the US, but only the two infliximab biosimilars are widely available at this time. No currently approved biosimilar has a designation as interchangeable. Based on scientific extrapolation, evidence from controlled trials and real-world experience in IBD, data supports the use of biosimilars for both treatment initiation and switching as safe, effective, and potentially cheaper alternatives to the originator biologic.

References


