THE ANTI-VEGF QUESTION: What's in Your Refrigerator?

With so many choices, how do retina specialists best manage their biologic agent inventory and select which drugs to stock? A look at the challenges underlying the decision-making process.

Mike Mott, Contributing Writer

ANTI-VEGF THERAPY IS THE CORNERstone for treating most pathology commonly seen in the retina practice. Beginning in 2005, repackaged bevacizumab (Avastin) and shortly thereafter ranibizumab (Lucentis), followed in 2011 by aflibercept (Eylea), rapidly and widely became adopted for the treatment of neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and other VEGF-driven ocular diseases. Less than two decades later, the continuing approval of several anti-VEGF therapeutics in just the past few years —including brolucizumab (Beovu, approved 2019), faricimab (Vabysmo, approved 2022), and aflibercept 8 mg (Eylea HD, approved 2023)—has further revolutionized the treatment of AMD, proliferative diabetic retinopathy, DME, and macular edema from retinal vein occlusion.

These additions to the armamentarium have undoubtedly provided new tools for preventing vision impairment and restoring visual function for patients—but not without a substantial price. In 2020, the total U.S. market sales of ranibizumab and aflibercept approached $1.5 billion and $5 billion, respectively, with individual doses ranging in the thousands of dollars.[1] As a result, pharmaceutical companies have pushed anti-VEGF biosimilars like ranibizumab-nuna (Byooviz, approved 2021) and ranibizumab-eqrn (Cimerli, approved 2022) to market to reduce costs relative to FDA-approved agents and compete with the originator biologics. Several other biosimilars are also in various stages of clinical research.

Disrupting practice management. These ongoing advancements are not only setting the stage for additional complexity in how retina specialists treat patients, but also forcing practices to reconsider how they maintain their own anti-VEGF inventory, said Alan E. Kimura, MD, MPH, at Colorado Retina Associates in Denver.

"Injectable drugs are central to the entire retinal practice," said Dr. Kimura. "They form the major work of the clinic." But they are also becoming the No. 1 pain point for both clinician and staff, he added. "There really are only so many vials we can carry in our refrigerators. How do we make space for rapidly growing biosimilars when we need to carry other mainstays as well?"

Because of this disruption to existing inventory management systems, more and more retina specialists are left wondering what exactly to stock and whether each drug is worth the price, said Ankoor R. Shah, MD, at Retina Consultants of Texas in Houston. "We have to carry more high-cost drugs than ever before. Making sure we manage just the right amount is increasingly important. If you're carrying too much inventory, you're misallocating valuable refrigerator space. If you're carrying too little, your patients can suffer because of subsequent delays in receiving medication."

Cynthia Turner

One of the challenges with keeping excess inventory, for example, is the declining reimbursement for many of these drugs quarter over quarter, said Judy E. Kim, MD, FARVO, FASRS, at the University of Texas Southwestern Medical Center in Dallas. "If you buy a large quantity of drug A at $x and the reimbursement decreases in the next quarter to $x-y, you can be in a situation where you lose money on a particular dose that has been sitting in your refrigerator for several months," she said. "On the opposite side of the spectrum, if you take a just-in-time approach, you can end up not having adequate drugs to treat the patients in your office on a particular day."

Although these intravitreal therapeutic agents may be a component of revenue for some practices, they also carry significant financial risks for the practice due to the cost of these agents, which must be balanced with anticipated patient need and careful tracking of the agents that are in the refrigerator, she said.

Inventory issues. Maintaining the Goldilocks perspective—not too little, not too much, just right—is not a simple one-size-fits-all proposition, said Dr. Shah. Proactive inventory management is unique to each practice, but there are several important components to consider when making the best decisions in the expanding world of biologics and biosimilars.

Sound medical decision-making with attention to outcomes and risk will trump all other considerations, said Dr. Kimura. Other factors include awareness of payer policies, step therapy implications, and novel treatments in the pipeline, to name a few.

Clinical Considerations

VA. If finances are not an issue because of your patient's insurance coverage, the most important factor when choosing what you want to carry in your refrigerator is whether one agent provides superior functional VA outcomes over another agent for a specific pathology, said Neil M. Bressler, MD, at Johns Hopkins Medicine in Baltimore.

