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THE ERA OF ANTI-VEGF BIOSIMILARS

Navigating the Treatment Paradigm for Retinal Vascular Diseases


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Content Source

This continuing medical education (CME) activity captures content from a live-virtual symposium.

Activity Description

This supplement summarizes in-depth discussions on biosimilar anti-VEGF therapies among a respected group of retina specialists. The faculty discuss how biosimilars compare with their reference products, the process by which they gain FDA approval, their risks and benefits, and the policies that may influence incorporation into clinical practice.

Target Audience

This certified CME activity is designed for retina specialists.

Learning Objectives

Upon completion of this activity, the participant should be able to:

- **Define** the term "biosimilar," focusing on the distinction between "biosimilar" and "generic"
- **Explain** why biosimilars may be introduced into the health care landscape and how they compare with innovator therapies
- **Describe** the process by which biosimilars go through clinical development and receive US FDA approval
- **Evaluate** the risks/drawbacks and benefits of using innovator and biosimilar products for the treatment of patients with retinal diseases

- **Assess** the feasibility of incorporating anti-VEGF biosimilars into clinical practice and adapting treatment algorithms based on regulation, legislation, and insurance policies
- **Summarize** the current and upcoming biosimilars in the retinal disease landscape and their associated trial data

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for credit.

1. Please rate your confidence in your ability to evaluate the risks/drawbacks and benefits of using innovator and biosimilar products for the treatment of patients with retinal diseases (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. How often do you use biosimilar agents to treat patients with retinal disease (on a scale of 1-5, with 1 = "Never" and 5 = "Always")?

a. 1
b. 2
c. 3
d. 4
e. 5

3. A 63-year-old patient presents to your office for evaluation of his neovascular age related macular degeneration (nAMD). He is on monthly ranibizumab intravitreal injections. He is interested in learning more about ranibizumab-nuna, a biosilimar agent. Which of the following is TRUE about this biosimilar?

a. Ranibizumab-nuna is considered safer than ranibizumab according to large scale studies
b. Cases of intraocular inflammation have been reported with the use of this biosimilar due to the presence of endotoxins in the manufacturing process
c. The immunogenicity and adverse event profile between ranibizumab and ranibizumab-nuna are comparable
d. Ranibizumab-nuna performed better than ranibizumab in trials with respect to mean letter gains from baseline

4. Which of the following statements is TRUE?

a. The regulatory approval process for biosimilars is not the same as the regulatory approval process for generic agents
b. Biosimilar agents have the same chemical structure as generic agents
c. Biosimilars have an equivalent safety profile compared to generic and branded agents
d. Biosimilars have an equivalent efficacy profile compared to generic and branded agents

5. A 79-year-old woman with bilateral tube shunts presents with new diagnosis of nAMD in her right eye. She prefers to receive an FDA-approved drug and asks you about the most appropriate initial treatment. Which of the following is the most reasonable response?

a. Port delivery system because she can be treated every 6 months
b. Observation because more durable agents will likely be available in the near future
c. There are five FDA-approved anti-VEGF agents including two recently approved ranibizumab biosimilars, which should initially be used monthly
d. Ranibizumab-eqrn because it has superior efficacy to the reference product and costs less

6. An 82-year-old man with nAMD in his right eye has been receiving off-label bevacizumab with suboptimal response and asks about switching to a ranibizumab biosimilar because his neighbor has received this treatment. When he asks you how these biosimilars compare to other branded anti-VEGF drugs, what is the best response?

a. Ranibizumab biosimilars appear comparable to ranibizumab in terms of efficacy and safety, but the trials are relatively smaller and evaluate earlier primary endpoints compared to traditional phase 3 registration studies
b. Ranibizumab biosimilars have equal efficacy and safety as their reference product, but are one-third the cost
c. Ranibizumab-eqrn has been tested head-to-head to ranibizumab-nuna and no significant differences were observed
d. In the phase 3 study evaluating ranibizumab-nuna, the mean letter gains from baseline at week 52 was +11 letters (ranibizumab-nuna) versus +9 letters (ranibizumab)

The Era of Anti-VEGF Biosimilars: Navigating the Treatment Paradigm for Retinal Vascular Diseases

Anti-VEGF therapy is the current standard of care for retinal vascular diseases. Currently, on-label anti-VEGF therapies include ranibizumab (approved in 2006),[1] aflibercept (approved in 2011),[2] brolucizumab (approved in 2019),[3] and faricimab (bispecific antibody targeting VEGF and angiopoietin-2; approved in 2022),[4] with bevacizumab being used off-label (first approved in 2004 for colorectal cancer).[5] Although these therapies are effective in a sizeable portion of patients with retinal disease, they are among the most expensive for Medicare.[5] Biosimilar anti-VEGF products may serve as potentially cost-effective alternatives that have clinically equivalent safety and efficacy.

Of the first generation of anti-VEGF therapies, originator molecules bevacizumab and ranibizumab went off-patent in 2019 and 2020, respectively, with originator molecule aflibercept following in 2023.[6] We have already seen the approval of two ranibizumab biosimilars during the past year. However, due to the novelty of ophthalmology biosimilars and the strict standards for intraocular treatments, there is some hesitation in the retina community regarding their use. With more biosimilars on the horizon, we convened a panel of experts in retinal diseases and biosimilars to discuss how biosimilars compare to their originator counterparts and the considerations for incorporating biosimilars into clinical practice.

– Sumit Sharma, MD, Program Chair

BIOSIMILARS AND GENERICS – WHAT'S THE DIFFERENCE?

