CLINICAL TRIAL DESIGNS IN WET AMD: A BRIEF REVIEW

Can newer therapies improve upon visual acuity and other outcomes for patients?

BY CARL D. REGILLO, MD

FDA approval of verteporfin photodynamic therapy (PDT; Visudyne, Novartis) in 1999 marked the era of pharmacotherapy for neovascular conditions of the retina.[1] Soon after, the landscape changed dramatically with the development of biologic therapies that targeted the VEGF family of proteins central to angiogenesis and vascular permeability.[2,3]

Pegaptanib (Macugen, Eyetech Pharmaceuticals), an intravitreally administered pegylated aptamer that targets the 165 isoform of VEGF-A, was the first approved in 2004.[4] It fell out of favor once pivotal trials of newer anti-VEGF-A agents, such as ranibizumab (Lucentis, Genentech/Roche), aflibercept (Eylea, Regeneron), and off-label use of bevacizumab (Avastin, Genentech/Roche), demonstrated more clinically meaningful improvements in vision.

Despite the strides made with standard-of-care intravitreal anti-VEGF-A agents for the treatment of wet AMD, patients' real-world results fall short of those attained in pivotal, phase 3 registration trials.[5-12] Subsequent treatments, also primarily inhibiting VEGF-A, demonstrate noninferiority to earlier agents but have mostly sought to improve durability without showing superior visual results. This article reviews design aspects of these registration trials, including those of next-generation therapeutic approaches.

MARINA AND ANCHOR: SETTING THE STANDARD

The pivotal superiority trials MARINA and ANCHOR compared ranibizumab with sham and PDT, respectively.[13,14] At 12 months, 95% of those randomized to 0.5 mg ranibizumab lost < 15 ETDRS letters versus 62% in the control group. Similarly, in the ANCHOR trial, 96% of the ranibizumab group lost < 15 ETDRS letters versus 64% in the PDT-treated group at 12 months.[15,16] No approved drug has been shown to be superior to monthly ranibizumab, thus setting the bar for newer therapeutic approaches.

NONINFERIORITY TRIALS

Active control studies seek to show that an investigational treatment is no worse than standard of care (ie, statistically noninferior). The specific noninferior margin and trial design affect the strength of the study's findings. Regulators require a functional visual acuity endpoint, which can be categorical (percentage of patients with a 15-letter loss or gain from baseline) or continuous (mean change in BCVA from baseline).

The phase 3 VIEW 1 and 2 studies of aflibercept were largely similar to MARINA and ANCHOR.[17] The primary endpoint analysis assessed noninferiority (margin of 10%) of aflibercept versus ranibizumab in the proportion of patients losing < 15 ETDRS letters at month 12. The aflibercept groups were noninferior to ranibizumab (0.5 mg every 4 weeks) and an integrated analysis found no statistically significant change in mean ETDRS letter improvement at 1 year. The trials demonstrated that 2 mg aflibercept dosed every 4 or 8 weeks (after three monthly loading injections) was noninferior to ranibizumab (0.5 mg every 4 weeks).

Monthly and bimonthly (every 8 weeks after 3-month loading) fixed regimens were used in the registration trials for ranibizumab and aflibercept, respectively. These fixed dosing regimens represent on-label standards of comparison for other follow-on therapies exploring similar or extended dosing schedules.

AT A GLANCE

- Active control studies seek to show that an investigational treatment is no worse than standard of care (ie, statistically noninferior).
- Most current wet AMD trials are designed to demonstrate noninferiority in mean cahnge in BCVA from baseline using extended dosing intervals of newer therapies.
- Combination therapy in wet AMD differs with regards to the primary endpoint; it must demonstrate superiority of effect on visual function outcomes.

The low cost of repackaged bevacizumab led to its widespread off-label use in wet AMD. The landmark CATT trial established the noninferiority of bevacizumab (1.25 mg every 4 weeks) to ranibizumab (0.5 mg every 4 weeks), validating its use in practice.[18]

IMPROVING DURABILITY

A majority of subsequent completed or ongoing trials in wet AMD have been designed to demonstrate noninferiority in mean change in BCVA from baseline using extended dosing intervals of newer therapies compared with fixed dosing with standard-of-care treatment.

