Ophthalmol Ther (2023) 12:639–655
https://doi.org/10.1007/s40123-023-00647-7

GUIDELINES

Brolucizumab in Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema: Ophthalmology and Diabetology Treatment Aspects

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Received: November 21, 2022 / Accepted: January 3, 2023 / Published online: January 12, 2023

ABSTRACT

Anti-vascular endothelial growth factor (anti-VEGF) therapies have become the standard of care in the treatment of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME), resulting in a remarkable decrease in disease-related vision loss. However, the need for regular injections places a significant burden on patients, caregivers, and the healthcare system and improvements in vision may not be maintained long term. As a result of its drying potency and duration of action, brolucizumab, an intravitreal anti-VEGF therapy approved for the treatment of nAMD and DME, could decrease injection frequency for patients and provide an efficacious treat-

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ment; however, balancing its benefits and risks can be challenging. There have been reports of intraocular inflammation (IOI) in patients treated with brolucizumab, which, if left untreated, may result in severe vision loss. Recent evidence, however, indicates that early recognition of IOI and prompt and aggressive systemic corticosteroid treatment in response to posterior segment involvement can lead to favorable outcomes in these relatively rare but severe cases. A series of consensus meetings were conducted in 2022 between Swiss medical retina experts and diabetologists, discussing the current data for brolucizumab and exploring various challenges to its use, including the associated risk of IOI. The outcome is a collation of practical insights and guidance for ophthalmologists on the use of brolucizumab in patients with nAMD and DME, including patient selection and assessment, treatment regimen and monitoring, and the recognition and management of adverse events.

Keywords: Brolucizumab; Diabetic macular edema (DME); Intraocular inflammation (IOI); Neovascular age-related macular degeneration (nAMD); Retinal vascular occlusion; Retinal vasculitis; Side effects; Steroid-induced diabetes; Treatment

Key Summary Points

Diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) have a high disease and treatment burden.

A number of clinical and real-world studies suggest that brolucizumab, an intravitreal anti-vascular endothelial growth factor therapy, could decrease injection frequency for patients with DME and nAMD and provide long-term improvements.

There have been rare reports of intraocular inflammation (IOI) in patients treated with brolucizumab; however, evidence has shown that prompt diagnosis and treatment of IOIs can lead to favorable outcomes.

This article provides practical guidance and insights from Swiss medical retina experts and diabetologists on the use of brolucizumab in patients with nAMD and DME.

INTRODUCTION

With an increasingly ageing population worldwide, more people are at risk of visual impairment due to chronic eye diseases, ageing processes, and ocular and systemic comorbidities [1–3]. Age-related macular degeneration (AMD), which is non-exudative or "dry" in early stages and may convert to exudative or "wet" in later stages (neovascular AMD, nAMD), is characterized by progressive loss of central vision that can become severe [3]. Although nAMD was previously one of the leading causes of blindness in the elderly [3], the use of anti-vascular endothelial growth factor (anti-VEGF) in clinical practice has reduced the incidence of nAMD-associated blindness dramatically [4]. Patients with unilateral late-stage AMD (including both nAMD and dry AMD) are at risk of conversion to macular neovascularization (MNV) in their fellow eye, at rates as high as 38% over 3 years [5].

Meanwhile, the prevalence of diabetic macular edema (DME), a manifestation of diabetic retinopathy, is continuously rising worldwide (4.07% based on data up to March 2020) and has become one of the major causes of vision loss in the working-age population [6–8]. VEGF

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plays an essential role in diabetic retinopathy and is involved in the development of DME. As such, anti-VEGF therapies have shown efficacy in DME [9], and DME-related vision loss has decreased since their introduction [10, 11]. Anti-VEGF therapy is now considered the standard of care, with additional laser photocoagulation and steroid injections as second-line options if required [12].

Despite the establishment of highly effective intravitreal anti-VEGF therapy as the standard of care for nAMD and DME [13, 14], a high treatment burden and thus an unmet need has still remained in this population. To achieve disease control in a real-world setting, many patients with nAMD and DME receive more than seven injections in the first year of treatment [12, 15–18]. An average patient spends 1.5 h at an injection appointment plus 1 h travelling to and from the appointment. With many relying on family and friends for transportation, this can place a considerable burden on the professional and private lives of both patients and their caregivers [19–21]. The need for regular injections also puts pressure on healthcare services, with ophthalmology appointments accounting for 10% of all outpatient appointments across the National Health Service, largely driven by the need for medical retina consultations [22]. On top of this, patients may require extra healthcare visits for comorbidities, since patients with DME and nAMD are also more likely to experience disease- and treatment-independent comorbidities than non-diabetic patients with DME and healthy controls, respectively, and visit healthcare facilities more often [23, 24].

