Expert Opinion on Management of Intraocular Inflammation, Retinal Vasculitis, and Vascular Occlusion after Brolucizumab Treatment

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Caroline R. Baumal, MD,[1] Bahram Bodaghi, MD, PhD,[2] Michael Singer, MD,[3] David J. Tanzer, MD,[4] András Seres, MD,[5] Mayur R. Joshi, MBBS,[6] Nicolas Feltgen, MD,[7] Richard Gale, MD[8]

Purpose: Recent reports have described a spectrum of uncommon findings of intraocular inflammation (IOI), retinal vasculitis, or retinal vascular occlusion in patients with neovascular age-related macular degeneration (nAMD) treated with intravitreal injection (IVI) of brolucizumab. We present guidance on the clinical presentation of this spectrum and propose recommendations for management of these events.

Design: PubMed literature review and expert opinion panel.

Participants: A working group of international medical experts and Novartis medical personnel.

Methods: The working group deliberated on the clinical presentations and used a 3-pronged approach to develop management recommendations based on (1) critical appraisal of scientific literature; (2) clinical insights from the HAWK and HARRIER trials, postmarketing reports, and assessments from an independent Safety Review Committee (SRC); and (3) their clinical experience.

Main Outcome Measures: Management recommendations for a spectrum of ocular inflammatory events after treatment with brolucizumab or other anti–vascular endothelial growth factors (VEGFs).

Results: Based on insights gained from the available information and the expertise of the contributors, recommendations were proposed for ocular examinations, imaging modalities, and treatment strategies for management of this spectrum of events. Patients should be educated to promptly report any relevant or persistent symptoms after IVI to facilitate timely intervention. Patients diagnosed with IOI should be evaluated for concomitant retinal vasculitis or retinal vascular occlusive events. Clinical examination can be augmented with multimodal imaging techniques, including widefield imaging, fluorescein angiography (with peripheral sweeps), and OCT. Once confirmed, the ongoing brolucizumab treatment should be suspended and intensive treatment with potent corticosteroids (topical, subtenon, intravitreal, or systemic) is recommended, which may be supplemented with other treatment strategies depending on the severity. Based on the clinical outcome of these events, individualized treatment with locally available standard of care should be considered for the underlying nAMD.

Conclusions: These recommendations emphasize the need for early diagnosis, prompt and timely intervention, intensive treatment, and frequent monitoring to minimize the risk of progression of these events. The proposed recommendations may facilitate a consistent management approach of this spectrum of ocular inflammatory events should they arise in nAMD after treatment with brolucizumab or other anti-VEGFs. *Ophthalmology Retina 2021;5:519-527 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Brolucizumab, an approximately 26 kDa single-chain antibody fragment, is the latest addition to the anti-vascular endothelial growth factor (VEGF) treatment armamentarium for patients with neovascular age-related macular degeneration (nAMD).[1] In the pivotal phase 3 HAWK and HARRIER trials, brolucizumab 6 mg demonstrated noninferior visual acuity (VA) gains (primary end point) and superior anatomic outcomes (central retinal subfield thickness reduction and fluid resolution) versus aflibercept 2 mg.[2,3] Also, in approximately 50% of the brolucizumab-treated eyes, the intravitreal injection (IVI) interval could be prolonged to 12 weeks at week 48, and more than 75% of these eyes continued at this 12-week treatment interval until week 96. These trials demonstrated that brolucizumab provides effective disease control with potential for reduced treatment burden.[2,3]

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In terms of safety, the incidence of intraocular inflammation (IOI) in HAWK and HARRIER was higher with brolucizumab 6 mg at 4% compared with 1% in aflibercept 2 mg–treated eyes, and most of these cases were reported as mild to moderate by the investigators.[3,4] However, as the proportion of eyes that lost ≥ 15 letters was comparable between the brolucizumab 6 mg and aflibercept 2 mg–treated groups at week 96, these trials concluded that brolucizumab exhibited an overall well-tolerated safety profile.[2,3] Based on the efficacy and safety results, brolucizumab is approved in more than 40 countries worldwide, including in the United States (October 2019), Switzerland, Australia, the European Union, Canada, and Japan.[4-11]

In February 2020, the American Society of Retinal Specialists (ASRS) circulated a safety update detailing 14 cases of retinal vasculitis in patients treated with brolucizumab, 11 of which were reported as occlusive retinal vasculitis that could potentially lead to vision loss.[12,13] In addition, Novartis (East Hanover, NJ) received postmarketing adverse event (AE) reports of retinal vasculitis, including occlusive retinal vasculitis.[12] The postmarketing incidence rate for retinal vasculitis or retinal vascular occlusion was 10.67 per 10 000 injections (as of August 28, 2020).[12] To elucidate and better understand these reports, Novartis commissioned an external Safety Review Committee (SRC) of 9 members, comprising global retina and uveitis specialists, imaging and ophthalmology experts from 2 separate external data monitoring committees, and an independent observer from the ASRS. The purpose of the SRC was to provide an independent and standardized assessment of postmarketing reports of patients treated with brolucizumab and to reassess ocular inflammatory AEs observed in HAWK and HARRIER.[12]

