

# Anti-VEGF Therapy: Past, Present, and Future



**These agents have fundamentally changed how we care for our patients. Here's my personal perspective on—and role in—the development of the story.**

**BY ROBERT L. AVERY, MD**

**O**f all the innovations that have improved the practice of retina in the past few decades, the development of anti-VEGF agents has had the most profound impact on our profession and our patients' vision. Here's a look at how it all started and what the future holds.

## **FACTOR X**

The earliest understanding of angiogenesis started in 1948, when I.C. Michaelson, MD, speculated that a diffusible, biologic "factor X" existed in the retina that controlled the growth and development of retinal neovascularization.<sup>1</sup> His theory was accurate, but it didn't start to take hold until 1971, when Judah Folkman, MD, published on the therapeutic implications of anti-angiogenesis.<sup>2</sup>

The search for factor X was taken up by Harold Dvorak, MD, who showed that tumor cells secreted vascular permeability factor. Independently, Napoleone Ferrara, MD, at Genentech, identified vascular endothelial growth factor (VEGF). When both entities were cloned, they turned out to be one and the same molecule, and the VEGF moniker prevailed. Dr. Ferrara pioneered the development of VEGF antibodies, which ultimately developed into bevacizumab (Avastin, Genentech) and ranibizumab (Lucentis, Genentech). Joan W. Miller, MD, and her team in Boston, including Anthony Adamis, MD, and many others, went on to demonstrate the role of VEGF and its inhibition in animal models of retinal disease.

I got swept up into this research just out of residency. In 1993, Lloyd P. Aiello, MD, PhD, previously a resident with me at Wilmer Eye Institute, was working with George L. King, MD, in Boston, and had access to antibodies to this newly discovered proliferative factor. Together, he and I collected and analyzed more than 200 aqueous samples and discovered VEGF concentrations in diabetic retinopathy (DR), vein occlusion, retinopathy of prematurity (ROP), and even

chronic retinal detachment.<sup>3</sup> We also showed a difference in VEGF concentrations between active proliferative DR (PDR) and quiescent DR, as well as before and after treatment with laser photocoagulation. Just 2 months prior to our publication, Dr. Adamis scooped us by publishing the presence of VEGF in 20 eyes of patients with diabetes.<sup>4</sup>

These findings opened the door to the general understanding that this protein is ubiquitous in many retinal vascular diseases.

## **PROS AND CONS**

Since then, research into VEGF and potential inhibitors exploded, leading to the first FDA approval of an anti-VEGF agent, pegaptanib (Macugen, Eyetech Pharmaceuticals), in 2004. At the same time, bevacizumab and ranibizumab remained under study for cancer and AMD, respectively. Despite Genentech's contention that the large bevacizumab molecule couldn't penetrate the retina, in 2005, Philip J. Rosenfeld, MD, PhD, and Carmen A. Puliafito, MD, first used bevacizumab in patients and found impressive benefits. They

## **AT A GLANCE**

- ▶ The therapeutic implications of anti-angiogenesis were first recognized in the 1970s for field of oncology.
- ▶ The development of anti-VEGF agents, with the first agent reaching ophthalmic clinical practice in 2004, has revolutionized the treatment paradigms for many retinal diseases.
- ▶ Innovations continue, with new agents, combinations of targets, and delivery methods in clinical trials.

shared this information and the details of compounding bevacizumab with me before their 2005 presentation at the American Society of Retina Specialists meeting. Our group put together a series of 79 AMD eyes,<sup>5</sup> which proved to be instrumental in obtaining insurance coverage for bevacizumab before ranibizumab was approved. In collaboration with Anat Loewenstein, MD, MHA, we evaluated bevacizumab toxicity in a rabbit model, using confocal microscopy to show that bevacizumab does, in fact, penetrate the retina.<sup>6</sup>

We helped pioneer the use of bevacizumab in PDR and diabetic macular edema (DME), first reporting the responses of patients with these indications.<sup>5,7</sup> We also noted fellow eye effects in PDR, prompting me to explore lower doses for this condition. Even when the dosage was reduced by a factor of 100 or 200, an effect on PDR neovascularization was seen.<sup>5</sup>

