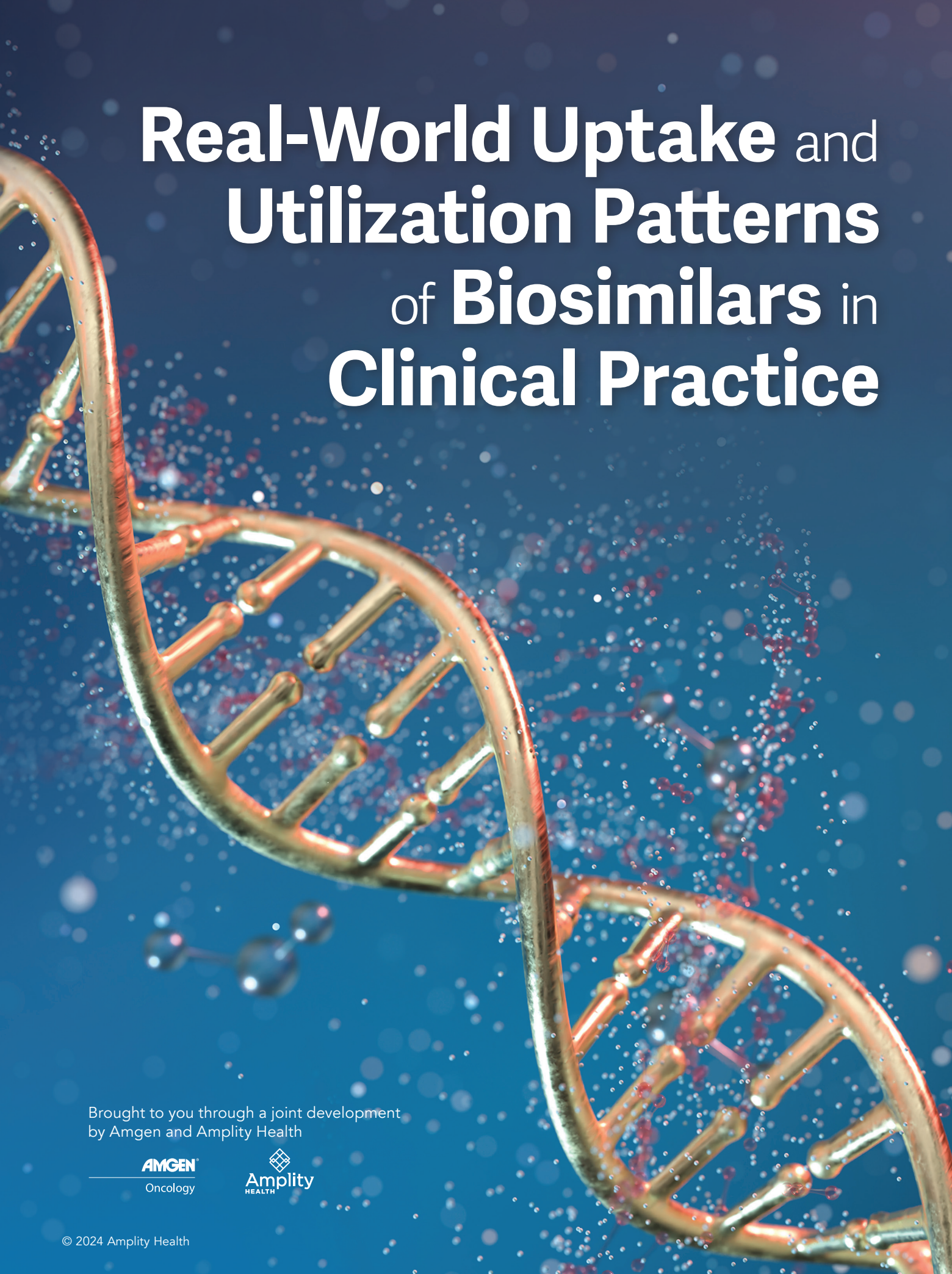
Real-World Uptake and Utilization Patterns of Biosimilars in Clinical Practice



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Faculty Perspectives™

In this supplement, expert faculty offer detailed perspectives based on their experience to summarize, examine, and analyze the emerging results from studies of anticancer biosimilars and provide recommendations to improve the adoption of and access to biosimilar products.

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Faculty Perspectives is published by Amplity Health, 1249 South River Rd, Suite 202A, Cranbury, NJ 08512.