Dr. S. Sharma, MD: In a survey of retina specialists, nearly 20% believed that biosimilars were the same as generic drugs,[7] highlighting a gap in understanding. We're more familiar with generic drugs – synthetic, identical copies, both in chemical formula and molecular structure, of their brand-name counterparts. Biosimilars are a little different. Like their reference products, biosimilars are biological entities, ie, proteins composed of amino acids that adopt complex structures to exert their effect. They tend to be 100 to 1,000 times larger than chemical drugs. As they are produced by live cells, they cannot be manufactured based on a predefined formula. Moreover, even with the same amino acid sequence, posttranslational modifications can differ, resulting in inherent variability in the final structure.[8]

Due to the nature of this manufacturing process, the FDA only requires biosimilars to be "highly similar" to their reference products, with minor variations allowed.[8] As such, there may or may not be differences in their efficacy and safety profiles. Currently, there are 35 FDA-approved biosimilars across medicine, with 21 available commercially.[9] In 2010, the Biologics Price Competition and Innovation Act (BPCIA) established an abbreviated pathway to FDA approval for biosimilars, with the goal of improving patient access to lower cost, high-quality products. By 2025, biosimilars could potentially reduce US drug expenditure by $130 billion.

The time and financial investment into biosimilar development and manufacturing are considerably greater than that for generic drugs.[8] The average small-molecule generic drug costs around $5 million to develop, compared to $100 to $200 million and 8 to 12 years for biosimilars, and $1.2 to $2.5 billion and 10 to 15 years for originator biologics.[8,10,11] Therefore, compared to the reference product, biosimilars can generate significant profit for the manufacturer and, by being priced 15% to 30% lower and instigating marketplace competition, they can also represent cost savings for patients and payers.[12] We've seen that in India during the past 7 years.

Q | Dr. S. Sharma: Dr. Sharma, what's been your experience?

Ashish Sharma, MD: The first ranibizumab biosimilar, which launched in 2015, was originally priced 30% below the reference product; however, during the past 2 years, two more ranibizumab biosimilars have entered the market and this has prompted price cuts of 40% to 50% and even discount schemes for the originator products.

Dr. S. Sharma: That's the hope for the US market as well.

Ankoor R. Shah, MD: What's happened in oncology, which has the longest duration of experience with biosimilars, may predict what will happen in ophthalmology. A presentation by Kathy W. Oubre, MS, chief operating officer at Pontchartrain Cancer Center, given during the American Society of Retina Specialists (ASRS) Business of Retina meeting, looked at 52 community practices and showed the first biosimilar was priced 20% to 30% lower but what's remarkable is the additional price reduction when the second biosimilar was introduced.[13] In ophthalmology, we've already seen two ranibizumab biosimilars approved in short order. It will be interesting to see whether the first mover advantage that was possible with oncology biosimilars will be replicated in our field.

Dr. S. Sharma: Great point. It's really a question of the price level for each and how long it can be sustained.

THE ROAD TO FDA APPROVAL

Sophie J. Bakri, MD: Biosimilars don't go through the same approval process as generic drugs, and up to one-third of retina specialists believe they do.[7] There are three main requirements – analytical studies to demonstrate high biosimilarity, animal studies for toxicity assessments, and a clinical study to assess

safety, efficacy, and immunogenicity in comparison to the reference biologic.[14] The BPCIA also includes a regulatory designation specific to the United States–"interchangeability"–which allows pharmacists to substitute the original drug with its generic or biosimilar without notifying or requiring the prescriber's approval.[5,12,14]

Some of the concerns raised with biosimilars pertain to the allowance of excipients in the biosimilar formulations, eg, the stabilizers or buffers, can be different to those used in the reference product.[8] This could be a source of inflammatory reactions not typically seen with the reference products. As mentioned previously, posttranslational modifications can differ, and result in structural changes that could lead to differences in safety and efficacy of the biosimilar. Anti-VEGF production incorporates several purification procedures to improve purity and reduce toxicity; however, as the manufacturing process remains a trade secret even after patent expiration, biosimilar manufacturers must "reinvent the wheel" to ensure consistency between batches.[8]

Q | Dr. S. Sharma: Dr. Sharma, given this and your experience with biosimilars in India, have you had any concerns of intraocular inflammation (IOI)?

Dr. A. Sharma: In 2015, when the first ranibizumab biosimilar was launched exclusively for distribution in India, the first few batches were associated with mild cases of anterior segment IOI. This was found to be due to the presence of endotoxins in the buffer used in the manufacturing process. At the time, all companies abided by the endotoxin limit of less than 0.5 endotoxin units (EU)/mL set by the International Standards Organization.[15,16] However, soon after, the FDA revised their limit to less than 0.2 EU/mL, an exceptionally high standard of purity to ensure the risk of IOI was further mitigated.[15,16] This limit was upheld by manufacturers and now, none of the three anti-VEGF biosimilars available in India have had unusual reports of IOI.

Dr. Bakri: Perhaps understandably then, 54% of retina specialists surveyed believe there is evidence to suggest that biosimilars may result in increased adverse events compared to the reference product.[7] Even with the resolution seen in India, it's important to consider that switching patients from the originator biologic to a biosimilar could be accompanied by unforeseen side effects.

Dr. S. Sharma: We published a study in 2021 about patients with uveitis who were switched from an infliximab reference product to its biosimilar, at the same dose, for nonmedical reasons.[17] Nearly two-thirds of patients experienced flares within 90 days of switching, whereas they did not have flares prior to the switch. The rheumatology literature deems the switch to biosimilars to be safe and effective, with very few instances of flare-ups.[18] However, other studies have also reported variable rates of flare-ups from switching to infliximab biosimilars in patients with uveitis, depending on the biosimilar employed.[19,20] While this may not apply directly to anti-VEGF biosimilars, and indeed there are other reports of no differences in outcomes in uveitis or other rheumatological diseases,[20-23] it's important to note there may be differences in efficacy which are, in part, to do with the approval process.

