SHORT-TERM OUTCOMES AFTER INTERIM TREATMENT WITH BROLUCIZUMAB

A Retrospective Case Series of a Single Center Experience

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Purpose: To examine outcomes of eyes with neovascular age-related macular degeneration that were switched to brolucizumab because of an unsatisfactory response to bevacizumab, ranibizumab, and/or aflibercept and then switched back because of the presence or risk of intraocular inflammation.

Methods: Retrospective case series of 51 eyes. Visual acuity and retinal anatomy on optical coherence tomography were recorded at the first brolucizumab injection (T1), the final brolucizumab injection (T2), and 6 months following the final brolucizumab injection (T3).

Results: At T2, 41 eyes (41/51%, 80%) had decreased subretinal fluid (31 eyes), intraretinal fluid (12 eyes), or pigment epithelial detachment height (12 eyes). At T3, decreased subretinal fluid was sustained in 17 eyes (17/31%, 55%), decreased intraretinal fluid was sustained in eight eyes (8/12%, 67%), and decreased pigment epithelial detachment height was sustained in eight eyes (8/12%, 67%). Mean logarithm of the minimum angle of resolution visual acuity at T1, T2, and T3 was 0.396 (~20/50), 0.441 (~20/55), and 0.468 (~20/59), respectively. During the brolucizumab treatment period, 11 eyes (11/51%, 22%) developed intraocular inflammation, including one case of retinal vasculitis.

Conclusion: Interim treatment with brolucizumab resulted in anatomical improvements in 41 eyes (41/51%, 80%) that were maintained in 22 of these eyes (22/41%, 54%) for at least 6 months after switching back to the original anti–vascular endothelial growth factor therapeutic. There were no corresponding significant changes in visual acuity.

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The advent of intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapies has revolutionized the management of neovascular age-related macular degeneration (nAMD). Current anti-VEGF therapies include off-label bevacizumab (Avastin, Genentech) and US Food and Drug Administration–approved ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), and—most recently—brolucizumab (Beovu, Novartis). Despite the overwhelming success of anti-VEGF therapy, response to therapy can be variable among individuals. Many patients experience suboptimal responses with one treatment compared with another.[1] Patients with persistent intraretinal fluid (IRF) or subretinal fluid (SRF) despite the maximum dosing frequency of one particular anti-VEGF therapy are referred to as refractory to the respective drug. Without clear evidence-based guidelines for the management of nAMD in refractory eyes, retina specialists are responsible for developing their own treatment protocols for such eyes.

Brolucizumab is a VEGF inhibitor that was approved for the treatment of nAMD in October of 2019 following two, Phase-3, randomized clinical trials: HAWK and HARRIER.[2] Based on the trial data, brolucizumab

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demonstrated superior anatomical results with greater fluid resolution and similar best-corrected visual acuity (VA) compared with aflibercept, with the capability of extending the dosing regimen to 12-week intervals in greater than 50% of treated eyes (56% [HAWK] and 51% [HARRIER]). The trials demonstrated an inflammatory rate of 4%, compared with 1% with aflibercept. However, within the first 4 months of approval, the American Society of Retina Specialists began to receive reports of inflammation, including cases of severe vision loss associated with occlusive retinal vasculitis, in patients treated with brolucizumab.[3] In response, Novartis completed a comprehensive product quality review of brolucizumab, and in April of 2020, the company released updated safety information that confirmed the risk of rare adverse events.[4–6] The fear of unpredictable severe inflammation and the need for patient monitoring postinjection, particularly in the setting of the coronavirus pandemic, has resulted in a decline of brolucizumab use in our practice, with many patients reverting back to their prebrolucizumab anti-VEGF agent.

To date, there is limited, real-world, clinical data available on patients who have received brolucizumab therapy.[7–10] To our knowledge, no previous work has addressed the outcomes of eyes switched back to bevacizumab, ranibizumab, or aflibercept after interim treatment with brolucizumab. The purpose of this study is to examine the visual and anatomical outcomes of patients who were refractory to a particular anti-VEGF therapy, switched to brolucizumab, but were subsequently switched back because of the presence of, or perceived risk of, intraocular inflammation.