For the aforementioned reasons, it is not surprising that patient compliance with intravitreal anti-VEGF regimens is limited. Data on 20,820 nAMD appointments and 1648 DME appointments scheduled in Europe between 2014 and 2015 showed that 14.5% of nAMD appointments were cancelled and 1.8% were no-shows, while 15.2% of DME appointments were cancelled and an additional 12.0% were no-shows [25].

Even with these burdensome treatment regimes, improvement in visual acuity may not be maintained over time [26–29] and many patients continue to have residual fluid. In a meta-analysis of real-world studies in nAMD, including 5629 patients who received ranibizumab, aflibercept, or brolucizumab, residual fluid was present in more than 40% of eyes after 2 years [15]. In 258 patients with DME, only 16% of patients had no fluid after 12 months of treatment with intravitreal aflibercept [30]. This lack of maintenance has been shown to differ depending on intensity of treatment, with increased healthcare visits and injection frequency associated with greater improvements in vision [11, 26, 31].

Brolucizumab is an intravitreal anti-VEGF drug indicated for use in adults for the treatment of nAMD and DME, approved in Switzerland since 16 January 2020 for nAMD and since 2 June 2022 for DME [32, 33]. With a molecular weight of 26 kDa, brolucizumab allows for higher molar dosing versus other anti-VEGF therapies, with a longer duration of action and improved tissue penetrability [34]. Preclinical data and phase II/III trials support the use of a once every 12 weeks (q12w) brolucizumab maintenance regimen immediately after the loading phase, offering a reduction in injection number/treatment burden for patients with nAMD and DME when compared with previous anti-VEGF options.

Clinical Data in nAMD

HAWK and HARRIER, two similarly designed phase III trials, compared brolucizumab (n = 1088 eyes) with aflibercept (n = 729 eyes) in treatment-naïve patients with nAMD. During the loading phase, both treatments were given as three injections at 1-month intervals. Brolucizumab treatment intervals were then extended to 12 weeks and later adjusted to 8 weeks if disease activity was present; aflibercept treatment was extended to fixed 8-week intervals. Brolucizumab 6 mg demonstrated non-inferiority for the primary endpoint, change in best-corrected visual acuity (BCVA) from baseline at week 48, in both studies: least squares (LS) mean, + 6.6 letters with brolucizumab vs + 6.8 letters with aflibercept (HAWK); + 6.9 (brolucizumab) vs + 7.6 (aflibercept) letters

(HARRIER); $p < 0.001$ for each comparison [35]. This was maintained to 96 weeks where the difference in the LS mean change from baseline between brolucizumab 6 mg and aflibercept was at most 0.6 letters in both studies [34]. In terms of fluid in the macula, eyes treated with brolucizumab 6 mg achieved greater reductions in central subfield thickness (CSFT) and had a significantly lower incidence of intraretinal fluid (IRF) and/or subretinal fluid (SRF) compared with aflibercept at weeks 16 and 48 [35], which was maintained through to week 96 [34]. In both studies, more than 50% of brolucizumab 6 mg-treated eyes were maintained on q12w dosing through week 48 [35] and approximately 40% were maintained on q12w dosing through week 96 [34].

Post hoc analyses of the HAWK and HARRIER studies further demonstrated the impact that the drying effect has on visual outcomes. Patients from HAWK/HARRIER who were early residual fluid (ERF)-free at week 12 showed greater improvements in visual outcomes vs patients with ERF [36] and fewer patients treated with brolucizumab had remaining fluid at weeks 48 and 96 compared with patients treated with aflibercept [37].

Another post hoc analysis demonstrated robust efficacy in the reduction of the pigment epithelial detachment (PED) thickness with brolucizumab 6 mg, with greater reduction vs aflibercept at weeks 16, 48, and 96 [38].

In these studies, brolucizumab exhibited an overall favorable benefit/risk profile. The most common adverse events (AEs) reported in the HAWK/HARRIER studies included cataract, conjunctival hemorrhage, reductions in visual acuity, and vitreous floaters and occurred at similar rates in all treatment arms. The exception to this was intraocular inflammation (IOI), which occurred at a higher rate with brolucizumab 6 mg vs aflibercept 2 mg in the pooled HAWK/HARRIER studies (4.4% [32/730] vs 1.0% [7/729]) [34]. Reassessment of the HAWK/HARRIER studies by an external safety review committee found concomitant retinal vasculitis (RV) and/or retinal occlusion (RO), AEs that can result in severe vision loss, in some patients with IOI. The incidence was 4.6% (50/1088) for IOI, 3.3% (36/1088) for IOI + RV, and 2.1% (23/1088) for IOI + RV + RO, and the risk of at least moderate vision loss due to IOI was 0.74% (8/1088). The median time from last injection to onset of IOI was 25.5 days and 74% occurred within 6 months of the first dose of brolucizumab [39].

