ADVANCES IN IBD

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Introduction to Biosimilar Use in Patients With Inflammatory Bowel Disease

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G&H What is a biosimilar?

GL According to the US Food and Drug Administration (FDA), a biosimilar is a product that is highly similar to a biologic agent (also referred to as an originator, reference, or innovator biologic) that has already been approved by the FDA. A biosimilar and originator biologic cannot have any clinically meaningful differences in terms of safety, purity, and potency, although they may have minor differences in terms of clinically inactive components. Thus, the biosimilar and originator biologic must have the same strength, form of dosage, and administration route.

A biosimilar cannot be superior to the originator biologic. There is a class of biologic agents known as biobetters (also referred to as biosuperiors or second-generation biologics). Instead of just being highly similar to the originator biologic, these agents include alterations in chemistry, formulation, and delivery.

G&H How does a biosimilar differ from a generic?

GL A biosimilar is manufactured to simulate the originator biologic, whereas a generic is manufactured to simulate a small molecule. Thus, biosimilars are not generics of biologics. There are several differences between biologics and small molecules. A biologic is a protein and has a 3-dimensional structure, whereas a small molecule is an organic chemical and has a well-defined structure that is not necessarily 3-dimensional. A biologic can use parenteral or intravenous administration, whereas a small molecule typically uses oral administration. Degradation of a biologic occurs via catabolism, whereas it occurs via metabolism in a small molecule. The mechanism of action of a biologic involves blocking or depletion, whereas it involves enzyme inhibition in a small molecule. Finally, the manufacturing cost of a biologic is higher than that of a small molecule.

G&H What is the rationale for using biosimilars in patients with inflammatory bowel disease?

GL The traditional medical armamentarium for inflammatory bowel disease (IBD) includes mesalamine products, corticosteroids, immune modulators, antibiotics, and biologics. IBD treatment can be quite expensive, particularly with biologics. Although biologics comprise only 1% of all written US prescriptions, these agents account for 28% of all drug spending, according to one estimate. Globally, it is expected that biologic sales will reach $180 billion this year, and approximately half of these sales will likely be attributed to 11 biologics that will lose exclusivity within the next 5 years. The use of biosimilars can reduce the cost of IBD treatment and potentially improve access to medication. Based on estimates from *IMS Health* published last year, the use of biosimilars could save health care systems in the European Union and the United States over $56 billion, and potentially up to $112 billion, over the following 5 years.

G&H Which IBD biosimilars are currently available in the United States?

GL The biologic agent infliximab (Remicade, Janssen) was approved by the FDA in August 1998. Currently, there are 2 biosimilars to infliximab that are commercially available in the United States: infliximab-dyyb (Inflectra,

Celltrion; approved in April 2016) and infliximab-abda (Renflexis, Merck; approved in April 2017). In August 2015, the FDA proposed a rule for drug naming in which each biosimilar, as well as the originator biologic, includes a unique suffix of 4 random lowercase letters so that providers cannot use the name to make assumptions about the drug's safety and efficacy. Under this rule, the originator infliximab is referred to as infliximab-hjmt.

Regulatory approval has also been granted to adalimumab-atto (Amjevita, Amgen; approved in September 2016, although not yet commercially available), which is a biosimilar to adalimumab (Humira, AbbVie).

In addition, numerous applications are currently being reviewed by the FDA for other infliximab and adalimumab biosimilars.

G&H What are the steps in the regulatory review process for production of biosimilars in the United States?

GL In the United States, biosimilarity is established via a 3-step process. First, the proposed biosimilar must be evaluated for quality (ie, structure and function). A biosimilar must have the same amino acid sequence and potency as the originator biologic. However, small glycosylation differences and posttranslation alterations may be permitted. Sensitive assays should be used to determine whether any differences are relevant. A biosimilar must also have the same effector functions and mechanism of action as the originator biologic. If the effector functions differ, the proposed biosimilar and the originator biologic are not highly similar, which means that they are not biosimilar to each other. The agent will have to be re-engineered to become a biosimilar.

Second, the proposed biosimilar must undergo pharmacologic evaluation. Healthy volunteers are used for this step because such a population is generally the most sensitive for evaluating similar pharmacokinetics between the proposed biosimilar and the originator biologic. The same dose of each of these agents must show equivalent potency and functions.

Third, a randomized, blinded, head-to-head study in a sensitive population with sensitive endpoints is used to establish clinical efficacy. For example, the endpoints that were used for FDA approval of the biosimilars to infliximab involved patients with psoriatic arthritis and ankylosing spondylitis. In addition, at least 1 sensitive patient population must be used to establish clinical safety. For example, the proposed biosimilar can be examined as monotherapy with adequate exposures per time. Finally, drug-tolerant assays must be used to evaluate immunogenicity in a sensitive population (eg, patients who are not on any immunosuppressive therapy or chemotherapy).

G&H What is meant by the concept of extrapolation of indication?

GL According to this concept, a biosimilar can be approved for an indication of an originator biologic even though the biosimilar was not evaluated in a comparative clinical trial for the indication. Under this scientific rationale, all of the collected data (ie, the totality of the evidence) from 1 of the biosimilar's indications can be applied to all of the originator biologic's approved indications. Thus, findings of 2 studies of infliximab-dyyb (then referred to as CT-P13) in rheumatoid arthritis and psoriatic arthritis were extrapolated to Crohn's disease and ulcerative colitis.