Dr. A. Sharma: Am I correct in remembering that you had to increase the dosage of the biosimilar to achieve equivalent control of inflammation?

Dr. S. Sharma: Correct. It required a 20% to 25% increase in dose, which made the cost equivalent to the reference product, and essentially resulted in no cost savings.

BIOSIMILARS IN RETINA

Dr. A. Sharma: There has been a lot of buzz around biosimilars in retina, and it's primarily because the patents of our stalwart anti-VEGF therapies have either recently expired or will expire during the next year. The US patent for bevacizumab expired in 2019 and we already have two bevacizumab biosimilars.[6] Their acceptance in the retina field has been low, even in the face of recent supply chain deficiencies for originator bevacizumab, because of the lack of experience with biosimilars and bevacizumab already being an off-label agent.

Decidedly, there is greater interest in the biosimilars of on-label ranibizumab and aflibercept, which expired/will expire in the US in 2020 and 2023, respectively.[6] Most are in the final stages of clinical development and will enter the market in the next 3 to 4 years. Biosimilars are differentiated from their originator counterparts by four-letter suffixes, eg, ranibizumab-nuna was the first ranibizumab biosimilar to be approved by the FDA.

Dr. S. Sharma: Going forward, both originator and biosimilar biologics will receive four-letter suffixes that are unique to the manufacturer. Older originator biologics are grandfathered and won't have this suffix.

Dr. A. Sharma: Good to know. Ranibizumab-nuna became commercially available in July 2022 priced at 40% of the cost of ranibizumab ($1,130) and is approved for all indications except diabetic retinopathy (DR) and diabetic macular edema (DME).[24] More recently, ranibizumab-eqrn 0.3 mg and 0.5 mg were not only approved for all five indications, but also designated as "interchangeable" with ranibizumab.[25] It became commercially available in October 2022 and is listed at $1,360 and $816 for the 0.5 mg and 0.3 mg doses, respectively.[25]

The lower pricing for biosimilars is a major advantage in India, as most patients pay out-of-pocket. How would this play out with insurance companies in the United States?

Dr. S. Sharma: It's complicated. A patient with Medicare typically has a 20% copay, but several foundations provide copay support. Commercial insurance companies can have much larger deductibles. However, across the board, biosimilars can reduce overall costs for the health care entity, eg, Medicare, and decrease the copay amount paid by the patient. Whether this

decrease will be significant, through foundation support, or nominal is difficult to predict.

Q | Dr. A. Sharma: Dr. Shah, you're in private practice; what is your take on savings?

Dr. Shah: First, we often compare the price of the biosimilar to the wholesale acquisition cost (WAC) of the originator biologic. For example, the list price for a single vial of ranibizumab-nuna 0.5 mg is $1,130, compared to the WAC of $1,950 for ranibizumab 0.5 mg.[24,26] The latter typically persists for about 6 months and then drops to the average selling price (ASP), which continues to erode over time. Right now, for ranibizumab, the ASP is around $1,290.[27] Depending on the biosimilar, there may still be some cost savings over the ASP or, in fact, none at all. The comparison with the ASP is not nearly as dramatic as the comparison to the WAC. Second, this decision may not even be ours to make. The payers may make the decision for us, for example, by way of step therapy.

Dr. Bakri: I agree. Payers do dictate that choice. However, clinical practices and hospitals also negotiate with the manufacturers of the originator biologics, and this may lead to price differences between types of health care practices and institutions. At the end of the day, we want to offer a varied menu of choice to our patients.

Dr. A. Sharma: Absolutely, I agree. The FDA approves biosimilars on a "totality-of-evidence" approach, ie, analytical, nonclinical, and clinical data. Retina specialists may not be familiar with the phase 3 clinical trial design for biosimilars, which is the only clinical study required for approval. Let's consider the trials evaluating ranibizumab-nuna/SB11 and ranibizumab-erqn/FYB201. The former included 705 patients receiving either the biosimilar or reference product, with 634 patients dosed up to week 52.[28,29] The predefined equivalence margins were -3 letters to +3 letters (90% confidence interval [CI]) for best-corrected visual acuity (BCVA) and -36 µm to +36 µm (95% CI) for central subfield thickness (CST). The primary endpoints of mean change in BCVA and CST were at weeks 8 and 4.[28] The mean gain in BCVA at week 52 was +9.8 letters versus +10.4 letters and the mean change in CST was -140.0 µm and -125.1 µm for SB11 and ranibizumab, respectively. The immunogenicity, pharmacokinetic, and adverse event profiles were comparable.[29]

FYB201 was evaluated in the phase 3 COLUMBUS AMD trial, with 239 and 238 patients in the reference and biosimilar arms, respectively.[30] The primary endpoint was met with mean gain in BCVA at week 8 being +5.1 letters versus +5.6 letters for FYB201 and ranibizumab, respectively, and the 90% CI (-1.6 to +0.9) falling within the predefined equivalence margin (-3.5 letters to +3.5 letters). Over 48 weeks, the mean change in BCVA was stable with +7.8 letters versus +8.0 letters for FYB201 and ranibizumab, respectively.[30]

The first point of difference between biosimilars and their reference products is that the primary endpoints for biosimilars are assessed much earlier than for originator biologics. In clinical practice, the greatest treatment effect is seen within the first 3 months. Assessing endpoints within 8 weeks, ie, the linear portion of the dose-response curve, is sensitive enough to detect potential differences in efficacy.[31] Note that the safety and efficacy are still monitored up to week 48/52, along with postmarketing surveillance and vigilance.