On June 4, 2020, the ASRS provided an update to its members on the initial findings of the SRC.[14] A critical contribution from the SRC analysis was to precisely identify the rate of these IOI events, which cannot be accurately determined based on voluntarily submitted postmarketing reports. The SRC conducted a post hoc unmasked analysis of the images from cases in HAWK and HARRIER that were reported as having IOI by investigators. The SRC reported that IOI of any form was identified in 50 of 1088 study eyes of patients treated with brolucizumab (4.6%) during the HAWK and HARRIER trials. Of these 50 eyes with IOI, 36 eyes had concomitant retinal vasculitis (3.3%), of which 23 had concomitant retinal vascular occlusion (2.1%).[14] Despite the risk of vision loss associated with these events after brolucizumab injection, the overall rate of at least moderate vision (≥ 15 ETDRS letters) loss in the HAWK and HARRIER trials' population was comparable between the brolucizumab (7.4%) and aflibercept (7.7%) treatment arms.[12,14] Based on these findings, a label update with additional safety information for brolucizumab was approved by the US Food and Drug Administration on June 11, 2020, and has been subsequently approved in Switzerland, Australia, and Japan (to date).[12,15]

An in-depth examination of the possible root cause, patient characterization, and development of approaches to mitigate these AEs is currently under way.[12] In the interim, in view of patient safety, it is important to put together recommendations to inform and guide ophthalmologists about the clinical management of the spectrum of IOI, retinal vasculitis, and retinal vascular occlusive events, should they present after treatment with brolucizumab or other anti-VEGFs. This article presents guidance on the clinical presentation, including ocular imaging, as well as potential treatment strategies to aid in the management of these ocular complications.

Methodology

A working group was established comprising 6 international medical experts (C.R.B., B.B., M.S., A.S., N.F., and R.G.) and 6 Novartis medical personnel (including D.J.T. and M.R.J.). The group adopted a 3-pronged approach to deliberate on the management of AEs within the spectrum based on (1) a critical review and appraisal of the currently available scientific literature; (2) clinical insights gained from the HAWK and HARRIER trials, postmarketing reports, and SRC assessments; and (3) clinical expertise and experience of the contributors. Human subjects were included in this study. IRB/Ethics Committee ruled that approval was not required for this study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

Literature Search

A comprehensive literature search was conducted on PubMed to identify relevant articles (published on or before August 28, 2020). Based on the list of MedDRA preferred terms and International Classification of Diseases 10th Revision codes, an extensive search list of 88 relevant clinical terms was identified. These ranged from general terms such as IOI, endophthalmitis, retinal vasculitis, and retinal vascular occlusion to more specific clinical terms such as Hollenhorst plaque, retinal artery embolism, and Harada disease. The detailed search strategy is available in the Supplementary Appendix (available at www.ophthalmologyretina.org). The resulting citations were reviewed for insights into the management of this spectrum of clinical presentations (Fig S1, available at www.ophthalmologyretina.org).

Data from HAWK and HARRIER Trials and the Spontaneous Postmarketing Reports

Deidentified information on IOI, retinal vasculitis, and retinal vascular occlusive events occurring during the HAWK and HARRIER trials and postmarketing cases, including the patient narratives and associated retinal images, was shared with the working group (as allowed by the legal and data sharing policies). Additional information from the SRC assessment of these cases was also shared via a member of the SRC.

Development of the Proposed Clinical Management Approach

Based on the available information, and their clinical expertise and experience, the working group provided recommendations on the management of this spectrum of clinical presentations. These were discussed with a wider group of retina specialists and further revised with participation and agreement from all authors.

Results

Literature Review

The initial literature search yielded a total of 974 publications. After further screening and review, 73 relevant articles were identified (Fig S1), most of which were case reports or retrospective case series.

Most of the identified articles reported on the management of IOI and endophthalmitis after anti-VEGF treatment in nAMD. In the reviewed articles, IOI was variably reported as uveitis, vitritis, anterior chamber inflammation, sterile inflammation, noninfectious inflammation, or, most often, as an umbrella term for any inflammation in the eye. The clinical manifestations of IOI may overlap with those of endophthalmitis, and many articles emphasized the importance of differentiating these conditions early on to manage them appropriately. Although imaging modalities were not described in detail in these articles, slit-lamp examination, fundoscopy, OCT, and intravenous fluorescein angiography (IVFA) were the most often used diagnostic tools. These events were primarily managed with topical or systemic corticosteroids, although in a few cases in which the diagnosis was equivocal, the patients were managed with antibiotics or observation.

