Expert opinions on benefit-risk profile and clinical use of brolucizumab

Nicholas Fung[1], *FHKAM, FCOphHK, MRCS, MBChB; Danny Ng*[2], *FRCSEd, FCOphthHK; Ian Wong*[3], *FRCOphth, MD; Raymond Wong*[4], *FHKAM, MRCSEd; Pui Pui Yip*[5], *FHKAM, FCOphHK; Alvin KH Kwok*[3], *MD, PhD, FHKAM, FRCOphth, FCOphth, FCSHK, FRCSEd, PDip Epidemiology and Biostatistics, MBBS; Wai Ching Lam*[1], *MD, FRCSC; Timothy YY Lai*[2], *MD, FRCOphth; Ramin Khoramnia*[6], *MD, FEBO*

[1]*Department of Ophthalmology, The University of Hong Kong, Hong Kong SAR, China*
[2]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China*
[3]*Hong Kong Sanatorium and Hospital, Hong Kong SAR, China*
[4]*C-MER Dennis Lam and Partners Eye Center, Hong Kong SAR, China*
[5]*Champion Eye and Refractive Surgery Centre, Hong Kong SAR, China*
[6]*University Eye Clinic, University Hospital Heidelberg, Germany*

Correspondence and reprint requests:
Dr Timothy YY Lai, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China. Email: tyylai@cuhk.edu.hk

Abstract

Brolucizumab is a next-generation anti–vascular endothelial growth factor (VEGF) agent for the treatment of neovascular age-related macular degeneration. It is highly potent and thus appropriate for those unresponsive to other anti-VEGF agents and those undertreated owing to the low adherence or the heavy burden of repeated injections. An expert panel of 10 retina specialists from Hong Kong and Germany convened in February 2021 to discuss the benefit-risk profile and clinical use of brolucizumab. Evidence suggests that brolucizumab provides comparable visual outcomes to aflibercept at a more relaxed injection schedule. Brolucizumab is superior to aflibercept in resolving intraretinal and subretinal fluids and decreasing disease activity. Brolucizumab is suitable for patients unresponsive to other anti-VEGF agents, especially for those with persistent intraretinal and subretinal fluids or disease activity. Injection intervals of brolucizumab can be extended to 8 to 12 weeks. However, brolucizumab has higher risk of adverse events such as intraocular inflammation, retinal vasculitis, and retinal occlusion, compared with aflibercept. Thus, regular monitoring for signs of intraocular inflammation and prompt management are important before and during treatment.

Key words: Brolucizumab; Injections, intraocular; Macular degeneration; Vascular endothelial growth factor A

Introduction

Brolucizumab is a next-generation drug for neovascular age-related macular degeneration (nAMD).[1] The general treatment goals are to maintain and improve visual acuity (VA), reduce vascular leakage, and induce regression of neovascularization.[2] Intravitreal injections of anti–vascular endothelial growth factor (anti-VEGF) agents (aflibercept, bevacizumab, ranibizumab, and brolucizumab) to inhibit abnormal blood vessel development are the most effective approach (**Table 1**).[2-5] Anti-VEGF agents are effective as long as strict and frequent regimens are followed, but in clinical settings undertreatment is the norm.[6-10] Over 70% of patients are undertreated during their first year,[11] and about 60% of patients are non-adherent after 2 years.[12] The low adherence may be partly due to the burden of repeated injections. Anti-VEGF agents that can be administered at less frequent intervals are needed.[13]

Brolucizumab (Beovu, Novartis, Basel, Switzerland)[14] is a single-chain antibody fragment comprising a scaffold attached to an anti-VEGF-A antibody that inhibits all isoforms of VEGF-A at a 2:1 ratio. It binds to VEGF-A isoforms and prevents their interaction with receptors VEGFR1 and VEGFR2, thereby suppressing endothelial cell proliferation, neovascularization, and vascular permeability.[15-20] The small molecular size of brolucizumab enables large molar dosages per injection, better penetration into ocular tissue, and greater fluid resolution.[1,17,18] These benefits result in longer injection intervals (up to every 12 weeks).[14] Furthermore, brolucizumab is easy to tolerate, as single-chain antibody fragments generally have high

stability and solubility *in vivo*.[15] Trials in animal models suggest rapid systemic clearance and low exposure.[17,18,21]

In February 2021, an expert panel comprising 10 retina specialists from public, private, and academic institutions convened to discuss evidence on the use of brolucizumab in clinical practice in Hong Kong. This study summarized the expert opinions on the benefit-risk profile and clinical use of brolucizumab.

