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Updates on the Use of Biosimilars for the Treatment of Inflammatory Bowel Disease

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Biologic therapy with monoclonal antibodies has been an effective strategy for improving outcomes in patients with inflammatory bowel disease. These therapies remain expensive. Over the past several years, biosimilars have entered the marketplace in the United States with the promise of reducing costs. Biosimilar's are biological products that are similar but not identical to the original biologic agent. This review discusses several aspects of biosimilars, including how they are approved as well as the latest data supporting their use in inflammatory bowel disease.

INTRODUCTION

Biologic therapy with monoclonal antibodies has been an effective strategy for improving outcomes in patients with inflammatory bowel disease. While they are effective, these therapies are also expensive. Over the past several years, biosimilars have entered the marketplace in the United States with the promise of reducing costs. Biosimilars are biological products that are similar, but not identical to an original biologic agent.[1] The first anti-TNF biosimilar was approved in the United States in 2016,[2] but they were used in Europe for a few years prior. As the number of biosimilars continues to increase, it will be important to understand how these agents are approved and what are the data supporting their use in patients with inflammatory bowel disease.

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The Basics

Biosimilars are biologic products that are highly similar to a previously approved reference or originator biologic therapy, notwithstanding minor differences in clinically inactive components (Table 1).[3] The United States Food and Drug Administration (FDA) stipulates that there should not be any clinically meaningful differences in terms of safety, purity, and potency (efficacy) with the originator biologic.[3] Biosimilars are characterized as having the same amino acid sequence as the originator biologic, however there may be subtle differences in glycosylation that could influence the pharmacology and immunogenicity of the biosimilar.[1] Hence, to be approved by the FDA, a biosimilar must demonstrate not only functional and structural similarities to the originator biologic, but also similar pharmacokinetics, immunogenicity, safety, and efficacy.[1,4]

As of December 2021, a total of 11 biosimilar

monoclonal antibodies for inflammatory bowel disease have been approved by the Food and Drug Administration in the United States.[2] Four of these are infliximab derived biosimilars and 7 are adalimumab derived biosimilars (Table 2). Although multiple adalimumab biosimilars have been approved, they will not be available for use in the United States until 2023.

Each biosimilar has a unique, nonproprietary name designed to distinguish it from the originator and from other biosimilars. Each biosimilar name consists of the base compound (i.e. infliximab or adalimumab) and then a 4-letter suffix that has no inherent meaning (Table 2).[5] Key definitions related to biosimilars are listed in Table 1.

How Biosimilars are Approved

In the United States, biosimilars are approved as part of the Biologics Price Competition and Innovation Act of 2009.[3] This act created an abbreviated licensure pathway for new biologic products to be marketed as either biosimilar or interchangeable with a previously approved originator product. Of note, biosimilarity and interchangeability are distinct categories, and not synonymous (Table 1).[4]

The *types* of studies required for biosimilar approval are similar to those for an originator biologic, however their *purpose* and *focus* is slightly different (Figure 1). An originator biologic must show safety and efficacy as a novel agent. In contrast, a biosimilar application must show similarity to an originator through the following: 1) analytical studies (structural and functional) showing the product is highly similar to the originator, 2) animal studies, including an assessment of toxicity, and 3) a comparative clinical study in one or more indications for which the originator is licensed that demonstrates safety, purity, and potency of the proposed biosimilar product as well as similar immunogenicity, pharmacokinetics, and pharmacodynamics as the originator biologic.[6]

Another key difference for biosimilar approval compared to originator biologic is the need for fewer clinical trials to obtain approval across all indications. This abbreviated approval process is based on a weighted reliance on analytic similarity with the originator product and the totality of the

Table 1. Key Definitions related to Biosimilars[4]

Biological Product	Large complex molecules regulated by the Food and Drug administration (FDA) and produced through biotechnology in a living system, such as a microorganism, plant cell, and animal cell to diagnose, prevent, treat, or cure medical conditions
Originator Product	A single biological product already approved by the FDA against which a proposed biosimilar is compared
Biosimilar Product	A biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved originator product
Interchangeable Product	A biosimilar product that meets additional FDA requirements, including information showing that it produces the same clinical result as the originator product in any given patient, as well as no significant reduction in terms of safety and efficacy by switching back and forth between an interchangeable product and an originator product
Extrapolation	The justification underlying "approval for other indications that were not directly studied by the biosimilar manufacturer." This is based on assessment of the totality of the evidence supporting "biosimilarity [to] at least one of the reference product's indications," combined with "knowledge and consideration of various scientific factors for each indication." These factors include "mechanism(s) of action, pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity."