For example, in the case of DME, the National Institutes of Health–sponsored DRCR.net Protocol T clinical trial demonstrated that the participant group assigned to aflibercept 2 mg, on average, had superior VA outcomes over two years compared with the bevacizumab or ranibizumab

Practice Considerations—Academic or Private?

Effective inventory management for retina practices and clinics requires a complex system dependent on various dynamics and workflows. A major factor to consider may be your practice type, said Dr. Shah, as academic and private settings may experience unique challenges.

Costs. "It is highly likely that smaller practices will choose to maintain a smaller anti-VEGF inventory than larger practices and perhaps academic practices due to economics," said Dr. Lim. The larger groups, universities, and hospitals have deeper pockets and more potential bargaining power for negotiating costs, she said.

Academic clinicians are "the last resort for many patients, including those with rare disorders," said Dr. Lim. "And because of our mission, we choose to stock the more expensive therapies and the more efficacious drugs that are used after first-line treatments have failed—and we accept the financial consequences."

Supply chain logistics. Unlike those in academic settings, retina specialists in private practice are managing the logistics of the entire supply chain, said Dr. Shah, from inventory and revenue cycles to accounts payable and cost assessment.

"Whether you have a single office or multiple satellite clinics, if you're in private practice, your group is bearing all of the risks," said Dr. Shah. "When a single anti-VEGF vial costs multiple thousands of dollars, the practice can suffer greatly and quickly with just a single mistake."

So efficiency—and prudence—are of paramount importance, said Dr. Shah. "It's a massive capital outlay to purchase the drugs sitting in your fridge," he said. And you need to balance the competing interests of what you know today and what's unexpected tomorrow. "Ideally you want your inventory to be turning around very quickly," he said. "And you also need to make space for your just-in-time inventory as well. When a patient you don't anticipate suddenly needs anti-VEGF treatment, you want to make sure you are able to treat them right away and effectively."

A robust inventory management system is therefore essential for a busy private practice to avoid stocking too much or too little medication, said Dr. Kim. These systems also allow the ophthalmologist to determine which doses they have been paid for and which have outstanding balances that need to be collected to avoid losing money on that particular drug.

Medication PA/Referral Resource

1

	EYLEA (2 UNITS)		LUCENTIS (5 UNITS)		VABYSMO		SYFOVRE		AVASTIN		SPECIAL INSURANCE REQUIREMENTS
	PA	REF	PA	REF	PA	REF	PA	REF	PA	REF	
HMA COMMERCIAL	CALL		CALL		CALL		CALL		CALL		Prior authorization via phone request only
USA MA PLAN	✔		✔		✔		✔				PA not required for Avastin
BB MA PLAN	✔		✔		✔		✔				Requires step therapy
MEDICARE PART B											**confirm secondary coverage if HMO and PA/REF requirements
CARE COMMERCIAL	✔	HMO	✔	HMO	✔	HMO	✔	HMO	✔	HMO	888-222-2222 REF needed for HMO plans (from PCP only)
MEDICAID HMO	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	
HMO INSURANCE	✔	HMO	✔	HMO	✔	HMO	✔	HMO	✔	HMO	REF needed for choice or medical home plans only

✔ Prior authorization is required
HMO HMO—Referral required
CALL Prior authorization is required, must call in request
No PA required
No referral required
Caution—Confirm other coverage requirements

REIMBURSEMENTS. *After checking payers' policies, identify carriers' referral and/or prior authorization requirements, per* The Profitable Retina Practice: Medication Inventory Management *(see page 39).*

groups when VA was 20/50 or worse, said Dr. Bressler, so you might consider aflibercept over those two agents.[2]

Similar advantages of aflibercept over bevacizumab or ranibizumab were suggested in the Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO) study of macular edema associated with retinal vein occlusions.[3]

Other benefits. If functional outcomes (for example, VA) are not superior with one agent over another—for example, faricimab or aflibercept 8 mg compared with aflibercept 2-mg for DME—then other advantages might be considered, such as the possibility of less frequent dosing, said Dr. Bressler. However, while clinical trials evaluating faricimab or aflibercept 8 mg show strong durability, the clinical trials were not head-to-head comparisons of different agents with the same treatment regimens to determine if one agent had stronger or greater durability than another agent. It's more important than ever to stay up to date on the appropriate interpretation of the latest research when making any treatment determinations, he said.