Methods

Eligibility and Ethics

This retrospective study evaluated patients treated with brolucizumab for nAMD between November 11, 2019, and August 20, 2020. This study received approval of the institutional review board and was conducted according to the tenets of the Declaration of Helsinki. Informed consent was not required for this study given its retrospective design. Included eyes were treated with any anti-VEGF therapy for a minimum of 12 months before switching to brolucizumab for one or more injections, after which they were switched back to an alternative anti-VEGF therapy. Eligible eyes had at least 6 months of follow-up after switching back from brolucizumab to an alternative anti-VEGF therapy.

Additionally, eligible eyes were on a fixed anti-VEGF regimen with stable dosing frequency and stable or worsening retinal anatomy for a minimum of 6 months before switching to brolucizumab. A fixed anti-VEGF regimen refers to the same agent being used for the 6 months before the switch to brolucizumab. A stable dosing frequency indicates a fixed treatment interval of ±3 days.

Measurement of Retinal Anatomy

Stable retinal anatomy was evaluated and defined as follows: In eyes with persistent SRF, peak SRF height was measured at the following locations[1]: subfoveal and[2] extrafoveal fluid on the central line scan as well as[3] extrafoveal fluid on the remaining B-scans. Stable retinal anatomy in the setting of SRF refers to stable SRF height (±20 μm to account for measurement errors) at all of the above locations during the visit at which brolucizumab was initiated compared with 6 months ago. Subretinal fluid height was measured using the measurement tool in the Cirrus software. Eyes with worsening SRF were also included as long as the treatment interval was not changed. Eyes with fluctuating SRF were also included as long as the treatment interval was not changed and as long as SRF never completely resolved from an area where it was previously noted. Eyes with consistent improvement over the 6 months before switching to brolucizumab were excluded.

Intraretinal fluid of eyes alone were graded semiquantitatively using a combination of qualitative review of the involved B-scans and review of OCT thickness maps. Eyes with IRF alone were excluded if IRF completely resolved at any visit in the 6 months before switching to brolucizumab or if there was consistent improvement leading up to the switch to brolucizumab. In eyes with both IRF and SRF, those with consistent improvement in one or both parameters were excluded. Eyes with stable or fluctuating IRF and SRF were included as long as IRF and/or SRF neither completely resolved during the 6 months before switch to brolucizumab.

In eyes with a subfoveal pigment epithelial detachment (PED), the central line scan was evaluated for a change in PED height at the visit at which brolucizumab was first used compared with the visit 6 months before switching. Subfoveal PED height was measured using the measurement tool in the Cirrus software. Any eyes in which the subfoveal PED height had reduced by >20 μm (which was felt to represent a true reduction in PED height) were excluded. The above parameters were used to ensure the study cohort was as homogenous a group of incomplete anti-VEGF responders as possible before the switch to brolucizumab.

Outcome Measures

Outcomes measured included VA, central macular thickness (CMT), and the presence and change SRF,

IRF, and subfoveal PED. Central macular thickness was measured on a Cirrus 5,000 spectral-domain optical coherence tomography (SD-OCT). The amount of SRF and IRF was measured as discussed previously. All measurements were measured by a single grader (A.T). The grader was blinded to the specific agent being administered at the given visit. Visual and structural parameters were recorded at the first brolucizumab injection (T1), the visit following the final brolucizumab injection (T2), and at 6 months following the final brolucizumab injection (T3).

Statistical Analysis

Categorical variables of SRF, IRF, and subfoveal PED were summarized using frequency and percentage calculations. Continuous variables were summarized with mean values and compared using a paired *t*-test. A *P* value of ≤ 0.05 was considered statistically significant. We used logistic regression to model the probability of presence of fluid across time points and fluid types. We used presence/absence of fluid as a response variable and time point, fluid (IRF/SRF), and their interaction as predictors.

Results

Patient Description and Prebrolucizumab Features

Fifty-one eyes from 46 patients were eligible for this study. A total of 70 eyes from 63 patients were managed with brolucizumab in our practice. Nineteen eyes were excluded because of the following reasons: 13 eyes did not have a fixed treatment interval or fixed anti-VEGF regimen over the 6 months before switching to brolucizumab, four eyes with a fixed treatment interval and treatment regimen had consistent improvement in retinal anatomy, and two eyes had brolucizumab as their first anti-VEGF agent. Of the 17 eyes that were switched to brolucizumab but excluded from this study, 11 eyes were switched for persistent SRF±IRF, 2 eyes were switched for persistent IRF, and 4 eyes were switched despite the lack of fluid for the prospect of better drug durability. All eyes treated with brolucizumab in our practice have been followed for at least 6 months, so no eyes were excluded based on the length of follow-up.

