

For this Practical Retina column, **Charles C. Wykoff, MD, PhD**, and **Brenda Zhou, BS**, from Houston, Texas, were asked to comment on the innovations taking place to benefit our patients with neovascular AMD (nAMD).

Retina specialists will agree that durability of our current therapies remains a shortcoming despite the monumental therapeutic advances that have taken place during the past decade and a half. We have seen many failed trials of therapies that were slated to improve management of patients with nAMD. Despite these failures, three potential therapies remain in the running to help us solve the durability issue that some of our patients face. These emerging therapies include brolocizumab (Novartis), abicipar (Allergan), and the ranibizumab port delivery system (Genentech). These anticipated U.S. Food and Drug Administration approvals will only add to the questions regarding the role of various approaches to manage patients with nAMD.

Dr. Wykoff and Ms. Zhou will review clinical trial data surrounding these emerging treatment approaches and will share their insights as to how these weigh against currently available therapies. They will discuss how innovation in this landscape will hopefully improve outcomes and decrease treatment burden. I am certain that the data presented in this piece will prove to be valuable for our community.



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Innovation in Neovascular Age-Related Macular Degeneration: Consideration of Brolocizumab, Abicipar, and the Port Delivery System

by Charles C. Wykoff, MD, PhD; and Brenda Zhou, BS

In the dawning years of the 21st century, pharmaceuticals that block all isoforms of vascular endothelial growth factor-A (VEGF-A) transformed the management of neovascular age-related macular degeneration (nAMD). Thirteen years following the first podium-level presentation by Philip Rosenfeld, MD, of the remarkable benefits possible with intravitreal delivery of anti-VEGF-A agents, we can, in some ways, pat ourselves on the back.¹ The widespread adoption of repeated intravitreal injections for management of nAMD has changed the face of blindness in many parts of the world. For example, a population-based Danish study reported that incident cases of blindness attributable to nAMD decreased by approximately 50% from 2006 to 2010, whereas new cases of blindness from other causes remained stable.²



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From other perspectives, however, we should withhold celebration in recognition that there is much yet to achieve. For example, if data are pooled from the 3,596 patients enrolled in the MARINA, ANCHOR, VIEW 1, and VIEW 2 trials, the average baseline visual acuity (VA) for these treatment-naïve nAMD eyes was approximately 20/100.³⁻⁵ Subsequently, under optimal consistent anti-VEGF-A treatments, if we achieve an average VA gain of 10 letters through 1 year, that leads to an average VA of approximately 20/63 — not an ideal visual outcome. Combined with humbling reports of remarkably poor real-world, long-term outcomes 5 to 7 years after initiation of anti-VEGF-A treatment without consistent dosing outside of clinical trials, these realities highlight a substantial amount of visual function left unrealized.^{6,7}

In recognition of these unmet needs, considerable capital continues to be invested. The National Institute of Health alone has dedicated \$82 million to \$106 million each fiscal year since 2014 to nAMD research.⁸ Along the way, we have endured many failed trials, including the recent discontinuation of programs focused on platelet-derived growth factor blockade.⁹ Despite these disappointments, three approaches involving new pharmaceuticals and novel hardware development with ongoing or recently completed phase 3 programs deserve attention.

BROLUCIZUMAB AND ABICIPAR PEGOL: INCREASED VEGF-A BINDING CAPACITY

Two late-stage approaches are aspiring to deliver clinical advantages by engineering more potent anti-VEGF-A pharmaceuticals.

Brolucizumab (RTH258) is a single-chain antibody fragment that inhibits all isoforms of VEGF-A.^{10,11} Its molecular weight is 26 kDa compared to 115 kDa for aflibercept (Eylea; Regeneron, Tarrytown, NY) and 48 kDa for ranibizumab (Lucentis; Genentech, South San Francisco, CA). On an anti-VEGF-A molar basis, a 6.0-mg 50- μ L dose is equal to approximately 12 times the 2.0-mg aflibercept dose and 22 times the 0.5-mg ranibizumab dose.^{12,13} In the HAWK and HARRIER phase 3 trials, 2,824 treatment-naïve nAMD eyes were randomized to brolucizumab versus aflibercept every 8 weeks after three monthly doses.^{14,15} Patients randomized to brolucizumab were treated with three monthly doses and then transitioned to injections every 12 weeks, with the opportunity to decrease to every 8-week dosing depending on examination and imaging findings at eight prespecified disease activity assessment visits through 96 weeks.¹⁶ Through year 1, 52% to 57% of brolucizumab-treated patients were maintained at 12-week dosing, and the primary endpoint of VA noninferiority between the drugs was achieved. Through the end of the second year, 75% to 82% of patients who completed the first year at quarterly dosing were maintained on quarterly dosing, for an absolute of 39% to 47% of HAWK and HARRIER patients being maintained on quarterly brolucizumab through 96 weeks after three monthly loading doses.¹⁷ Anatomically, brolucizumab appeared to be a statistically significantly superior drying agent, with between 31% to 41% more eyes having resolved intraretinal and subretinal fluid by OCT at the 16-week, 48-week, and 96-week time points compared with eyes treated with aflibercept.

