ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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How Biosimilars Will Impact Costs and Care in Oncology

Gary H. Lyman, MD, MPH, FASCO, FACP, FRCP(Edin)
Senior Lead, Healthcare Quality and Policy
Hutchinson Institute for Cancer Outcomes Research
Fred Hutchinson Cancer Research Center
Professor of Medicine, Public Health and Pharmacy
University of Washington
Seattle, Washington

H&O How does a biosimilar compare to a biologic therapy or a generic formulation?

GL To start, it is necessary to distinguish biologic molecules from simple chemical molecules, which represent the earlier types of medications that we are all familiar with. Biologic agents are produced in living systems, such as cells or bacteria. Compared with a simple chemical molecule, a biologic molecule is far more complex and often much larger. It cannot be replicated exactly because of the complexity. It is possible to synthesize a simple chemical in a test tube at a laboratory or production facility. The production of biologic therapies is far more complicated and can be altered by minor differences in the components or the manufacturing process.

Most biologic therapies are very expensive. One opportunity to increase competition and lower prices as the patents expire on biologic therapies is for other companies to replicate them as biosimilars, which represent a highly similar biologic to the originator. The challenge arises from the complexity of these biologic molecules; replicating them is no easy task. A formula can be used to exactly replicate simple small molecules in the laboratory to produce a generic molecule. For all intents and purposes, the generic drug should be exactly the same chemical as the original molecule. In contrast, a biologic agent cannot be replicated exactly, but it can be reproduced as a highly similar agent or biosimilar. As defined by the US Food and Drug Administration (FDA), a biosimilar is a molecule that is highly similar to a biologic agent in terms of chemical characteristics; mechanism of action; behavior in preclinical systems, such as animals; activity in humans; pharmacokinetics; and pharmacodynamics. A biosimilar must meet certain quality benchmarks that confirm close similarity, suggesting that it will function the same as the original molecule.

H&O What are the goals for the use of biosimilar drugs?

GL The goals revolve around competition and cost reduction to increase access and affordability. The biologic therapies developed in the past 10 to 20 years have revolutionized medicine, most notably oncology and hematology. They have dramatically improved the treatability and clinical outcomes of several forms of cancer, as well as several noncancerous conditions. As one example, human epidermal growth factor receptor 2 (HER2)-positive breast cancer used to be considered the worst form of the disease and was highly lethal in most patients. It is now one of the most successfully treated forms of breast cancer because several biologic therapies target the specific genetic mutation in this subtype. Trastuzumab was the first biologic agent approved for HER2-positive breast cancer, and it is still the most common biologic treatment in this setting. Trastuzumab and subsequent forms of anti-HER2 biologic therapies have tremendously improved curability and long-term disease control in these patients.

A challenge to the use of biologic therapies is their high cost. They may be unaffordable or cause dire financial hardship to patients and their families. Rates

of bankruptcy are at least 2 times higher among cancer patients compared with the general population. In some cases, patients may choose to avoid treatment altogether, stop treatment early, or assume the enormous financial burden. Although the potential price reduction associated with biosimilars is important, it is also necessary to ensure that all patients who should get treated with these drugs can access them, are able to receive them, and can complete their treatment. These issues are interwoven with the cost and affordability of these drugs.

H&O What can be learned from the development and use of biosimilars in Europe?

GL The Europeans are approximately a decade ahead of us in terms of access to and use of biosimilars in clinical practice. They have been using biosimilars for more than 10 years, and many more biosimilars are approved in Europe than in the United States. In Europe, no biosimilars have been removed from the marketplace because of toxicities or unexpected complications. While the European experience is very reassuring, it is still necessary to be vigilant, and to follow the process we have established in the United States to ensure the efficacy and safety of biosimilars. Postmarketing surveillance is another important way to monitor these drugs.

H&O What are some biosimilar drugs currently approved in oncology?

GL Currently, 23 biosimilars are approved in the United States, of which more than half are utilized in oncology and hematology, including 9 for the actual treatment of cancer (Table). The first approved biosimilar, filgrastim-sndz (Zarxio, Sandoz), is a supportive care drug. It was approved by the FDA in 2015. Filgrastim is a granulocyte colony–stimulating factor that reduces the side effects of chemotherapy by raising the white blood count. Another version, filgrastim-aafi (Nivestym, Pfizer) was approved in 2018. Also in 2018, the FDA approved 2 biosimilars of the long-acting version of this drug: pegfilgrastim-jmdb (Fulphila, Mylan) and pegfilgrastim-cbqv (Udenyca, Coherus). A biosimilar of epoetin alfa, known as epoetin alfa-epbx (Retacrit, Pfizer), was approved in 2018.