TALON is a 64-week ongoing head-to-head phase IIIb study, which aims to prove superiority of brolucizumab 6 mg over aflibercept 2 mg in extending duration of treatment intervals and non-inferiority of brolucizumab 6 mg relative to aflibercept 2 mg in BCVA, using a matched treat and extend treatment regimen in treatment-naïve patients with nAMD. The 32-week interim results found that brolucizumab was superior to aflibercept in the distribution of the last treatment interval with no disease activity (defined as the absence of any IRF and/or SRF in the central macular subfield; $p < 0.0001$). According to this interim analysis, the last treatment interval at which absence of disease activity was maintained was 12 weeks for 19.8% of patients receiving aflibercept vs 38.5% of patients receiving brolucizumab [40].

Clinical studies and real-world experience in pretreated eyes have also demonstrated brolucizumab efficacy; in a recent study of 36 eyes in patients with nAMD who had received at least 10 prior anti-VEGF injections and had persistent retinal fluid following five monthly injections with aflibercept or bevacizumab, brolucizumab significantly decreased CSFT over 4 weeks ($p < 0.001$) and led to complete resolution of fluid in 66.67% of patients [41]. In the SHIFT study, switching to brolucizumab did not significantly change BCVA in 63 eyes with recalcitrant nAMD but it produced significant reductions in CSFT (− 66.76 µm) and macula volume (− 0.27 mm^3) at 4 weeks after the first brolucizumab injection ($p < 0.001$ for both) [42]. In the first real-world Canadian analysis of brolucizumab, outcomes were assessed retrospectively at a mean follow-up of 28 weeks in 73 patients with nAMD who switched to brolucizumab after treatment with at least one other anti-VEGF agent. Non-significant improvement in BCVA was observed (+ 4.3 letters), while reductions in mean CSFT (− 36.6 µm) and proportion of patients with any macular fluid (56.1%) were significant ($p = 0.0002$ and

$p < 0.001$, respectively). IOI was detected in 4.1% patients in this study, which is in line with the incidence rate reported in HAWK and HARRIER post hoc analyses [43].

Post-Approval Safety Data in nAMD

Data from brolucizumab-treated eyes were analyzed in a cohort study of patients with nAMD from the Intelligent Research in Sight (IRIS) Registry ($n = 10,654$ eyes), a US eye disease database, and the Komodo healthcare map ($n = 11,161$ eyes), a US claims database. The majority of patients included had switched to brolucizumab from another anti-VEGF therapy. The overall incidence of IOI and/or RO in each registry was 2.4%. Patients with a history of IOI and/or RO in the preceding 12 months had an increased observed risk rate (IRIS 8.7% [95% CI 6.0–11.4%] and Komodo 10.6% [95% CI 7.5–13.7%]) for an IOI and/or RO event in the 6 months following the first brolucizumab treatment compared with patients without prior IOI and/or RO. Female sex was identified as an independent risk factor for IOI and/or RO (increased observed risk rate IRIS 2.9% [95% CI 2.5–3.3] and Komodo 3.0% [95% CI 2.6–3.4]); however, limitations associated with database analyses should be taken into account when considering risk factors for IOI and/or RO in practice [44].

The MERLIN phase III study compared fixed q4w regimens of brolucizumab 6 mg and aflibercept 2 mg in patients with recalcitrant nAMD and found a two times higher incidence of IOI with brolucizumab vs aflibercept (9.3% vs 4.5%). The q4w dosing in the MERLIN study, which was designed before IOI issues occurred, is not in line with current brolucizumab posology, where injection intervals are extended to 8 or 12 weeks after the first three loading doses [45]. Given the reported frequency of IOI, the MERLIN study was prematurely terminated and, importantly, injection intervals of a minimum of 8 weeks are now recommended after the loading phase [46, 47].

The non-interventional BASIC study was conducted from June to August 2020 to investigate potential immunological factors that could contribute to the development of brolucizumab-associated RV and/or RO. The blood samples of patients with brolucizumab-related RV/RO had higher anti-drug antibody (ADA) titers and higher frequency of neutralizing ADAs than those of patients without the manifestation of RV/RO. Increased T cell activation and platelet aggregation (supposably via the formation of immune complexes) upon in vitro stimulation with brolucizumab was also described. These findings are consistent with a mature B and T lymphocyte activation against brolucizumab and support the conclusion that treatment with brolucizumab should be permanently stopped upon diagnosis of RV/RO [48].

That this inflammation is driven by induced and/or boosted antibodies as well as systemic brolucizumab-specific B and T lymphocytes strongly suggests that a rapidly acting systemic anti-inflammatory therapy, at the earliest possible point of time, could be effective in treating IOI. Indeed, severe vision loss, regularly encountered in untreated IOI, can successfully be prevented with prompt and intensive treatment in the majority of instances. In the SHIFT study, where seven patients developed IOI (including one with RV) and were treated promptly with steroids according to IOI severity, none of the patients experienced persistent, clinically relevant worsening in visual acuity once the IOI was resolved [42]. In the REBA study, one patient developed RO and presented 4 h after symptom onset, at which point their BCVA had dropped from 20/60 prior to RO to 20/200. The patient was referred immediately for treatment and, upon recovery, their BCVA was restored to 20/60 [49].