There is limited literature reporting on retinal vasculitis or retinal vascular occlusive events after anti-VEGF treatment in nAMD.[16-24] These include 5 published articles that discuss the presentation and management of IOI, retinal vasculitis, and retinal vascular occlusion in brolucizumab-treated patients with nAMD (Table 1).[16,17,19,23,24] Although these articles provide initial insights, there is still a need for guidance on consistent management of these ocular conditions.

Recommendations for the Clinical Management of IOI, Retinal Vasculitis, and Retinal Vascular Occlusive Events

Investigation of postmarketing reports and reassessment of HAWK and HARRIER cases by the SRC revealed that some eyes treated with IVI of brolucizumab may present with a spectrum of IOI, retinal vasculitis, or retinal vascular occlusive events.[2,3,12,16,17,19,23,24] Although IOI has been reported after IVI of all anti-VEGF agents, there is limited evidence on the occurrence of noninfectious retinal vasculitis and retinal vascular occlusive events after anti-VEGF treatment in nAMD.[4,25-30] We propose recommendations to inform the management of this spectrum of events. It is important to rule out endophthalmitis related to IVI as well as any underlying systemic or infectious diseases that can potentially contribute to or aggravate these ocular events and manage them appropriately with the available standard of care.

Intraocular Inflammation

After intravitreal brolucizumab injection, any patient experiencing floaters or ocular discomfort persisting for more than 2 days should be investigated for the presence of IOI (Fig 1). In addition, patients presenting with vision loss or light sensitivity at any time after injection should be assessed. Clinicians should emphasize to their patients the importance of reporting any of the described symptoms as a matter of urgency to ensure timely intervention.

A complete ocular investigation, including dilated fundus and slit-lamp examination, direct or indirect ophthalmoscopy, should be performed; color fundus photography (widefield, if available) should also be considered. It is important to assess both the anterior and posterior segments carefully.[31] OCT is recommended to visualize cells in the posterior vitreous.[32] In patients with inflammation precluding clinical examination of the retinal details or with reduced vision, IVFA with peripheral sweeps (if available) may be performed to visualize the entire extent of retinal vasculature and exclude occult vasculitis and vascular occlusion.

Clinically, it is also important to differentiate noninfectious IOI from infectious endophthalmitis, a severe vision-threatening condition that needs urgent evaluation and treatment. These 2 conditions may have some common features on clinical presentation; thus, distinguishing between these may be a practical challenge for clinicians.[27,33] Infectious endophthalmitis typically develops within 1 week after IVI of the anti-VEGF agent and is characterized by acute or subacute onset of pain, discomfort, reduced VA, epiphora, conjunctival hyperemia, chemosis, lid edema, hypopyon, and vitreous and anterior segment cellular reaction or fibrin.[27,34] Vitreous and aqueous sampling can be used to confirm an infectious etiology and should be managed with antibiotics as per local standard practice.[27,35] In contrast, IOI after brolucizumab may present in a delayed fashion, many weeks after IVI, and usually lacks acute features and hypopyon.

Once the diagnosis of IOI is confirmed, initiation of corticosteroid therapy is recommended. Based on the severity of inflammation, clinicians may consider the most potent topical corticosteroid from the locally available options. If necessary, topical therapy may be supplemented with subtenon, intravitreal, and systemic corticosteroids. Treatment can be tapered once the inflammation is under control. If the symptoms worsen with the use of corticosteroids, the patient should be reevaluated for infectious etiology.

In patients treated with brolucizumab, noninfectious retinal vasculitis or retinal vascular occlusive events have been reported to occur in the presence of IOI.[16,17,19,23,24] Therefore, it is recommended to frequently monitor these patients and proactively rule out or confirm (and if confirmed, appropriately treat) the clinical findings of retinal vasculitis or retinal vascular occlusive events in patients presenting with IOI.

Retinal Vasculitis

Patients with retinal vasculitis have varied clinical presentations that can be central, affecting the optic nerve and macula, or involve the peripheral retina, or multifocal, affecting both the large and small caliber vessels. It usually involves the retinal arteries first, affecting retinal veins later in the course (with perivenular hemorrhages) with the presence or absence of occlusive changes.[36] In cases of retinal vasculitis involving the posterior pole or associated vitritis, patients usually present with symptoms such as blurred or decreased vision, floaters, or scotomata.[37]

Fundoscopic examination may be useful to reveal typical clinical findings of retinal vasculitis, including perivascular sheathing (focal or multifocal cuffing or sheathing of blood vessels), that are usually accompanied by signs of IOI.[37,38] Intravenous fluorescein angiography is recommended for a

Table 1. Summary of Recently Published Reports on the Management of IOI, Retinal Vasculitis, and Retinal Vascular Occlusive Events after Brolucizumab Treatment in Patients with nAMD