Benefit-risk profile

In the HAWK and HARRIER phase III trials, treatment-naïve patients aged >50 years were randomly assigned to receive brolucizumab or aflibercept (HAWK: 3 mg brolucizumab [n=358], 6 mg brolucizumab [n=360], 2 mg aflibercept [n=360]; HARRIER: 6 mg brolucizumab [n=370], 2 mg aflibercept [n=369]) and were followed up for 96 weeks.[22,23] Both trials began with a loading phase of injections at weeks 0, 4, and 8, followed by 8 weeks with no injection. The 16-week loading phase was identical between arms. Then, brolucizumab was administered every 12 weeks (or every 8 weeks in patients with disease activity), whereas aflibercept was administered every 8 weeks. Patients were assessed at weeks 16, 20, 32, and 44 for best-corrected visual acuity (BCVA), disease activity, intraretinal fluid (IRF), subretinal fluid (SRF), sub-retinal pigment epithelium (sub-RPE) fluid, and central subfield thickness (CST). Patients in the HARRIER trial were additionally assessed at weeks 28 and 40. Non-inferiority of brolucizumab against aflibercept was determined by the BCVA change from baseline to week 48, whereas safety was determined by the incidence of adverse events.

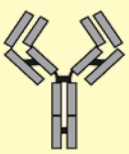
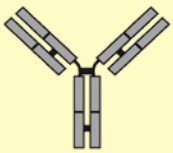
Benefits

In the HAWK and HARRIER trials, brolucizumab achieved comparable BCVA results to aflibercept despite having longer intervals (**Table 2**).[22,23] Brolucizumab was superior to aflibercept in controlling disease activity and IRF/SRF. Compared with 2 mg aflibercept, 6 mg brolucizumab resulted in about 36% less disease activity at 16 weeks after first dose, and 30% to 50% less IRF/SRF and sub-RPE fluid. Brolucizumab resulted in stronger and more consistent reduction in CST than aflibercept, with better improvement in the morphology of the macula.

In a study that pooled data from the HAWK and HARRIER trials and presented at the European Society of Retina Specialists 2020 Congress, brolucizumab resulted in quicker resolution of IRF/SRF than aflibercept, with lower incidence of persistent IRF/SRF over the first 12 weeks (12.5% vs 20.4%).[24] In patients with early persistent IRF/SRF, VA improvement was greater after brolucizumab treatment, with 8%, 48%, and 59% more patients achieving BCVA gain of ≥15 letters at 16, 48, and 96 weeks, respectively.

Retrospective reviews and case studies confirm brolucizumab's effectiveness at suppressing disease activity (in terms of reduction in CST, fluid compartments, and large pigment epithelial detachments, and improvement in VA outcomes) in the short-term, especially for patients unresponsive to other anti-VEGF agents.[25-30] In the BRAILLE chart review of 20 treatment-naïve patients and 74 recalcitrant patients who received a mean of 1.36 injections of brolucizumab and were followed up for 5 to 30 weeks, those recalcitrant patients who switched to brolucizumab had significant improvement in BCVA from 0.91 logMAR at baseline to 0.73 logMAR at final checkup, whereas all patients had an average reduction in CST of >100 μm, and >80% of treated eyes showed reduction or complete resolution of SRF, IRF, and pigment epithelial detachments.[27] In the REBA study of 23 treatment-naïve patients and 55 recalcitrant patients who switched to brolucizumab and were followed up for >9 months, >70% of treatment-naïve eyes had complete resolution of IRF/SRF by the end of the loading phase, whereas all recalcitrant patients who switched to brolucizumab had complete resolution of disease activity by their third brolucizumab injection.[29] Both groups of patients showed a gain of an average of 10 ETDRS (Early Treatment Diabetic Retinopathy Study) letters and a reduction of CST of >150 μm.

Table 1. Comparison of anti–vascular endothelial growth factor agents[16]

	Aflibercept	Bevacizumab	Ranibizumab	Brolucizumab
Molecular structure	VEGFR1/2-Fc fusion protein 	IgGI antibody 	Antigen-binding fragment 	Single-chain antibody fragment 
Molecular weight, kDa	97-115	~149	~48	26
Clinical dose, mg	2.00	1.25	0.30-0.50	6.00
Equivalent molar dose (to aflibercept)	1.0	0.4-0.5	0.5-0.6	11.2-13.3
Injection interval	Every 8 weeks	Every 4 weeks	Every 4 weeks	Every 8 to 12 weeks

Risks

In the HAWK and HARRIER trials, over half of the patients had adverse events such as conjunctival hemorrhage, cataracts, vitreous floaters, and VA reduction, and the rate was comparable in the brolucizumab and aflibercept arms (**Table 3**).[22,23] In the pooled brolucizumab group, nine patients had suspected endophthalmitis.[1] Of them, three were negative and two were positive for *Staphylococcus* or *Streptococcus mitis*, and the others were not tested or uninterpretable.