In one particularly severe case, an 81-year-old woman presented with severe bilateral loss of vision 8 days after receiving a second set of bilateral brolucizumab injections for the treatment of nAMD. She was diagnosed with vasculitis and immediately treated with steroids; however, her visual acuity deteriorated further and remained unchanged thereafter. The patient had complained of a dark spot in her peripheral field of vision 2 weeks after her first set of injections, which may have been a warning sign of vasculitis, but no additional

examinations were performed before her next injections. This highlights the importance of patient education and early recognition of AEs during the use of brolucizumab [50].

Clinical Data in DME

KITE and KESTREL were two 100-week phase III trials that evaluated the safety and efficacy of brolucizumab 6 mg (n = 368) versus aflibercept (n = 368) in patients with DME. Aflibercept was given as five loading doses at 4-week intervals, followed by fixed 8-weekly maintenance dosing, in line with its label. The five brolucizumab loading doses were given at extended intervals of 6 weeks and were followed by 12-weekly maintenance dosing with the option to adjust to 8-weekly if disease activity was present. Brolucizumab 6 mg was non-inferior (NI; margin 4 letters) to aflibercept 2 mg for the primary endpoint of mean change in BCVA from baseline at week 52 in both studies (KESTREL, + 9.2 letters vs + 10.5 letters; KITE, + 10.6 letters vs + 9.4 letters; $p < 0.001$) [51] and this was maintained to week 100, where the difference in the LS mean change from baseline between brolucizumab 6 mg and aflibercept was at most 2.5 letters in both studies [52]. In addition, at weeks 32, 52, and 100 numerically more subjects achieved CSFT less than 280 μm, and fewer had persisting SRF and/or IRF vs aflibercept. In KITE, brolucizumab 6 mg showed superior improvements in the change of CSFT in the first-year vs aflibercept (p = 0.001) [51]. Of the brolucizumab 6 mg patients who successfully completed the first q12w cycle immediately after the loading phase in KITE and KESTREL, approximately 70% remained on the q12w/q16w interval until week 100 [52].

At week 100 in the KESTREL study, the incidence of IOI was 5.3% (brolucizumab 3 mg), 4.2% (brolucizumab 6 mg), and 1.1% (aflibercept) and the incidence of RO and RV was 1.6% and 1.6% (brolucizumab 3 mg), 1.6% and 0.5% (brolucizumab 6 mg), and 0.5% and 0% (aflibercept). At week 100 in the KITE study, the incidence of IOI was 2.2% (brolucizumab 6 mg) and 1.7% (aflibercept), the incidence of RO was 0.6% in the brolucizumab 6 mg and the aflibercept arms, and there were no new cases of RV [52].

As a result of the more recent approval of brolucizumab for DME [32, 33], real-world data in this indication is limited; one case series reported off-label use in three eyes with recalcitrant DME that had received at least 10 prior anti-VEGF injections before switching to brolucizumab. All patients showed notable improvement in BCVA and a reduction in fluid at 12 weeks after first injection. BCVA changes were maintained at 16 weeks; however, increases in fluid were noted at this time [53].

RATIONALE FOR THE GUIDANCE

There is wide variation in clinical practice patterns for the treatment of nAMD and DME and many clinicians are uncertain about how the scientific evidence for emerging therapies will fit into the existing patient pathways. Recently, a number of guidelines for the use of brolucizumab have been published [54–56]. However, these guidelines are global or specific to certain countries and therefore may not be directly applicable to Swiss ophthalmologists. The guidance provided in the current article was developed by a group of Swiss retina specialists, with support from Swiss diabetologists, to provide expert opinion on the use of brolucizumab in nAMD and DME with a focus on the management of IOIs.

METHODOLOGY

A series of medical expert consensus meetings, sponsored but not influenced by Novartis, were held throughout 2022 to discuss the role of brolucizumab for the treatment of nAMD and DME. All members of the steering committee work in Swiss hospital ophthalmology departments or as private practitioners and have experience in leading and managing retinal services involved in delivering intravitreal therapy. The consensus meetings facilitated the development of this article, to explore how brolucizumab could best fit within the current standard of care.