"Depending on the biosimilar, there may still be some cost savings over the average selling price or, in fact, none at all."

—Ankoor R. Shah, MD

A second misconception about biosimilar clinical trials is that they do not evaluate a reasonable number of patients. The landmark ANCHOR and MARINA trials had 140 and 240 patients, a total of 380 patients, which is similar to the 354 patients assigned to the SB11 arm. The sample size is chosen based on the equivalence margin (a narrow margin requires a larger sample size) and ability to detect signals.[31]

A third concern is that of IOI, which we previously discussed. Undoubtedly, we all begin as skeptics. However, in India, most of us now use biosimilars, even in cases of retinopathy of prematurity. Remember, the rate of IOI in ANCHOR and MARINA was 17.1% and 20.9%, respectively.[32] That rate was much lower for SB11 (0.9%) and even ranibizumab now.[29] Given that IOI stemmed from the buffers and excipients, rather than the biologic itself, we can control these components well and adhere to the stricter FDA-recommended endotoxin limit of 0.2 EU/mL to ensure safety. As a result, SB11, FYB201, and the two other biosimilars approved within India haven't presented with new safety concerns.

Lastly, biosimilar trials are often conducted in only one indication, but approved for several.[33] The FDA's rationale is that if the biosimilar doesn't show differences in safety compared to the originator biologic in one indication, this can reasonably be extrapolated to others. Indeed, we've shown in retrospective studies that this extrapolation is safe and effective.[33]

Dr. S. Sharma: I'll also note that if the study was done with one dose, eg, 0.5 mg, the biosimilar will be approved for all indications using that dose. If the 0.3-mg dose has not been studied, those indications are not included. That is why the approval for SB11 in DR and DME is still pending.

INCORPORATING BIOSIMILARS INTO YOUR PRACTICE

Dr. Shah: Retina specialists are certainly open and willing to try biosimilars, as seen by the 62% of survey respondents who

said they would use biosimilars in their practices.[7] This number will change over time with increasing real-world experience in the United States. As we discussed, biosimilars have significant potential to reduce financial burdens. The question remains as to who gets the benefit – payers, health care system, or patients – but cost savings do accrue. What's unique in ophthalmology is the off-label use of bevacizumab, a medication that already provides significant cost-savings with good efficacy. With the newer therapies that are approved, the goalpost for treatment success keeps moving forward, and we must ask ourselves whether anti-VEGF biosimilars will gain traction.

Q | Dr. S. Sharma: Where do you see new therapies and biosimilars fitting into the treatment paradigm?

Dr. Shah: I maintain the status quo. There's significant literature and real-world experience for off-label bevacizumab, ranibizumab, and aflibercept. If I have a patient who isn't well controlled on one of these, I'll use faricimab. Given the recent precedent of an anti-VEGF agent that had promising efficacy but increasing reports of IOI in the real world, I am hesitant to make more sweeping changes.

Dr. A. Sharma: One of the reasons for the biosimilar stronghold in India is the poor access to compounding pharmacies that could've allowed us to use off-label bevacizumab more readily. That's a major differentiator between the United States and India in terms of biosimilar adoption. Private practitioners in India needed a cheaper, single-vial option and biosimilars filled that gap. Considering the United States does have a good system for compounding in place, it'll be interesting to see how biosimilars will be used in practice.

Dr. Bakri: There's a lot to unpack when thinking about where these products will fit. For new products, I'd first consider nonresponders, maybe try a better drying agent. With ranibizumab, we know it's a safe drug and, in fact, many of my patients on ranibizumab have experienced IOI with other drugs. Switching to biosimilars only gives me pause because of the possible IOI, but we have seen waves of IOI with other very widely used anti-VEGF agents. Practices that use ranibizumab as first-line therapy may be comfortable replacing them outright. Others use bevacizumab first and while it remains available, I could see us still using it. Payer mandates are what will really change our practice. With more drug choices, we might have to re-examine why a patient is on a specific drug in the first place, and advantages and risks to switching. Much of what we do is driven by our own experience and clinical trials, so being comfortable with switching is really a matter of becoming comfortable with biosimilar safety.

Dr. Shah: That was the experience in oncology as well, ie, the first biosimilar to market had slow adoption, but subsequent biosimilars were more readily accepted. While payers may make some of these decisions, it behooves us as retina specialists to steer the decision-making ship and not relinquish too much control. As Dr. Bakri said earlier, having additional tools in the toolkit is only going to be favorable for us and our patients. I do welcome these choices, but it's a matter of finding where they fit and how to implement them.

We previously mentioned that two bevacizumab biosimilars have been approved; however, the American Academy of Ophthalmology (AAO) doesn't endorse them, partly because the manufacturers explicitly note they aren't intended for intraocular use.[14] Clearly, there's an understanding that the eye is a challenging space and equivalence in other areas may not preclude incidences of IOI, eg, reports pertaining to infliximab biosimilar use in uveitis and rheumatology.[17] However, there is strong clinical evidence, particularly safety, for ranibizumab biosimilars, so there wouldn't be AAO opposition on that standpoint. Their policy statement does recommend reviewing rules around substitution of biosimilars, because these can vary.[14] The interchangeability clause is interesting because, as Dr. Bakri mentioned, pharmacists can swap Part D (retail prescription) drugs without informing anyone. For Part B (administered by physicians) medications, clinicians are the ones swapping medications. I would, personally, still have a discussion with the patient because these are biosimilars, not bioequivalents.

Q | Dr. Shah: What do you foresee happening here?