Brolucizumab is associated with greater risks of intraocular inflammation (IOI) than aflibercept.[22,23] According to an independent safety review committee, brolucizumab carries risks of severe vision loss secondary to retinal vasculitis or retinal artery/vascular occlusion, which tend to occur in the presence of IOI.[31,32] Thus, the consensus is to discontinue brolucizumab in any case of IOI.[31-34] Adverse events tend to develop within the first three injections of brolucizumab and after 3 weeks of the preceding injection, but the time from first injection to first IOI-related adverse event can

Table 2. Clinical outcomes of the HAWK and HARRIER phase III clinical trials at 16, 48, and 96 weeks[22,23]

	HAWK trial			HARRIER trial		
	6 mg brolucizumab (n=360)*	2 mg aflibercept (n=360)*	p Value	6 mg brolucizumab (n=370)*	2 mg aflibercept (n=369)*	p Value
Change in best-corrected visual acuity, No. of ETDRS letters						
Week 48	6.6±0.71	6.8±0.71	<0.001	6.9±0.61	7.6±0.61	<0.001
Week 96	5.9±0.78	5.3±0.78	-	6.1±0.73	6.6±0.73	-
Disease activity						
Week 16	24.0	34.5	0.001	22.7	32.2	0.001
Presentation of intraretinal/subretinal fluid						
Week 16	33.9	52.2	0.001	29.4	45.1	<0.001
Week 48	31.2	44.6	<0.001	25.8	43.9	<0.001
Week 96	24.0	37.0	-	24.0	39.0	-
Presentation of sub-retinal pigment epithelium fluid						
Week 48	13.5	21.6	0.004	12.9	22.0	<0.001
Week 96	11.0	15.0	0.121	17.0	22.0	0.037
Change in central subfield thickness, μm						
Week 16	-161.4	-133.6	<0.001	-174.4	-134.2	<0.001
Week 48	-172.8	-143.7	0.001	-193.8	-143.9	<0.001
Week 96	-174.8	-148.7	0.012	-197.7	-155.1	<0.001

** Data are presented as least squared mean±standard error, least squared mean, or % of eyes*

Table 3. Incidences of adverse events reported by the HAWK and HARRIER phase III clinical trials and an independent safety review committee[22,23,31,32]

Adverse event	HAWK trial		HARRIER trial		Safety review committee	
	6 mg brolucizumab (n=360)	2 mg aflibercept (n=360)	6 mg brolucizumab (n=370)	2 mg aflibercept (n=369)	Brolucizumab (n=1088)	Aflibercept (n=729)
	No. (%) of patients or % of patients					
Ocular adverse event at 96 weeks	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)	-	-
Serious ocular adverse event at 96 weeks	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)	-	-
Intraocular inflammation	17 (4.7)	2 (0.6)	3 (0.8)	4 (1.1)	50 (4.6)	8 (1.1)
Retinal vasculitis	-	-	-	-	36 (3.3)	-
Retinal artery and vascular occlusion	4 (1.1)	0 (0.0)	2 (0.5)	1 (0.3)	23 (2.1)	-
Endophthalmitis	4 (1.1)	0 (0.0)	1 (0.3)	1 (0.3)	9 (<0.1)	-
Loss of ≥15 ETDRS letters at 96 weeks	8.1	7.4	7.1	7.5	7.4 (at 48 weeks)	7.7 (at 48 weeks)

be up to 18 months.[35] The mechanism of brolucizumab-related adverse events may be associated with a delayed hypersensitivity response, impurities in the serum, or excessive VEGF inhibition.[36,37]

Intraocular inflammation

The safety review committee identified 50 definite or probable cases of IOI in all brolucizumab-treated eyes (n=1088) in the HAWK and HARRIER trials, compared with eight cases in the aflibercept arms (**Table 3**).[31] IOI tends to occur early in treatment, with about 50% and 80% occurring within 3 and 12 months, respectively; earlier occurrence is associated with greater risk of vision loss.[1,31,32,35] According to medical claim data in the IRIS Registry and Komodo study, the incidence of IOI within 6 months of the first brolucizumab injection was 2.4%, with prior IOI or retinal occlusion being a risk factor.[38] Most IOI cases in the HAWK and HARRIER trials were mild to moderate and were resolved without sequelae.[1,35] Most severe IOI cases did not result in diminished VA outcomes; of 49 patients with severe IOI, only 14 had loss of BCVA, whereas 23 had improved and 12 had stable BCVA.[1]

