ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Benefits, Concerns, and Future Directions of Biosimilars in Inflammatory Bowel Disease

BIOSIMILARS SPOTLIGHT
Part 3 of a 3-part series

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G&H What are the main benefits of using biosimilars for the treatment of patients with inflammatory bowel disease?

BF The main benefit of using biosimilars in patients with inflammatory bowel disease (IBD) is reduced drug acquisition costs. Biosimilars are not generic drugs—they are highly similar to originator biologic agents—but, like generics, biosimilars are less expensive than the originators. In most countries, biologic drugs have become a burden on pharmacy budgets. In IBD specifically, biologic agents are currently the fastest-growing budget items. This situation is an important concern for both pharmacy benefits managers and patients, who are increasingly covering part of drug costs. Biosimilars are less costly than originator biologic agents primarily because biosimilars do not have to undergo the intensive clinical development process associated with approval of an originator. Furthermore, biosimilars do not incur high costs for marketing, market access, and postmarketing research and development. Thus, an opportunity exists for savings, and those savings can, potentially, be passed onto consumers and payers.

G&H Currently, what are the main concerns associated with using biosimilars for the treatment of IBD?

BF One of the concerns is the potential threat of immunogenicity. Biosimilar monoclonal antibodies are large molecular weight proteins. Although the amino acid sequence of a biosimilar is the same as that of the originator biologic agent, when proteins subsequently fold and, most importantly, when they are glycosylated, the quaternary structure—that is, the 3-dimensional shape—is defined. That configuration is what the immune system recognizes, resulting in either sensitization or tolerization. Molecules made in living cells have very complex quaternary structures primarily because they undergo glycosylation (enzymes placing carbohydrate molecules on the protein backbone). Glycoproteins have long carbohydrate chains with very complicated branching structures that can be highly variable depending upon culture conditions. Thus, it is not possible to produce a molecule that is the same as, for example, originator infliximab (Remicade, Janssen), and that is why these new agents are called biosimilars, not bioidenticals or generics.

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Immunogenicity is relevant if the immune system recognizes that a molecule is foreign and, thus, produces

antidrug antibodies, leading to the loss of efficacy or the development of side effects (with the former result being more important). Gastroenterologists first learned about this problem when originator infliximab was initially introduced and given to patients intermittently and without immunosuppressants; in a very short period of time, unacceptably high rates of immunogenicity were seen. Over the past decade, considerable attention has been directed to the prevention of this problem. Even drugs in which the proteins are "fully humanized" (ie, antibodies are exclusively derived from human gene sequences in distinction to those that originate from a mouse) can have problems with the formation of antidrug antibodies and loss of response. Given that each person's immune system is unique, "fully human" antibodies are capable of inducing antidrug antibodies once they are recognized as foreign.

Thus, immunogenicity is a potential concern for the use of biosimilars. If a drug is introduced in a patient who is in stable remission on infliximab that is very similar, but not identical, to the originator drug, tolerance may break down. In addition, it is highly likely that there will be multiple biosimilars in the future, leading to a complex environment in which patients are exposed to multiple similar yet not identical agents. We do not understand the consequences of such an environment for patient safety.

G&H Thus far, have patients with IBD had any concerns regarding treatment with biosimilars?

BF Patients may be concerned if they are already in remission and are doing well on maintenance therapy on an originator biologic agent but then have to switch to a biosimilar. These are usually patients who are at high risk for complications and poor outcomes. Although these patients are a small part of the overall IBD population (just 20%), they generate up to 80% of the total costs to the health care system. If a patient is already in remission and is doing well, switching the therapy will not make the patient any better (biosimilars are not better than originator biologic agents); however, the potential for harm exists.

G&H What are the most important questions that still need to be answered involving biosimilars?

BF More information is needed regarding switching between biosimilars and originator biologic agents. The US Food and Drug Administration (FDA) recently released a white paper indicating the types of trial designs that would be required before nonmedical switching of biosimilars in stable patients could be endorsed—in distinction to substitution by a pharmacist in patients starting therapy. These types of trials would involve multiple crosses between an originator biologic agent and a biosimilar. Thus, we need more studies on switching, especially multiple-switch studies.

G&H Has there been any research thus far on this issue?

BF There are some limited data on one-way switching. The study that has received the most attention has been NOR-SWITCH, the results of which were recently published in *The Lancet*. This was a multicenter study conducted in Norway in which patients in stable remission with originator infliximab were randomized to switch unidirectionally either to the infliximab biosimilar or to continue originator infliximab.

> Biosimilars will be an important component of the future of IBD treatment.

Several methodologic issues have been raised regarding this study. One of these is the noninferiority design of the trial. Very large sample sizes are needed to discern meaningful differences. The researchers of this study chose a clinically insignificant difference of 15%, but, in my opinion, the study was underpowered to show noninferiority, making the results difficult to interpret.

Another issue is that, to conduct the study exclusively in a country with a relatively small population, the researchers had to combine a total of 6 patient populations in remission on infliximab (patients with rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease, psoriatic arthritis, or ankylosing spondylitis), resulting in a mixed patient population. A composite endpoint was established, which was essentially failure after randomization to either the originator drug or the biosimilar. Most clinicians find the results of NOR-SWITCH difficult to interpret because of the heterogeneic patient population.

Thus, NOR-SWITCH, in my opinion, does not adequately answer the critical questions regarding switching to biosimilars. In particular, the study evaluated a one-way switch, so it did not address the issue of immunogenicity and the formation of antidrug antibodies because the patients were not challenged with reswitching. Therefore, additional studies are needed to assess nonmedical switching.

G&H Are there any other important questions involving biosimilars in IBD that need to be answered?

BF How immunogenicity is measured requires advanced chemistry. It is important to be able to differentiate antibodies directed against a biosimilar vs those directed against the originator drug during switching studies. However, this has not been adequately studied.

G&H What do you think is the future of biosimilars for patients with IBD?

BF Biosimilars will be an important component of the future of IBD treatment. Biosimilar development will continue because of cost considerations. From a cost perspective, biosimilars are extremely beneficial. Currently, there are multiple biosimilars that are in development, and the FDA has already approved 4 biosimilars: infliximab-dyyb (Inflectra, Pfizer) and infliximab-abda (Renflexis, Merck), which are biosimilars to infliximab, as well as adalimumab-atto (Amjevita, Amgen) and adalimumab-adbm (Cyltezo, Boehringer Ingelheim), which are biosimilars to adalimumab (Humira, AbbVie). The FDA has accepted the concept of extrapolation of indications; we just need additional high-quality research on nonmedical switching and the risk of immunogenicity.

Dr Feagan has been a consultant to all of the manufacturers of originator monoclonals used in IBD and the biosimilar product Inflectra.

Suggested Reading

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