Dr. S. Sharma: It will be difficult to switch those patients who are doing well on their current anti-VEGF agent, especially if cost isn't a concern for them, because they will question the decision to use a biosimilar that doesn't have the same wealth of supporting data. Most biosimilar use will likely happen with treatment-naïve patients. While we don't need to discuss the switch with them, I think all clinicians will at least inform their patients. If a patient was complaining about cost, most of us likely already use compounded bevacizumab for those cases. At this point, I don't think biosimilars will be cheaper than off-label bevacizumab.

Dr. Bakri: If I used ranibizumab first line, it might be an easier conversation. I would explain to the patient what a biosimilar is, the evidence behind it, and the other possible drug choices. The situation may arise, however, that an insurance company forces everyone on ranibizumab to switch to a biosimilar or risk not being covered. What happens, then, if we switch the patient to a completely different originator biologic?

Dr. A. Sharma: As an aside, some colleagues may want to make the switch because of a lack of response with the originator. Biosimilars will not provide an efficacy benefit over their reference product. You're better off switching to a completely different agent.

With regard to the patient conversation, it wasn't difficult for us in India because we explained that the price benefit stems from the biosimilar being made within India and ranibizumab being made outside India.

Dr. Shah: To round out this discussion, incorporating biosimilars into practice also hinges on regulatory, legal, and insurance

"It will be difficult to switch those patients who are doing well on their current anti-VEGF agent, especially if cost isn't a concern for them, because they will question the decision to use a biosimilar that doesn't have the same wealth of supporting data."

—Sumit Sharma, MD

policies, which will vary between states and payers. This lack of familiarity with biosimilars encompasses all the major stakeholders in retina. We're all adapting and learning.

A survey of retina specialists showed that 40% believe that payers have considerable influence on which biosimilars/anti-VEGF agents are used, with 76% stating they have little to no influence on payer formulary decisions.[12] This is only going to continue to increase and we're seeing some of that through the Medicare Advantage plans that mandate "step therapy" or "fail-first policies." These cost-controlling measures require beneficiaries to try a "step," typically off-label bevacizumab, before switching to another medication. While many major societies like AAO and ASRS don't support this, preferring instead for the physician and patient to make the decision together, the expectation is that biosimilars may become another "step" after off-label bevacizumab.

A more recent development, the Inflation Reduction Act (IRA) of 2022, authorizes the government to negotiate prices for certain high-priced, single-source branded drugs covered under Part D or B.[34,35] These negotiated prices don't come into effect until 2026 for Part D drugs, and 2028 for Part B medications. In practice, we may not see this affect anti-VEGF drugs because once there is competition in the market, eg, biosimilars, prices fall by natural mechanisms and there is no need for government-mandated negotiation. Given the slew of biosimilars waiting in the wings, we may just have a fair market. The IRA does incentivize biosimilar development by providing an 8% add-on payment over the originator biologic's ASP for qualifying biosimilars for the first 5 years, because it's seen as a cost-saving mechanism for the health care system as a whole.[34]

Q | Dr. S. Sharma: **From a practice management standpoint, how many anti-VEGF originators and biosimilars will you stock, and would that depend on each of your practice locations?**

Dr. Shah: What's efficient from a storage and logistics perspective is to stock at least one biosimilar. In oncology, trastuzumab has multiple biosimilars, and Dr. Oubre's study showed that 60% of the 52 practices examined had to stock at least two biosimilars.[13] As the number of approved anti-VEGF biosimilars increase, this will become a logistical challenge because often we want to be able to treat patients on the same day they present with certain issues.

Dr. S. Sharma: When we added faricimab to our formulary, we were asked which drug would be removed to accommodate the inclusion.

Dr. Bakri: We were asked the same question. We usually provide the rationale of patient care to be able to maintain a small stock of everything, but it depends on how hard we're pushed to make that decision. I like to preserve choice for physicians and patients.

Dr. S. Sharma: What's the standard in India?

Dr. A. Sharma: We predominantly use the first ranibizumab biosimilar that was approved. It's slower going with the newer biosimilars that have just become available in the past 2 years.

Q | Dr. S. Sharma: **Do biosimilars have other benefits besides cost savings?**

Dr. Bakri: Cost savings is the only one but, remember, it's not just for the patients and payers. It's also reducing the cost of health care over time so we can make way for new innovative treatments that are coming down the pipeline. It's about preserving choice in the long term and sustaining the ability of payers to pay on the patients' behalves. We'll be asked to reduce our costs more and more because the budget isn't exactly increasing.

Dr. S. Sharma: Excellent point. Medicare's budget neutrality requirements mean that every time we spend more in one area, we take pay cuts as physicians. The cost advantage is not just for drug development, it's also for us.

Dr. Bakri: Certainly. It's in everybody's interest to provide the best patient care at the lowest cost. It's not just about today, it's about the long term, and I really welcome innovation. Every product has its lifecycle, and we need to realize that.

Dr. Shah: Cost is the main point, but there may be other nuanced advantages, eg, with the Medicare merit-based incentive payment system (MIPS) program. Biosimilar use may show that we're not only high-quality but also low-cost physicians.

BIOSIMILARS ON THE HORIZON

Dr. S. Sharma: There are two more ranibizumab biosimilars in the pipeline, one that has completed phase 3 studies, and another that's on hold. Since aflibercept's US patent will expire next year, there are six aflibercept biosimilars waiting in the wings, currently in phase 3 trials. As aflibercept is the US market leader in terms of usage, these biosimilars may induce a significant change in our use patterns.