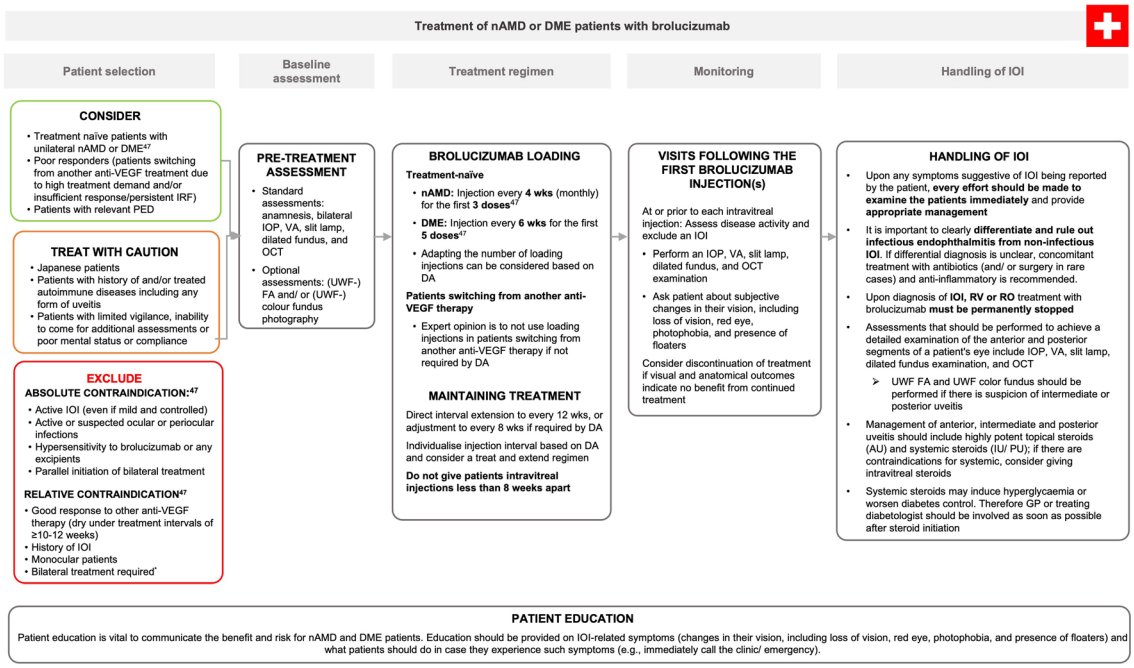

Fig. 1 Brolucizumab treatment overview. *Although bilateral treatment is not universally recommended, it is the experts' opinion that brolucizumab may be considered in the second eye if well tolerated in the first eye over a period of at least 6 months. *AU* anterior uveitis, *DA* disease activity, *DME* diabetic macular edema, *IOI* intraocular inflammation, *IU* intermediate uveitis, *nAMD* neovascular (wet) age-related macular degeneration, *OCT* optical coherence tomography, *PU* posterior uveitis, *Q8W* every 8 weeks, *Q12W* every 12 weeks, *RO* retinal occlusion, *RV* retinal vasculitis, *UWF-FA* ultra-wide field fluorescein angiogram, *VA* visual acuity, *VEGF* vascular endothelial growth factor

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

A summary of the key points from the meetings can be found in Fig. 1.

Patient Selection

Brolucizumab is indicated for the treatment of nAMD or DME, unless contraindications are present (Table 1, Fig. 1). The HAWK/HARRIER and KITE/KESTREL studies only included patients who were naïve to intravitreal anti-VEGF treatment, meaning the strongest clinical evidence exists for treatment-naïve eyes. Nevertheless, patients switching to brolucizumab from another anti-VEGF drug are likely to represent the main group of patients treated initially, and there is already a wealth of real-world data available in this population [42, 44, 49, 53, 57–59].

Baseline/Pre-treatment Assessment

Pre-treatment assessments that should be conducted before brolucizumab initiation include standard assessments used for all anti-VEGF therapies (Fig. 1). On top of this, additional assessments such as ultra-wide field (UWF; where available) fluorescein angiogram (FA) and UWF (where available) color fundus photography may be considered, according to the individual center's standards, in order to provide baseline information (Fig. 1).

Table 1 Eligibility for brolucizumab treatment

Patients to be considered for treatment	
Treatment-naïve patients with unilateral nAMD or DME [47]	
Poor responders (patients switching from another anti-VEGF treatment because of high treatment demand and/or insufficient response/persistent IRF)	
Patients with relevant PED [60]	
Patients to be treated with caution	
Japanese patients [61]	
Patients with history of and/or treated autoimmune diseases including active rheumatoid disease, multiple sclerosis, Behcet's disease, lupus, and any form of uveitis (authors' opinion)	
Patients with limited vigilance, inability to come for additional assessments, or poor mental status or compliance	
Patients to be excluded	
Absolute contraindications	**Relative contraindications**
Active IOI (even if only mild and controlled with topical corticosteroids)	Good response to other anti-VEGF therapy (dry under treatment intervals of $\geq$ 10–12 weeks) and no significant risk of severe vision loss due to disease progression
Active or suspected ocular or periocular infection	History of IOI
Known hypersensitivity to brolucizumab or any excipients	Monocular patients[a]
Parallel initiation of bilateral treatment	Switching from unilateral to bilateral treatment with brolucizumab after $\geq$ 6 months of unilateral treatment[a]