Abicipar pegol (MP0112) is a 34-kDa designed ankyrin repeat protein (DARPin) that also inhibits all isoforms of VEGF-A.¹⁸ When comparing abicipar pegol to current anti-VEGF-A medications, a 2.0-mg

dose is equal to approximately 3.4-times the 2.0-mg aflibercept dose and 5.6-times the 0.5-mg ranibizumab dose on an anti-VEGF-A molar basis. In the CEDAR and SEQUOIA phase 3 trials, 1,885 treatment-naïve nAMD eyes were randomized to either 0.5 mg ranibizumab monthly, 2.0 mg abicipar pegol every 8 weeks after 3 initial monthly doses, or 2.0 mg abicipar pegol every 12 weeks after doses at baseline, week 4, and week 12. In contrast to the HAWK and HARRIER designs, CEDAR and SEQUOIA had true-fixed quarterly dosing arms with no mechanism for patients to receive more frequent dosing without exiting the trial. The primary endpoint at week 52 of noninferiority to ranibizumab was met. Specifically, between 91.2% and 96% of each arm maintained VA, defined as losing less than 15 letters compared to baseline at 52 weeks.¹⁹ Remarkable to clinicians, patients were more likely to experience inflammatory events with abicipar pegol at more than 15% compared to less than 1% with ranibizumab. Although more information is needed describing the predictability and severity of these events, as well as the incidence of inflammation following re-challenge, it may be worthwhile noting that it is common for biological pharmaceuticals to undergo improvements in the manufacturing process, and this appears to be needed for abicipar pegol based on the data available to date.

Will brolucizumab and/or abicipar pegol allow us to reach the 12-week mark between re-treatments reliably in most nAMD patients? First, it is important to recognize that many patients can be successfully managed with quarterly ranibizumab or aflibercept treatment, and such dosing is now contained within both U.S. Food and Drug Administration-approved medication labels. Although average VA gains were not maintained with quarterly dosing in PIER, a substantial proportion of patients did maintain VA during the quarterly dosing phase.^{20,21} Similarly, during the VIEW 1 extension study, a clinically relevant proportion of patients were maintained on quarterly aflibercept dosing.²² Finally, successful quarterly dosing has been reported in 17% to 37% of ranibizumab-treated eyes in prospective treat-and-extend trials.²³⁻²⁵

Nevertheless, there are grounds to be optimistic that the greater anti-VEGF-A molar-binding capacity conferred by brolucizumab and/or abicipar pegol may translate into tangible benefit in some patients. From a durability perspective, the median number of pro re nata (PRN) injections through 2 years in the HARBOR trial was 27% higher with 0.5 mg compared to 2.0 mg ranibizumab at 14 compared to 11 injections.²⁶ From an efficacy perspective, some trials that enrolled pa-

tients with an incomplete anatomic response to conventional anti-VEGF-A dosing have reported visual gains when transitioned to a higher dose of the same anti-VEGF-A agent.^{26,27} Finally, suboptimal treatment frequencies in the real-world, coupled with the observation that multiple exudative disease recurrences may limit ultimate VA gains indicate that a more potent drying agent associated with increased durability may translate into better long-term VA outcomes.^{28,29}

PORT DELIVERY SYSTEM: SUSTAINED VEGF-A INHIBITION

A hardware solution to the unmet needs surrounding nAMD is also in development. The port delivery system (PDS) is slightly longer than a grain of rice and is surgically implanted in the operating room such that a release mechanism within the vitreous cavity is contiguous with a reservoir spanning the sclera. An external port covered by tenons capsule and conjunctiva is accessible for fluid exchange in the office using a customized needle. In the phase 2 LADDER study, 220 treatment-naïve nAMD eyes were randomized to either the control arm of monthly 0.5 mg ranibizumab or three PDS arms employing different ranibizumab concentrations: 10 mg/mL (58 patients), 40 mg/mL (62 patients), and 100 mg/mL (59 patients).³⁰ Patients in the PDS arms had their device reservoir flushed and refilled in clinic in a PRN fashion when prespecified VA, OCT, and/or examination findings were identified.

Results from LADDER indicated that approximately 80% of PDS patients randomized to the highest concentration of ranibizumab were stable without refill through at least 6 months with a median time to refill of 15 months.^{30,31} These patients experienced a mean change of +4.3 letters and a mean change in central foveal thickness of $-3.4 \mu\text{m}$, comparable to improvements achieved in the monthly ranibizumab arm of +3.3 letters and $-6.9 \mu\text{m}$. Such hardware carries possible risks, such as conjunctival erosion and subsequent exposure long appreciated by our glaucoma colleagues related to surgically implanted aqueous drainage implants.³² Nevertheless, the PDS may afford more consistent anti-VEGF-A dosing and move the field away from the peak-and-trough phenomenon inherent to repeated intravitreal injections. The PDS is currently being evaluated in the phase 3 Archway and Portal trials.^{33,34}

CONCLUSIONS

Outside of the approaches described above, the field of nAMD management will invariably be shaped by other developments also in late-stage clinical trials. Biosimilars to both ranibizumab and aflibercept are being developed. Conbercept (KH902), a 143-kDa

biologic capable of inhibiting all isoforms of VEGF-A, has been utilized widely across China for nAMD treatment and is currently being studied in the U.S. in ongoing phase 3, randomized trials compared to aflibercept (PANDA-1 and PANDA-2).³⁵⁻³⁸ Peering further up the pipeline, anti-VEGF-A pharmaceuticals with the capacity to potentially extend biological activity well beyond 3 months, including KSI-301 and sunitinib, are in early-stage human trials.^{39,40} Finally, novel molecular targets in combination with VEGF-A blockade are being pursued, including angiopoietin-2 and VEGF-C plus VEGF-D blockade; such alternative targets may improve retinal deturgescence, but may also allow for the tantalizing possibility of fluid-independent visual gains.⁴¹

Although the current commentary has focused on nAMD, the atrophic form of AMD remains a tremendous unmet need when considering AMD management more broadly.⁴² Despite the recent failure of lampalizumab, the complement cascade remains a clear target and multiple alternative pharmaceuticals are progressing through human trials.^{43,44}

The bar set by anti-VEGF-A monotherapy for the treatment of nAMD is indeed high when compared to what clinicians had in their armamentarium before its development. However, there remains tremendous opportunity for improving outcomes for our patients from both efficacy and durability perspectives.

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