All study eyes had previously been treated with bevacizumab without complete resolution of SRF and/or IRF and were subsequently receiving treatment with either aflibercept or ranibizumab before switching to brolucizumab. During the 6 months before the first injection of brolucizumab, eyes were on a fixed regimen of either aflibercept (n = 28) or ranibizumab (n = 23). Eyes were switched to brolucizumab because of persistent SRF, IRF, and/or inadequate drug durability requiring treatment intervals shorter than 4 weeks. Specifically, 29 patients were switched because of persistent SRF and short treatment interval, eight patients were switched because of persistent CME and short treatment interval, three patients were switched because of both persistent CME and SRF, five patients were switched because of persistent IRF, persistent CME, and short treatment interval, and six patients were switched because of short treatment interval alone. Average treatment frequency before treatment with brolucizumab was 4.49 weeks (range, 2–12 weeks). At T1, 37 of 51 eyes (73%) had persistent SRF, 17 of 51 eyes (33%) had persistent IRF, and 41 of 51 eyes (80%) had a subfoveal PED.

Brolucizumab Treatment Period

Eyes received a mean of 1.78 brolucizumab injections (range, 1–4 injections) at a mean interval of 4.74 weeks in eyes that received more than one brolucizumab injection. Twenty-four eyes (47%) received one injection, 18 eyes (35%) received two injections, five eyes (10%) received three injections, and four eyes (8%) received four injections. At T2, 41 of 51 eyes (80%) had decreased SRF, IRF, or PED height. Specifically, 31 of 37 eyes (84%) had decreased SRF, 12 of 17 eyes (71%) had decreased IRF, and 12 of 41 eyes (29%) had decreased PED height at T2. Three of 51 eyes (6%) showed worsening of SRF or IRF. Two of 51 eyes (4%) showed no improvement in fluid.

During the brolucizumab treatment period, 11 of 51 eyes (22%) developed intraocular inflammation: 5 of 11 eyes (45%) developed iritis, 2 of 11 eyes (18%) developed endotheliitis with corneal edema, 2 of 11 eyes (18%) developed vitritis, 1 of 11 eyes (9%) developed iritis and vitritis, and 1 of 11 eyes (9%) developed iritis, vitritis, and retinal vasculitis. Eight of the 11 eyes (73%) that developed inflammation received one injection, two eyes (18%) received two injections, and one eye (9%) received three injections. Topical steroids were used in all nine eyes with a component of iritis or endotheliitis. Two eyes with isolated vitritis were monitored without anti-inflammatory therapy.

The decision to switch back was because of a combination of mounting postmarketing data regarding brolucizumab-related inflammation as well inflammation noted in some study eyes. The decision to stop using brolucizumab as well as the timing of the switch back was at the discretion of the treating physician. Eyes were switched from brolucizumab to either aflibercept (n = 33) or ranibizumab (n = 18). All 28 eyes that had been on a fixed regimen of aflibercept before receiving brolucizumab were switched back to

aflibercept. Eighteen of the 23 eyes that had been on a fixed regimen of ranibizumab were switched back to ranibizumab, and the remaining five eyes that had been on a fixed regimen of ranibizumab were switched to aflibercept. After the final brolucizumab injection, eyes received a mean of 5.29 injections (range: 2–9) of aflibercept or ranibizumab during the 6-month follow-up period.

Among those with decreased SRF at T2 (n = 31), this improvement was maintained at T3 in 17 of 31 eyes (55%) (Figure 1). Eyes with decreased SRF (n = 31) at T2 had the following SRF findings at T3: further decrease in SRF in 3 of 31 eyes (9.8%), stable SRF in 14 of 31 eyes (45%), and increased SRF in 14 of 31 eyes (45%). Eyes with decreased IRF (n = 12) at T2 had the following IRF findings at T3: stable IRF in 8 of 12 eyes (67%) and increased IRF in 4 of 12 eyes (33%). Eyes with decreased subfoveal PED height (n = 12) at T2 had the following PED findings at T3: stable PED height in 8 of 12 eyes (67%) and increased PED height in 4of 12 eyes (33%). Overall, 41 of 51 eyes (80%) had anatomical improvements at T2, with sustained improvements in 22 of these eyes (22/41, 54%) at T3 (Figure 2).