[a]Some experts may consider brolucizumab for monocular patients since these patients are likely to immediately detect any corresponding symptoms and report them promptly. Bilateral treatment is not universally recommended; however, there is no explicit contraindication. It is the experts' opinion that treatment of the second eye may be considered if brolucizumab was tolerated in the first eye over a 6-month period, as the risk of developing severe IOI at this stage is low

Table 2 Key symptoms of IOI

IOI symptoms to be aware of[a]
Floaters
Redness of the eye
Decreased or blurred vision (including sudden vision loss, changes in reading vision, etc.)
Photophobia
Foggy vision
New onset scotoma
Ocular discomfort

[a]Caveat: symptoms can be painful or painless

Patient Education

Patient education is vital to ensure the patient is able to provide informed consent and to encourage compliance with treatment. Patients should be informed of the benefits and risks of brolucizumab, be aware of other treatment options available to them, and be given enough time to fully consider their options.

Importantly, education should include information on IOI-related symptoms (Table 2), how to recognize them, and what to do if they experience them, e.g., immediately call the clinic/emergency department, even if symptoms are painless. This should be reiterated throughout treatment (Fig. 1) and patients should have a direct contact number for emergencies.

Treatment with brolucizumab is recommended for institutions with 24/7 availability for emergencies and those in cooperation with an institution providing 24/7 availability. If possible, a dedicated service can be organized to enquire about patient well-being after injections in order to increase awareness and allow direct reporting of symptoms. Education of applicable colleagues (e.g., residents) at the emergency department is mandatory.

Treatment Regimen (Dosage and Administration)

In general, brolucizumab treatment fits into the existing daily practice pathways after informing the patient about IOI risk and symptoms. Additional pre-injection assessments may be required during the loading phase and are described in the monitoring section.

The recommended dose is 6 mg brolucizumab (0.05 ml solution) administered by intravitreal injection [47].

Loading phase for treatment-naïve patients

- nAMD: q4w for the first three doses
- DME: q6w for the first five doses
- The authors recommend that after the first two loading injections, the physician may consider adapting the number of remaining injections according to a treat and extend protocol if the patient shows a good anatomical response

Loading phase for patients switching from another anti-VEGF therapy

- If not indicated by disease activity, the authors do not generally recommend using a fixed re-loading regimen in patients switching from another anti-VEGF therapy
- In the experts' view, physicians may keep the initial post-switch interval the same as the last pre-switch interval before adapting the interval thereafter depending on disease activity (note: a maximum of three consecutive q4w and five consecutive q6w brolucizumab injections are recommended for patients with nAMD and DME, respectively, prior to extending to q8w intervals)

Maintenance phase for treatment-naïve patients and for patients switching from another anti-VEGF therapy

- Injection intervals may be extended to 8–-12 weeks if the eye is completely dry after the loading phase, or adjusted to every 8 weeks if disease activity (fluid) is present
- The authors recommend individualizing treatment intervals on the basis of disease activity

- Extended treatment intervals are favorable, particularly in patients switching from another anti-VEGF treatment
- If disease stability is reached under brolucizumab q12w, the physician may consider further interval extension
- If disease activity worsens, treatment intervals should be shortened but must not be less than 8 weeks. Switching to another therapy should be considered if disease activity continues to worsen at 8-week brolucizumab intervals

Criteria for Stopping Treatment

Anti-VEGF treatment should not be continued if visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment (e.g., absence of visual potential, diagnosis of IOI, RO, or RV) [62–64]. Upon diagnosis of IOI, RV, or RO, treatment with brolucizumab must be permanently stopped and the eye should be switched to treatment with another anti-VEGF agent if required (ideally not before the inflammation has resolved).

Monitoring

The expert panel recommends a patient examination prior to each injection to check the efficacy of brolucizumab treatment as well as to detect any side effects that may be present, particularly IOI (Fig. 1). Therefore, prior to each intravitreal injection (including loading doses), visual acuity (VA), intraocular pressure (IOP), slit lamp and dilated fundus examination, as well as optical coherence tomography (OCT) examination should be routinely performed. After the loading phase, and for yearly controls, physicians may consider conducting a UWF (where available) FA and UWF (where available) color fundus photography. At all visits, physicians should ask patients about subjective changes in their reading vision and ask if the patient has experienced foggy vision, red eye, photophobia, or the presence of floaters.

Additional post-injection control in asymptomatic patients is not generally recommended but can be considered, if justified, at the discretion of the treating physician. One-time post-injection control 1–2 weeks after the first injection, either face-to-face or by telephone call, may be used for educational purposes to retrain the patient on IOI-related warning symptoms.

Handling of IOI in nAMD and DME

Careful monitoring, prompt diagnosis, and timely intervention are key to managing potential AEs associated with brolucizumab (Fig. 1). It is important to educate all stakeholders on the possible AEs associated with brolucizumab injection, in particular the risk of IOI, and to reinforce vigilance throughout the treatment course to ensure that patients recognize signs and symptoms and report any changes immediately.