CASE STUDIES – SWITCHING TO BIOSIMILIARS IN INDIA

Dr. A. Sharma: I want to share our experience with the three ranibizumab biosimilars that are now approved in India. This first case involves a patient with treatment-naïve DME with subfoveal neurosensory detachment, presenting with a BCVA of 20/63 (Figure 1). Four weeks after one injection of the most recently approved ranibizumab biosimilar, the intraretinal fluid (IRF) and retinal detachment had resolved and BCVA improved to 20/20.

The next case features a patient with nAMD who was treated with 10 bevacizumab injections and was switched to a monthly regimen of the second ranibizumab biosimilar approved in India; patient's BCVA was 20/63 (Figure 2). After the first injection, BCVA improved to 20/40 and IRF was significantly reduced. After the second injection, there was no fluid and BCVA further improved to 20/30.

The last case involves a treatment-naïve patient with type 1 macular neovascularization (MNV) who presented with a BCVA of 20/40 in December 2019 (Figure 3). Over 31 months and 10 injections of the first ranibizumab biosimilar approved in India, the patient is now stable and treated on a quarterly basis.

In fact, a survey of the Vitreoretinal Society of India found that between 2018 and 2020, the use of ranibizumab biosimilars increased from 41% to 56% and the use of bevacizumab biosimilars decreased significantly from 9% to 2%.[1] Respondents were more likely to continue using ranibizumab biosimilars over bevacizumab biosimilars, due to the compounding requirement of the latter.[2]

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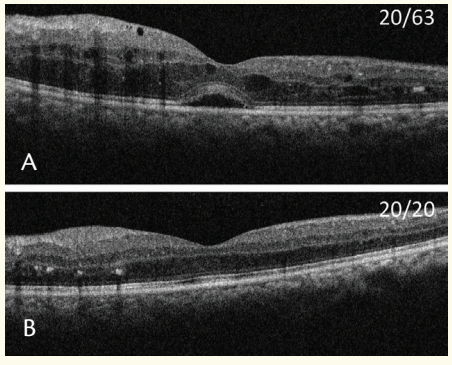

Figure 1. Case 1: Treatment-naïve patient with center-involved DME at presentation (A) and 4 weeks after an injection of the third ranibizumab biosimilar approved in India (B). Courtesy of Ashish Sharma, MD.

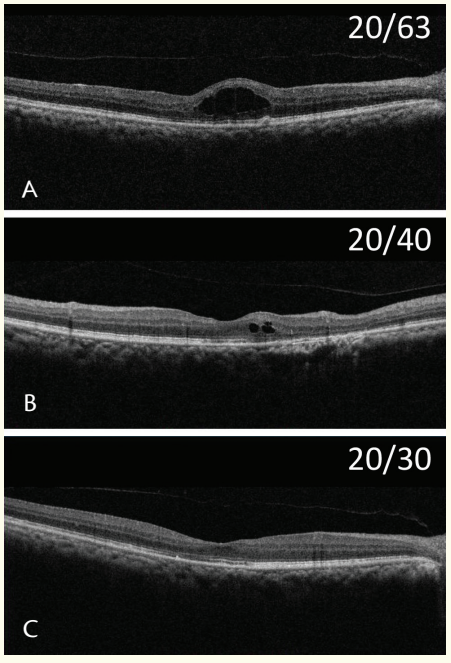

Figure 2. Case 2: Patient with nAMD pretreated with 10 bevacizumab injections (A), switched to the second ranibizumab biosimilar approved in India (B, C). (B) Four weeks after the first biosimilar injection. (C) Four weeks after the second biosimilar injection. Courtesy of Ashish Sharma, MD.

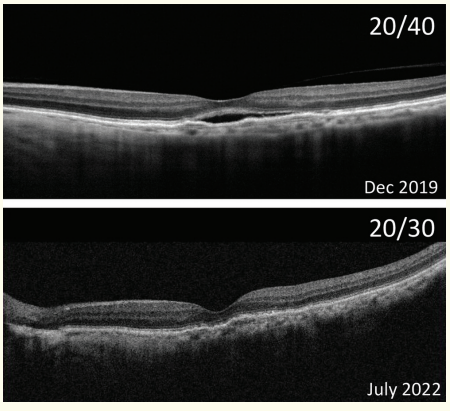

Figure 3. Case 3: Long-term treatment of a patient with type 1 MNV with the first ranibizumab biosimilar approved in India. Courtesy of Ashish Sharma, MD.

A large number of practices use bevacizumab first line, so an interesting pipeline candidate is the noncompounded, on-label, ophthalmic formulation of bevacizumab-vikg, which was designed to address some of the issues with compounded bevacizumab. The manufacturer submitted their biological license application (BLA) to the FDA in March 2022, but voluntarily withdrew it to provide additional information. It was resubmitted at the end of August 2022.[35]

If on-label bevacizumab was approved, a potential complication could be the unavailability of compounded bevacizumab, because compounding of any medication that is FDA approved for an indication is prohibited.[36]

Dr. Shah: To protect their patent, the manufacturer could go after pharmacies producing compounded bevacizumab. We have had some precedent of this, and often those pharmacies are forced to shut down after expensive legal battles. However, for every one that closes, three others pop up. It will be interesting to see how this will be enforced. For patients who are uninsured, off-label compounded bevacizumab is a lifesaver. Hopefully, there will be some built-in protection and they won't go after compounded bevacizumab as aggressively.

Dr. S. Sharma: There is a lot of consternation in the field right now, but we don't know how it will pan out. Dr. Sharma, do you think it will be used in India, if approved?

Dr. A. Sharma: No, I doubt it, but it all depends on pricing. If it were priced significantly below the biosimilars we use now, maybe. However, it is technically an innovator molecule, so I wouldn't expect a big enough price cut to encourage adoption.