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TLG2383

Real-World Uptake and Utilization Patterns of Biosimilars in Clinical Practice

Biologic therapies have advanced the treatment of many serious diseases, including cancer and a broad range of inflammatory conditions.[1,2] With the patent expiration of many of these medications, utilization of biosimilars is expected to rise.[1,3] Biosimilars are biologic products that are highly similar to an FDA-approved reference biologic with no meaningful clinical differences in safety or efficacy.[1]

Although the relatively high cost of biologics has been cited as a deterrent to broad patient access, they are also expensive to develop and manufacture.[3] In particular, the research and development cost for new anticancer drugs is estimated to range from $944 million to $4.54 billion.[4] The development of lower-cost, alternate versions of licensed biologic drugs, known as "biosimilars," was driven by the Biologic Price Competition and Innovation Act, which paved the way for the FDA to design an abbreviated approval pathway for biosimilar biologic products.[1,5]

Despite the abbreviated approval pathway of biosimilars, they undergo a multistage evaluation process to confirm biosimilarity to the reference product.[5,6] A comparative clinical trial is often conducted to demonstrate clinical comparability in a sensitive patient population before a biosimilar can be approved.[5] In a meta-analysis that included 31 cancer biosimilar studies of 3 reference products involving 12,310 patients, biosimilar anticancer drugs were found to undergo rigorous clinical evaluations. When surrogate measures of efficacy were evaluated, results were statistically indistinguishable from those for original products across cancer types, drugs, and treatment outcomes.[7]

The rigorous FDA approval process, which is different from new therapeutics, is founded on the totality of evidence and involves the submission of a comprehensive data package by the drug sponsor. The "totality-of-the-evidence" concept of biosimilarity requires that sufficient structural, functional, nonclinical, and clinical data are acquired in a stepwise manner to demonstrate that no clinically meaningful differences in quality, safety, or efficacy are observed compared with the reference product.[5,6]

Biosimilars are biologic products that are highly similar to an FDA-approved reference biologic with no meaningful clinical differences in safety or efficacy.

Generation of evidence to support the approval of a biosimilar begins with analytical studies, moving on to preclinical animal studies and clinical pharmacokinetics (and pharmacodynamics studies where possible), followed by a clinical immunogenicity assessment and clinical studies demonstrating equivalent efficacy compared with the reference biologic product in a randomized, phase 3, head-to-head comparison trial. At each step, regulators evaluate the totality of evidence, determining whether additional studies are needed to demonstrate the similarity between the biosimilar and the reference product.[5,6] Furthermore, additional studies are required for the proposed biosimilar to be granted interchangeability designation by the FDA. The proposed interchangeable product should induce the same clinical effect as the reference product in any given patient, and switching between the proposed interchangeable product and the reference product should not increase safety risks or decrease effectiveness compared to using the reference product without switching between products.[5]

Trends in the adoption of biosimilars have been

identified in the clinic, particularly through real-world evidence (RWE).[7,8] Observational studies have found that educational initiatives effectively improve healthcare professionals' knowledge of biosimilars, enhancing their adoption and utilization in the clinic.[8] Additionally, a systematic review and meta-analysis of randomized controlled trials revealed biosimilars have shown comparable efficacy to reference products.[7] Moreover, clinicians' confidence in these biosimilars has often led to rapid adoption following the launch of new products.[8] Finally, the cost-effectiveness of these products has been a significant driver for payers to incorporate biosimilars into formularies, subsequently leading to increased utilization in clinical practice.[1,3]

Observational studies have found that educational initiatives effectively improve healthcare professionals' knowledge of biosimilars, enhancing their adoption and utilization in the clinic.

With the expanding landscape of approved biosimilars for oncology indications, there is a need to examine their adoption, utilization patterns, and clinical performance in real-world settings and determine whether the safety and effectiveness in such settings are comparable to the findings of controlled clinical studies.[8] Therefore, the main objective of this review is to summarize, examine, and analyze the emerging results from RWE studies of anticancer biosimilars and provide recommendations to improve the adoption of and access to biosimilar products. Additionally, expert guidance to overcome persisting barriers to biosimilar adoption will be discussed.