Trials of brolucizumab (Beovu, Novartis) and faricimab (Vabysmo, Genentech/Roche) marked the beginning of noninferiority studies of treatment durability for many next-generation therapies, with most employing fixed dosing with aflibercept as a control comparator arm and incorporating designs that tailored the retreatment interval based on protocol-defined disease activity. Key entry criteria largely remained consistent with earlier studies.

The HAWK and HARRIER phase 3 trials investigated 6 mg and 3 mg brolucizumab versus 2 mg aflibercept.[19] A 3-month loading phase was followed by every 12-week dosing for the brolucizumab groups, with an option to decrease to 8-week dosing based on evidence of disease activity. At 2 years, brolucizumab demonstrated noninferiority in mean change in BCVA compared with aflibercept with a similar safety profile. More than half of 6 mg brolucizumab eyes were maintained on dosing every 12 weeks through 48 weeks. Despite better treatment duration, widespread adoption of the drug has been hampered by the risk of occlusive retinal vasculitis and intraocular inflammation.[20]

The phase 3 TENAYA and LUCERNE trial patients were randomized in a 1:1 ratio to 6 mg faricimab or 2 mg aflibercept.[21] Faricimab patients were initially dosed with four injections every 4 weeks up to week 12 and then were assigned dosing intervals of every 8, 12, or 16 weeks based on active disease criteria up to week 60. Both trials met the primary endpoint of mean change in BCVA from baseline, with faricimab showing noninferiority to aflibercept. Faricimab treatment was durable, as 80% of patients in each study achieved at least every 12-week dosing and 45% reached the maximum dosing interval of every 16 weeks by year 1.[21]

It remains to be seen how these extended treatment paradigms from the clinical trial setting perform in the real world, where retreatment decisions vary.

New Drugs Under Investigation

The FDA accepted Regeneron's biologics license application for 8 mg aflibercept based on data from PULSAR that met the primary endpoint of noninferiority in vision gains for both the 12- and 16-week 8 mg aflibercept dosing regimens after initial monthly doses at 48 weeks compared with patients treated with 2 mg aflibercept in an 8-week dosing regimen.[22] A majority of the high-dose treatment patients were able to maintain the dosing regimens. The safety profile was similar to that of the approved aflibercept dose and consistent with the agent's known safety profile.

KSI-301 (Kodiak Sciences) is an anti-VEGF-A antibody biopolymer conjugate with a high molecular weight that is intended to increase residence time in the eye and extend durability. The phase 2b/3 DAZZLE trial randomized patients to either 5 mg KSI-301 on a flexible treatment schedule of 3, 4, or 5 months versus 2 mg aflibercept every 8 weeks following three monthly loading doses. DAZZLE did not meet the primary endpoint of noninferiority of mean change in BCVA from baseline to 12 months. A second trial, DAYLIGHT, is evaluating a more frequent monthly KSI-301 dosing regimen for noninferiority to aflibercept.[23,24]

TKIs and gene therapies hold promise for controlling wet AMD in the maintenance phase of therapy with the potential for greater durability.[25-30] However, these therapies are still in clinical trials, and the relative efficacy and safety of these treatments compared with standard fixed, frequent anti-VEGF-A injections have yet to be shown in large scale, pivotal studies.[31]

SUPERIORITY TRIALS

Combination treatment approaches in wet AMD differ with regards to the primary endpoint, as they need to demonstrate superiority of effect on visual function outcomes (with favorable safety) to be considered for regulatory approval. Key entry criteria are mostly consistent with earlier noninferiority studies; however, patients presenting with worse BCVA at baseline are preferred to avoid any potential ceiling effects of the combination treatment, which could hamper the ability to achieve the superiority primary endpoint.