Based on these observations, I became interested in systemic safety, particularly in the treatment of ROP. When asked to comment on the observation of fellow eye effects in the pediatric population, I voiced my concerns in editorials in the *Journal of AAPOS*.<sup>8,9</sup> Bevacizumab has a serum half-life of 20 days compared with 2 hours for ranibizumab, raising concerns about systemic levels in babies with total blood volume 1/40th that of an adult. These infants are also in the process of organogenesis, and systemic suppression of VEGF could have detrimental effects on an infant's growth and development.<sup>8</sup> Current retrospective studies remain inconclusive, and the ROP population is difficult to study. But Wallace et al performed a dose de-escalation study in ROP down to 1/40th of an adult intravitreal dose of bevacizumab, and nine of nine patients had ROP resolution without recurrence—demonstrating that low doses can work.<sup>10</sup> Further study will determine if there is a significant safety concern.

2011 was a pivotal year, with the Comparison of Age-Related Macular Degeneration Treatments (CATT) trial results and aflibercept (Eylea, Regeneron) approval.<sup>11</sup> The CATT trial first showed comparable results for bevacizumab and ranibizumab for AMD and has provided numerous reports since. Aflibercept provided another agent with superior drying effects and has taken significant market share over the years.

#### ▶ WATCH IT NOW ◀



Track the History—and Future—of Anti-VEGF Therapy

▶ [bit.ly/ARDSAVERY](https://bit.ly/ARDSAVERY)

#### NEXT WAVE

Conbercept (Chengdu Kanghong Biotech), an anti-VEGF agent approved in China since 2014, is making its way to the United States. The molecule is about the same size as aflibercept but reportedly has a higher binding affinity.<sup>12</sup> The company finished 36 months of follow-up in both of its pivotal studies, but there is concern that missed visits due to COVID-19 may impact the results.<sup>13</sup>

Kodiak is another company to watch; its drug candidate, KSI-301, is an anti-VEGF–biopolymer conjugate with a significantly longer half-life in the vitreous cavity than other anti-VEGF agents, given its molecular weight of almost 1 million daltons. The company is projecting an ocular equivalent concentration at 3 months postinjection of about 1,000-fold what would be expected of other agents—giving the potential for a sustained treatment effect for up to 6 months.<sup>14</sup>

Other pathways being investigated involve tyrosine kinase inhibitors (TKIs), with GB-102 (sunitinib malate, Graybug Vision) being the farthest along. Preliminary data from the company's phase 2b ALTISSIMO trial showed that median time to supportive therapy was 5 months; however, patients lost an average of 9 letters in that treatment arm.<sup>15</sup>

Ocular Therapeutix is developing a bioresorbable hydrogel implant that contains a TKI (OTX-TKI). Other formulations can also hold antibodies such as ranibizumab or aflibercept.<sup>16</sup> The implants are designed to deliver drugs for many months, potentially reducing the treatment burden.

Although nothing has been reported recently from PanOptica, the company has been working on a novel eye drop containing a TKI for the treatment of wet AMD. In a phase 1/2 trial, more than 50% of study participants receiving once-daily topical PAN-90806 ophthalmic suspension for 12 weeks did not need rescue with anti-VEGF intraocular injection at the study conclusion.<sup>17</sup>

We are also seeing developments in the anti-angiopoietin pathway. Roche/Genentech conducted global phase 3 clinical trials in wet AMD investigating faricimab, an antibody that binds to and inactivates angiopoietin-2 and VEGF-A. In two phase 3 trials in wet AMD, TENAYA and LUCERNE, approximately 50% of patients eligible for extended dosing were able to be treated every 4 months in the first year.<sup>18</sup>

The Port Delivery System (PDS, Roche) is moving through trials, and we will likely see it approved by the end of this year. In clinical trials, 98% of patients receiving the PDS filled with ranibizumab were able to go 6 months between refill injections.<sup>19</sup> Patients in the treatment group also maintained stable vision comparable with that in the monthly ranibizumab group.