Educational Gaps as Barriers to the Adoption of Biosimilars by Providers

Historically, educational gaps have been one of the factors hindering biosimilar adoption. Several factors have been identified as critical drivers of physician hesitancy to prescribe and adopt biosimilars, including concerns about immunogenicity, interchangeability with originator drugs, extrapolation, and a general lack of understanding of the regulatory process for the approval of biosimilars.[8]

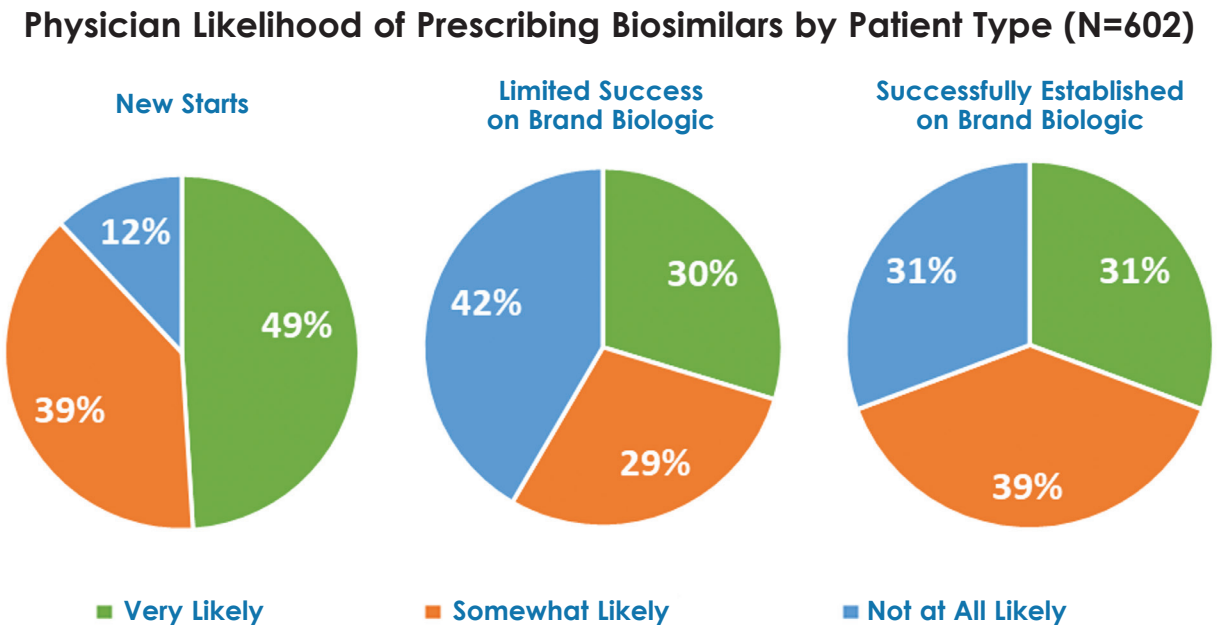
A published survey of 77 oncology clinicians (52 physicians, 16 pharmacists, and 9 advanced practice providers) identified critical knowledge gaps related to biosimilars. Notably, only 20 (26.0%) participants were able to provide a satisfactory definition of biosimilars, and 31 (40.3%) participants thought that a biosimilar was the same as a generic drug.[9] Furthermore, findings from a systematic review that assessed data from 20 US and European healthcare provider surveys concluded that oncology healthcare professionals in the United States and Europe had inadequate knowledge, familiarity, and understanding of biosimilars, which directly impacted their prescribing patterns of biosimilars due to safety and efficacy concerns, which limited biosimilar use. Moreover, the results of this analysis suggested that educational programs directed at healthcare providers and critical physician stakeholders could improve confidence in biosimilars.[10]

How is your organization speaking to physicians about biosimilars?

LEE SCHWARTZBERG, MD, FACP, Chief, Medical Oncology and Hematology, Renown Institute for Cancer – *"Because the biosimilar approval process is very different than what medical oncologists are used to for a novel agent, it's taken repetitive education to get the majority of medical oncologists comfortable with the idea. However, once they understood the process, the comfort level went up dramatically. In my practice we conducted sessions for all of our medical oncologists on a repetitive basis. The presentations by webinar and at in-person meetings probably had more impact than written papers only because of the vast amount of information that's coming at medical oncologists today is very difficult to parse and it's too difficult for any one medical oncologist to read everything or to learn everything."*

