Clinical Ophthalmology

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REVIEW

Brolucizumab: evidence to date in the treatment of neovascular age-related macular degeneration

This article was published in the following Dove Press journal:
Clinical Ophthalmology

Nicolas A Yannuzzi[1]
K Bailey Freund[2–4]

[1]Department of Ophthalmology, Bascom Palmer Eye Institute/University of Miami Miller School of Medicine, Miami, FL, USA; [2]Luesther T. Mertz Retinal Research Center, Manhattan Eye, Ear and Throat Hospital, New York, NY, USA; [3]Vitreous Retina Macula Consultants of New York, New York, NY, USA; [4]Department of Ophthalmology, New York University School of Medicine, New York, NY, USA

Abstract: Age-related macular degeneration (AMD) is a global health concern and the leading cause of vision loss in the developed world. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has revolutionized the treatment of neovascular AMD, but there are still challenges with delivery of care and treatment burden with currently available medications. Brolucizumab is a single-chain antibody fragment inhibitor of all isoforms of VEGF-A. Its small molecular weight allows for high solubility and tissue penetration. Brolucizumab has most recently been evaluated in 2 parallel phase 3 randomized controlled trials which demonstrated its safety and efficacy in an extended dosing regimen. The present review summarizes the safety, visual and anatomic outcomes, and durability of brolucizumab in the treatment of neovascular AMD and discusses some of the extended dosing regimens explored with currently approved medications and other therapies still under clinical investigation.

Keywords: neovascular age-related macular degeneration, brolucizumab, vascular endothelial growth factor

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in the developed world and is projected to be of increasing importance in the coming years with an estimated 196 million affected by 2020 and 288 million by 2040.[1] Intravitreal anti-VEGF therapy has revolutionized the treatment of neovascular AMD. There are currently 4 available intravitreal anti-VEGF therapies: pegaptanib,[2] bevacizumab,[3] ranibizumab,[4,5] and aflibercept.[6] While the initially approved agent, pegaptanib, has comparatively reduced potency (presumably because of targeting only the VEGF-165 isoform), the other 3 treatments are all highly effective. Yet, challenges still remain. Intravitreal anti-VEGF therapy initially stabilizes vision, but long-term visual outcomes are less promising with almost one third of eyes developing atrophy and significant vision loss after 5–7 years of therapy.[7,8] Furthermore, there is a significant economic and caregiver burden of repeated intravitreal injections. Consequently, many patients do not receive treatment as frequently in a real-world setting as in standardized clinical trials,[9–11] resulting in a negative impact on visual outcomes.

Current treatment strategies include dosing at fixed intervals or pro re nata (PRN) regimens as evaluated in initial clinical trials. Ranibizumab received approval for q4 weeks or PRN dosing. Aflibercept received approval for q4 weeks initially followed by q8 weeks, with some eyes still requiring q4 week dosing. The most commonly used dosing strategy, however, is treat and extend

Correspondence: K Bailey Freund
Vitreous Retina Macula Consultants of New York, 950 Third Avenue, New York, NY 10022, USA
Tel +1 212 861 9797
Email kbfreund@gmail.com

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http://doi.org/10.2147/OPTH.S184706

(TER)[12–15] which has also been validated in several prospective trials and found to be non-inferior to PRN or fixed dosing.[16,17] Given the challenges to patients and the health care system with repetitive injections, there has been an effort to develop longer, more potent intravitreal anti-VEGF agents and other strategies. Brolucizumab (RTH258, also previously known as ESBA1008) is the most recent biologic to have demonstrated efficacy in an extended dosing regimen in late phase clinical trials. This review summarizes the currently available clinical evidence for the use of brolucizumab in the treatment of neovascular AMD.

Pharmacology of brolucizumab

Brolucizumab is a humanized single-chain antibody fragment inhibitor of all isoforms of vascular endothelial growth factor-A (VEGF-A). In comparison to a full antibody or a Fab fragment, brolucizumab is a single-chain antibody fragment, the smallest functional subunit of an antibody that still maintains full binding capacity to its intended target.[18] In comparison to bevacizumab (a full antibody, 149 kDa), aflibercept (a VEGFR 1/2 - Fc fusion protein, 115 kDa), and ranibizumab (a Fab fragment, 48 kDa), brolucizumab has the smallest molecular weight (26 kDa).[19] The stability and solubility of brolucizumab allows it to achieve high doses in a single 50 microliter intravitreal injection.[20] At a dose of 6 mg, its equivalent molar dose is approximately 10 times greater than aflibercept and approximately 20 times greater than bevacizumab and ranibizumab. Animal studies have also suggested that brolucizumab's small size might provide better retinal and choroidal penetration and faster systemic clearance.[19]