Gene therapy is an exciting treatment possibility under investigation. In the phase 1 OPTIC trial, patients treated with ADV-022 (Adverum Biotechnologies), an intravitreal injection gene therapy producing an aflibercept-like molecule, experienced an 85% reduction in annualized anti-VEGF injections, and two-thirds of patients did not require supplemental



## AN OPHTHALMIC FORMULATION OF BEVACIZUMAB

An ophthalmic preparation of bevacizumab, bevacizumab-vikg (ONS-5010, Outlook Therapeutics), is moving through clinical trials. The drug is designed to address the potential complications of off-label use of repackaged bevacizumab (Avastin, Genentech), including the risks of inconsistent dosing, injection impurities, syringe concerns, and silicone oil bubble issues, according to Firas Rahhal, MD, a partner at Retina-Vitreous Associates Medical Group and Associate Clinical Professor of Ophthalmology at the UCLA School of Medicine.

In two registration trials, NORSE ONE and NORSE THREE, the new formulation showed a safety profile in line with published data for off-label use of bevacizumab, such as the 2011 CATT trials conducted by the US National Eye Institute. In press releases, the company said it expects efficacy and safety data from NORSE TWO, the ongoing pivotal trial of 228 patients being treated with bevacizumab-vikg monthly for 11 months, in the third quarter of 2021.<sup>1,2</sup>

Pending the results of these trials, the company hopes to have the data necessary to file a biologics license application under the PHSa 351(a) regulatory pathway, not as a biosimilar.<sup>1</sup> If approved, bevacizumab-vikg will be the first approved and cGMP-manufactured ophthalmic formulation of bevacizumab.

### Pricing Considerations

The significant cost disparity between off-label repackaged bevacizumab and current FDA-approved anti-VEGF agents has many wondering how this new formulation will be priced. Larry Kenyon, Outlook's President, CEO, and CFO, said the price is expected to be closer to the current cost of off-label bevacizumab than that of the FDA-approved ophthalmic anti-VEGF options.

### Future Indications

While Outlook Therapeutics moves forward with bevacizumab-vikg for treatment of wet AMD, it's already working with the FDA to start registration for clinical programs for bevacizumab-vikg indications for diabetic macular edema and branch retinal vein occlusion, according to the company.<sup>1</sup>

1. Outlook Therapeutics reports positive safety profile from Norse three open-label safety study for ONS-5010 / LYTENAVA (bevacizumab-vikg) [press release]. Outlook Therapeutics. March 31, 2021. <https://ir.outlooktherapeutics.com/news-releases/news-release-details/outlook-therapeutics-reports-positive-safety-profile-norse-three>. Accessed April 5, 2021  
2. Outlook Therapeutics reports topline results and positive proof-of-concept for ONS-5010 / LYTENAVA (bevacizumab-vikg) from Norse 1 [press release]. Outlook Therapeutics. August 26, 2020. <https://ir.outlooktherapeutics.com/news-releases/news-release-details/outlook-therapeutics-reports-topline-results-and-positive-proof>. Accessed April 5, 2021

anti-VEGF injections with median follow up of 68 weeks.<sup>20</sup>

Subretinal delivery of RGX-314 (Regenxbio), an adeno-associated virus vector that encodes an anti-VEGF antibody extremely similar to ranibizumab, continues to look promising. In new interim data, a meaningful reduction in anti-VEGF treatment burden was seen in two of the trial's treatment cohorts (4 and 5) compared with the injection rate during the 12 months prior to RGX-314 administration.<sup>21</sup> In addition, suprachoroidal delivery is being tested in trials in AMD and DR.

### FINAL THOUGHTS

The introduction of anti-VEGF therapy has had a greater effect on the world of retina than any other advance in the past few decades. It has changed our offices, our clinic flows, our pharmaceutical purchasing patterns, and myriad other aspects of our daily routines; but, most important, it has changed our patients' visual outcomes.

I was lucky enough to be an observer of, and sometimes a participant in, the development process. I'm fascinated by all of the innovations in the pipeline, and it will be interesting to see which ones will be the game-changers of the future. ■

9. Avery RL. Extrapolating anti-vascular endothelial growth factor therapy into pediatric ophthalmology: promise and concern. *J AAPOS*. 2009;13(4):329-331.

10. Wallace DK, Kraker RT, Freedman SF, et al. Assessment of lower doses of intravitreal bevacizumab for retinopathy of prematurity: a phase 1 dosing study. *JAMA Ophthalmol*. 2017;135(6):654-656.

11. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011; 364:1897-1908.

12. Liu K, Song Y, Xu G, et al. Conbercept for treatment of neovascular age-related macular degeneration: Results of the randomized phase III PHOENIX study. *Am J Ophthalmol*. 2019;197:156-167.