Another study of 602 physicians found that >75% believed that biosimilars are just as safe and effective as their originator counterparts. However, a substantial proportion of the surveyed physicians were uncomfortable with switching patients from a reference biologic to a biosimilar. While about half

Figure. Physicians more likely to prescribe a biosimilar for patients newly starting a biologic therapy[2]



Adapted from Wilde S, et al. NORC at the University of Chicago. www.norc.org. © NORC 2021.

indicated that they were very likely to prescribe a biosimilar to a patient just starting biologic therapy, only 31% were very likely to prescribe a biosimilar to a patient responding to a reference biologic (**Figure**).[2]

These knowledge gaps reinforce the need for educational efforts to improve prescribers' comfort levels and stimulate broader adoption of biosimilars. To that end, the Advancing Education on Biosimilars Act was signed into law on April 23, 2021. The legislation provides for increased federal efforts to educate patients, doctors, and caregivers about biosimilar drugs, including funding to develop continuing education programs, webinars, and other resources intended to address the prescribing of biologic products and biosimilars.[11]

Why is it so important to educate the clinical team about biosimilar adoption?

BHAVESH SHAH, RPh, BCOP, Chief Pharmacy Officer, Specialty and Hematology Oncology Pharmacy, Boston Medical Center – *"Education is one of the key factors that help successful biosimilar adoption. If every single stakeholder that's involved in the care of that patient is not educated and on board with that biosimilar, there will be a disconnect when that patient is switched. Providers need to be able to speak to patients not only about clinical comparability, but also about the financial aspects, because some patients may initiate discussions that providers are not accustomed to having. I think that talking points can help them navigate through those conversations. Similarly, nursing staff needs to be prepared to have these discussions. I believe that there should be a shared decision with patients when it comes to biosimilar adoption."*

Educational initiatives directed at healthcare providers have improved their knowledge and utilization of biosimilars. In one study designed to enhance oncology providers' knowledge of biosimilars, 12 biosimilar training sessions were conducted for oncology staff over a 4-month period. Before training, 86%

of nurses and 43% of physicians were unaware of the term "biosimilar/biosimilarity" in the previous month, and 40.1% of participants were uncertain if biosimilars are equally as effective as originator biologics. After training, participants' confidence in using biosimilars grew from mean (standard deviation) scores of 3.1 (3.2) to 7.1 (2.1; *P*<.001), and 95% believed biosimilars had the same efficacy as bio-originators.[10]

As providers' experience and confidence have grown over time, many have also become more comfortable in engaging patients about the rationale for prescribing a biosimilar, including therapeutic oncology biosimilars.

The evidence from RWE studies could increase physician comfort and confidence in prescribing biosimilars and switching patients from originator drugs to a biosimilar alternative.

When you prescribe anticancer biosimilars, how and when do you engage your patients?

LEE SCHWARTZBERG, MD, FACP – *"We explain that there are different versions of the same drug that are highly similar and approved by the FDA, and this is the one that our institution or clinic keeps in stock and recommends for our patients. The patient conversation has become much easier and usually does not necessitate an in-depth discussion. We're comfortable that we're going to get the same results from a biosimilar that we would've gotten from the reference product, and therefore it has become our default oncology therapeutic agent."*

The Need for Real-World Evidence Studies of Biosimilars

As biosimilars are increasingly adopted in the clinical practice setting, there is an opportunity to develop observational evidence that further supports their use. Although randomized clinical trials represent the gold standard for evaluating new drugs, they are not able to control for all potential variabilities in real-world clinical practice settings. For example, in the community treatment setting, there are several sources of variability caused by heterogeneous patient populations, a broad range of comorbidities, and disease severity. These variables may impact patients' response to treatments and medical interventions, resulting in deviations from the findings of clinical trials that typically include more homogenous patient populations.[12]

Thus, RWE studies can bridge knowledge gaps and further support the evidence base by providing a complete picture of treatments' and medical interventions' effectiveness, tolerability, and clinical impact in heterogeneous populations. The evidence from RWE studies could increase physician comfort and confidence in prescribing biosimilars and switching patients from originator drugs to a biosimilar alternative. Furthermore, real-world studies (postmarketing surveillance and observational) are designed to monitor patient outcomes over several years in diverse patient populations, which could be highly valuable for assessing the efficacy of biosimilars in extrapolated indications.[13] In addition, RWE studies can provide data that differentiate a single biosimilar from competitors by evaluating outcomes specific to the biosimilar product that were not assessed by other competitors. Collectively, RWE studies offer the opportunity to generate additional long-term effectiveness and safety evidence, particularly for extrapolated indications, and their findings may bolster physicians' confidence in integrating biosimilars in their routine clinical practice.[13]

How important are real-world studies in supporting the overall evidence base for biosimilars?