Publication	Treatment Status and No. of Patients (Eyes)	Time to Onset of Event after Brolucizumab Injection (Days)	Spectrum of Clinical Presentations	Treatment Given	Follow-up Duration*	VA Outcome (Preinjection VA vs. VA at Last Examination)
Haug et al[17]	• Prior IVI anti-VEGF treated • N = 1 (2)	28	OD: IOI and retinal vascular sheathing OS: IOI, retinal vasculitis, retinal arteriovenous occlusion	• OU: Topical corticosteroid • OS: Intravitreal corticosteroid implant	• 9 wks after first brolucizumab IVI	• OD: 20/30 vs. 20/40 • OS: 20/25 vs. 20/40
Jain et al[19]	• Prior IVI anti-VEGF treated • N = 1 (1)	16	OS: Retinal arteriolar occlusion secondary to IOI	• Topical corticosteroid	• 4 wks after third brolucizumab IVI	• OS: 20/150 vs. CF at 1 ft
Baumal et al[16]	• Prior IVI anti-VEGF treated • N = 12 (15)	30.3 (mean)	IOI or retinal vasculitis or retinal artery occlusion	Corticosteroids:[†,‡] • Topical: 9 patients • Systemic: 9 patients • IVT: 2 patients • Subtenon corticosteroids: 1 patient • IVT corticosteroid implant: 1 patient Vitrectomy: 2 patients	• 25 days (mean; diagnosis of event to last evaluation visit)[§]	• VA improved: 4 eyes • VA maintained: 3 eyes • VA worsened: 8 eyes
Witkin et al[23]	• Prior IVI anti-VEGF treated • 25 (26)[‖]	25 (mean)	• IOI: 24 eyes • Retinal vasculitis: 26 eyes • Occlusive vasculitis: 22 eyes	Corticosteroids:[†,¶] • Topical: 24 eyes • Systemic: 11 patients • IVT: 5 eyes Vitrectomy: 4 eyes No treatment: 2 eyes	• 53 days (mean follow-up after last brolucizumab IVI)	• Mean logMAR VA: 0.3557 vs. 1.0861[#]
Kondapalli[24]	• Prior IVI anti-VEGF treated • N = 1 (ns)	21	• OD: Occlusive retinal vasculitis	• Topical and systemic corticosteroids	• 5 wks after second brolucizumab IVI	• OD: 20/50 vs. 20/200 • OS: 20/30 vs. 20/200

CF = count fingers; IOI = intraocular inflammation; IVI = intravitreal injection; logMAR = logarithm of the minimum angle of resolution; N = number; nAMD = neovascular age-related macular degeneration; ns = not specified; OD = right eye; OS = left eye; OU = both eyes; VA = visual acuity; VEGF = vascular endothelial growth factor.
*From last brolucizumab IVI to last examination visit.
[†]A combination of corticosteroids were administered according to severity of the event, and patients may have been counted more than once depending on the mode of therapy received.
[‡]Some patients received other concomitant medications (heparin: 1; valacyclovir: 1; cycloplegic: 1).
[§]Time interval from last brolucizumab injection to last follow-up visit not reported.
[‖]This case series includes some cases already reported by Baumal et al.[16]
[¶]One eye received intravitreal antibiotics, and 2 patients received antiviral medications.
[#]The VA outcomes by individual patients are not available.

thorough assessment and characterization of the disease activity. Typical findings include delayed arterial filling, retinal vasculature nonperfusion, hyperfluorescence and staining of the vessel wall, and late fluorescein leakage from the dilated capillaries of the optic nerve head.[37,39] Figure 2 shows representative images of the spectrum, including features typical of retinal vasculitis. Clinicians are encouraged to use widefield imaging with peripheral sweeps for a quantitative examination of the entire retina to detect any peripheral inflammation, leakage, or ischemia. OCT may evaluate for vitreous cells and macular