Clinical trials

Phase I/II

A Phase I/II trial was conducted to assess for the safety, tolerability, and effect of brolucizumab at a range of doses compared to ranibizumab.[21] The study was conducted in two phases: a dose escalation phase and a dose expansion phase. In the dose escalation phase, patients were randomized to receive brolucizumab 0.5 mg, 3.0 mg, or 4.5 mg or ranibizumab 0.5 mg. In the first portion of the dose expansion phase, patients were randomized to receive brolucizumab 4.5 mg or ranibizumab 0.5 mg and in the second portion, either brolucizumab 0.5 mg, 3.0 mg, or 6.0 mg or ranibizumab 0.5 mg. This was a single dose protocol. The primary endpoint was change from baseline to 1 month in central subfield thickness (CSFT).

In this study, brolucizumab met its primary endpoint at a dose of 4.5 mg and 6.0 mg and demonstrated noninferiority to ranibizumab 0.5 mg. The least squares mean (LSM) reductions in mean change from baseline to month 1 CSFT were 21 microns and 10 microns greater for brolucizumab 4.5 mg and 6.0 mg in comparison to ranibizumab 0.5 mg respectively. Overall, there was a trend towards a longer duration of action in the brolicizumab treated eyes, although the time course of improvement in best corrected visual acuity (BCVA) was similar between the two groups. There were no significant differences in ocular or systemic adverse effects.

Phase II – OSPREY

A Phase II 56-week prospective, randomized, double-masked, multicenter, 2-arm study compared the safety and efficacy of brolucizumab 6.0 mg and aflibercept 2.0 mg for the treatment of neovascular AMD.[22] The trial enrolled 89 treatment naïve patients. The trial was designed to test for non-inferiority of brolucizumab to aflibercept. The study was divided into 3 intervals: q4w dosing for 3 injections ending on week 8, followed by q8w dosing from weeks 8 until 32, followed by either q12 week dosing for brolucizumab or q8 week dosing for aflibercept from weeks 32 until 56. During study visits without scheduled treatments, investigators were allowed to treat when deemed clinically necessary. During sham injection visits, investigators could elect to treat with active drug instead of the scheduled sham injection.

The primary and the key secondary endpoints were the change in BCVA from baseline to week 12 and week 16. Additional secondary endpoints were change in BCVA from baseline at week 40, average changes from week 12 BCVA for week 16 to week 40, corresponding endpoints for central subfield thickness (CSFT) stability (a post hoc analysis), and assessment of potential for less frequent treatment for brolucizumab over two cycles of q12 week treatment (from weeks 32 until 56). Exploratory endpoints included presence of subretinal fluid and intraretinal fluid at each follow-up visit (a post hoc analysis). The primary safety evaluation was incidence of ocular and non-ocular adverse events during treatment.

The trial demonstrated noninferiority of brolucizumab to aflibercept with respect to visual acuity outcomes. Brolucizumab was found to be noninferior at both time points (weeks 12 and 16). The LSM BCVA change from baseline at week 12 was 5.75 and 6.89 letters in the brolucizumab and aflibercept groups respectively with a difference

of −1.13 letters (80% CI, −4.19 to 1.93 letters) and at week 16 was 6.04 and 6.62 letters with a difference of −0.58 letters (80% CI, −3.72 to 2.56 letters). Additionally, there was no significant difference between the two treatments in terms of change from baseline visual acuity to week 40 with an LSM BCVA change of 6.25 and 5.75 letters respectively for brolucizumab and aflibercept representing a treatment difference of 0.50 letters (80% CI, −3.39 to 4.36). Thus, it was found that brolucizumab had roughly equivalent and possibly very slightly better visual acuity gains than aflibercept.