In June 2019, the FDA approved the fifth biosimilar version of trastuzumab, which is known as trastuzumab-anns (Kanjinti, Amgen/Allergan). Also in June 2019, the FDA approved the second biosimilar of bevacizumab, a treatment for malignancies such as colon cancer and ovarian cancer, known as bevacizumab-bvzr (Zirabev, Pfizer). Finally, the biologic rituximab has changed the treatment landscape for lymphoma. In 2018, the FDA approved the first biosimilar version, rituximab-abbs (Truxima, Celltrion/Teva). A second biosimilar version, rituximab-pvvr (Ruxience, Pfizer), was approved in July 2019.

Table. Biosimilars Approved by the FDA

Biosimilar	Approval Date
Hadlima (adalimumab-bwwd)	July 2019
Ruxience (rituximab-pvvr)	July 2019
Zirabev (bevacizumab-bvzr)	June 2019
Kanjinti (trastuzumab-anns)	June 2019
Eticovo (etanercept-ykro)	April 2019
Trazimera (trastuzumab-qyyp)	March 2019
Ontruzant (trastuzumab-dttb)	January 2019
Herzuma (trastuzumab-pkrb)	December 2018
Truxima (rituximab-abbs)	November 2018
Udenyca (pegfilgrastim-cbqv)	November 2018
Hyrimoz (adalimumab-adaz)	October 2018
Nivestym (filgrastim-aafi)	July 2018
Fulphila (pegfilgrastim-jmdb)	June 2018
Retacrit (epoetin alfa-epbx)	May 2018
Ixifi (infliximab-qbtx)	December 2017
Ogivri (trastuzumab-dkst)	December 2017
Mvasi (bevacizumab-awwb)	September 2017
Cyltezo (adalimumab-adbm)	August 2017
Renflexis (infliximab-abda)	May 2017
Amjevita (adalimumab-atto)	September 2016
Erelzi (etanercept-szzs)	August 2016
Inflectra (infliximab-dyyb)	April 2016
Zarxio (filgrastim-sndz)	March 2015

FDA, US Food and Drug Administration.

This list was prepared in August 2019, based on data from: FDA-Approved Biosimilar Products. FDA.gov. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information. Updated July 23, 2019. Accessed September 17, 2019.

H&O Are these biosimilars in widespread clinical use?

GL Several biosimilars have already been integrated into clinical practice and guideline recommendations as viable alternatives to the originator. In the area of supportive care, more than half of the drugs now in use are biosimilars.

However, not all of the FDA-approved biosimilar

cancer therapies are available in pharmacies yet owing to challenges with patents. Although they should be available soon, there may still be some reluctance among clinicians to use a biosimilar for the treatment of cancer, rather than simply as supportive care. I anticipate that cancer therapies may be adopted in a somewhat irregular fashion, and used in certain clinical contexts but not others. Broad utilization of biosimilars is expected over the next 2 or 3 years, if the US experience mirrors that in Europe. It will be interesting to see how the availability of multiple biosimilars as a mainstay of cancer treatment will impact prices, competition, access, and choices for patients.

In many ways, biosimilars that are approved today are more carefully scrutinized and manufactured than the original agents.

H&O What is the FDA approval process for biosimilars?

GL The FDA wants to encourage competition among highly similar agents. At the same time, the FDA wants to establish a reliable process to ensure that a biosimilar is highly similar to the original biologic and can be expected to behave the same in terms of treatment outcomes and adverse events.

The FDA requires data that focus on molecular characteristics to ensure that the biosimilar is as close as possible to the original biologic molecule. There must be evidence in both animals and humans that the biosimilar has the same mechanism of action as the originator and has the same pharmacokinetic and pharmacodynamic effects in the body. The FDA uses approximately 60 different criteria to judge similarity.

If any uncertainty remains after this appraisal, the FDA can require direct comparative studies. Studies comparing biosimilars to their originators have generally demonstrated similarity, or noninferiority, meaning that they will behave and function in essentially the same way. Generally, these are not large studies, as were required for approval of the original drug. They are far more limited in size and scope. The FDA does not want the cost of developing biosimilars to become a barrier to manufacturers or to add to the price of the drug.

H&O What is the role of postmarketing surveillance for biosimilars?