LEE SCHWARTZBERG, MD, FACP – *"To expand the knowledge base of biosimilars, understanding how these agents work in a real-world setting is important. As with any therapeutic agent, clinicians are seeing a much broader range of patients that participate in clinical trials. Since less clinical trial evidence is required for biosimilar approval, it actually heightens the importance of real-world evidence for biosimilars."*

BHAVESH SHAH, RPh, BCOP – *"Real-world evidence is very important because it gives providers and patients additional comfort that the drug has the same effect in the practice setting than in clinical*

trials, especially when the data sets are large, and it's been helpful that the FDA has developed a framework for evaluating real-world data for use in regulatory decisions because the framework applies to biosimilars as well as novel treatments."

Real-World Uptake, Treatment Patterns, and Clinical Comparability of Anticancer Biosimilars

To date, there are more than 40 FDA-approved biosimilar products in the United States, several of which are anticancer or supportive care biosimilars for patients with cancer.[14] As the number of approved biosimilars continues to grow and expand into additional specialties, observational data can provide essential insights into how biosimilars are incorporated into clinical practice.[15-18]

Adoption patterns for oncology biosimilars

In oncology, biosimilar versions of VEGF inhibitors and HER2 receptor antagonists have been marketed in the United States for over 4 years, beginning in July 2019. Despite the aforementioned knowledge gaps, some providers quickly adopted oncology biosimilars at launch, with prescribing observed across the approved indications. A 2021 analysis found that biosimilar anticancer agents were used across approved indications, regardless of patient demographics or clinical characteristics.[15]

Recent RWE studies demonstrated that biosimilars are initiated to treat a substantial proportion of both reference product–naïve and prior reference product–treated patients requiring treatment with a biologic. In a retrospective observational study of patients with metastatic colorectal cancer, 47% of those who initiated a biosimilar oncology agent were naïve patients, and 53% received prior treatment with the reference product. Interestingly, 78% of patients with cancer initiated the oncology biosimilar as a first-line treatment.[16]

Another RWE study demonstrated the rapid uptake of biosimilars when multiple biosimilar versions of a reference product became available. For example, when one anticancer biosimilar was launched in the United States, 7.3% of initiating treatment–naïve patients were prescribed the biosimilar over the reference product. Interestingly, during the same period 1 year later, when 5 other biosimilars to the same reference product were available, 80.5% of initiating treatment–naïve patients began treatment on a biosimilar, indicating substantially broader uptake by providers.[17]

Switching from a reference anticancer agent to a biosimilar

The US switching data for oncology biosimilars are somewhat limited compared to therapeutic categories where biosimilars have been in use for a more extended period of time. Nevertheless, analyses indicate that switching has been taking place, although studies may not be designed to elucidate the reason for the switch. For example, one study found that 18.2% of patients were switched to an oncology biosimilar product within the first 90 days post-launch.[17] In a retrospective study examining patient characteristics and treatment patterns of an oncology biosimilar, 66% of patients with metastatic colorectal cancer and previous reference anticancer agent use continued treatment with a biosimilar anticancer agent in the same line of treatment. The majority of these patients received the biosimilar in the first line within 28 days and without evidence of progression, indicating treatment change occurred within the same line of therapy, suggesting that physicians appear comfortable using the biosimilar similarly to the reference product.[18]

To date, there are more than 40 FDA-approved biosimilar products in the United States, several of which are anticancer or supportive care biosimilars for patients with cancer.