Of the 37 eyes with persistent SRF at T1, SRF completely resolved in 18 of 37 eyes (49%) at T2 and did not recur by the T3 visit in 11 of 37 eyes (30%). Of the 17 eyes with persistent IRF at T1, IRF completely resolved in 8 of 17 eyes (47%) by T2 and did not recur at T3 in 5 of 17 eyes (29%). Of the 41 eyes with persistent subfoveal PED at T1, the PED completely resolved in 2 of 41 eyes (5%) at T2 and did not recur at T3 in 1 of 41 eye (2%).

Thirty-three eyes were switched from brolucizumab to aflibercept. Twenty-five of these 33 eyes (76%) had anatomical improvements following treatment with brolucizumab. Of these eyes, 15 of 25 eyes (60%) had sustained improvements at T3. Of the 18 eyes that switched to ranibizumab, 16 of 18 (89%) had anatomical improvements at T2. Eight of these 16 eyes (50%) had sustained improvements at T3.

Of the five eyes that were switched from ranibizumab before brolucizumab to aflibercept after brolucizumab, 1 of 5 eyes (20%) had subfoveal PED resolution at T2 that was sustained at T3. One of five eyes (20%) had no improvements from T1 to T2 but did have decreased SRF at T3. The remaining 3 of 5 eyes (60%) showed no anatomical changes throughout the study period.

Mean CMT at T1 was 264 μm. Mean CMT reduced to 245 μm at T2 ($P = 0.023$) but increased back to 263 μm at T3. Eyes with and without brolucizumab-related inflammation had similar rates of anatomical improvement at T2 ($P = 0.17$). A similar proportion of these patients had sustained improvement at T3 ($P = 0.38$).

Mean logarithm of the minimum angle of resolution (logMAR) VA for all eyes at T1, T2, and T3 was 0.396 (~20/50 Snellen), 0.441 (~20/55 Snellen), and 0.468 (~20/59 Snellen), respectively. Among eyes that were switched back to aflibercept, mean logMAR VA at T3 was 0.514 (~20/65 Snellen). Among eyes that were switched back to ranibizumab, mean logMAR VA at T3 was 0.307 (~20/41 Snellen). Among eyes that developed intraocular inflammation (n = 11), mean logMAR VA was 0.309 (~20/40) at T1, 0.335 (~20/43) at T2, and 0.325 (~20/42) at T3. The difference in vision between T1 and T3 in eyes that developed inflammation was not statistically significant ($P = 0.78$). Among eyes that did not develop intraocular inflammation (n = 40), mean logMAR VA was 0.420 (~20/53) at T1, 0.470 (20/50) at T2, and 0.508 at T3 (~20/64).