Extrapolation of indication is used for biosimilars in the United States and several other countries, although this concept is considered to be somewhat controversial.

G&H Are biosimilars interchangeable with the originator biologic?

GL Interchangeability is a higher standard than biosimilarity. To be interchangeable, drugs must meet the criteria for biosimilarity, as well as be able to achieve the same clinical result in a given patient, and providers must be able to switch these agents with each other without decreasing safety or efficacy. Thus, biosimilars and originator biologics are not necessarily interchangeable in all scenarios. Interchangeability is currently determined on a state-by-state basis in the United States. To date, there are no interchangeable infliximab or adalimumab products available. Recently, the American Gastroenterological Association made 6 recommendations to the FDA regarding the concept of interchangeability in response to the FDA's draft guidance (Table).

G&H Is nonmedical switching between biosimilars and originator biologics appropriate?

GL In nonmedical switching, a patient is in a clinical state of well-being on an agent (eg, infliximab) and an insurance company or provider decides that the individual needs to switch to another agent (eg, a biosimilar to infliximab) not because of a medical reason but to save money. There have been several studies on this issue, but there is not yet adequate large-scale, well-powered evidence to suggest whether nonmedical switching is appropriate. The NOR-SWITCH study attempted to look at this issue, but it did not look at factors such as mucosal healing, it was of a relatively short duration, and it looked at many different endpoints with different disease states. Also, it only looked at a single switch from the originator infliximab to the biosimilar. Another short-term study was presented at this

Table. The American Gastroenterological Association's Recommendations to the FDA Regarding Interchangeability of Biosimilars[a]

- Extrapolation of data should not be allowed for any indication where the pathophysiology is known to be different or is yet to be elucidated.
- The agency should use caution when allowing extrapolation for pediatric indications.
- Sponsors should exclusively use US-licensed reference products in switching studies.
- "Real-world" data on biosimilar and interchangeable products must be collected through formal postmarketing observational studies to ensure the longitudinal safety and efficacy for all patient populations being treated with these products.
- Gastroenterologists with appropriate disease expertise should be engaged by the FDA when interchangeable products are reviewed for approval.
- Prescribing physicians must be empowered with the ability to prevent non-medical switching from a reference product to an interchangeable product.

FDA, US Food and Drug Administration.

[a]These 6 recommendations are quoted directly from "AGA makes six recommendations to FDA on interchangeable biosimilars. American Gastroenterological Association. http://www.gastro.org/news_items/aga-makes-six-recommendations-to-fda-on-interchangeable-biosimilars. Updated May 25, 2017. Accessed September 8, 2017."

year's European Crohn's and Colitis Organisation meeting. The authors found that, up to week 6, CT-P13 and the originator infliximab had similar efficacies and safety profiles, thus supporting the use of nonmedical switching. However, these were not large studies that were powered, for example, for regulatory approval. As previously mentioned, the studies that were used to gain regulatory approval for biosimilars were not performed in patients with IBD.

G&H Is immunogenicity the same for a biosimilar and for the originator biologic?

GL It should be. There are many questions that need to be addressed regarding immunogenicity, or the formation of antibodies against a foreign protein (ie, the biologic agent). Is it possible to switch from an originator biologic to a biosimilar without immunizing the patient? To answer this question appropriately, patients on immune modulators, as well as patients not on immune modulators, should be evaluated to prospectively assess whether antibodies form. To date, studies have suggested that there are similar levels of antibody formation in patients receiving the originator biologic and the biosimilar. However, many uncertainties exist. What happens if the patient undergoes a double switch of therapy—ie, the patient is on an originator biologic and then is switched to a biosimilar, and subsequently the insurance company or provider decides to switch the patient to a different biosimilar? Currently, there are no data available on this issue. It would be best to formally study patients over a time period of 6 months to a year, and test large numbers of patients. However, these studies are, unfortunately, unlikely to be conducted because the mandate for biosimilars being approved differs from the mandate for approval of the originator biologics. In addition, the FDA does not require large registries of patients taking biosimilars, as it does with patients taking originator biologics (eg, with the TREAT [Therapy, Resource, Evaluation, and Assessment Tool] registry [ClinicalTrials.gov Identifier: NCT00553176] and SECURE [Cimzia Crohn's Disease Post-Marketing Registry; ClinicalTrials.gov Identifier: NCT00844285]).

Dr Lichtenstein has consulted for Abbott Corporation/AbbVie, Actavis, Alaven, Celgene, Ferring, Hospira, Janssen Orthobiotech, Luitpold/American Regent, Pfizer Pharmaceuticals, Prometheus Laboratories, Romark, Salix Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, Takeda, and UCB; conducted research for Celgene, Janssen Orthobiotech, Salix Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, and UCB; received honorarium (CME Program) from Ironwood, Luitpold/American Regent, Merck, and Romark; and received funding to the University of Pennsylvania (IBD Fellow Education) from Janssen Orthobiotech, Pfizer Pharmaceuticals, and Takeda.

Suggested Reading

AGA makes six recommendations to FDA on interchangeable biosimilars. American Gastroenterological Association. http://www.gastro.org/news_items/aga-makes-six-recommendations-to-fda-on-interchangeable-biosimilars. Updated May 25, 2017. Accessed September 8, 2017.

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