GL Many clinicians recognize that the process of regulatory approval for biosimilars is highly developed. Even the ability to characterize a molecule and its function are much further along than 20 years ago, when many of the original biologics were developed. In many ways, biosimilars that are approved today are more carefully scrutinized and manufactured than the original agents. Nonetheless, it is necessary to vigilantly monitor the manufacture and utilization of biosimilars, as well as to identify any rare or delayed adverse events that were not apparent at the time of regulatory approval.

Postmarketing surveillance has an important role for biosimilars, and the FDA is taking it very seriously. I believe that the main roles of postmarketing surveillance are to ensure safety and provide reassurance. The medical community is naturally skeptical because FDA approval of biosimilars is based on fewer comparative clinical data than are required for originator therapies. Clinicians want evidence showing that biosimilars are as safe and effective as the original products. Clinicians can be assured that biosimilars will be monitored very closely even after they are approved by the FDA and enter the marketplace. The FDA is working with the American Society of Clinical Oncology (ASCO), as well as certain companies, to emphasize how important it is for clinicians and patients to report the adverse events seen with biosimilars. Rare or unexpected adverse events are of particular importance, as toxicities may develop with long-term use.

There is a similar postmarketing surveillance process in Europe. After 10 years, no biosimilar has been removed from the market. I anticipate that clinicians in the United States will embrace biosimilars as they gain individual experience, and as more widespread use raises no safety issues. Postmarketing surveillance will likely provide reassurance that biosimilars can be safely and effectively used as part of the solution to the high cost of health care delivery in the United States.

H&O Does it appear that the use of biosimilars has already reduced the cost of treatment?

GL It will likely be another 1 or 2 years before we see how biosimilars impact the cost of cancer care. Published data for 2015 to 2017 show that the price of a supportive care biosimilar is approximately 10% less than the originator. Of course, we would like to see a larger reduction. Data from Europe suggest a price reduction of 20% or 25%. These reductions are far less than those seen with generic medicines, which can lower prices by 70% or 80%. Such a drastic price reduction will not

be seen with biologics, however, as they are much more complicated and expensive to produce. Nevertheless, even a 20% or 25% reduction in price would be substantial, since the field of biologics for cancer treatment is a multibillion dollar industry worldwide.

If a biosimilar has been shown to be highly similar to the originator—essentially as effective and safe—but the price is much lower, there may be opportunities to reduce the cost of health care. I expect that major price reductions will occur when there are multiple biosimilar versions of an originator, and companies compete to have their product selected for use in clinical practice. Biosimilars may also increase the ability to negotiate drug prices directly with industry. For practicing oncologists/hematologists, particularly those in large health care systems, the decision of which drug to use is often made by the institution or a pharmacy and therapeutics committee based on negotiations with payers or industry to purchase a drug at the lowest price. Although there is concern among physicians that they are being told which drug to use, there is also hope that this process leads to price reductions. Medicare is precluded by the US Congress from negotiating with industry to obtain lower prices. The United States is the only developed country where the health care system is not allowed to negotiate with industry for a more reasonable price on drugs. At least until this issue is resolved, another approach to price reduction might be competition. Companies can try to outbid one another by lowering the price of a drug, so that drug is selected for use by a particular institution.

We also need to limit the cost of new drugs; the average newly approved cancer therapy costs more than $10,000 a month. Biosimilars will allow competition that should decrease the cost of cancer care, while improving patient access to very effective but expensive medications.

H&O What was the goal of ASCO's statement on biosimilars?

GL I was privileged to chair this panel of experts on cancer therapies and biologics, which developed ASCO's statement on biosimilars. The major goal of the statement was education. ASCO is the largest professional oncology society in the world. The 2019 annual meeting drew more than 30,000 oncology professionals from around the world. Therefore, ASCO carries enormous influence. One of its primary objectives is continuing education of the oncology community. We saw the rapid advent of biosimilars, and we heard questions about them from the community. ASCO therefore responded by publishing a statement that reviewed the entire subject and addressed common questions of practitioners and patients about biosimilars. Since the first statement was published in February 2018, the FDA has approved more than 10 biosimilars. The FDA has ramped up their approval process, with an emphasis on developing and approving biosimilars. It may be necessary in the near future to provide an updated ASCO statement on the rapidly changing availability and use of biosimilars in oncology. At the same time, there may be lingering concern within the oncology community. ASCO will continue to provide educational programs at the annual meeting, as well as webinars and podcasts.

Disclosure

Dr Lyman has consulted for Agendia, Amgen, Genomic Health, Halozyme, Mylan, Partners Healthcare, Pfizer, Samsung Bioepis, and Spectrum Pharmaceuticals.

Suggested Readings

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