Biosimilars in Breast Cancer

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Medical Writer
Jonathan Bell, MS
Associate Medical Writer

The American Journal of Hematology/Oncology® Editorial Board
Debu Tripathy, MD
Professor and Chairman
Department of Breast Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX

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Faculty
Adam M. Brufsky, MD, PhD, FACP
Professor of Medicine
Associate Division Chief
Department of Medicine
Division of Hematology/Oncology
University of Pittsburgh School of Medicine
Pittsburgh, PA

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This activity is designed to inform physicians about the current availability and use of biosimilars in breast cancer.

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with breast cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Explain the approval process of biosimilar drugs and the differences between biosimilar drugs and their references
- Describe the benefits and potential drawbacks of using biosimilars to treat patients with breast cancer
- Discuss the emerging equivalence data surrounding FDA-approved biosimilars

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Contact information for questions about the activity:
Physicians' Education Resource®, LLC
2 Clarke Drive, Suite 110
Cranbury, NJ 08512
Phone: (888) 949-0045
E-mail: info@gotoper.com

Introduction

Breast cancer accounts for approximately 15% of all new cancers in American adults.[1] The median age at diagnosis is 62 years.[1] In 2017, it is estimated that 252,710 new cases of breast cancer will be diagnosed in women and 2470 new cases will be diagnosed in men.[2,3] Breast cancer is the second most prevalent cancer in American women, behind skin cancer.[2] It is estimated that 40,610 women and 460 men will die of breast cancer this year.[1,4] At the time of diagnosis, 62% of breast cancers are confined to the localized stage, 31% have spread to regional lymph nodes, and 6% are considered metastatic.[1] Overall, the median 5-year survival of patients with breast cancer is almost 90%: 99% in patients with localized disease, 85% in patients with regional disease, and 27% in patients whose cancer has metastasized.[1] Currently, more than 3 million breast cancer survivors are living in the United States.[1,2]

Breast cancer status is usually defined by the presence or absence of mutations in estrogen receptors, progesterone receptors, or human epidermal growth factor receptor 2 (HER2); cancers lacking mutations in all 3 receptors are referred to as triple negative. Treatment strategies for breast cancer are dependent on this mutational status.

The average cost for the treatment of breast cancer varies by mutation status, and stage at diagnosis, as well as insurance coverage. A recent retrospective analysis of insurance claims data found that the average costs per patient in the 2 years following initial diagnosis were $72,000, $97,000, $159,000, and $183,000 for patients with stage 0, I/II, III, and IV breast cancer, respectively.[5] An emerging shift in the treatment of breast cancer includes the increased approval and usage of biosimilars. Biosimilars may be a potential solution to the costly nature of current treatment options and may lead to a wider range of treatment options for patients with breast cancer.

What Are Biosimilars?

Stated simply, biosimilars are biological products—drugs made of carbohydrates, amino acids, and nucleic acids, or combinations thereof and produced in organisms including bacteria, yeast, or higher life forms—shown to be highly similar in structure, safety, and efficacy to existing, FDA-approved biological products.[6] A further differentiation is the class of products known as interchangeable drugs, which are biosimilars shown to achieve the same clinical result as a given reference drug in any patient. As a result, interchangeable drugs may be substituted without consulting health care providers who prescribed the reference drug.[6]

Biosimilars are unique in their approval process by the FDA. This process was detailed in the Biologics Price Competition and Innovation (BPCI) Act of 2009 as part of the Affordable Care Act.[7] Under the BPCI Act, biosimilar agents may be approved if "the biological product is similar to a reference product based upon data derived from"[8]:

- Analytical studies that demonstrate that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); and
- A clinical study of studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency.

A biosimilar product is approved under section 351(k) of the Public Health Service (PHS) Act, based upon biological products licensed under section 351(a) of the PHS.[7,8] Overall, the approval timeframe of biosimilar agents is abbreviated, as it is able to rely on clinical data from the reference drug. To date, 5 biosimilars have been approved in the United States: 1 biosimilar each of filgrastim, etanercept, and adalimumab, and 2 biosimilars of infliximab.[9,10] Trials of many other biosimilars, including those for the treatment of breast cancer, are ongoing.