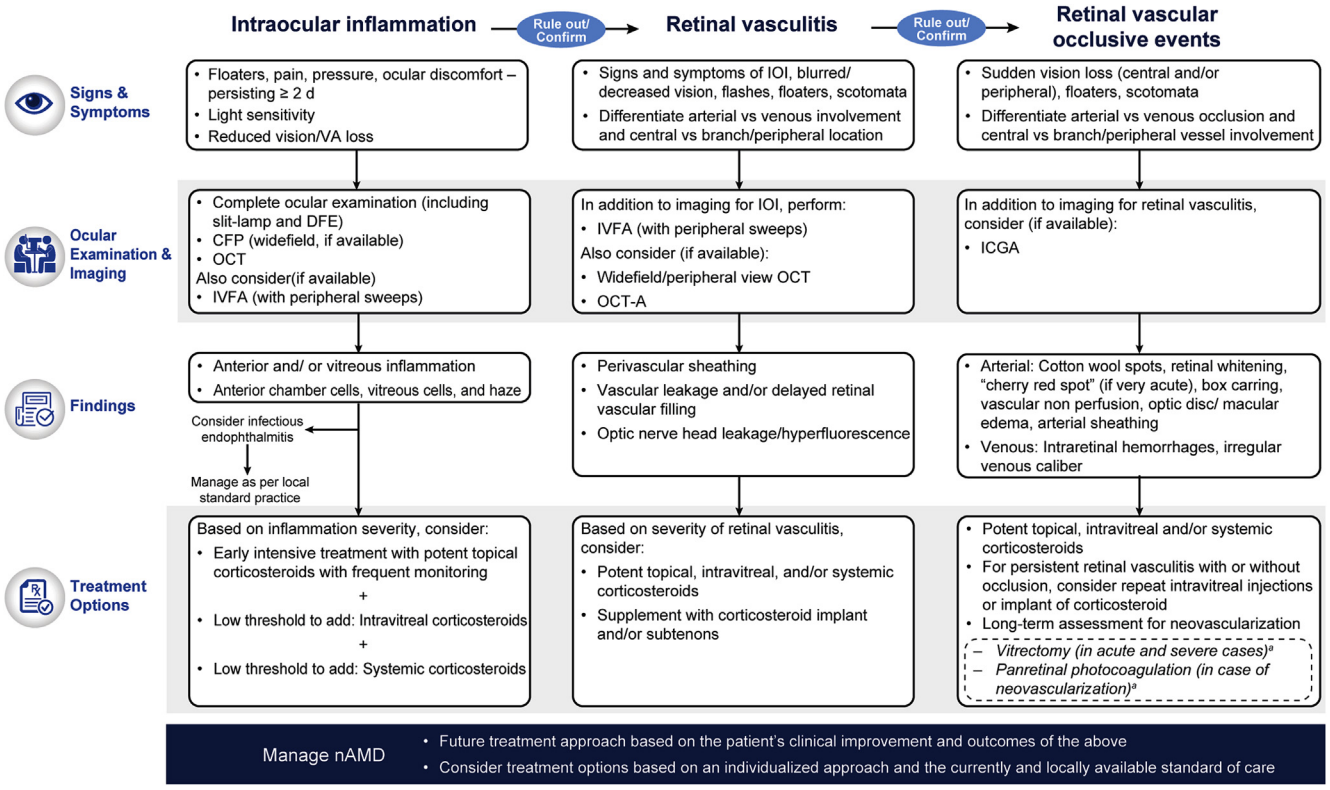

Figure 1. Proposed recommendations for management of intraocular inflammation (IOI) ± retinal vasculitis ± retinal vascular occlusive events. [a]May be considered in select cases but may have limited clinical value. CFP = color fundus photography; d = days; DFE = dilated fundus examination; ICGA = indocyanine green angiography; IOI = intraocular inflammation; IVFA = intravenous fluorescein angiography; OCTA = OCT angiography; VA = visual acuity.

changes, whereas noninvasive OCT angiography (OCTA) may be considered, when available, to characterize microvascular flow changes in the retinal vascular plexuses and choriocapillaris.[40]

Based on the severity of retinal vasculitis, clinicians are recommended to treat these patients intensively with potent topical, intravitreal, or systemic corticosteroids of their choice, as indicated in Figure 1. Treatment may be supplemented with intravitreal steroid implants or subtenon steroid injection, as needed. It is important to carefully monitor patients with retinal vasculitis to assess the extent and severity of vascular leakage and identify any occlusive complications early on to allow timely intervention.

Retinal Vascular Occlusive Events

Retinal vascular occlusion has been described as part of the IOI and retinal vasculitis spectrum after brolucizumab treatment.[16,17,19,23,24] Of note, the post hoc analysis of cases from HAWK and HARRIER trials, as well as those reported to Novartis in the postapproval setting that were reviewed by the SRC, found occult retinal vascular occlusion in some eyes presenting with this spectrum.[12,13]

The clinical presentation, VA, and management of these patients depend on the location of occlusion (central vs. peripheral vessels), type of vasculature involved (arterial vs. venous), and degree of ischemia and nonperfusion. Patients may present with symptoms such as loss of vision (central or peripheral) due to retinal vascular occlusion involving the macula, floaters, ischemia-related scotomata, and color vision abnormalities.[37,41]