With respect to its drying effect, brolucizumab appeared to be a slightly more potent agent than aflibercept by some measures. The LSM change from baseline in CSFT at week 12 was −197 microns and −189 microns and at week 40 was −198 microns and −178 microns for brolucizumab and aflibercept respectively. A post-hoc analysis disclosed that the proportion of eyes with subretinal fluid at week 12 was 9.3% and 20.9% in the brolucizumab and aflibercept groups respectively (difference, −11.6% [80% CI, −21.4% to −1.9%] and at week 40 was 14.6% and 32.5% (difference, −17.9% [80% CI, −29.7% to −6.0%]). This difference was not observed for intraretinal fluid where there was no significant difference detected between the two groups at 12 or 40 weeks. The proportion of eyes that were completely dry without subretinal or intraretinal fluid at week 12 was 48.8% and 41.9% respectively for brolucizumab and aflibercept (difference, 7.0% [80% CI, −6.7% to 20.7%]), but, by week 40 brolucizumab was found to be superior with 61.0% versus 35.0% (difference, 26.0% [80% CI, 12.2% to 39.7%]). Fluctuations in the proportions of eyes with IRF and SRF were observed in both treatment groups; peak values occurred 8 weeks after treatment and trough values occurred 4 weeks after treatment.

A key question addressed in the third portion of the trial was whether brolucizumab could maintain its effect at longer dosing intervals than aflibercept. There were fewer rescue injections during the q8 weekly treatment phase given to brolucizumab eyes than aflibercept eyes (6 injections in 5 patients versus 15 injections in 10 patients respectively). During the q12 week dosing portion of the trial, brolucizumab treated eyes appeared to maintain stable visual acuity from weeks 36 until 44, but then lost an average of 1.3 letters from weeks 48 to 56, possibly representing waning efficacy at this dose interval. In total, 50% of brolucizumab treated eyes had stable visual BCVA and did not receive unscheduled treatment from weeks 36 to 52 at the q12 week dosing interval. Furthermore, during the q12 week phase, 14 brolucizumab-treated patients received unscheduled treatment while, during the same period, 10 aflibercept treated patients received unscheduled treatment. In total during the extension period to q12 weekly dosing over two years, the brolucizumab group had 60 additional injections in comparison to 94 additional injections in the aflibercept group.

Adverse events were comparable between the brolucizumab and aflibercept groups. There were no cases of intravitreal injection associated endophthalmitis, and the number of eyes with significant intraocular inflammation was comparable between the two groups (2.3% and 2.2% respectively). There were no clearly attributable adverse systemic effects.

Phase 3 – HAWK and HARRIER

HAWK and HARRIER were both two-year, randomized, double-masked, multicenter studies comparing the efficacy and safety of brolucizumab versus aflibercept in neovascular AMD.[23] While HAWK examined 2 doses of brolucizumab (3 mg and 6 mg) versus aflibercept 2 mg, HARRIER compared brolucizumab 6 mg to aflibercept 2 mg. The primary endpoint for both studies was noninferiority of mean BCVA change at week 48. In each trial, eyes were given 3 q4 week loading doses of their assigned drug followed by q12 weekly treatment for brolucizumab or q8 week treatment for aflibercept. The secondary endpoints were average change in BCVA from baseline for weeks 36 to 48, proportion of eyes receiving brolucizumab still receiving q12 weekly dosing through week 48 (brolucizumab group only), change in BCVA and CSFT from baseline at each post-baseline visit, SRF and IRF at each post-baseline visit, and disease activity status at week 16. Disease activity status was defined as a composite clinical assessment based on multiple indicators including BCVA, CSFT, and the presence of intraretinal cysts or fluid.

In both HAWK and HARRIER, brolucizumab demonstrated noninferiority with respect to its primary endpoint (BCVA at week 48). In HAWK, brolucizumab 3 mg and brolucizumab 6 mg showed a −0.6 and −0.2 letter difference in mean change in BCVA versus aflibercept and met statistical significance for noninferiority. With respect to the secondary endpoint of change in BCVA over weeks 36 to 48, broluicizumab was also found to be noninferior. The average change was +6.2, +6.7, and +6.7 letters in brolicizumab 3 mg, 6 mg and aflibercept 2 mg respectively. In HAWK, fewer brolucizumab 6 mg-treated eyes had disease activity versus aflibercept (24% versus 34.5%, p=0.0001) at week 16.