Benefits and Risks of Biosimilars

Biosimilars, by definition, should not incur an increased clinical benefit; they are functionally biologically equivalent to the reference drug. Therefore, the most immediate benefit of biosimilar use is to drive down the cost of care. Quality-adjusted life years, which measure the cost of both the quality and quantity of life achieved, may be more attainable with the use of biosimilars.[11] In Europe, it has been shown that the average uptake, or penetration, of biosimilar use increases 6% on average every year after approval; additionally, the cost of a given reference drug has been shown to decrease approximately 3% each year after a biosimilar enters the market.[12] Barriers to entry include the complexity of manufacturing, need for further clinical trials, lack of automatic usage and substitution, and potential marketplace competition.[13]

Risks of biosimilars are more nuanced. Biosimilars are copies of existing biological agents whose patents have expired; however, they are manufactured in different cell lines, potentially resulting in unknown changes in folding or posttransational structure. They are then purified using a different process or possibly new technology.[14] Biosimilars are not exact copies of the reference drug, and as a result, before implementation can or will occur, specific safety and efficacy data must be validated.[14]

Biosimilars in Breast Cancer

While there are currently no FDA-approved biosimilars of drugs that treat breast cancer, many biologic antibodies are under investigation. Trastuzumab, a monoclonal antibody that targets HER2, was shown to inhibit the proliferation of breast cancer cells that overexpress HER2; in 2001, it was shown to improve the overall response rate (ORR), duration of response, and median survival in combination with chemotherapy compared with chemotherapy alone.[15] This led to the approval of trastuzumab in treating HER2-positive metastatic breast cancer in 2006.[16] Since then, trastuzumab approval has expanded to cover additional settings, treatment regimens, and cancer types. As of 2008, more than 420,000 women with HER2-positive breast cancer had received treatment with trastuzumab[17]; it is considered the standard of care. The US patent for trastuzumab is set to expire in June 2019; it expired in July 2014 in Europe.[18] The success of trastuzumab, in combination with its expired patent, has prompted the investment into competing biosimilars.

Although 19 biosimilars for trastuzumab are currently being investigated, MYL-1401O has shown the most success.[18] Results from the phase III HERITAGE trial in patients with HER2-positive metastatic breast cancer have been presented and published.[19,20] As progression-free survival or overall survival may be insufficient to demonstrate biosimilarity between reference products and their biosimilars, bodies such as the European Medicines Agency (EMA) have recommended using an activity-measuring clinical endpoint such as partial complete response (pCR) or ORR as the primary endpoint.[21] The primary outcome measure of this study was a comparison of the best ORR at week 24 between the combination of biosimilar trastuzumab (MYL-1401O) with taxane and reference trastuzumab with taxane. The study showed that patients receiving reference trastuzumab plus a taxane had an ORR of 64.0% at 24 weeks; patients receiving biosimilar trastuzumab plus a taxane had an ORR of 69.6%, a rate within predefined equivalence boundaries.[19,20] Progression-free survival at 48 weeks was 44.7% and 44.3% for reference and biosimilar trastuzumab, respectively; overall survival was 85.1% and 89.1%, respectively; adverse events affected 94.7% and 98.6% of patients, respectively.[19] MYL-1401O was submitted to the EMA for approval in August 2016 and to the FDA for approval that November.[22,23] PF-05280014, another biosimilar of trastuzumab, was reported as having demonstrated equivalence in its primary endpoint in November of last year; data from this study have not yet been presented.[24]

Important questions still remain in the testing of biosimilars. Thus far, the biosimilarity of MYL-1401O has only been evaluated in patients with metastatic disease, a population that differs from patients with early stage breast cancer. Further, the establishment of ORR as a primary endpoint has drawn concerns. Finally, biosimilar trastuzumab has been investigated only as a single agent, while trastuzumab plus pertuzumab is considered the standard of care.[11]

The development and testing of biosimilar drugs may continue to change the ways doctors treat their patients. Increased understanding of the approval and testing process, as well as potential benefits and risks of the use of biosimilars, is essential for practicing oncologists. Biologic pharmaceutical options remain costly, and incorporation of biosimilars may lead to health care savings of 30% or more, with market entry costs, pricing reactions, and many other factors establishing the ultimate level of cost reduction that may be seen.[25]

Adam M. Brufsky, MD, PhD, FACP, is professor of medicine at the University of Pittsburgh School of Medicine and the associate division chief for the Division of Hematology/Oncology at the University of Pittsburgh School of Medicine's Department of Medicine. He is also the medical director of the Women's Cancer Center at Magee-Womens Hospital of University of Pittsburgh Medical Center and the University of Pittsburgh Cancer Institute (UPCI), associate director for clinical investigations at UPCI, and codirector of the Comprehensive Breast Cancer Center.

Moderator: What benefits, considerations, and potential drawbacks do you see to utilizing biosimilars? How comfortable would you be using a biosimilar over a reference drug?