,evidence based on the above types of studies for the biosimilar. This process is called extrapolation and involves using the biosimilar clinical trial data from one or two indications as rationale for approval across other indications for which the originator biologic is approved.[6] Extrapolation is a key for reducing biosimilar development costs and expediting time to market. Extrapolation is not automatic and requires scientific justification through a totality of the evidence from human pharmacokinetic/pharmacodynamic studies, clinical safety/efficacy studies (including immunogenicity), and pharmacovigilance studies for that biosimilar and disease state in question.[5]

Although the above approval process for biosimilars is regulated by the FDA, both IBD patients and providers may still have concerns when a biosimilar is approved for IBD but not formally tested via a phase III clinical trial in IBD patients. Although observational studies from Europe were reassuring with regard to similarity in outcomes before biosimilars were approved in the US, it is nonetheless helpful to have both controlled and updated real world data conducted specifically in IBD patients to help inform their use in this population.

Clinical Studies Evaluating Biosimilars in IBD

Clinical studies evaluating biosimilar use in IBD patients can be categorized into those that examine outcomes for new starts (biosimilar vs. originator), non-medical switching (group of originator patients are switched to biosimilar), true switch (originator and biosimilar patients are each switched to the other agent), and interchangeability studies. Interchangeability studies require specially designed trials to receive this designation from the FDA. These studies typically include at least 3 switches between products for at least 2 exposure periods.[1,4]

Clinical Trial Data for Biosimilarity in IBD Patients

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.[7] 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.[7] 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. [7]

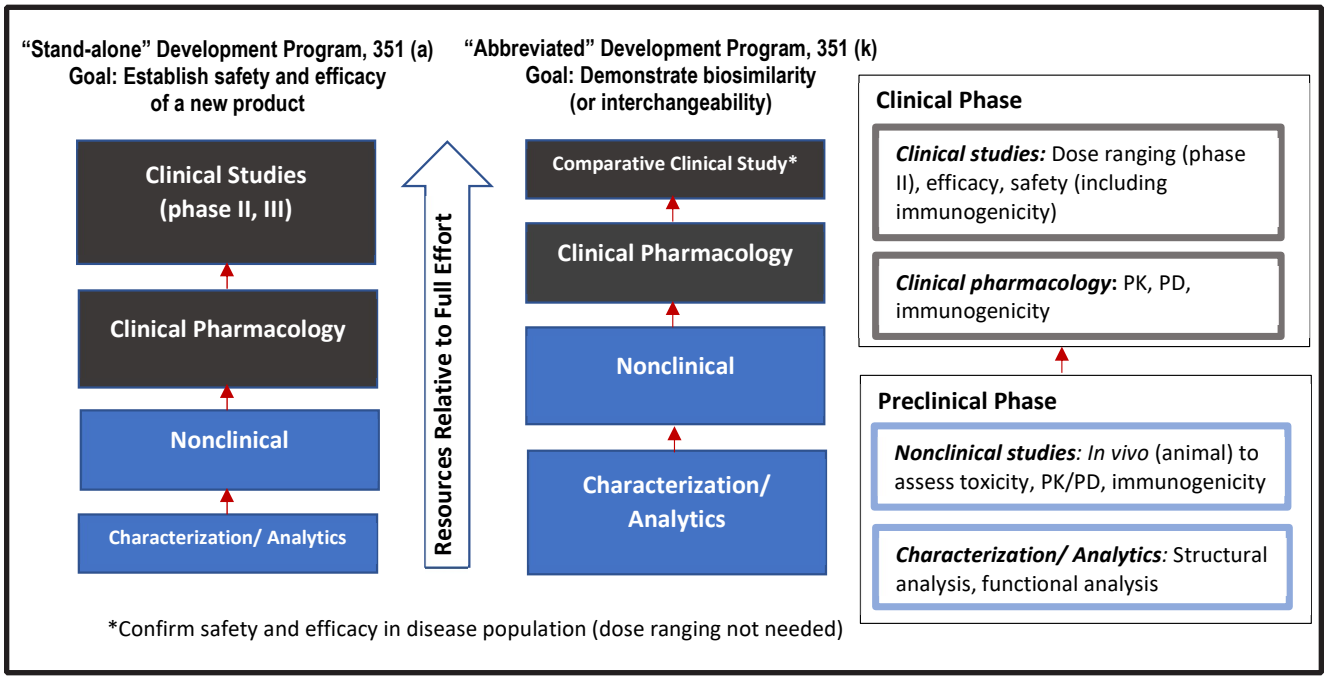
A controlled trial in biologic-naïve patients with active Crohn's randomized participants to infliximab vs. infliximab-dyyb for 30 weeks, and subsequently re-randomized patients to continue versus crossover and continue through 54 total weeks of observation.[8] The investigators assessed

Table 2. FDA Approved Biosimilars for IBD and Date of Licensure[2]

Infliximab (originator approved 8/1998)	Adalimumab (originator approved 12/2002)
1. Inflectra (infliximab-dyyb)- 4/2016	1. Amjevita (adalimumab-atto)-9/2016
2. Renflexis (infliximab-abda)-5/2017	2. Cyltezo (adalimumab-adbm)-8/2017*
3. Ixifi (infliximab-qbtx)-12/2017	3. Hyrimoz (adalimumab-adaz)-8/2018
4. Avsola (infliximab-axxq)-12/2019	4. Hadlima (adalimumab-bwwd)-7/2019
	5. Abrilada (adalimumab-afzb)-11/2019
	6. Hulio (adalimumab-fkjp)-7/2020
	7. Yusimry (adalimumab-aqvh)-12/2021

*Designated as interchangeable by FDA: 10/2021

Figure 1.