Despite positive phase 2 data, the results of phase 3 trials of the anti-PDGF molecule, pegpleranib (Fovista, Ophthotech), reported that in combination with ranibizumab or aflibercept/bevacizumab, the primary endpoint of superior mean change in BVCA at 12 months was not met in any of the studies. Reasons for the disappointing data may include changes in trial design from the phase 2 study and potential limited pathophysiological role of PDGF in treatment-naïve disease.[32,33]

OPT-302 (Opthea Limited), an intravitreally administered VEGF-C and -D 'trap' inhibitor biologic, is being investigated in two phase 3 clinical trials in combination with ranibizumab (ShORe) and aflibercept (COAST).[34-36] OPT-302 is given once every 4 or 8 weeks after three monthly loading doses in combination with anti-VEGF-A therapy. Both studies' primary endpoint is superiority in change in BCVA gains from baseline at 12 months for combination therapy versus anti-VEGF-A monotherapy. The completed phase 2b study of OPT-302 plus ranibizumab achieved the primary endpoint of

OLD DRUG, NEW APPROACH

Outlook Therapeutics has an investigational ophthalmic formulation of bevacizumab for the treatment of wet AMD, ONS-5010. The pivotal NORSE TWO trial was designed as a superiority study that compared the safety and efficacy of ONS-5010 (dosed every 4 weeks) against ranibizumab (dosed according to the PIER dosing regimen). The trial met both the primary and secondary endpoints: 41.7% (P = .0052) of patients gained ≥ 15 letters of vision, 56.5% (P = .0016) gained ≥ 10 letters of vision, and 68.5% (P = .0116) gained ≥ 5 letters. The data showed that the drug was well-tolerated, consistent with previously reported data. The FDA accepted the company's biologics license application and set a Prescription Drug User Fee Act goal date of August 29, 2023.[1]

1. Outlook Therapeutics announces acceptance of BLA by FDA for ONS-5010 as a treatment for wet AMD [press release]. Eyewire+. October 28, 2022. Accessed May 1, 2023. eyewire.news/news/outlook-therapeutics-announces-acceptance-of-biologics-license-application-by-fda-for-ons-5010-as-a-treatment-for-wet-amd

a statistically significant mean change in BCVA from baseline to week 24 of +14.2 letters—an additional gain of +3.4 letters (P = .0107) over the ranibizumab plus sham control group.[37]

Phase 2b results also showed that OPT-302 combination therapy had a mean BCVA gain of an additional +5.7 letters over the control group (16.1 vs 10.3 letters) at 24 weeks in a prespecified analysis of treatment-naïve patients with minimally classic and occult lesions. Thus, the phase 3 ShORe and COAST endpoints will be analyzed in a hierarchical fashion, starting with the primary endpoint in these two lesion types (high responders), followed by the total population (including predominantly classic lesions).[34,35]

A LOOK AHEAD

As new therapeutic approaches have been developed for the treatment of patients with wet AMD, pivotal registrational trial designs have evolved to assess for further improvements in efficacy or durability of responses over existing standard of care. Our current anti-VEGF-A therapies work well, but we can still do better to gain back more vision, maintain initial visual gains, or decrease the burden for many patients who currently have a real unmet need for better long-term vision outcomes. ■