Comparative efficacy and safety of oncology biosimilars

Recent RWE studies also confirmed that anticancer biosimilars have comparable efficacy to reference products.[19-21] One RWE study demonstrated that a biosimilar anti-HER2 product has similar efficacy and safety to the reference product in the neoadjuvant

setting in patients with HER2-positive early breast cancer. The study included 77 patients who received the reference product and 59 patients treated with the biosimilar alternative. The total pathological complete response rates were similar for patients in the biosimilar group compared to the reference product and comparable to pivotal phase 3 trials.[19]

In a registry-based analysis, a similar percentage of early-stage breast cancer patients achieved a pathological complete response with a biosimilar anticancer agent versus the reference agent (74.4% [93/125] vs 69.8% [90/129], *P*=.411). For patients with metastatic breast cancer, median progression-free survival did not differ significantly between the 2 groups. The overall response rate, disease control rate, and cardiac safety profiles did not show a significant difference in outcomes between the 2 groups.[20]

Overall, RWE studies continue to demonstrate the utility of biosimilars in real-world clinical practice, which is raising physicians' confidence in utilizing them in routine clinical practice and paving the way for broader adoption.

In an observational cohort study of 353 patients with advanced non–small cell lung cancer initiated on a biosimilar (n=58) and the reference agent (n=295), mortality outcomes were similar, and there were no differences in serious adverse events, including bleeding, gastrointestinal perforation, thromboembolism, and severe hypertension, between the study groups.[21]

What is a practical application of real-world evidence as it pertains to biosimilars?

LEE SCHWARTZBERG, MD, FACP – *"Real-world evidence can be developed to ensure that efficacy and safety is comparable across biosimilars and in comparison to the reference agent. We have some therapeutic agents now that have multiple biosimilar versions. We believe that once approved, all of these agents should work very similarly to each other and very similarly to the reference product. Real-world evidence can be very useful in confirming that hypothesis."*

Overall, RWE studies continue to demonstrate the utility of biosimilars in real-world clinical practice, which is raising physicians' confidence in utilizing them in routine clinical practice and paving the way for broader adoption in the United States.[15-21]

Potential Economic Impact of Accelerated Biosimilar Adoption

Despite the positive impact of broad biosimilar adoption, competing stakeholder priorities and complicated reimbursement incentives continue to limit biosimilar adoption in the United States, where overall biosimilar volume share in accessible markets remained less than 30% in 2021.[22] As a result, current savings are insufficient to promote the broad use of biosimilars. Achieving savings comparable to those in some European countries may not be possible without systemic reform.[23]

Current models of acquisition and reimbursement may create economic complexities favoring use of biologics. Modeling studies demonstrated that the implementation of alternative reimbursement models for oncology biosimilars, such as value-based care approaches, could result in positive payer savings that could facilitate an economic compromise wherein commercial payers can save on biosimilars while provider reimbursement remains stable.[24]

How can real-world studies support the economic advantages of broad biosimilar adoption?

BHAVESH SHAH, RPh, BCOP – *"When there are multiple biosimilars in the market, we know that the ASP (average sales price) can drop 40% to 50% depending on the number of approved biosimilars of a reference agent. If providers or institutions are actually not able to take advantage of switching from one biosimilar to another, then I think that blunts the savings that you can actually achieve by having multiple biosimilars. The only way we can resolve this is having that real-world evidence of that switch, and showing that there was no difference in clinical response or difference in immunogenicity."*

Table. Factors influencing US payers' positive perception of biosimilars[24]

Factors	Number of Payer Mentions (n=20)
Cost-effectiveness	13 (65%)
Physician comfort level	10 (50%)
Number of marketed biosimilars for a specific category	9 (45%)
Efficacy	8 (40%)
Safety	6 (30%)
National Comprehensive Cancer Network guidance	6 (30%)
FDA interchangeability designation	6 (30%)

Note: Other mentions include patient comfort level (n=4); extrapolation, speed of adoption of biosimilars (n=3); duration of medication, manufacturer reputation, and manufacturer supply reliability (n=1).

As the stewards of the premium dollar, US payers are particularly sensitive to drug costs, and biologics account for a sizable proportion. According to a recent report from the US Department of Health and Human Services, biologics are estimated to cost Medicare Part D as much as $12 billion annually.[25] Biosimilars represent a substantial cost-savings opportunity. Although the availability of biosimilars has provided patients with reduced-cost therapeutic options, reference product prices have remained relatively stable despite increased biosimilar competition.[17] According to an Association for Accessible Medicines report, total savings from biosimilars were estimated at $7.9 billion in 2020.[22]

US payers can also be vital in stimulating broad biosimilar adoption via formularies and utilization management strategies. In a series of qualitative interviews, US payers indicated that cost-effectiveness was the most critical factor influencing positive perceptions of biosimilar adoption (**Table**).[24]