Dr Brufsky: The bottom line of biosimilars is that they are at least closely structurally similar to the reference drug, but they are slightly different. What you worry about with a biosimilar is changes in the conformation and the posttranslational processing of the protein. Remember, you are developing the biosimilar based on the amino acid sequence that you are getting from a DNA sequence. You have the DNA sequence, but you have no idea how the protein is processed because you are expressing this protein in a different cell line that's secreting it, or in bacteria. The biggest drawback is you have no idea—you are supposed to have an idea, but you may not—about all the posttransational processing that goes on that may be slightly different between new drugs. And for that reason, you really should do some sort of an equivalence study of the biosimilar, to be sure that the drug acts in the same way that the FDA and other organizations have required. We could be critical about how they do that testing and what they require, but nonetheless, that is the essential biggest drawback with these drugs.

On the other side, if you have another drug, a competitor drug, in this space where you've never had one, that's going to drive down the cost. Sunil Verma, MD, MSEd, a Canadian oncologist, has done some very nice speaking and analyses on the fact that biosimilars could drive the cost of care down by about 25%. I think they looked at it in Europe and they found that when biosimilars were introduced, it drove the cost of care down. And that is really the only reason to use a biosimilar.

I do not have a problem using these drugs as long as I am sufficiently satisfied with the data of equivalence. In oncology now, there are a number of equivalence trials. At least when it comes to biosimilar trastuzumab, presented by Hope Rugo, MD, at ASCO [the American Society of Clinical Oncology meeting] last year, the data looked pretty good. It looks fairly similar compared with reference trastuzumab. My view is that I am okay with using biosimilars in this setting as long as I am comfortable with equivalence data.

In your opinion, what are the barriers for physicians to adopting biosimilars?

I think it is the comfort level with the equivalence data. I think that is the biggest one. If physicians had a comfort with the equivalence data, they would likely adopt it. Again, I think that if the reference drug is the same cost, there is no reason to adopt the biosimilar.

When considering study design, aside from providing evidence of biosimilarity, how important is it to test a proposed biosimilar in combination with other therapeutic agents?

It is a good question, and I think it is one that we ask ourselves all the time. The example is trastuzumab. We do not have a trial with biosimilar trastuzumab with pertuzumab, and I think that could be concerning because there may be—again, because of the posttransational processing differences—potential differences. Situations may arise where the biosimilar is not going to work; the antibodies are not going to bind to each other. You do not know that. I think that there should be some data. Doctors are going to have to make decisions

based on this, and hopefully there will be some data with combinations that we could use to help us make our decisions.

The phase III HERITAGE trial results presented at the 2016 ASCO meeting, as you already mentioned, showed similar overall response rates for MYL-1401O to branded trastuzumab. Would you be able to provide us with a brief overview of the findings from this study and its clinical implications?
The bottom line is that the progression-free survival was the same roughly in both arms of the study. Those are the top-line data of this particular trial, and there were no additional safety signals that were found. In a phase III trial in first-line metastatic breast cancer treatment, there was no difference in HER2-positive metastatic breast cancer.

Now, the issue is, of course, the standard of care now in HER2-positive first-line metastatic breast cancer is trastuzumab and pertuzumab together with chemotherapy, and that was not tested. So, that is a flaw in this particular trial.

So, again, it sounds like the fact that there was a lack of combinations, of trastuzumab with pertuzumab, is a pitfall of this study. Would you agree?
Yes, absolutely.

If there is a new indication for a biosimilar drug, does that change the indication of the reference?
The FDA is going to give approval based on original trials. The thing is, the trial data are the trial data, whether it is with the biosimilar or not. I think if there is a trial with a biosimilar that shows efficacy in a new indication, then the reference drug can be used that way, too. They are interchangeable. It should not make a difference. The drug is the drug, as far as I am concerned.

What gaps in awareness, usage, and education exist among patients, caregivers, and/or advocacy groups about biosimilars? What can physicians do to increase awareness among patients and caregivers?
I think they are already aware to some degree. Again, they will be aware because it is going to reduce the cost of care. We need an overall educational piece for the advocates and patients, just to let them know that these are likely the same drugs and will drive down cost. But where there are differences, we have to find out.

Researchers have to show biosimilarity compared with a reference drug. However, the FDA does not require that you show efficacy of the biosimilar drug itself.
That is correct.

Do you just focus on the bioequivalence or would you as a physician like to see that additional data?
I like additional data when I can get them. Especially with a biosimilar because it is really a different kind of drug.

Finally, do you think that biosimilars will be the future standard of care?
I do. I think there will be biosimilars that become the future standard of care because they are going to drive the cost down.

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