"Regardless of the type of drug, it's a matter of gaining more experience and being comfortable with them."

—Sophie J. Bakri, MD

Dr. S. Sharma: In terms of pricing, it will have to compete against the ranibizumab biosimilars. Otherwise, there's no incentive to use it. The 12-month phase 3 NORSE TWO trial that evaluated bevacizumab-vikg has also drawn some criticism due to its trial design. Treatment-naïve patients with active nAMD were given monthly injections of bevacizumab-vikg 1.25 mg or three doses of monthly ranibizumab 0.5 mg, followed by q12w dosing (PIER trial protocol).[37] The primary criticism pertained to the use of this protocol for ranibizumab, which is technically on-label, but we know it's less effective than monthly dosing. Is this good clinical trial design? Does this disadvantage the patients in the ranibizumab group and bias the trial outcomes in favor of bevacizumab-vikg? I think it's a suboptimal comparison, and while we may see noninferiority in the trial, I question whether it provides enough confidence for us to say bevacizumab-vikg is noninferior to monthly ranibizumab.

Dr. Bakri: As a community, retina specialists follow the data. We care greatly about how the clinical trials are conducted, and FDA approval and drug availability don't automatically guarantee that we will use them. We saw that early on with bevacizumab – after the first few promising case reports, we started using it off-label. We also saw this more recently with approved drugs that were associated with reports of IOI, vasculitis, and occlusion – we stopped using them. Even if payers mandate that we use a certain biosimilar, we can justify our reasons for switching to other branded drugs. We care about safety. We love to study things on a case-by-case basis. Regardless of the type of drug, it's a matter of gaining more experience and being comfortable with them.

PARTING THOUGHTS ON BIOSIMILARS

Q | **Dr. S. Sharma: What would do for your patients who are stable on a drug?**

Dr. Bakri: I wouldn't switch them. Why rock the boat, especially if the patient is stable, on a good interval, and happy? If there's a payer issue or the patient's copay has changed, then I look at all the options.

Q | **Dr. A. Sharma: Do you believe the "interchangeability" designation confers any advantage?**

Dr. Shah: I don't foresee that having a real advantage, and although ranibizumab-nuna will receive that designation soon as well, it will be a moot point going forward. The office and clinic discussions around biosimilars in the United States may start with a consent form. For now, it will be ranibizumab and its biosimilars, which is a significant enough switch to initiate that discussion with the patient. Again, they're biosimilar, not bioequivalents. We can't hang our hats on "interchangeability" and believe that swaps can be made without having that discussion. The cost component, which is the real advantage, is almost negated for a lot of the US population.

Dr. Bakri: It's negated as of right now, but that may not always remain the case. That's my concern.

Q | **Dr. S. Sharma: I worry about how payer models will change once intravitreal anti-VEGF biosimilars become available, and what that might mean for us. Will they allow us to keep using the branded product and still provide cover but hold us responsible for the difference in price? Will they increase the copay percentage? Will the rules around step therapy change?**

Dr. Bakri: Dr. Shah, what happens currently in oncology when a patient wants to continue using the branded drug? Do clinicians point to the insurance company and explain that these are the options provided by their chosen insurance provider? In ophthalmology, will premium insurances allow a larger choice of branded drugs? At the end of the day, they must cover the population, and we have several new therapies that are getting more and more expensive. We also have more treatable diseases.

Dr. Shah: Those are tough questions and there are no clear answers. The cost containment component of newer innovator therapies is challenging. They potentially allow less frequent treatments and are priced accordingly, ie, if they save us six treatments, they're priced for five treatments. The cost savings here are incremental. One of the real challenges and significant cost burdens for the health care system will be diseases currently without treatment, and geographic atrophy is a timely one that comes to mind. If we can achieve value, where we get the same safety and efficacy with lower costs, that's always a good thing. The adoption rate and how quickly retina specialists will make that move is difficult to predict.

Dr. S. Sharma: From the uveitis point of view for example, for infliximab, we didn't get a choice. That's why we made the switch. One of the impetuses for publishing that study on infliximab biosimilars was to justify a need for either the originator drug or the higher biosimilar dose. I was able to get one or the other approved by the medical director based on that paper.

Unless we do a large study, I don't believe we'll see the same type of data in the ophthalmology anti-VEGF space. The efficacy will be very similar. I will always question safety and that's because all of us are a little shell shocked by some of the other products that have come to market that have had major safety concerns.

However, I'm hopeful, based on the experience in India, that we won't see that for anti-VEGF biosimilars.

Q | Dr. S. Sharma: Dr. Sharma, I believe ranibizumab is now marketed under a different brand name in India and that has brought the cost down by 50%, despite being the originator product from the same company. How does that play into your practice?

Dr. A. Sharma: That's right, we predominantly use the rebranded ranibizumab product and the original brand is mainly used by some government institutes. When it was first launched in India, the original branded ranibizumab was priced around $1,200. Rebranded ranibizumab is now approximately $350. The ranibizumab biosimilars started out at approximately $200 and are currently priced around $100.

Dr. S. Sharma: That's a big price pressure.

Dr. A. Sharma: Yes. We also had a scheme with rebranded ranibizumab, whereby if we used three vials, the fourth was free. During the past year or so, pricing pressures have changed so that if we use two vials, the third is free. Ultimately, in these situations, the patients win.

Dr. S. Sharma: I'm very curious to see if the United States will experience the same pricing pressure on brand-name products now that biosimilars are becoming available. It will be interesting to see how the ASP may change for different practices and prescribers. Dr. Shah, any thoughts in this regard, from a large private practice standpoint?