Fundoscopic examination may reveal signs of retinal ischemia as shown in Figure 2A, D, and G, including cotton-wool spots (consistent with precapillary retinal arteriolar occlusion), retinal whitening, arterial sheathing, and "cherry red spot" at the fovea (observed in acute retinal artery occlusion). Other findings include retinal arterial attenuation, segmentation of blood column in the retinal vessels (boxcarring), optic disc edema, irregular venous caliber, and intraretinal perivenular hemorrhages.[39,41] OCT is recommended to assess for posterior vitreous cells and macular thickening or edema.[37] Intravenous fluorescein angiography and OCTA may be considered to evaluate the degree of ischemia and delineate areas of capillary nonperfusion.[37,41,42] If available, indocyanine green angiography (ICGA) may be considered to assess inflammatory or ischemic changes in the choriocapillaris and choroidal vasculature.[43,44] Widefield imaging techniques are recommended to document the entire extent of areas of nonperfusion and detect any disease activity and progression that could be missed using conventional imaging. In the clinical setting of multiple foci of vessel involvement (vasculitis with or without occlusion) in the presence of IOI, the likelihood of an embolic etiology (i.e., carotid artery or cardiac) is extremely low and a systemic workup for a potential source (as would be considered in the presence of a Hollenhorst plaque) may not be indicated in most of these cases.