"In this exercise of what to stock for treating DME, while bevacizumab is needed when finances preclude use of other anti-VEGF agents, we have sound efficacy data to suggest leaning toward aflibercept 2 mg over bevacizumab or ranibizumab agents," said Dr. Bressler. "We also have 15 years of safety experience with aflibercept [2 mg] that is not available for faricimab or aflibercept 8 mg."

This is not to say the other more recently available agents should not be a part of your inventory, if feasible, said Dr. Bressler, especially for patients who aren't doing as well as you might have expected with first-line treatment. "But there is no way to know if these cases would do better, the same, or worse with one of the more recently available agents, reiterating that you need compelling evidence to be confident that switching from one agent to another is worth considering, assuming there's no sacrifice to safety with the switch."

Be discerning. When it comes to physician preference, said Dr. Bressler, it's going to be very important for the individual retina specialist to educate and reeducate themselves to understand what's hype and what's fact about anti-VEGF agents, what's being marketed, and what needs to be considered both from clinical trial research and each specialist's own expertise and practice-setting experience.

Quirks of Payer Policies

Because of the high cost of anti-VEGF medications, retina practices need to stay aware of payer policies, said Jennifer I. Lim, MD, FARVO, at the University of Illinois at Chicago. It's not only essential to maximizing reimbursement, but also critical to maintaining the best balance of anti-VEGF inventory.

Prior authorization. Many commercial, Medicare Advantage, and Medicaid HMO plans may require prior authorizations for coverage, said Dr. Lim. And each carrier has unique policies that can change frequently (see Fig. 1). So identifying these policies and monitoring updates is an inherent part of the retina practice because of their impact on what anti-VEGF agents you should carry.

"Prior authorizations are ongoing challenges that are now compounded by the growing number of anti-VEGF formulations," said Dr. Shah. "It can really extend your time to delivering care. We see a patient, we identify and diagnose a condition, and now we want to treat the patient. But how quickly can we get the medication into the eye?" Those waits from the insurance companies can exacerbate the already complex timing of how to keep the optimal supply of medication in your inventory, said Dr. Shah.

Step therapy. Insurance payer policies may also require a preferred drug therapy for intravitreal injections, typically a lower-cost drug (for example, bevacizumab), along with a documented failed

response before initiating a more expensive drug (for example, faricimab). Step therapy is a tool that more and more insurers are using to reduce health care costs, at the expense of patient and physician choice, said Dr. Lim. These types of "fail first" policies can dramatically impact the prior authorization process and can wreak havoc on inventory planning, she said.

Increasing and improving therapeutic options for the management of potentially blinding retinal diseases continues to enhance patient care. The choice of drug should be made by the patient and their ophthalmologist after a detailed discussion of the risks and benefits of all available options. Coverage policies that vary by insurer such as prior authorization and step therapy limit treatment options and contribute to disparities in care between patient populations.

—George A. Williams, MD, Academy Senior Secretary for Advocacy

Step therapy ultimately forces ophthalmologists to stock older drugs, such as ranibizumab, that they maybe wouldn't normally stock any longer in favor of newer drugs, said Dr. Lim. "For example, I'm sometimes mandated to start with bevacizumab or ranibizumab," she said. "But what if my preference for a patient with poor vision from DME is to skip those drugs and start with faricimab or aflibercept 8 mg because of better efficacy and/or durability?" Compared with aflibercept 2 mg, phase 3 studies show faricimab dosed every 16 weeks is noninferior,[4] and results in press hint at promise for aflibercept 8 mg dosed every 20 or 24 weeks. "Step therapy increases my inventory, increases my overhead, and overstuffs my refrigerator—all unnecessarily," she said.

Biosimilars

Biosimilars and step therapy. With the introduction of newer and newer retina drugs, payers have continued to revise their step therapy policies, with some requiring the use of biosimilars after failure with bevacizumab before more expensive drugs are covered. For example, in 2023, Blue Cross Blue Shield of Michigan and Care First in Maryland announced that new patient approvals for aflibercept will first require a failure to both off-label bevacizumab and ranibizumab-nuna, said Dr. Kimura.