13. Conbercept: New Generation of Product for Treatment of nAMD Completes 36-week Primary Endpoint Visits of Phase III Trial [press release] December 23, 2020. Accessed April 1, 2021. [www.prnewswire.com/news-releases/conbercept-new-generation-of-product-for-treatment-of-namd-completes-36-week-primary-endpoint-visits-of-phase-iii-trial-301197992.html](http://www.prnewswire.com/news-releases/conbercept-new-generation-of-product-for-treatment-of-namd-completes-36-week-primary-endpoint-visits-of-phase-iii-trial-301197992.html)

14. Kodiak. Our Pipeline. Accessed April 1, 2021. <https://kodiak.com/our-pipeline>

15. Graybug vision reports preliminary topline results from phase 2b ALTISSIMO trial [press release]. Graybug Vision. March 9, 2021. Accessed April 1, 2021. <https://investors.graybug.vision/news-releases/news-release-details/graybug-vision-reports-preliminary-topline-results-phase-2b>

16. Ocular Therapeutix. OTX-TKI. Accessed April 1, 2021. [www.ocutx.com/research/otx-tki](http://www.ocutx.com/research/otx-tki)

17. PanOptica anti-VEGF eye drop shows promise in treatment of neovascular (wet) AMD [press release]. PanOptica. October 10, 2019. Accessed April 1, 2021. [www.panoptica.com/wp-content/uploads/2019/10/PanOptica-PAN-90806-Data-Summary-Release-Clean-Final-Oct-09-2019.pdf](http://www.panoptica.com/wp-content/uploads/2019/10/PanOptica-PAN-90806-Data-Summary-Release-Clean-Final-Oct-09-2019.pdf)

18. New phase III data show Roche's faricimab is the first investigational injectable eye medicine to extend time between treatments up to four months in two leading causes of vision loss, potentially reducing treatment burden for patients [press release]. Roche. February 12, 2021. Accessed April 1, 2021. [www.roche.com/media/releases/med-cor-2021-02-12.htm](http://www.roche.com/media/releases/med-cor-2021-02-12.htm)

19. Phase III data show Roche's Port Delivery System with ranibizumab enabled over 98% of patients to go six months between treatments for neovascular age-related macular degeneration [press release]. Roche. July 22, 2020. Accessed April 1, 2021. [www.roche.com/media/releases/med-cor-2020-07-22b.htm](http://www.roche.com/media/releases/med-cor-2020-07-22b.htm)

20. Adverum Biotechnologies presents long-term data through March 10, 2021 from the OPTIC trial of ADVVM-022 intravitreal gene therapy in Treatment-experienced wet AMD patients at ARVO 2021 [press release]. Adverum Biotechnologies. May 1, 2021. Accessed May 17, 2021. <https://investors.adverum.com/news-releases/news-release-details/adverum-biotechnologies-presents-long-term-data-through-march-10>

21. Regenxbio announces additional positive interim phase I/IIa and long-term follow-up data of RGX-314 for the treatment of wet AMD [press release]. Regenxbio. February 16, 2021. Accessed April 1, 2021. <https://regenxbio.com/news-releases/news-release-details/regenxbio-announces-additional-positive-interim-phase-iiia-and>

1. Patz A. Retinal neovascularisation: early contributions of Professor Michaelson and recent observations. *Br J Ophthalmol*. 1984;68:42-46.

2. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285:1182-1186.

3. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331:1480-1487.

4. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol*. 1994;118(4):445-550.

5. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina*. 2006;26:262-269.

6. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology*. 2006;113:363-372.

7. Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina*. 2006;26(3):352-354.

8. Avery RL. Bevacizumab (Avastin) for retinopathy of prematurity: Wrong dose, wrong drug, or both? *J AAPOS*. 2012;16(1):2-4.

### ROBERT L. AVERY, MD

- Founder and CEO, California Retina Consultants, Santa Barbara, California
- Associate Medical Director, *Retina Today*
- bobave@gmail.com
- Financial disclosure: Consultant (Adverum, Allergan, Amgen, Apellis, Asclepix, Eyepoint, Clearside, Genentech, Novartis, Ocular Therapeutix, Regenxbio, Revana); Equity (Adverum, Eyepoint, Kodiak, Novartis, Regeneron, Revana)