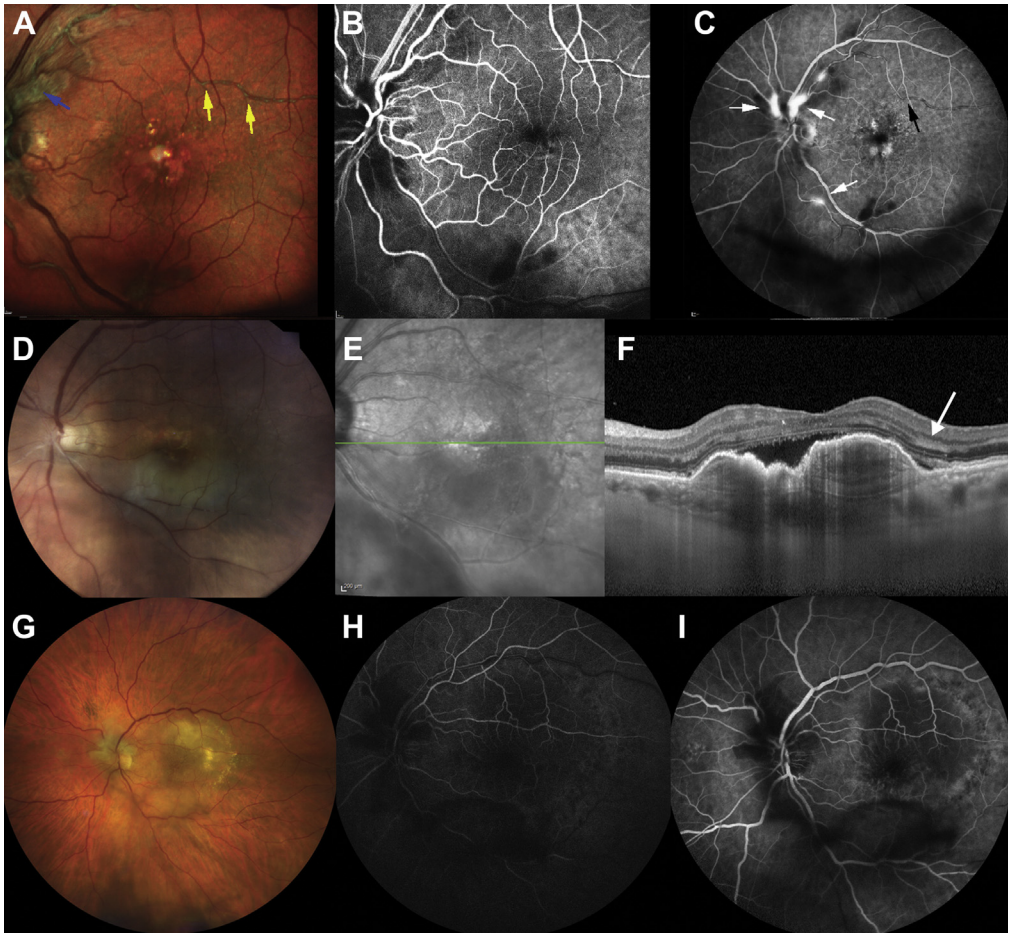

Figure 2. Three representative cases demonstrating the spectrum of ocular findings related to IOI and occlusive retinal vasculitis. Case 1 **(A–C)**: An 88-year old woman was diagnosed with retinal vasculitis in her left eye at 6 weeks after bilateral intravitreal brolucizumab injection. Color fundus photograph **(A)** reveals multiple intra-arterial foci of gray material **(yellow arrow)** and retinal whitening extending from the optic nerve along the superotemporal arcade **(blue arrow)**. Fluorescein angiography (**B** early, **C** late) shows delayed flow along the inferotemporal arcade, with late focal staining of the retinal arteries **(white arrow)**. A region of nonperfusion is noted superior to the fovea **(black arrow)** corresponding to the foci of intra-arterial gray material in 2A. Case 2 (**D–F**): An 80-year-old woman presented with reduced vision and a superior scotoma at 7 days after her second brolucizumab injection. Fundus photograph **(D)** shows retinal whitening involving the inferior macula, arterial sheathing, and focal interruptions of the blood column within an inferotemporal macular branch retinal artery. Near-infrared **(E)** and OCT **(F)** show subretinal fluid that was improved from prior OCT evaluations and intraretinal foci of hyperreflectivity **(white arrow)**. Case 3 **(G–I)**: A 75-year-old woman had persistent subretinal fluid despite 18 previous anti-VEGF injections (14 aflibercept/4 ranibizumab), comprising the reason to switch to brolucizumab. She presented with floaters and reduced vision and was diagnosed with IOI and occlusive retinal vasculitis 30 days after her first brolucizumab injection. Fundus photograph **(G)** shows multiple cotton wool spots around the optic nerve and perimacular and subtle periarterial whitening. There is some vitreous opacity along the inferotemporal arcade. Fluorescein angiography (**H**, early 28 seconds) shows globally delayed retinal arterial filling, notable around the optic nerve. At 68 seconds **(I)**, there remains delayed arterial filling around the optic nerve and inferiorly, and blockage from vitreous opacity. **A to C** courtesy of Haug et al[17] and **D to G** courtesy of Baumal et al.[16] IOI = intraocular inflammation; IVFA = intravenous fluorescein angiography; VEGF = vascular endothelial growth factor.

Retinal vascular occlusive events require prompt evaluation and intensive management in an effort to minimize secondary ischemic changes.[41] In the setting of inflammation, treatment with potent corticosteroids (systemic, intravitreal, or topical) is recommended to ensure adequate inflammation control. In patients with persistent retinal vasculitis (with or without occlusion), repeat IVIs of corticosteroids or corticosteroid implants may be given (Fig 1). Careful attention should be given to the patient's ocular and medical history to ensure that the patient is not at increased risk of a corticosteroid-induced side effect. Consultation with the primary care physician may be indicated to co-manage patients on oral corticosteroids. In cases of intolerance, major side effects, or contraindication to steroids, other treatment options such as immunomodulatory agents or nonsteroidal agents may be considered. There is currently no evidence regarding the utility of these therapies in this setting, but there may be a role when more information on the pathogenesis of the inflammatory event is available. In severe cases, or when signs and symptoms are acutely associated after the IVI, vitrectomy may have a theoretical benefit, although clinical evidence to support this option is currently limited. Patients with retinal vascular occlusive events may be at risk of developing secondary ocular complications such as neovascularization; therefore, it is important to carefully monitor them. Panretinal photocoagulation may be used in the event of

neovascularization and considered in patients with extensive peripheral ischemia before the appearance of new vessels.[41]

Management of nAMD

The previous sections provide recommendations on how best to manage the spectrum of ocular inflammatory events should they arise after treatment with brolucizumab or other anti-VEGFs. However, it is also important to effectively manage nAMD in these patients. As soon as the patient is diagnosed with IOI, retinal vasculitis, or a retinal vascular occlusive event, anti-VEGF treatment should be suspended. The patient must be monitored regularly, and future treatment options for nAMD may be determined based on the outcomes of the described events and the patient's clinical status. The clinician may consider treatment modalities based on an individualized approach and the locally available standard of care (Fig 1).

Discussion

In the pivotal HAWK and HARRIER trials, brolucizumab demonstrated comparable efficacy to aflibercept with respect to vision gains while providing superior anatomic outcomes with an overall well-tolerated safety profile.[2,3] Postapproval, spontaneous reports and published case series revealed a spectrum of ocular inflammatory events with brolucizumab IVI.[12,13,16,17,19,23,24] The exact incidence of these vascular occlusive events is not clear, but it seems to be uncommon. The SRC review of HAWK and HARRIER data found approximately 2% of eyes with IOI had concomitant retinal vasculitis and vascular occlusion, whereas a recent multicenter real-world study did not have any cases of occlusive retinal vasculitis related to brolucizumab.[12,13,45]

The root cause of these events is unknown and currently under investigation. One of the possible hypotheses for the pathogenic mechanism of this spectrum of events that is under investigation is the formation of local antibodies.[16,17,19,23] Other proposed hypotheses include patient factors such as prior anti-VEGF treatment use, human leukocyte antigen, immune status, and causative comorbidities.[16,17,19,23]

In publications reporting on the spectrum of ocular inflammatory events, patients presented with varying severities of IOI, retinal vasculitis, and retinal vascular occlusion, typically within 2 months of their last brolucizumab injection.[16,17,19,23,24] Most patients received topical or systemic corticosteroids, whereas some of them additionally required intravitreal or subtenon corticosteroid injections. A small number of eyes from these reports also underwent vitrectomy but were not noted to gain any additional clinical benefit from the procedure.[16,23] Differences in the management of these events, including the time of diagnosis, mode, frequency and duration of treatment, and follow-up period, may have contributed to the variable visual outcomes. Although these reports do provide some preliminary clinical insights, there is a need for guidance to facilitate a more consistent management approach of this spectrum.