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.[8]

Finally, the VOLTAIRE-CD trial randomized patients with Crohn's to receive either adalimumab or adalimumab-adbm for 4 weeks (induction), and then continue therapy until week 46. At week 24, patients were unmasked and those on originator adalimumab were switched to adalimumab-adbm.[9] Investigators found similar response and remission rates at week 4, 24, and at week 48, based on Crohn's disease Activity Index-70 (CR-70) criteria, CR-100 criteria, and a CDAI score less than 150 points (remission). The investigators reported that adalimumab-adbm met the non-inferiority margin for pre-specified outcomes and showed no concerning differences in adverse events or drug related adverse events.[9]

Clinical Trial Data for Interchangeability

An interchangeable biosimilar is one that meets the additional requirement of showing it produces the same clinical result as the reference product in any given patient and that the risk in terms of safety and efficacy is not reduced by switching back and forth between the biosimilar and originator biologic (Table 1).[10] The design of studies for a designation of interchangeability are outlined by the FDA and are different than those needed to receive approval as a biosimilar. A biosimilar approved as an interchangeable product means that the FDA has concluded it may be substituted for the reference product without consulting the provider. The specific implications and regulations are governed by each state's pharmacy board.[10]

In 2021, the FDA designated the first interchangeable anti-TNF biosimilar.[11] In a phase III randomized trial (Voltaire-X, NCT 03210259), 238 patients with moderate to severe plaque psoriasis were first all treated with originator adalimumab during a lead in period. They were then randomized to either continue originator adalimumab or undergo a switch to adalimumab-adbm, then switch back to originator adalimumab, and finally switch back again to adalimumab-adbm. At week 32, the authors found no meaningful difference in PK, efficacy, safety, and immunogenicity. At the time of this writing, only one other biosimilar, not used in IBD, has received an interchangeable designation by the FDA (insulin glargine-yfgn).[11]

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Real World Data for Biosimilars in IBD Patients

The number of publications, whether editorials, patient surveys, clinical trials, or observational studies regarding the use of biosimilars in inflammatory bowel disease has increased from 6 publications in 2013 to an average of 70-90 per year since 2017. Real world-data on biosimilar use specific to IBD patients, while not a substitute for a controlled clinical trial, nonetheless have been useful in bridging knowledge gaps that have resulted from extrapolating biosimilar trial data in other disease states to IBD patients. These real-world studies have been critical for answering the safety and efficacy of biosimilars in IBD patients for new starts and medical switches,[12-16] and more recently for newer biosimilars and multiple switches.[17-19] To date, studies continue to confirm that biosimilars are highly similar to originator biologics and do not show any meaningful difference in terms of safety, efficacy, or immunogenicity.[20]

Society Statements on Biosimilars

The Crohn's and Colitis Foundation published an updated position statement in 2020 regarding biosimilars and IBD. Among several recommendations, they stated the Foundation was not opposed to single transitions of patients in clinical remission but was opposed to multiple switches due to lack of data supporting the safety and efficacy of such a strategy in patients with IBD.[21] They also emphasized a process for shared decision making and transparency, for both the provider and patient, when a substitution was to occur.[21] These recommendations are in line with the 2017 position statement from the European Crohn's and Colitis Organization (ECCO),[22] but a bit different that the 2020 Joint Canadian Association of Gastroenterology/Crohn's and Colitis Canada Position statement, which did not endorse non-medical switching from originator to biosimilar infliximab.[23]

The Future

The biosimilar landscape for the future holds significant promise but also some risk for confusion and uncertainty as more of the currently approved anti-TNF biosimilars become fully available and on the market. Competition holds the best promise for increasing affordability and access for biologic therapies. However increased competition leads to more choices and an increased probability of patients on different biosimilars from one year to the next as patients change insurance plans. Thus it is likely we will see more de-facto multiple switch situations rather than care guided by FDA designated interchangeability or switch trials. Add to this, the increase likelihood over time that patients may not be switching from an originator to a biosimilar but from one biosimilar to another, and it is likely that there will not be a clean clinical trial to inform all permutations of clinical scenarios. Even so, there is reason for optimism as the GI community continues to do what it has been doing to date, looking at the totality of the data regarding the role of biosimilars in IBD care, applauding those that invest in high quality trials assessing interchangeability and efficacy/safety specifically in IBD patients, and continuing to encourage high-quality real-world studies to fill in the remaining clinical information gaps. To date, studies continue to confirm that biosimilars are highly similar to their originator biologic and do not show any meaningful difference in terms of safety, efficacy, or immunogenicity. ■

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