bpc BiologicsPrescribers COLLABORATIVE
A PROJECT OF AfPA

Indication Extrapolation

If a prescription medication is approved to treat a specific disease or condition, do you assume that it has undergone full testing for that condition?

This assumption is usually valid. Shortcuts do exist, however, for generic drugs—conventional medications with exactly the same chemical composition as the original innovator drug. Because drugs such as generic aspirin and ibuprofen are chemically identical to the innovator brand drugs, it is assumed that they will act the same way as the brand drugs in all diseases and conditions.

But this logical assumption doesn't apply to biological medications—those made from living organisms or cells.

BIOLOGICS, BIOSIMILARS & INDICATION EXTRAPOLATION

Unlike generic drugs, biological medications cannot be exact copies of one another. Policymakers must navigate, therefore, to what extent biosimilars should be tested in patients with different diseases—or whether they should be automatically approved for all of the innovator biologics' indications through a process known as indication extrapolation.

Given that biosimilars cannot be exact copies of the original innovator biological medications, they may not act the same way in every disease state, possibly triggering unforeseen adverse effects. For this reason, each biosimilar should be considered on a case by case basis to determine the extent of evidence required for patients with different diseases.

WHY INDICATION EXTRAPOLATION POSES CHALLENGES FOR BIOSIMILARS

Biological Medications Impacts the Immune System

One of the ways that the underlying chemical differences in biosimilars may cause different effects in patients is via their impact on the immune system. Even minor differences in biological medications can affect the immune response in ways that may not always be predictable.[2]

In some cases, this may lead to unforeseen adverse events that could compromise patient safety, as happened with a biologic known as epoetin used for the treatment of chronic kidney disease. In this case, a small change to the biologic's manufacturing process led to an increase in the development of antibodies, which caused a condition of severe anemia in some patients.[3]

Route of Administration and Dose

Another important situation in which differences between biosimilars and innovator biologics may be apparent is when they are administered at different doses and/or via different routes (eg, intravenous, intramuscular, or subcutaneous).

For example, a medication may be more rapidly distributed or eliminated from the body following intravenous administration than intramuscular administration. Additionally, when administered subcutaneously, a biological medication is generally more likely to stimulate the immune system than when administered intravenously.[4,5]

Given the different composition of body tissues, it cannot be automatically assumed that a biological product will act the same way when administered via different routes and at different doses.

Mechanism of Action

As complex proteins, many biologics have more than one mechanism of action. For example, a group of medications known as monoclonal antibodies may act through multiple mechanisms. In one disease, the medication may act through only one of these mechanisms, whereas in another disease, all of the mechanisms may be important.[2] Even one single change in a chemical group can change the mechanism of action.

Consequently, it cannot be assumed that a biosimilar has the same mechanism of action as an innovator biologic unless their structures are identical.

Differences In Disease States and Patient Characteristics

Finally, differences in disease states and patient characteristics present problems for indication extrapolation. In some diseases, the immune system may be more active than others, leading patients to respond differently to biosimilars. Patients with some diseases may be older, more prone to certain adverse effects of the medication, or taking other medications that could alter the effects of a biosimilar.

Particular caution may be warranted in attempting to extrapolate indications to diseases that are highly dissimilar. Some biological medications, such as the monoclonal antibodies, are indicated for very different diseases; for instance, rituximab is indicated for both rheumatoid arthritis and a type of cancer known as non-Hodgkin's lymphoma.[2]

Not only are the disease mechanisms likely quite different in these two conditions, but the patient characteristics are also dissimilar.

CONCLUSIONS

Given the complex chemical nature of large biological medications, even minor differences between innovator biologics and biosimilars raise serious concerns for patient safety. Therefore, caution is warranted when attempting to extrapolate the indications from an innovator biologic that has undergone extensive clinical trials in actual patients to a biosimilar that has not.

In order to err on the side of safety, the extent of evidence required for a biosimilar to grant indication extrapolation should be considered extremely carefully and on a case by case basis.

References

1. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. Ann Oncol. 2008;19:411-9. 2. Scott BJ KA, Wang J. Biosimilar monoclonal antibodies: a Canadian regulatory perspective on the assessment of clinically relevant differences and indication extrapolation. J Clin Pharmacol. 2014;In Press: 3. Woodcock J, Griffin J, Behrman R, et al. The FDA's assessment of follow-on protein products: a historical perspective. Nat Rev Drug Discov. 2007;6:437-42. 4. Allergan, Inc. . BOTOX® Prescribing Information. Available at: http://www.allergan.com/assets/pdf/botox_pi.pdf. Accessed August 22, 2014. 5. Brennan FR, Morton LD, Spindeldreher S, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. Monoclonal Antibodies. 2010;2:233-55.

bpc BiologicsPrescribers COLLABORATIVE

A PROJECT OF AfPA

The Biologics Prescribers Collaborative works to ensure that the voices of clinicians who prescribe complex biological treatments inform policies that shape the use of these medicines. Member organizations represent specialty prescribers of biologics for chronic, life-threatening illnesses.

Adapted from "What is Indication Extratpolation and Should it be Allowed with Biological Medicines?" by David Charles, MD, and Mary Ann Chapman, PhD; Institute for Patient Access, November 2017.