In a survey of 20 payers, 75% (including representatives from managed care organizations, integrated delivery networks, and pharmacy benefit managers) cited a preference for biosimilars over reference products in treatment-naïve patients and indicated that step therapy protocols were the preferred vehicle to drive biosimilar use.[24]

In addition to providers, payers can also benefit from educational efforts to enhance their comfort level in managing biosimilar use. When asked about their primary concerns regarding biosimilars, payers identified evidence from switching studies and FDA guidance on pharmacy-level substitution of reference products with biosimilars as the highest-rated strategies to overcome biosimilar adoption challenges in the United States.[24]

In addition to the potential economic impact of broad biosimilar adoption, biosimilars are improving patient access to potentially life-saving treatment. Improved access to biosimilars can be driven by both prescribers and health insurers. Pharmacists can fulfill an important operational role in this effort.[24]

How can oncology pharmacists help to overcome barriers and drive systemwide adoption of biosimilars?

BHAVESH SHAH, RPh, BCOP – *"Although there must be a provider champion, (oncology) pharmacy has the understanding of how to navigate through the administrative process of systemwide adoption, and is responsible for coordinating communications and driving all the operational aspects of biosimilar adoption. That is critical because there is considerable administrative burden involved, when you consider*

the formulary process, setting up the EMR for multiple biosimilars, coding and billing, and leading educational efforts for nursing staff and patients.

After adoption, follow-through is equally important. Pharmacists need to ensure that patients are converted to the biosimilar that is covered by their payer. It can be challenging to keep track of payer formulary changes as multiple biosimilars of a reference agent come to market. In my view, it's critical to have a dedicated biosimilar pharmacist for every institution in your system if you want successful adoption."

Organized systemic adoption by medical practices and health systems can benefit patients. A recent study by the Community Oncology Alliance showed that for 2 oncology biosimilars, biosimilar use had expanded rapidly and significantly, and the lower cost of these agents has enabled many more patients to access expensive treatments.[26] Likewise, payers have the ability to structure their benefit designs to reduce patient out-of-pocket spending for biologics. An analysis by Rand found that in many cases, especially when coinsurance plays a major role in patient out-of-pocket spending, lower biologic prices will benefit patients.[27]

Modeling studies indicated that introducing affordable biosimilars over the next 10 years could boost access to biologic treatments for an additional 1.2 million patients in 2025.[28] Biosimilars may reduce healthcare disparities by improving access to biologics for lower-income Americans. Lower-income individuals have been affected in the past by higher incidence rates of disease and worse disease progression, and they often experience overall worse health outcomes compared to the rest of the population.[28]

How are biosimilars directly benefitting patients?

LEE SCHWARTZBERG, MD, FACP – *"Biosimilars are one discrete way where we can make an impact (on healthcare costs), because the development costs are less, and generally speaking, the price of biosimilars are less. That results in patients having to pay less. On an individual basis, it can increase access for patients and it can also lead to lower patient direct costs depending on their particular plan."*

Conclusion

Despite more than 7 years of biosimilar experience in the United States, considerable barriers to broad systemic adoption of biosimilars continue to persist. For example, surveys demonstrate that educational gaps remain among clinicians as well as payers. However, growing observational evidence indicates that biosimilars exhibit comparable effectiveness and safety profiles to reference biologics, bolstering the evidence base from prospective randomized clinical trials.[15-21,24]

RWE indicates that tangible opportunities exist for key stakeholders—providers, patients, government and private payers, and manufacturers—to align on the clinical comparability and potential cost savings that can be realized by broad biosimilar adoption. Given the broad economic and societal benefits, it is in the interests of public and private sector stakeholders to prioritize wide biosimilar adoption, including therapeutic oncology biosimilars, accordingly.[1,3,24]

What do you see as the future of oncology biosimilar adoption?

BHAVESH SHAH, RPh, BCOP – *"I think the trend toward greater adoption will continue. NCCN Guidelines endorse biosimilars across multiple indications, across multiple disease types, regardless of whether patients are treated in the neoadjuvant, adjuvant, or metastatic setting. We've seen leading institutions like Kaiser and Mayo Clinic publish real-world evidence indicating that biosimilar adoption is safe. All of this has raised the comfort level with biosimilar adoptions in the oncology setting, and I think the trend will continue."*

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USA-CBU-81650