In HARRIER, brolucizumab 6 mg showed a −0.7-letter difference in mean change in BCVA in comparison to aflibercept, also meeting statistical significance for noninferiority. Regarding the secondary endpoint in HARRIER, the average change in BCVA over weeks 36 to 48 was +6.5 letters with brolicizumab 6 mg versus +7.7 letters with aflibercept 2 mg. In HARRIER, fewer brolucizumab 6 mg-treated eyes had disease activity than aflibercept (22.7% versus 32.2%, p=0.002) at week 16. BCVA gains achieved by week 48 in both HAWK and HARRIER were maintained through week 96.[24]

Adverse ocular and systemic events were comparable between brolucizumab and aflibercept in HAWK and HARRIER with the exception of uveitis and endophthalmitis. With brolucizumab 6 mg, across both HAWK and HARRIER, there were 11 uveitis events through 48 weeks and no further uveitis events by 96 weeks versus 1 event with aflibercept through 48 weeks and no further events by 96 weeks. With brolucizumab 6 mg, there were 3 cases of endophthalmitis at 48 weeks and an additional 2 cases through 96 weeks versus 0 cases at 48 weeks and 1 case through 96 weeks with aflibercept.

Notably, both trials showed that only half of the enrolled eyes receiving brolucizumab were able to maintain a q12w dosing interval through week 48. Forty-nine percent of patients receiving 3 mg and 56% of patients receiving 6 mg brolucizumab in the HAWK trial maintained their q12 week dosing interval through week 48. In contrast 51% of eyes receiving 6 mg brolucizumab in HARRIER maintained a q12 weekly dosing interval. An interesting finding from HAWK and HARRIER was that eyes receiving brolucizimab which did not require a rescue treatment between the final q4 week loading dose and the first q12 week dose were likely to be maintained at q12 week dosing for the remainder of the study. In HAWK, 85% of such eyes treated with 6 mg brolucizumab that successfully passed the first q12 week dosing interval could be maintained through week 48 at q12 week dosing. Similarly, in HARRIER, 82% of such eyes were able to be maintained at q12 weekly dosing throughout the study. Furthermore, in HAWK and HARRIER, 82% and 75% of those patients who reached week 48 on a q12 week 6 mg brolucizumab interval remained on q12 doing through week 96. Though not reported directly, since 56% of eyes in HAWK and 51% in HARRIER reached 48 weeks at q12 dosing, this would imply that of the total cohort 46% of eyes in HAWK and 38% of eyes in HARRIER maintained q12 week dosing.

In both HAWK and HARRIER, study eyes initially received three q4 week doses of their assigned drug. Notably, in both trials, brolucizumab appeared to produce greater average CSFTs reductions than aflibercept eyes at weeks 4, 8, 12, and 16. The LSM change in CSFT for brolucizumab at 3 mg and 6 mg dosing was similar at each of these timepoints in the HAWK trial. In HAWK At week 16, the LSM average CSFT for 3 mg and 6 mg brolucizumab and 2 mg aflibercept was −153, −161, and −133 microns respectively. In HARRIER, the average change in LSM CSFT at week 16 was −174 microns for brolucizumab 6 mg and −134 microns for aflibercept 2 mg. Anatomic endpoints at week 48 were maintained through week 96.

Comparison to other extended dosing trials

A number of trials have explored the durability of currently approved medications with extended dosing regimens. ALTAIR is a randomized phase 4 trial conducted in Japan that compared aflibercept 2.0 mg with 2 different treat and extend regimens in neovascular AMD.[25] The two arms included extension at either 2- or 4-week intervals, and all extensions were made based on preset criteria of the presence of subretinal or intraretinal fluid. The minimum interval was 8 weeks and the maximum interval was 16 weeks. In ALTAIR, 57% of eyes in the 2 week adjustment arm and 60% of eyes in the 4 week adjustment arm were maintained at a dosing interval greater than or equal to 12 weeks by week 96. Furthermore, 49% of patients reached an interval of q16 week dosing.

A post hoc analysis of VIEW-1 and VIEW-2 explored the sustainability of aflibercept 2.0 mg at extended dosing intervals. Following 52 weeks of either q4 weekly or q8 weekly fixed dosing with aflibercept, patients were evaluated monthly on a PRN basis for retreatment between weeks 52 and 96. The post hoc analysis showed that 50% and 43% of those patients previously treated with q4 week and q8 week aflibercept respectively in VIEW 1 and 58% and 53% of those patients previously treated with q4 week and q8 week aflibercept respectively in VIEW 2 could be maintained at q12 week dosing or longer.

