

ADVANCES IN IBD

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Nonmedical Switching of Biosimilars in Patients With Inflammatory Bowel Disease



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G&H What are the most common reasons for nonmedical switching of biosimilars?

RC In nonmedical switching, a patient is stable on a therapy, for example an originator biologic, but is switched to another drug, such as a biosimilar to the biologic, for a reason that is not medically necessary—usually to save money. The switch may be initiated by the insurance company (or whoever pays for the drug, whether it is the originator biologic or the biosimilar) to move to the option that is cheaper. Because these treatments are expensive, patients do not usually pay for them on their own. On the other hand, patients themselves may decide to switch because their copayment may be eliminated or much less with the other drug. The third group that could originate the switch is the physician, in an attempt to decrease costs specifically to the health care system in which the physician practices or to the health care system overall.

One could argue that all drug switches involving biosimilars (from the originator drug to a biosimilar or from a biosimilar to the originator drug) would, in fact, be nonmedical switches. The essence of a biosimilar is that the drug is highly similar to the originator product without any clinically meaningful differences in the safety profile, purity, and potency of the drugs. Thus, if the patient experiences a medical problem with either the originator drug or the biosimilar (eg, an adverse reaction or development of antibodies against the drug), simply switching from one to the other would not help, as they are essentially just different versions of the same drug. The patient would need to be switched to a completely different drug.

G&H What types of switching studies can be performed with biosimilars?

RC Currently in inflammatory bowel disease (IBD) with monoclonal antibody biosimilars, the US Food and Drug Administration (FDA) has approved infliximab-dyyb (Inflectra, Celltrion) and infliximab-abda (Renflexis, Merck), which are biosimilars to infliximab (Remicade, Janssen), as well as adalimumab-atto (Amjevita, Amgen) and adalimumab-adbm (Cyltezo, Boehringer Ingelheim), which are biosimilars to adalimumab (Humira, AbbVie).

During the development and testing of biosimilars, several types of studies are conducted. The first type examines the biosimilar against a placebo to determine whether the biosimilar works better than the placebo, while other studies within this category start patients on a biosimilar or on the originator biologic and then follow them for a period of time to determine whether the biosimilar is noninferior to the originator biologic. In some of these studies, after a period of time being on the originator biologic, some patients are switched to the biosimilar blindly, while other patients stay on the originator biologic. Both groups of patients are followed to see whether there is any difference in outcomes over the course of the study (typically 6 or 12 months). This is known as a single-switch study because patients are switched once.

There are more complex single-switch studies whereby patients start on either the biosimilar or the originator biologic. Some patients stay the entire study with the drug on which they started, while other patients switch from the biosimilar to the originator biologic or from the originator biologic to the biosimilar. These are

still known as single-switch studies because there is only 1 switch. At the end of the study period, there are 4 groups of patients: the patients who started on the biosimilar, the patients who started on the originator biologic, the patients who switched from the biosimilar to the originator biologic, and the patients who switched from the originator biologic to the biosimilar. The purpose of this type of study would be to show noninferiority among all 4 of these groups.

Finally, there are multiple-switch studies. Currently, I do not believe that any multiple-switch studies have been published in patients with IBD, although there has been a multiple-switch study published in psoriasis with originator etanercept (Enbrel, Amgen) and biosimilar etanercept (GP2015, Sandoz) that did not show concerning safety or immunogenicity issues.

G&H Could you discuss any findings from single-switch studies using biosimilars in IBD patients?

RC Most of the published studies or abstracts to date have shown that the infliximab biosimilars that are approved in the United States are noninferior to the originator infliximab. Less research has been published on the adalimumab biosimilars; at this point, I believe that only abstracts have been published.

The study that has been receiving the most attention in this area is the NOR-SWITCH study, the results of which were recently published in *The Lancet*. This was a single-switch study in Norway of adult patients who were stable on the originator infliximab for at least 6 months and then underwent double-blind randomization 1:1 to either stay on the originator drug or switch to the biosimilar. Patients with a variety of inflammatory diseases, including IBD, were followed for 52 weeks, and the primary endpoint of the study was disease worsening. There were 155 Crohn's disease patients and 93 ulcerative colitis patients; the rest of the patients had other diseases. Over the 52-week period, outcomes (change in the Harvey-Bradshaw Index in Crohn's disease patients and change in the partial Mayo score in ulcerative colitis patients) did not show statistically significant differences. Overall, the biosimilar was found to be noninferior to the originator infliximab in terms of efficacy, trough drug levels, anti-drug antibody rates, fecal calprotectin levels, C-reactive protein levels, and safety-related issues.

G&H Are there any limitations to this study that should be taken into account?