1. Klein R. Prevalence of age-related macular degeneration in the US population. *Arch Ophthal*. 2011;129(1):75-80.
2. Klein BEK. Forecasting age-related macular degeneration through 2050. *JAMA*. 2009;301(20):2152-2153.
3. Fine SL. Macular photocoagulation study. *Arch Ophthalmol*. 1980;98(5):832.
4. Boyer DS, Antoszyk AN, Awh CC, et al. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*. 2007;114(2):246-252.
5. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548.
6. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5:e1221-1234.
7. Arepalli S, Kaiser PK. Pipeline therapies for neovascular age related macular degeneration. *Int J Retina Vitreous*. 2021;7(1):55.
8. Ehlken C, Jungmann S, Böhringer D, et al. Switch of anti-VEGF agents is an option for nonresponders in the treatment of AMD. *Eye*. 2014;28(5):538-545.
9. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report. *Arch Ophthalmol*. 1999;117(10):1329-1345.
10. Miller JW, Le Couter J, Strauss EC, et al. Vascular endothelial growth factor A in intraocular vascular disease. *Ophthalmology*. 2013;120(1):10-14.
11. Holmes DIR, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome Biol*. 2005;6(2):209.
12. Gragoudas ES, Adamis AP, Cunningham ET, et al. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*. 2004;351(27):2805-2816.
13. Kaiser PK, Blodi BA, Shapiro H, et al. Angiographic and optical coherence tomographic results of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*. 2007;114(10):1868-1875.
14. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432-1444.
15. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. *Am J Ophthalmol*. 2007;144(6):850-857.
16. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology*. 2009;116(1):57-65.
17. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548.
18. Martin DF, Maguire MG, CATT Research Group, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908.
19. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84.
20. Witkin AJ, Hahn P, Murray TG, et al. Occlusive retinal vasculitis following intravitreal brolucizumab. *J Vitreoretin Dis*. 2020;4(4):269-279.
21. Heier JS, Khanani AM, Ruiz CO. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399(10326):729-740.
22. Aflibercept 8 mg BLA for treatment of wet age-related macular degeneration and diabetic macular edema accepted for FDA priority review [press release]. Regeneron. February 23, 2023. Accessed May 1, 2023. bit.ly/44IUMUC
23. A study to evaluate the efficacy and safety of intravitreal KSI-301 compared with intravitreal aflibercept in participants with neovascular (wet) age-related macular degeneration (wAMD) (DAYLIGHT). Accessed May 1, 2023. bit.ly/44rr0Tp
24. Stern HD, Hussain RM. KSI-301: an investigational anti-VEGF biopolymer conjugate for retinal diseases. *Expert Opin Invest Drugs*. 2022;31(5):443-449.
25. A depot formulation of sunitinib malate (GB-102) compared to aflibercept in subjects with wet AMD (ALTISSIMO). Accessed May 1, 2023. clinicaltrials.gov/ct2/show/NCT03953079
26. Safety and tolerability study of suprachoroidal injection of CLS-AX following anti-VEGF therapy in neovascular AMD (OASIS). Accessed May 1, 2023. clinicaltrials.gov/ct2/show/NCT04626128
27. Study evaluating the treatment of OTX-TKI for subjects with neovascular age-related macular degeneration. Accessed May 1, 2023. clinicaltrials.gov/ct2/show/NCT04989699
28. Study of EYP-1901 in subjects with wet age related macular degeneration (wAMD). Accessed May 1, 2023. bit.ly/3NEhqSo
29. Safety and efficacy of ADVM-022 in treatment-experienced patients with neovascular age-related macular degeneration (LUNA). Accessed May 1, 2023. clinicaltrials.gov/ct2/show/NCT05536973
30. Regenxbio announces additional positive interim data from trials of RGX-314 for the treatment of wet AMD [press release]. Regenxbio. October 3, 2022. Accessed May 1, 2023. bit.ly/3AQy3mh
31. Cabral de Guimaraes TA, Georgiou M, Bainbridge JWB, Michaelides M. Gene therapy for neovascular age-related macular degeneration: rationale, clinical trials and future directions. *Br J Ophthalmol*. 2021;105(2):151-157.
32. Ophthotech announces results from third phase 3 trial of fovista in wet age-related macular degeneration [press release]. Iveric Bio. April 14, 2017. Accessed May 1, 2023. bit.ly/44uxeNh
33. Rosenfeld PJ, Feuer WJ. Lessons from recent phase III trial failures: don't design phase III trials based on retrospective subgroup analyses from Phase II trials. *Ophthalmology*. 2018;125:1488-1491.
34. OPT-302 with ranibizumab in neovascular age-related macular degeneration (nAMD) (ShORe). Accessed May 1, 2023. bit.ly/3ASlUgH
35. OPT-302 with aflibercept in neovascular age-related macular degeneration (nAMD) (COAST). Accessed May 1, 2023. bit.ly/3ny1aYr
36. Dugel PU, Boyer DS, Antoszyk AN, et al. Phase 1 study of OPT-302 inhibition of vascular endothelial growth factors C and D for neovascular age-related macular degeneration. *Ophthalmol Retina*. 2020;4(3):250-263.
37. Jackson TL, Slakter J, Buyse M, et al. A randomized controlled trial of OPT-302, a VEGF-C/D inhibitor for neovascular age-related macular degeneration [preprint published online February 6, 2023]. *Ophthalmology*.

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