If a patient reports a change in vision or any other IOI symptom (Table 2), every effort should be made to examine them immediately (i.e., same day) and provide appropriate management. It is important, though frequently difficult, to clearly differentiate infectious endophthalmitis (which arises mostly 2–7 days after injection) from non-infectious IOI (which may arise 2–60 days after injection). If the differential diagnosis is unclear, concomitant treatment is decided on clinical grounds, i.e., antibiotics, anti-inflammatory drugs, and/or, on rare occasions, vitreoretinal surgery [64].

If IOI is suspected, physicians should confirm the presence of inflammation and determine the severity (Table 3). A variety of assessments, including IOP, VA, slit lamp and dilated fundus examination, as well as OCT, can be used to achieve a detailed examination of the anterior and posterior segments of a patient's eye. If there is any suspicion of intermediate or posterior uveitis, the addition of UWF FA and UWF color fundus photography is strongly recommended in order to detect the presence of clinically missed vascular occlusions. The experts recommend retaining the intravenous line after FA until a clinical decision has been made, in order to enable the initiation of systemic steroid therapy if required.

IOI should always be assessed by an experienced physician who is familiar with the most

Table 3 Key IOI findings to confirm presence of inflammation

Anterior uveitis	Intermediate/posterior uveitis[a]
Corneal precipitates	Precipitates
Single cells in the anterior vitreous/Tyndall effect	Vitreous and pre retinal cells (hyperreflective spots)
Conjunctival hyperemia	Intraretinal hyperreflective spots
Red eye/ciliary injection	Intraretinal hemorrhages
	Macular or optic disc edema (hyperfluorescence)
	(Peri)vascular sheathing
	Vasculitis
	Retinal vascular occlusions
	Cotton wool spots
	Vascular leakage
	Retinal ischemia
	Media opacities
	Paracentral acute middle maculopathy
	Retinal whitening
	Retinal nerve fiber layer edema around the optic nerve
	Kyrieleis plaques
	Segmental blood flow in the retinal vessels (boxcarring)

[a]Caveat: can present with or without anterior segment involvement

important imaging features of an IOI (Table 3). Angiographic findings in such cases are prone to misinterpretation, owing, among other reasons, to the strong anti-VEGF effect of brolucizumab that may ameliorate or mask typical signs of vasculitis and lead to underestimation of IOI severity [65].

Brolucizumab must be permanently stopped upon diagnosis of IOI, RV, or RO, regardless of association to the drug and severity of IOI. Since IOI is an immunologic response to brolucizumab, rather than a toxic one, dose reduction does not impact the IOI risk and severity and is therefore not recommended.

Management of Anterior Uveitis

The management of anterior uveitis includes highly potent *topical* steroids, and eventually pupil-dilating agents, based on individual needs and physician preference [65]. Disease dynamics and treatment response should be monitored closely (i.e., daily), during the first days of treatment. The experts recommend a control visit after 1–2 days and again at 7 days, with treatment escalation if there are any signs of worsening or of newly developing posterior segment involvement. If there are signs of improvement, topical steroids can be tapered, but brolucizumab treatment must not be resumed.

Management of Intermediate/Posterior Uveitis

In the case of intermediate/posterior uveitis, the severity should be determined at diagnosis using UWF FA and UWF fundus photography in order to aid treatment decisions. Patients should be treated with highly potent *systemic* corticosteroids, either oral administration for at

least 6 weeks or intravenous administration over 3–5 days, followed by oral administration [64]. Systemic steroid treatment should be commenced immediately and continued in cooperation with the patient's general practitioner (GP). In acute and more severe cases, high-dose intravenous steroids (pulse therapy) are preferred over oral steroids by the expert steering committee, owing to their quick bioavailability. Topical steroids may be added if the anterior segment is involved. Upon improvement, steroids can be tapered gradually but brolucizumab treatment must not be resumed [64].

As in other vasculitic entities, physicians may consider thrombocyte aggregation inhibition (for a period of up to 3 months) if there are signs of RV or RO [66, 67]. Intravitreal steroids may be considered to reduce the duration of systemic therapy in patients with very strong contraindications for systemic steroids, e.g., uncontrolled diabetes, or any kind of systemic infectious diseases. However, the physician should be aware that while intravitreal steroids may reduce inflammation locally, they are not likely to prevent further vascular occlusion which seems to be rather associated with a systemic immune reaction.

Management of IOI in Patients at High Risk of Hyperglycemia

The management of IOI is largely the same in patients with DME or nAMD, and the guidance above should be followed for both. However, it is important to be aware that treatment with systemic steroids may induce hyperglycemia or worsen diabetes control in patients with diabetes. In otherwise healthy patients, the risk for severe hyperglycemia is low and, if it occurs, is usually transient. However, in patients with diabetes and other risk factors such as age > 60 years and BMI > 25 kg/m^2, the chance of glucocorticoid-induced hyperglycemia is increased [68].