RC There was some concern that patients with Crohn's disease initially seemed to do better on the originator

infliximab. However, those differences did not reach statistical significance and disappeared over the course of 52 weeks. There was no discernible difference between the originator infliximab or the biosimilar in patients with Crohn's disease past week 16. Findings from the 2 drugs almost completely overlapped from weeks 24 to 52 for patients with Crohn's disease. Drug findings tended to overlap for the entire course of the study for patients with ulcerative colitis.

Another concern was that the study was not large enough. A noninferiority study has to be quite large to be able to show any differences because both sets of patients are receiving active drug. However, again, the curves overlapped almost completely over time. In fact, the week 40 findings were nearly identical for both drugs. Thus, it is difficult to fathom that a larger study would show much of a difference over the 52 weeks of the study.

G&H Could you discuss findings from any other clinical trials or real-world data involving switching of biosimilars?

RC In the EGALITY trial, the results of which were recently published in the *British Journal of Dermatology*, 264 patients with psoriasis were given a biosimilar to etanercept and 267 patients with psoriasis were given the originator etanercept. Some patients stayed on the same drug for the entire study, while others switched at week 12, then switched back at week 18, and then switched again at week 24. All patients were followed for 52 weeks. There did not seem to be a difference in efficacy, treatment-emergent adverse events, or antidrug antibodies, at least from what has been published to this point.

G&H Has there been any research on the switching of biosimilars specifically in children with IBD?

RC There have been several studies in pediatric IBD, although these studies have generally been small. For example, a study from South Korea examined originator and biosimilar infliximab in 51 pediatric Crohn's disease patients and 23 pediatric ulcerative colitis patients. In the Crohn's disease group, 26 were naive and 25 switched once, while in the ulcerative colitis group 16 were naive and 7 switched once. There did not seem to be much difference between patients who were naive to therapy and those who switched during the study, which lasted 30 weeks.

G&H Thus far, what has been the reception from physicians and patients regarding switching of biosimilars?

RC In the United States, biosimilar use for IBD is still new and not yet widespread. The first US biosimilars for IBD were approved just last year. Thus, it is important for physicians and prescribers to become educated about biosimilars so that they can inform their patients, who often have no or little knowledge of biosimilars. Biosimilars have become very routine in other markets, such as Europe, where there are many patients with Crohn's disease and ulcerative colitis. In these countries, many physicians seem to have wholeheartedly moved forward with switching to whichever is cheaper between the originator and the biosimilar. In some cases, this is because the government or entity that is paying has enacted a mandatory switch.

As for patient reactions, my understanding is that switching has been well received in Europe because patients do not have a choice. In addition, physicians do not show much concern because the published data have not shown statistically significant differences when switching. There have been no alarming findings over the several years that biosimilars have been used in Europe, so it is unlikely that there would be alarming findings as biosimilars become more widespread in the United States.

G&H What are the next steps in research in this area?

RC One area that is of much concern to gastroenterologists is whether multiple switches will be found to be equivalent or noninferior in patients with Crohn's disease and ulcerative colitis. This issue is particularly important in Crohn's disease because of the early data from the NOR-SWITCH trial that seemed to favor the originator.

In addition, more research is needed on the use of biosimilars specifically in IBD patients, as there are some differences between the use of these agents in IBD patients vs in patients with other diseases. One difference is that the doses used for Crohn's disease and ulcerative colitis are higher than those traditionally used for rheumatoid arthritis and psoriasis, which may or may not make a difference when using biosimilars that were tested just at lower doses. None of the biosimilars were tested in patients with Crohn's disease or ulcerative colitis as

part of their FDA approval; they were typically tested in patients with rheumatoid arthritis and psoriasis, and then the indications were extrapolated to adult and pediatric Crohn's disease and adult ulcerative colitis (but not pediatric ulcerative colitis) for the infliximab biosimilars, as well as to adult Crohn's disease and adult ulcerative colitis (but not pediatric Crohn's disease) for the adalimumab biosimilars. We also know that Crohn's disease and ulcerative colitis require a loading dose for both infliximab and adalimumab, while the other indications generally do not. Another difference is the presumed loss of antibodies in the stool of patients with inflamed bowels. This is not much of an issue in patients who are receiving these drugs for conditions other than IBD. Several earlier studies have suggested that there was more immunogenicity in Crohn's disease and ulcerative colitis patients than in rheumatoid arthritis patients, but I do not think that has panned out as results from postmarketing studies with different biologics have been released.

Dr Cohen has served on the speakers bureau (for disease state only, not promotional drug talks) for AbbVie, Pfizer, and Takeda. He has also served as a consultant and/or on the advisory and/or scientific advisory board for AbbVie Laboratories, Celgene, Eli Lilly, Hospira, Janssen, Pfizer, Sandoz Biopharmaceuticals, Takeda, and UCB Pharma.

Suggested Reading

Glintborg B, Sørensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis*. 2017;76(8):1426-1431.

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