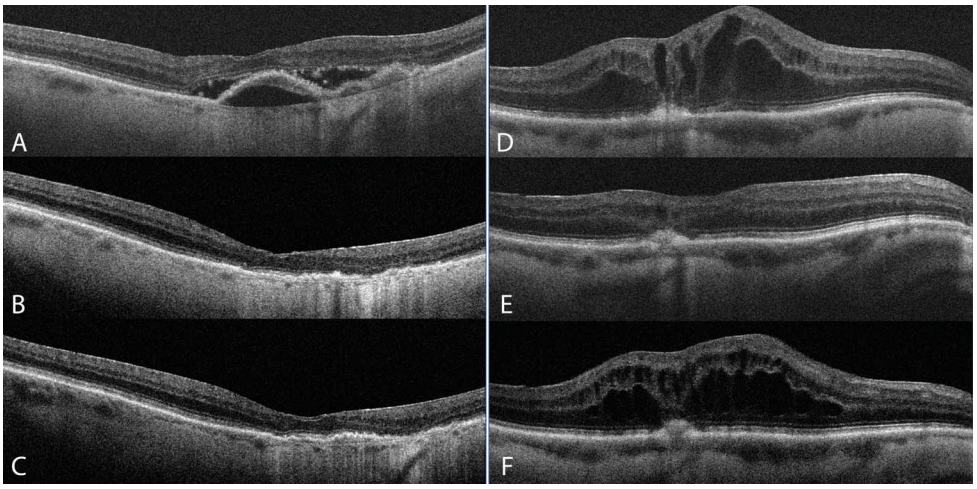

Fig. 1. Representative cases from this study. Patient A (**A**–**C**) had persistent subretinal fluid (SRF) and a subfoveal pigment epithelial detachment (PED) on a fixed regimen of aflibercept every 4 weeks (**A**). After four doses of brolucizumab, the SRF had resolved, and the PED had flattened (**B**). Six months following switching back to aflibercept, the anatomical improvement was maintained, and aflibercept frequency had been extended to every 8 weeks (**C**). Patient B (**D**–**F**) had persistent intraretinal fluid (IRF) on a fixed regiment of aflibercept every 4 weeks (**D**). After one treatment with brolucizumab, IRF improved (**E**), but 2 months after switching back to monthly aflibercept, IRF worsened (**F**).

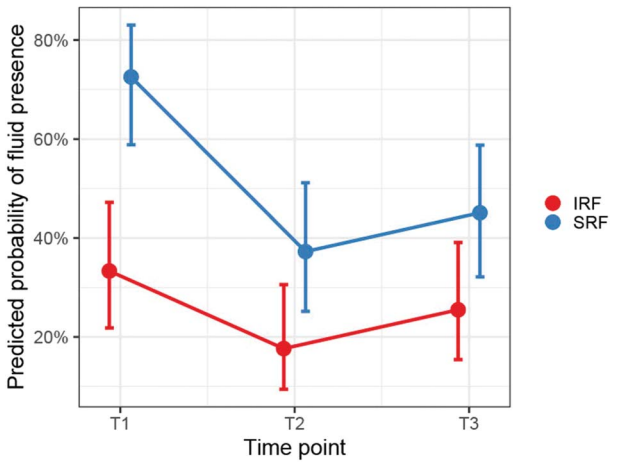

Fig. 2. Prevalence of subretinal fluid (SRF) and intraretinal fluid (IRF) at the time of the first brolucizumab injection (T1), the visit after the last brolucizumab injection (T2) and 6 months following the final brolucizumab injection (T3). The individual dots represent the prevalence of IRF and SRF at various time points. The error bars were generated using logistic regression and represent the probability of presence of SRF and IRF using the time point, fluid (irf/srf), and their interaction as predictors.

Mean logMAR VA in all eyes with SRF was 0.367 (~20/47 Snellen) at T1. At T2, mean logMAR VA was 0.340 (~20/44 Snellen) in eyes with persistent SRF and 0.469 (~20/59 Snellen) in eyes with completely resolved SRF. At T3, mean logMAR VA was 0.403 (~20/51 Snellen) in eyes with persistent SRF and 0.419 (~20/52 Snellen) in eyes with resolved SRF.

Mean logMAR VA in all eyes with IRF at T1 was 0.565 (~20/73 Snellen). At T2, mean logMAR VA was 0.690 (~20/98 Snellen) in eyes with persistent IRF and 0.607 (~20/81 Snellen) in eyes with completely resolved IRF. At T3, mean logMAR VA was 0.687 (~20/97 Snellen) in eyes with persistent IRF and 0.610 (~20/81 Snellen) in eyes with resolved IRF.

Mean logMAR VA in all eyes with subfoveal PED at T1 was 0.331 (~20/43 Snellen). At T2, mean logMAR VA was 0.563 (~20/73 Snellen) in eyes with persistent PED and 0.358 (~20/81 Snellen) in eyes with completely resolved PED. At T3, mean logMAR VA was 0.428 (~20/54 Snellen) in eyes with persistent PED and 0.389 (~20/49 Snellen) in eyes with resolved PED.

