The Practical Oncologist

The Use of Biosimilars in Hematology/Oncology Practice

Charles L. Bennett, MD, PhD, MPP
Frank P. and Josie M. Fletcher Chair
SmartState Chair and Director
SmartState Center for Medication Safety and Efficacy
University of South Carolina
Columbia, South Carolina

Marc L. Fishman, MD, CM
Assistant Adjunct Professor
University of South Carolina College of Pharmacy
Columbia, South Carolina
Oncology Analytics, Inc.
Plantation, Florida

Kevin Knopf, MD, MPH
Assistant Clinical Professor
University of California, San Francisco
Division Chief of Hematology/Oncology
Highland Hospital
Oakland, California

What is the aim of biosimilars in hematology/oncology practice?

Dr. Charles Bennett: The US Food and Drug Administration (FDA) established the biosimilars licensure pathway to provide additional treatment options, increase medication access, and potentially, lower health care costs as a result of competition.[1] Of these aims, lowering the cost of care in biologic therapy is quite important.

A major driver of interest in biosimilars is the huge anticipated growth of the overall global market for cancer biologics. From 2020 to 2021, the global cancer biologics market grew by 6.9%, from $66 billion to $71 billion. It's expected that the market will reach $93 billion by 2025.[2]

We know that biologic drug therapies are integral to treat cancer patients, but can be expensive. These products, such as cell therapies, cytokines, growth factors, monoclonal antibodies, and monoclonal antibody-drug toxin combinations, are all manufactured in living systems, which makes them complex to produce. That complexity translates into a higher price tag: the median annual cost of oncology/hematology biologic therapies today is nearly $143,000 per patient.[3]

What exactly is a biosimilar?

Dr. Charles Bennett: The FDA has defined biosimilars as biological products that are *highly similar* to an existing FDA-approved reference product, with *no clinically meaningful differences* as compared to that reference product in terms of safety, purity, and potency.[1] This is demonstrated through human pharmacokinetic/pharmacodynamic studies and assessment of clinical immunogenicity.

Of note, clinicians should not confuse biosimilars with generics. They are very different from each other, even though they sound like they should be the same. Biosimilars are based on FDA-approved reference products that are biologics, or complex large-molecule drugs, while generics are based on simpler small-molecule drugs.

What are some of the fundamental principles for establishing clinical biosimilarity?

Dr. Kevin Knopf: The goal of biosimilars is to lower the cost of care in cancer by establishing similar efficacy and safety compared with a reference product—not to re-establish benefit. The clinical trial program includes the assessments of pharmacokinetics, if feasible, pharmacodynamics, efficacy, and safety, and the use of short-term surrogate endpoints such as overall response rate in one- or two-arm studies. In some settings, no clinical trials of cancer patients are needed for FDA approval of the oncology biosimilar, and preclinical data can constitute 90% of the dossier.

Are biosimilars truly as effective and safe as the reference product?

Dr. Charles Bennett: We are starting to see meta-analyses that compare the efficacy and safety of biosimilars to their reference product. For example, Botteri and colleagues conducted a meta-analysis showing no significant differences in clinical efficacy and safety between granulocyte colony-stimulating factor (G-CSF) biosimilars and their reference products, ie, filgrastim and pegfilgrastim. Eight randomized controlled trials were included. The overall difference in duration of severe neutropenia was not statistically significant between the biosimilars and reference products (0.06 d; 95% CI, 0.05-0.17). Likewise, there were no differences in secondary efficacy endpoints, bone pain events, myalgia events, or serious adverse events.[4]

What is the US experience with biosimilars?

Dr. Marc Fishman: To date, the FDA has approved at least 29 biosimilars. Many of these are relevant to hematology/oncology, including biosimilars to bevacizumab, epoetin alfa, filgrastim and pegfilgrastim, rituximab, and trastuzumab.

Dr. Charles Bennett: Although use is on the rise, currently biosimilars make up only about 2.3% of the overall biologics marketplace in the United States. More than 90% of biosimilar sales are in the EU, despite 60% of biologic sales overall taking place in the US.[5] Part of the reason is that biosimilars have been in place in Europe since about 2005, or 10 years before the United States. The US experience is clearly less mature as a result, but some reports are available that illustrate rapid uptake.

One such report shows a very rapid uptake of biosimilar filgrastim among large insurers, with the product achieving 50% market share one year after its approval.[6] A couple of factors contributed to this, including designation of the biosimilar as the preferred drug over reference filgrastim, oncologist acceptance of the biosimilar as having equivalent efficacy and safety versus reference filgrastim, and lower pricing after rebates for the biosimilar. Another example is the experience with biosimilar

epoetin for cancer and chemotherapy-induced anemia. One Medicare insurer indicated that this use of biosimilar epoetin increased from 0.4% in 2018 to 45.3% in 2019, and to 82.1% in 2020, while for the related commercial insurer, uptake increased from 1.6% to 17.1% to 62.5% over that same time period.[6]

What is the economic impact of biosimilars?