Ranibizumab has been evaluated in an extended dosing regimen. The EXCITE study compared monthly and quarterly dosing of ranibizumab after three monthly loading doses in a 12-month randomized study. Although visual gains were seen in the monthly and the quarterly dosed eyes, those treated with 0.3 mg and 0.5 mg quarterly gained 4.9 and 3.8 letters while those treated monthly

gained 8.3 letters, demonstrating inferior visual acuity outcomes when dosed at a quarterly interval. Another study exploring the efficacy of ranibizumab dosed quarterly after an initial loading dose of 3 monthly intravitreal injections disclosed similar outcomes.[26]

Other therapies still under clinical evaluation have been evaluated for extended dosing regimens. Abicipar pegol (abicipar) was compared to ranibizumab in a phase 2 trial and showed durability of effect in visual acuity and CSFT but had a notable incidence of intraocular inflammation (10.4%) that ultimately resolved without sustained vision loss.[27] The phase 3 data demonstrated that abicipar at a dosing interval of q12 weeks can achieve similar visual outcomes to q4 week ranibizumab but still had a higher incidence of intraocular inflammation than the ranibizumab group.[28] A second phase 3 trial using a modified formulation of the drug showed a lower rate of intraocular inflammation (8.9%).[29]

In addition to novel biologics, other delivery mechanisms are anticipated to be available in the future including the port delivery system (PDS) for ranibizumab. Results from the randomized phase 2 LADDER trial showed that the surgical placement of the PDS could achieve favorable visual outcomes with a schedule of refilling every 8.7–15 months as determined by OCT.[30] Although the complication rate was favorable in the short term (vitreous hemorrhage rate of 4.5% was the most notable adverse event), long-term safety data are needed. A phase 3 multicenter, randomized trial comparing q24 week PDS delivery of ranibizumab to q4 week intravitreal ranibizumab 0.5 mg in AMD is fully enrolled, and data are expected in the near future.

Trials of gene-based delivery of anti-VEGF proteins for neovascular AMD are still in their infancy, although the early data look promising and these treatments could represent a highly durable therapeutic option.[31] Regenxbio has announced interim phase I data on the use of RGX-314 for the treatment of neovascular AMD via subretinal injection with durability of protein expression at 6 months,[32] and Adverum has announced an investigational new drug application for ADVM-022 delivered by intravitreal injection.[33]

Discussion

Current evidence suggests that brolucizumab 6.0 mg is a potent intravitreal anti-VEGF agent showing efficacy and safety similar to drugs currently used to treat neovascular AMD. In addition, brolucizuamb may be a more durable drug, primarily due its low molecular weight allowing for higher molar dosing. At the dosing intervals examined in trials to date, brolucizumab showed noninferiority to aflibercept 2.0 mg with respect to BCVA gains and stability of BCVA over 96 weeks.

The phase III data from HAWK and HARRIER showed that about 50% of patients treated with brolucizumab could be maintained on q12 week dosing without requiring rescue treatments. Eyes that could not be maintained on a regimen of q12 week brolucizumab tended to show a need for early re-treatment during the 12 weeks following the initial loading phase. This finding could be useful for identifying eyes for which q12 week dosing may not be appropriate. In HAWK and HARRIER, unlike for eyes assigned to receive brolucizumab, the dosing of eyes assigned to aflibercept was not extended beyond q8 week, so there was no head to head comparison of q12 week dosing between drugs. However, head to head data at identical q8 dosing intervals suggest that fewer brolucizumab eyes required rescue treatments than aflibercept treated eyes.

Clinical practice and published data suggest that many aflibercept treated eyes may be extended to q12 dosing using either a PRN regimen or TER. It remains unclear whether some brolucizumab treated eyes on a TER regimen could be extended beyond 12-week intervals without sacrificing efficacy.

Clinical trials have demonstrated that brolucizumab 6.0 mg may be a more potent drying agent than aflibercept 2.0 mg as observed with multiple measures including CSFT and fluid compartment assessments. The ocular and systemic safety of brolucizumab also appear comparable to other intravitreal anti-VEGF agents. In summary, brolucizumab appears to offer the potential for less frequent intravitreal injections in eyes treated for neovascular AMD without sacrificing efficacy. Fewer injections would decrease the treatment burden for patients and healthcare providers and reduce the frequency of injection-related complications.

Acknowledgments

This work was supported by the Heed Foundation and The Macula Foundation, Inc., New York, NY. The funding organizations had no role in the design or conduct of this research.

Disclosure

K Bailey Freund is a consultant for Optovue, Allergan, Heidelberg Engineering, Zeiss, and Novartis. He also receives research support from Genentech/Roche. The authors report no other conflicts of interest in this work.

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