Treatment Interval

The average treatment interval before treatment with brolucizumab was 4.49 weeks (range, 2–12 weeks). At the visit 6 months after the final brolucizumab injection, the average recommended treatment interval was 4.61 weeks (range, 2–16 weeks). Overall, 31 eyes (61%) maintained the same recommended treatment interval as before receiving brolucizumab; 13 eyes (25%) had an extended recommended treatment interval, and 7 eyes (14%) had a shorter recommended treatment interval. Among eyes that were switched back to aflibercept, mean injection interval at T3 was 4.7 weeks. Among eyes that were switched back to ranibizumab, mean injection interval at T3 was 4.5 weeks.

Before treatment with brolucizumab, 15 eyes were on an extended treatment interval of ≥5 weeks. Ten of these eyes maintained a recommended ≥5-week interval after the 6-month follow-up visit, and the remaining 5 eyes had a recommended 4 weeks of interval. Seven eyes that had previously been on a <5-week interval before treatment with brolucizumab had a recommended ≥5-weeks interval after the 6-month follow-up visit.

Among eyes that developed inflammation, average treatment interval before treatment with brolucizumab was 4.55 weeks, compared with a recommended 4.27 weeks 6 months after the final brolucizumab injection. The eyes that developed inflammation had an average of 6.4 weeks (range, 4–9 weeks) between their last brolucizumab injection and their first anti-VEGF injection postbrolucizumab (T2), compared with an average of 4.7 weeks (range, 3–10 weeks) in eyes that did not develop inflammation.

Discussion

The October 2019 Food and Drug Administration approval of brolucizumab marked the first new anti-VEGF therapy for nAMD since the approval of aflibercept in November 2011. The Phase-3 clinical trial data that supported a better drying effect and durability created initial enthusiasm for use in eyes with recalcitrant fluid. However, subsequent reports of brolucizumab-associated intraocular inflammation, which in some cases included an occlusive retinal vasculitis and severe vision loss, resulted in the near cessation of brolucizumab use in our practice.

Our expectation was that anatomical gains would subside following withdrawal of brolucizumab. A parallel can be drawn to the development and post-marketing surveillance of aflibercept. Anatomical improvements in eyes that were refractory to ranibizumab, once switched to aflibercept, were widely reported. However, clusters of aflibercept injection-related sterile inflammation were reported to the American Society of Retina Specialists Research and Safety in Therapeutics Committee, leading to several reports characterizing the inflammation.[11–13] As a result, many retina specialists temporarily switched away from aflibercept. Subsequently, a retrospective review of patients who switched from aflibercept to ranibizumab revealed worsening functional and anatomical outcomes.[14]

In this retrospective case series, we reviewed outcomes of eyes with persistent intra- or subretinal fluid and/or inadequate drug durability requiring treatment intervals shorter than 4 weeks while receiving treatment with bevacizumab, ranibizumab, and/or aflibercept, which were switched to brolucizumab and were then switched back after a relatively short duration of brolucizumab therapy. We found that 54% of eyes with improvements in SRF, IRF, and/or subfoveal PED height associated with brolucizumab treatment maintained these improvements for at least 6 months after switching back to the original anti-VEGF therapeutic.

Despite improvements in SRF, IRF, and subfoveal PED, there were no corresponding significant improvements in VA. The value of complete fluid resolution, independent of corresponding improvement in VA, in the treatment of nAMD is frequently debated. Although it is generally accepted that persistent IRF is a marker of poorer visual outcomes and justifies aggressive treatment, some studies suggest that persistent SRF may be well-tolerated and may, in fact, be associated with better visual outcomes.[15–17] Our study found sustained improvements in both SRF and IRF in a subset of patients at the 6-month follow-up following brolucizumab discontinuation. We did observe a slight worsening of vision initially in those eyes whose SRF had completely resolved after the course of brolucizumab, but this difference was not maintained at the 6-month follow-up. We also observed a slight worsening of vision in eyes with persistent IRF compared with eyes with resolved IRF both at the first postbrolucizumab injection and at the 6-month follow-up. Interpretation of VA differences between eyes with persistent subfoveal PED and resolved subfoveal PED are limited by low numbers (only 4 and 2 patients with persistent PED at T2 and T3, respectively, compared with 37 and 39 patients with resolved PED.