The recommendations proposed may be considered to aid in diagnosis and management of these events should they arise with brolucizumab or other anti-VEGFs in nAMD. Patients should be educated on the importance of reporting any symptoms as soon as they arise to ensure an early diagnosis. Imaging techniques, including IVFA with peripheral sweeps, OCT, and widefield imaging, are recommended to confirm or rule out retinal vasculitis or retinal vascular occlusive events in patients presenting with IOI. Early and intensive treatment of IOI with potent corticosteroids and regular monitoring of patients may play a role in preventing progression within the spectrum. In the situation that the IOI progresses, it is imperative to follow a more aggressive treatment approach. It is also critical to distinguish IOI from infectious endophthalmitis because their clinical course and management are different. Management of the underlying nAMD should be determined based on the outcomes of these events, and clinicians should consider an individualized patient approach using the locally available standard of care.

It is important to note that these recommendations are primarily based on the authors' expert opinion and should be considered as guidance in managing these events, rather than a formal protocol or guidelines. Because treatment practices and available therapies vary in different regions and centers, clinicians can choose what they consider the most appropriate from the selection locally available to them.

Conclusions

The spectrum of IOI, retinal vasculitis, and retinal vascular occlusive events is uncommon; accordingly, there is limited knowledge about the pathogenesis that would serve to precisely direct therapeutic intervention. Clinicians are encouraged to report these events as per their local practices with as much detail as available, including images when possible. This will allow the clinical community to better understand this spectrum of events so that the management of these patients can be improved in the future. While we continue to increase our clinical understanding, the proposed recommendations can be used for timely management in an effort to minimize the risk of progression of this spectrum.

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[1] Tufts University School of Medicine, New England Eye Center, Boston, Massachusetts.

[2] Ophthalmology, IHU FOReSIGHT, Sorbonne University, APHP, Paris, France.

[3] Medical Center of Ophthalmology, University of Texas Health Science Center, San Antonio, Texas.

[4] Novartis Pharmaceutical Corporation, East Hanover, New Jersey.

[5] Budapest Retina Associates, Budapest, Hungary.

[6] Novartis Pharmaceuticals UK Limited, London, United Kingdom.

[7] Ophthalmology, University Goettingen, Goettingen, Germany.

[8] York Teaching Hospital NHS Foundation Trust, University of York, York, United Kingdom.

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D.J.T.: Employee – Novartis Pharmaceuticals Corporation, East Hanover, NJ.

A.S.: Consultant – Novartis, Roche; Speakers Bureau – Roche.

M.R.J.: Employee – Novartis Pharmaceuticals UK Limited.

N.F.: Consultant – Alimera Sciences, Novartis, Roche; Speaker – Allergan, Alimera, Bayer, Heidelberg Engineering, Novartis, Roche.

R.G.: Consultant – AbbVie-Allergan, Bayer, Novartis, Roche; Investigator – AbbVie-Allergan, Bayer, Novartis, Roche.

HUMAN SUBJECTS: Human subjects were included in this study. IRB/Ethics Committee ruled that approval was not required for this study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Baumal, Bodaghi, Singer, Tanzer, Seres, Joshi, Feltgen, Gale

Data collection: Baumal, Bodaghi, Singer, Tanzer, Seres, Joshi, Feltgen, Gale

Analysis and interpretation: Baumal, Bodaghi, Singer, Tanzer, Seres, Joshi, Feltgen, Gale

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Overall responsibility: Baumal, Bodaghi, Singer, Tanzer, Seres, Joshi, Feltgen, Gale

Abbreviations and Acronyms:
AE = adverse event; **ASRS** = American Society of Retinal Specialists; **ICGA** = indocyanine green angiography; **IOI** = intraocular inflammation; **IVFA** = intravenous fluorescein angiography; **IVI** = intravitreal injection; **nAMD** = neovascular age-related macular degeneration; **OCTA** = OCT angiography; **SRC** = Safety Review Committee; **VEGF** = vascular endothelial growth factor.

Keywords:
Anti−vascular endothelial growth factor, Brolucizumab, Intraocular inflammation, Neovascular age-related macular degeneration, Retinal vascular occlusion, Retinal vasculitis.

Correspondence:
Caroline R. Baumal, MD, Tufts University School of Medicine, New England Eye Center, 800 Washington St., Box 450, Boston, MA 02111. E-mail: cbaumal@gmail.com.

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