The expectation is that more "steps" will follow as more biosimilars enter the market, further complicating the logistics of inventory management, said Dr. Kimura. We don't know quite yet whether the growth of biosimilars will be "exponential" or will stall, he said. "But we do know that even with the smallest addition of biosimilars to step therapy and prior authorizations, there's major complexity on the horizon. From just a revenue cycle and inventory management perspective, how will we possibly keep track of what to stock in our refrigerators when there are so many requirements from multiple payers?"

The burden of navigating payer policies. In his practice, Dr. Kimura currently hires several full-time staff to manage the drug supply across multiple clinics. But it's his hope that artificial intelligence can help alleviate the burden in the near future. "I think we are going to be able to remove the human element from part of the equation," he said. "With machine learning, we can hope to enter the medical records of patients A through Z, including their insurance policies, their diagnoses, and the preferred treatments, and output all of our options at once in real time."

Biosimilars and patient safety. Ultimately, the impact of anti-VEGF biosimilars on the retina practice will largely be determined by the agents that insurers choose to cover and encourage for first-line therapy, said Dr. Bressler. But, because biosimilars usually undergo a smaller number of clinical trials with fewer participants than is typical with new anti-VEGF agents, retina specialists who do adopt their usage need to monitor patients carefully for adverse events and stay educated about the current biosimilar landscape to ensure they are using new agents in the most safe and effective manner, he said.

"Retina specialists are not fundamentally opposed to using biosimilars on a case-by-case basis," said Dr. Shah. "But like all physicians, we are data driven and tend to be a little gun-shy jumping onto the latest and greatest medication or being mandated to do so. There have been several medications in the past, such as brolucizumab, that have received FDA approval and later had side effects with higher incidence rates than were known at the time [of approval]."

Furthermore, said Dr. Shah, some payer policies have inappropriately required off-label indications prior to the use of the physician's preferred anti-VEGF drugs—for example, the use of ranibizumab-nuna, which only comes in the 0.5-mg dosage, prior to aflibercept for DME—though the FDA-approved dosage for ranibizumab is 0.3 mg.

Off-label use of biosimilars. Of concern, he said, some insurers require off-label usage of Avastin biosimilars as part of their step therapy programs. This is troubling on two levels because, first, the drugs are not approved for ophthalmic usage and, second, there are patient concerns about at least one of these drugs because of its excipients. Insurers that implement these steps

need to consider limiting requirements to appropriate products with FDA-approved indications that demonstrate safety and efficacy for the disease being treated, he said. For any such off-label use of biosimilars in the eye, the ophthalmologist should also be careful to assess any associated medicolegal risks, he advised.

"In the end, we need to remember that every patient has a story," said Dr. Kim. "And each story is different. We treat the patient and not just the disease, and we cannot treat them with protocols or mandates that put financial outcome above patient health."

New Treatments and Unanticipated Safety Issues

Novel therapy. Last year, both injectable pegcetacoplan (Syfovre) and avacincaptad pegol (Izervay) were approved by the FDA for the treatment of geographic atrophy. Over the next few years, the expectation is that pharmaceutical companies will release similar drugs, each having different FDA-approved indications and limitations as well as specific routes to receive payer coverage, said Dr. Kimura.

Tricky decisions on what to stock. Any novel treatments like these requiring injection will also impact your inventory levels and be part of the calculus for determining what to store in your shrinking refrigerator, said Dr. Kimura. "Not only are we seeing more drugs for the existing diseases that we treat," he said. "We're also seeing more diseases that we can treat. So we're all having some very important discussions about what exactly to stock."

How to decide. At the University of Illinois at Chicago, Dr. Lim's group has taken the democratic route. "Everybody gets a vote," she said. "We hear each retina physician's opinions, weighing the pros and cons of a new drug and then decide as a group if the drug should be put on formulary. For example, when it first came out, we considered brolucizumab because of its efficacy data. But after learning about the associated incidence of occlusive vasculitis, we decided it wasn't worth the risk."