Dr. Shah: We've seen how ranibizumab-erqn 0.5 mg ($1,360) and ranibizumab-nuna 0.5 mg ($1,130) were similarly priced and comparable to ranibizumab's current ASP (approximately $1,290).[24,25,27] As Dr. Sharma noted, the manufacturer of the originator may push back with lower pricing schemes, rebate offers, or mechanisms of the like. Again, the presence of off-label bevacizumab, which works very well, is a strong pricing pressure on its own, as it is so much lower in price than the ranibizumab biosimilars that are now available. It will be interesting to see where biosimilar prices start in relation to the originators and off-label bevacizumab.

I think we're going to see two evolutions. First, with the ranibizumab biosimilars and once that's sorted, the whole deck will be reshuffled in anticipation of the aflibercept biosimilars. ■

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THE ERA OF ANTI-VEGF BIOSIMILARS: NAVIGATING THE TREATMENT PARADIGM FOR RETINAL VASCULAR DISEASES

Release Date: November 2022
Expiration Date: December 2023

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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Define the term "biosimilar," focusing on the distinction between "biosimilar" and "generic"	_____	_____	_____
Explain why biosimilars may be introduced into the health care landscape and how they compare with innovator therapies	_____	_____	_____
Describe the process by which biosimilars go through clinical development and receive US FDA approval	_____	_____	_____
Evaluate the risks/drawbacks and benefits of using innovator and biosimilar products for the treatment of patients with retinal diseases	_____	_____	_____
Assess the feasibility of incorporating anti-VEGF biosimilars into clinical practice and adapting treatment algorithms based on regulation, legislation, and insurance policies	_____	_____	_____
Summarize the current and upcoming biosimilars in the retinal disease landscape and their associated trial data	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to evaluate the risks/drawbacks and benefits of using innovator and biosimilar products for the treatment of patients with retinal diseases (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Based on this activity, how often do you plan to use biosimilar agents to treat patients with retinal disease (on a scale of 1-5, with 1 = "Never" and 5 = "Always")?

a. 1
b. 2
c. 3
d. 4
e. 5

3. A 63-year-old patient presents to your office for evaluation of his neovascular age related macular degeneration (nAMD). He is on monthly ranibizumab intravitreal injections. He is interested in learning more about ranibizumab-nuna, a biosilimar agent. Which of the following is TRUE about this biosimilar?

a. Ranibizumab-nuna is considered safer than ranibizumab according to large scale studies
b. Cases of intraocular inflammation have been reported with the use of this biosimilar due to the presence of endotoxins in the manufacturing process
c. The immunogenicity and adverse event profile between ranibizumab and ranibizumab-nuna are comparable
d. Ranibizumab-nuna performed better than ranibizumab in trials with respect to mean letter gains from baseline

4. Which of the following statements is TRUE?

a. The regulatory approval process for biosimilars is not the same as the regulatory approval process for generic agents
b. Biosimilar agents have the same chemical structure as generic agents
c. Biosimilars have an equivalent safety profile compared to generic and branded agents
d. Biosimilars have an equivalent efficacy profile compared to generic and branded agents

5. A 79-year-old woman with bilateral tube shunts presents with new diagnosis of nAMD in her right eye. She prefers to receive an FDA-approved drug and asks you about the most appropriate initial treatment. Which of the following is the most reasonable response?

a. Port delivery system because she can be treated every 6 months
b. Observation because more durable agents will likely be available in the near future
c. There are five FDA-approved anti-VEGF agents including two recently approved ranibizumab biosimilars, which should initially be used monthly
d. Ranibizumab-eqrn because it has superior efficacy to the reference product and costs less

6. An 82-year-old man with nAMD in his right eye has been receiving off-label bevacizumab with suboptimal response and asks about switching to a ranibizumab biosimilar because his neighbor has received this treatment. When he asks you how these biosimilars compare to other branded anti-VEGF drugs, what is the best response?

a. Ranibizumab biosimilars appear comparable to ranibizumab in terms of efficacy and safety, but the trials are relatively smaller and evaluate earlier primary endpoints compared to traditional phase 3 registration studies
b. Ranibizumab biosimilars have equal efficacy and safety as their reference product, but are one-third the cost
c. Ranibizumab-eqrn has been tested head-to-head to ranibizumab-nuna and no significant differences were observed
d. In the phase 3 study evaluating ranibizumab-nuna, the mean letter gains from baseline at week 52 was +11 letters (ranibizumab-nuna) versus +9 letters (ranibizumab)

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low____

This activity improved my competence in managing patients with this disease/condition/symptom. ____ Yes ____No

Probability of changing practice behavior based on this activity: ____High ____ Low ____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy ____
Change in nonpharmaceutical therapy ____
Change in diagnostic testing ____
Choice of treatment/management approach ____
Change in current practice for referral ____
Change in differential diagnosis ____
My practice has been reinforced ____
I do not plan to implement any new changes in practice ____

Please identify any barriers to change (check all that apply):

____ Cost
____ Lack of consensus or professional guidelines
____ Lack of administrative support
____Lack of experience
____ Lack of time to assess/counsel patients
____ Lack of opportunity (patients)
____ Reimbursement/insurance issues
____ Lack of resources (equipment)
____ Patient compliance issues
____ No barriers
____ Other. Please specify: _____

The design of the program was effective for the content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relative to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
You would you recommend this program to your colleagues	___ Yes	___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

____ Patient Care
____ Practice-Based Learning and Improvement
____ Professionalism
____ Medical Knowledge
____ Interpersonal and Communication Skills
____ System-Based Practice

Additional comments:

_____

This information will help evaluate this activity. May we contact you by email in 3 months to inquire if you have made these changes?
If so, please provide your email address below.

_____

_____


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