Dr. Marc Fishman: The typical list price for a biosimilar in the United States is about 15%, and sometimes up to 35%, lower than the reference product—not dramatic reductions, but significant. We do see large insurers starting to identify biosimilars as preferred therapy over reference biologics. In 2019, US health plans covered biosimilars as preferred in 14% of decisions, and that number seems to be going up quite significantly.[7,8] There's also a question of rebates, which are key to inclusion of biosimilars on formularies. Manufacturers negotiate rebate agreements with pharmacy benefit managers to ensure that their drug remains on the formulary, or on a preferred formulary tier. Rebate agreements are not publicly disclosed, and I think we would think all like to see more clarity and more transparency on rebates.

What are some of the factors behind the economic impact of biosimilars?

Dr. Marc Fishman: The economic effect of biosimilars is said to hinge on a wide array of factors, such as pharmacovigilance and safety, endorsement by the medical community, patient acceptance, price, competition, insurers, and reimbursement programs. In my experience, however, I don't think endorsement by the medical community or patient acceptance have been of particular concern. We don't see clinicians demanding the originator pharmaceutical over the biosimilar, and I've never heard of a patient saying, "I want the brand-name drug." The patient *will* be interested in the price—we know that because cancer patients endure a lot of financial stress and they will generally prefer a lower co-pay. In general, "price" is a pretty broad term and can mean many things – the cost to the patient, the cost to the health plan, and by inference, there's also profitability that's related to price.

Since they help reduce cost, can biosimilars help overcome healthcare disparities and access challenges?

Dr. Kevin Knopf: I'm interested in healthcare disparities and health economics, and a lot of healthcare disparities are related how assets are allocated among different patient populations. The high cost of biologic therapies exacerbates some healthcare disparities and leads to inequities in the use of these agents, and probably affects cancer outcomes disproportionately for certain patient populations in the United States. The biosimilars represent a cost-effective alternative to the reference product. They provide the same quality and efficacy of care at a lower cost. In the broader healthcare

system, they're a win-win situation in that they may enhance health equity.[9] However, to increase uptake of these agents, awareness must be increased among providers and patients. Most Americans have never heard of biosimilars, although the majority of them are aware of generic drugs. The negative perceptions of any patients or physicians around biosimilars must also be addressed.

How does the use of oncology biosimilars translate into clinical practice? Can you provide an example that illustrates best practices in implementation?

Dr. Kevin Knopf: My healthcare system is a public hospital. We care for the underserved, those with public insurance, either Medicare or Medicaid, or uninsured. We collaborated with a local Medicaid HMO that also interested in cost-effective care to look at our utilization of biosimilar medicines. As soon as biosimilars become available, we put them on our formulary. We have quickly moved to 100% adoption in the hematology-oncology space. Our other specialties, including neurology, rheumatology, and gastroenterology are not yet at 100%, but they are getting closer and closer, and I anticipate that they will be at 100% within the next 6 to 12 months. Our system requires that the product be on market for 6 months and go through our Pharmacy and Therapeutics (P&T) committee. To date, 100% of biosimilars that have come on the market have been approved by our P&T committee. I have mandated that all our oncologists use biosimilars unless there's a strong and valid objection, in which case exceptions can be made.

For more information on biosimilars, **click here**.

Provided by MediCom Worldwide, Inc.
This activity is supported by an educational grant from Pfizer, Inc.

References

1. US Food and Drug Administration. Biosimilars. Accessed February 15, 2022. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars.

2. Cancer biologics Global Market Report 2021: COVID-19 Growth and Change to 2030. Accessed February 15, 2022. https://www.researchandmarkets.com/reports/5446217/cancer-biologics-global-market-report-2021-covid.

3. Hernandez I, Bott SW, Patel AS, et al. Pricing of monoclonal antibody therapies: higher if used for cancer? *Am J Manag Care*. 2018;24(2):109-112.

4. Botteri E, Krendyukov A, Curigliano G. Comparing granulocyte colony-stimulating factor filgrastim and pegfilgrastim to its biosimilars in terms of efficacy and safety: A meta-analysis of randomised clinical trials in breast cancer patients. *Eur J Cancer*. 2018;89:49-55. doi:10.1016/j.ejca.2017.10.034

5. Generics and Biosimilar Initiative (GABI). The sluggish US biosimilars market. Accessed February 15, 2022. https://www.gabionline.net/reports/The-sluggish-US-biosimilars-market.

6. Bennett CL, Nagai S, Bennett AC, et al. The First 2 Years of Biosimilar Epoetin for Cancer and Chemotherapy-Induced Anemia in the U.S.: A Review from the Southern Network on Adverse Reactions. *The Oncologist*. 2021;26(8):e1418-e1426. doi:10.1002/onco.13713

7. Whalen J. Recognizing and addressing challenges to the adoption of trastuzumab biosimilars and HER2-targeted therapies. *Am J Manag Care*. 2020;26(2 Suppl):S23-S31. doi:10.37765/ajmc.2020.42899

8. Chambers JD, Lai RC, Margaretos NM, Panzer AD, Cohen JT, Neumann PJ. Coverage for Biosimilars vs Reference Products Among US Commercial Health Plans. *JAMA*. 2020;323(19):1972-1973. doi:10.1001/jama.2020.2229

9. Baumgart DC, Misery L, Naeyaert S, Taylor PC. Biological Therapies in Immune-Mediated Inflammatory Diseases: Can Biosimilars Reduce Access Inequities? *Front Pharmacol*. 2019;10:279. doi:10.3389/fphar.2019.00279