Given all of the new retina therapeutics in the pipeline, there's no better time than now to start having these internal conversations about what to stock, said Dr. Lim. She suggests starting with three basic questions.

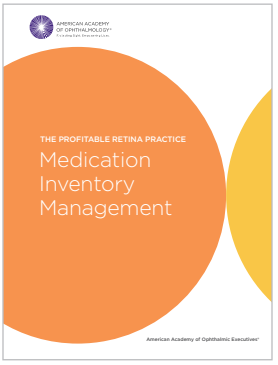
- First, what are the new drugs' risks and benefits? Is there such a great benefit that you're willing to risk an adverse effect?
- Second, do these new drugs give your patients a better chance of improving their vision? What kind of add-on benefits do they provide in terms of better efficacy or longer durability?
- Finally, do these new drugs help your patients economically? If the efficacy and durability are the same as the alternative, will it save them money?

Down the road. In addition to the expansion of anti-VEGF biosimilars and high-dose variations, additional treatments are in the pipeline such as VEGF-C/D inhibition and tyrosine kinase inhibitors, to name a few, that might soon have a substantial impact on what you'll want to carry in your inventory and how much, said Dr. Shah.

Dual-action treatment. "Combination therapy will be more common in the very near future," said Dr. Lim. And it's going to present yet another challenge for refrigerator management. "We're moving from one-drug-per-eye monotherapy to scenarios in which we're combining the injection of anti-VEGF drugs with additional agents, which is going to add that much more complexity to what you need to stock."

Extended duration treatments. Other therapeutics might offer pathways for reducing your

Resources



The Profitable Retina Practice: Medication Inventory Management handbook serves as a guide for analyzing your current system and identifying steps for improvements around the three key components necessary to effectively manage your inventory: control, reimbursement, and monitoring. The booklet is intended to help maximize efficiency and profitability in any practice by developing a comprehensive medication inventory management system.

The digital version is free to Academy and AAOE members, $120 for nonmembers. The print booklet is $99 for Academy and AAOE members, $150 for nonmembers.

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- Geographic Atrophy—How to Get Paid for New Treatments (November 2023).

refrigerator stock—to a degree, said Dr. Shah. "Reducing patient burden is a major focus now for retina practices," he said. "Our patients, especially older and working-age individuals, can get exhausted with monthly treatments. And so if I can treat you half as often, without sacrificing vision outcomes by maintaining or improving your vision, all while giving you back time for family and work, that can be a real boon."

Gene therapy. Gene therapy, for example, may be an exciting alternative to continued intravitreal injections, said Dr. Shah, and may offer a one-time treatment regimen to provide sustained anti-VEGF protein expression after the initial administration. "Whether it be suprachoroidal injection or subretinal delivery of gene therapy, establishing an intraocular biofactory to produce an anti-VEGF agent could be a tremendous step forward."

If sustainable, this technology could drastically reduce the amount of anti-VEGF medication you need to stock, said Dr. Shah, but there are caveats. "Gene therapy could be of tremendous help from a refrigerator management standpoint," he said. "But, unfortunately, any gains here could very well be offset by the as-yet unknown increase in biosimilars, novel therapies, and new lines of diseases that we can treat with intravitreal injections."

The Art of Inventory Management

With so many anti-VEGF choices flooding the market in the coming years, there is no easy formula to best manage your inventory, said Dr. Shah. "Trying to determine how much of each drug to stock is an art," he said. "Different practices will have different patient populations and different patient demographics, so if you ask 10 different retina specialists, you're going to get 10 different answers."

The bottom line. Physician preference, step therapy implications, and prior authorization considerations must all be top of mind, said Dr. Lim. But in the end, your patients will always come first. "When you're deciding what goes in your fridge, you have to be honest with yourself and ask, 'If I were the patient, what drug would I want the doctor to have in there for me?' The answer should always be focused on safety and efficacy first and then, at a much lower bar, cost and reimbursement."

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Meet the Experts

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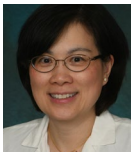

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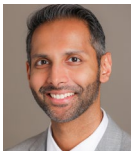

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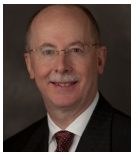

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