If intermediate/posterior uveitis is diagnosed in these patients, the expert panel recommends initiating systemic steroid treatment immediately, despite any inherent complications that may be anticipated. The patient's GP or treating diabetologist, if already involved, should be contacted as soon as possible (ideally within 1–2 days), but this may vary depending on patient risk status and should not preclude the immediate onset of steroid treatment if indicated. Monitoring and control of blood glucose is mandatory in the first 1–3 days after steroid initiation. For patients at higher risk of hyperglycemia, i.e., those with pre-existing type 1 diabetes, patients already taking insulin, and those with HbA1c > 7.5%, a quick referral to the GP or treating diabetologist has to be considered to ensure timely glucose monitoring and adaptation of insulin treatment if required. Alternatively, physicians can opt to refer patients to a diabetologist or the clinic's emergency department for initiation of steroids, but this must not cause a delay in treatment initiation.

It is the physician's responsibility to ensure that their patients are educated on glucose management and informed to measure their blood glucose on a daily basis (fasting blood glucose every morning and, ideally, additional blood glucose before the main meals) during steroid therapy and for at least 3 days after steroid therapy has been ceased (continued monitoring for 1 week after steroid therapy is recommended by the expert committee for intravenous application).

Ongoing management, conducted by the diabetologist/GP will vary depending on the patient's risk status and initial response to steroids.

- Escalation (immediate monitoring and/or increased insulin dose) may be required for:
  - Patients who develop blood glucose > 10 mmol/L for 3 days or fasting blood glucose > 15 mmol/L for > 24 h during steroid treatment
- Referral to the emergency department for evaluation of hospitalization need is recommended if:
  - Patients have ongoing hyperglycemia with fasting blood glucose > 15 mmol/L *and*
  - Patients experience possible warning symptoms of hyperglycemia during

steroid treatment, e.g., polyuria, polydipsia or feeling generally unwell, *or*
- Patients are thought to be non-compliant with their treatment

CONCLUSION

Despite advances in the treatment of nAMD and DME, unmet needs remain. Patients face considerable treatment burden [19, 23], and improvements in vision and absence of fluid may not be maintained long term [16, 26]. Brolucizumab received marketing authorization in Switzerland for the treatment of patients with nAMD in January 2020, and for patients with DME in June 2022 [32, 33]. Brolucizumab offers physicians an anti-VEGF option with an extended duration of action and an improved drying effect on retinal fluid (compared with aflibercept) [34, 35, 40, 51] that could reduce the treatment burden of patients and treatment costs for the health system. Severe IOIs, serious events that can result in complete vision loss if untreated, have been associated with brolucizumab treatment. However, the incidence of severe IOIs is low and the recovery of IOI-related vision loss is likely if they are diagnosed and treated early. It is vital, therefore, that patients and physicians are educated on the symptoms and management of IOIs, in order to ensure prompt treatment. This article provides ophthalmologists with a collation of data and guidance to support them in delivering brolucizumab in their service and managing IOIs.

ACKNOWLEDGEMENTS

Funding. Sponsorship for this manuscript and the group that developed it, and the journal's Rapid Service Fee, were funded by Novartis. All authors received honoraria from Novartis for participation in the consensus meetings; however, they contributed to the development of the manuscript without any financial support and retained final control of the content and editorial decisions.

Medical Writing Assistance. Medical writing assistance was provided by Dr. Gabrielle Olley of Rock Unlimited. Support for this assistance was funded by Novartis. Novartis has checked that the content was factually accurate.

Author Contributions. All named authors contributed to the consensus meetings that were carried out to determine the direction of the review and gather the clinical opinions and evidence required to write the manuscript. The first draft of the manuscript was written by Gabrielle Olley and critically reviewed by all authors. All authors read and commented on each version of the manuscript and read and approved the final manuscript. The views and opinions of the authors are not necessarily those of Novartis or the publisher. Springer Healthcare is not responsible for the validity of guidelines it publishes.

Disclosures. Justus G. Garweg acts as an advisor to AbbVie, Bayer, Novartis and Roche and contributes to several international studies, including those investigating brolucizumab, which had no bearing on the outcomes presented here. Katja Hatz provides consultancy/advisory services and contract research for Novartis, Bayer, Roche and Allergan (AbbVie). Claudine A. Blum has received funding for congress participation from Novo Nordisk. Chiara M. Eandi provides consultancy/advisory services and contract research for AbbVie, Bayer, Novartis, and Roche. Gábor M. Somfai provides consultancy/advisory services for AbbVie, Bayer, Novartis, Roche and Carl Zeiss Meditec and contributes to several international studies, including those investigating brolucizumab, which had no bearing on the outcomes presented here.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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