The most dreaded manifestation of brolucizumab-associated inflammation is an occlusive retinal vasculitis leading to severe vision loss.[18] The American Society of Retina Specialists Research and Safety in Therapeutics Committee reported that 92% of retinal vasculitis cases after brolucizumab administration were associated with other signs of intraocular inflammation.[19] We observed inflammation in a total of 11 of 51 eyes (22%), including retinal vasculitis in 1 eye. A review of 172 eyes treated with brolucizumab for nAMD found an 8.1% rate of intraocular inflammation, including 1 case of occlusive retinal vasculitis with severe loss of vision.[10] The BREW and SHIFT studies reported intraocular inflammation in 0 of 42 (0%) and 7 of 63 (11%) eyes treated with brolucizumab, respectively.[8,9] It is unclear why the rate of inflammation was so high in our cohort. It may have been in part because evidence of even a few vitreous cells was classified as vitritis even when asymptomatic. In fact, only three patients (representing four study eyes with inflammation) presented before their scheduled visit with symptoms of inflammation. It is unclear whether brolucizumab-associated inflammation had any effect on treatment burden or anatomical improvement. There is some data to suggest that severe inflammation following intravitreal injections (e.g., following endophthalmitis) can lead to reduction in treatment burden.[20] In our cohort, the proportion of eyes with sustained anatomical improvement at T3 was similar in eyes with and without brolucizumab-related inflammation. Additionally, the extent of inflammation in the majority of cases was mild and therefore unlikely to have meaningfully impacted anatomical outcomes or treatment burden. There was no significant different in average visual acuity between T1 and T3 in eyes that developed intraocular inflammation.

Longer intervals between anti-VEGF treatments help reduce treatment burden for patients and their caregivers. The HAWK and HARRIER trials found that more than 50% of eyes treated with brolucizumab were able to extend their dosing regimen to 12-week intervals. In our cohort of patients treated with brolucizumab, the average treatment interval before treatment with brolucizumab was 4.49 weeks (range, 2–12 weeks) compared with 4.61 weeks at 6 months following the final brolucizumab injection. This difference is not significant. Of note, eyes that developed inflammation had a longer average treatment interval between their last brolucizumab injection and the first anti-VEGF injection postbrolucizumab (6.4 weeks) than those that did not develop inflammation (4.7 weeks). However, this difference was not related to a delay or postponement in treatment but rather that this subset of eyes required less frequent dosing intervals.

The results of our study suggest that a short course of brolucizumab may provide anatomical benefits for eyes with persistent fluid while being treated with aflibercept, bevacizumab, or ranibizumab. These anatomical benefits may be maintained for at least 6 months in a subset of patients after switching back to an alternative anti-VEGF treatment. It is unclear whether the observed effect is from significant durability of brolucizumab in a subset of patients or from combination anti-VEGF therapy. Some of the observed effects were from switching to aflibercept following brolucizumab in eyes that had only previously received bevacizumab and ranibizumab. For example, we observed one patient refractory to bevacizumab and ranibizumab who had no improvement after brolucizumab therapy but had decreased SRF after subsequent treatment with aflibercept. We observed another patient refractory to bevacizumab and ranibizumab who had subfoveal PED resolution after treatment with brolucizumab that was maintained after switching

to aflibercept. These findings may be attributable to switching to aflibercept rather than residual effects of brolucizumab. Several studies have demonstrated benefits of switching anti-VEGF agents in refractory nAMD patients.[21–24] One study examined patients with nAMD who switched from ranibizumab to aflibercept and back to ranibizumab. The authors found that patients who received less than three aflibercept injections had improved VA and decreased CMT at three months after the switch back to ranibizumab compared with before the initial switch.[25] To our knowledge, use of an alternating or combination anti-VEGF regimen has not otherwise been studied in the literature.

The treatment strategy described in our study may limit the risk of brolucizumab-associated inflammation while still providing some of its treatment benefits. This may be a reasonable option for patients for whom the threat of persistent fluid seems great. We do not yet know whether these benefits will be sustained for significantly longer than 6 months or whether a subsequent short-term course of brolucizumab treatment would provide similar benefits.

This study has certain limitations including a retrospective design and a small sample size. We tried to account for these by studying a relatively homogeneous study group. It is our hope that the results of this study will provide physicians with further information to guide treatment for these challenging patients.

Key words: age-related macular degeneration, anti-VEGF, brolucizumab, inflammation, retina.

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