IOI may precede retinal vasculitis or retinal occlusion by 16 to 171 days.[35] Uveitis, iritis, vitritis, and iridocyclitis are the most common initial presentations of IOI before retinal vasculitis or retinal occlusion.[35] Signs of IOI include inflammatory cells in anterior and/or posterior segments, vitreous cells or opacities, non-granulomatous keratic precipitates, conjunctival injection, Descemet's membrane, and corneal edema.[35]

The incidence of IOI appeared to be higher in Japanese patients.[39,40] According to the Japan AMD Research Consortium study of 127 eyes treated with brolucizumab, the rate of IOI during the first 6 months was notably high at 9% to 10%,[39] which was nevertheless lower than the 13% reported by the safety review committee for Japanese patients in the HAWK trial. In a post-hoc analysis of Japanese patients with polypoidal choroidal vasculopathy in the HAWK trial, the rate of IOI was higher in brolucizumab users than aflibercept users (15% vs 0%), but the sample size was too small to perform post-hoc statistical analysis.[40] Ophthalmologists should be aware that Japanese populations may be at greater risk of IOI, but the evidence remains inconclusive.

Retinal vasculitis, retinal occlusion, and vision loss

Of the 50 eyes with IOI identified by the safety review committee, 36 involved retinal vasculitis and 23 involved retinal vasculitis and retinal occlusion (**Table 3**).[31,32] Nonetheless, the overall risk of moderate or severe vision loss was <1%, which is similar to that for aflibercept. For all vision loss cases, brolucizumab was associated with a 7.4% risk of vision loss within 2 years, compared with 7.7% for aflibercept. Most vision loss cases were caused by the degenerative nature of nAMD and were not drug-related.[1]

Records for adverse events associated with brolucizumab are submitted by practitioners worldwide to the website: https://www.brolucizumab.info/. From October 2019 to September 2021, for every 10,000 injections, there were 5.4 cases of retinal vasculitis, 3.3 cases of retinal occlusion, and 7.0 cases of both (15.7 cases overall), of them 4.9 cases were severe vision loss.

Recommendations

Brolucizumab is comparable with aflibercept in terms of VA outcomes but has a more relaxed treatment schedule that may facilitate adherence. Brolucizumab achieves better outcome in terms of resolving fluids, controlling disease activity, and improving macula morphology. Brolucizumab-associated adverse events are rare. Nevertheless, patients should be regularly assessed for IOI signs after administering brolucizumab, as onset may be nonspecific and may develop weeks after injection. Early diagnosis is important for timely intervention, treatment, and monitoring. Brolucizumab is contraindicated when IOI is suspected.[35] Measures to reduce risk are the same as those for other anti-VEGF agents. It is important to avoid injecting any anti-VEGF agent into an inflamed eye. Ophthalmologists should arrange the times of assessment and injection close to each other and follow up on any reports of suspicious symptoms. A management plan for the clinical use of brolucizumab is shown in the **Figure**.

Patient selection

Brolucizumab can be used in both treatment-naive patients and patients with ongoing anti-VEGF therapy. Currently, brolucizumab is mostly used in patients with ongoing anti-VEGF therapy. It is advisable to keep using the existing agents if effective; there is no need to switch to brolucizumab if the injection schedule can be extended to at least every 8 weeks. Brolucizumab should be avoided in patients with a history of IOI or retinal occlusion in the preceding 12 months. Brolucizumab can be considered in treatment-naïve patients with persistent SRF and sub-RPE fluid (eg, polypoidal choroidal vasculopathy). Brolucizumab can also be considered in patients with difficulty controlling disease activity or improving macula morphology and in patients struggling to extend treatment interval beyond 4 to 6 weeks.[22,23] Brolucizumab is appropriate in patients unresponsive to other anti-VEGF agents including those with polypoidal choroidal vasculopathy or pigment epithelial detachments.[25,40] Guidelines are helpful to avoid selecting patients at risk of adverse events and to provide treatment approaches.[33,34] Screening patients for IOI risks may help alleviate concerns.

Monitoring

Pre-existing IOI and signs of inflammation should be ruled out with a dilated-pupil fundus examination before the loading injection. When switching to brolucizumab, patients should be closely monitored for any manifestation of drug-associated IOI during the initial 6 months and even 18 months, as IOI can develop up to 18 months from the first injection.[35] Complete ophthalmic examination with

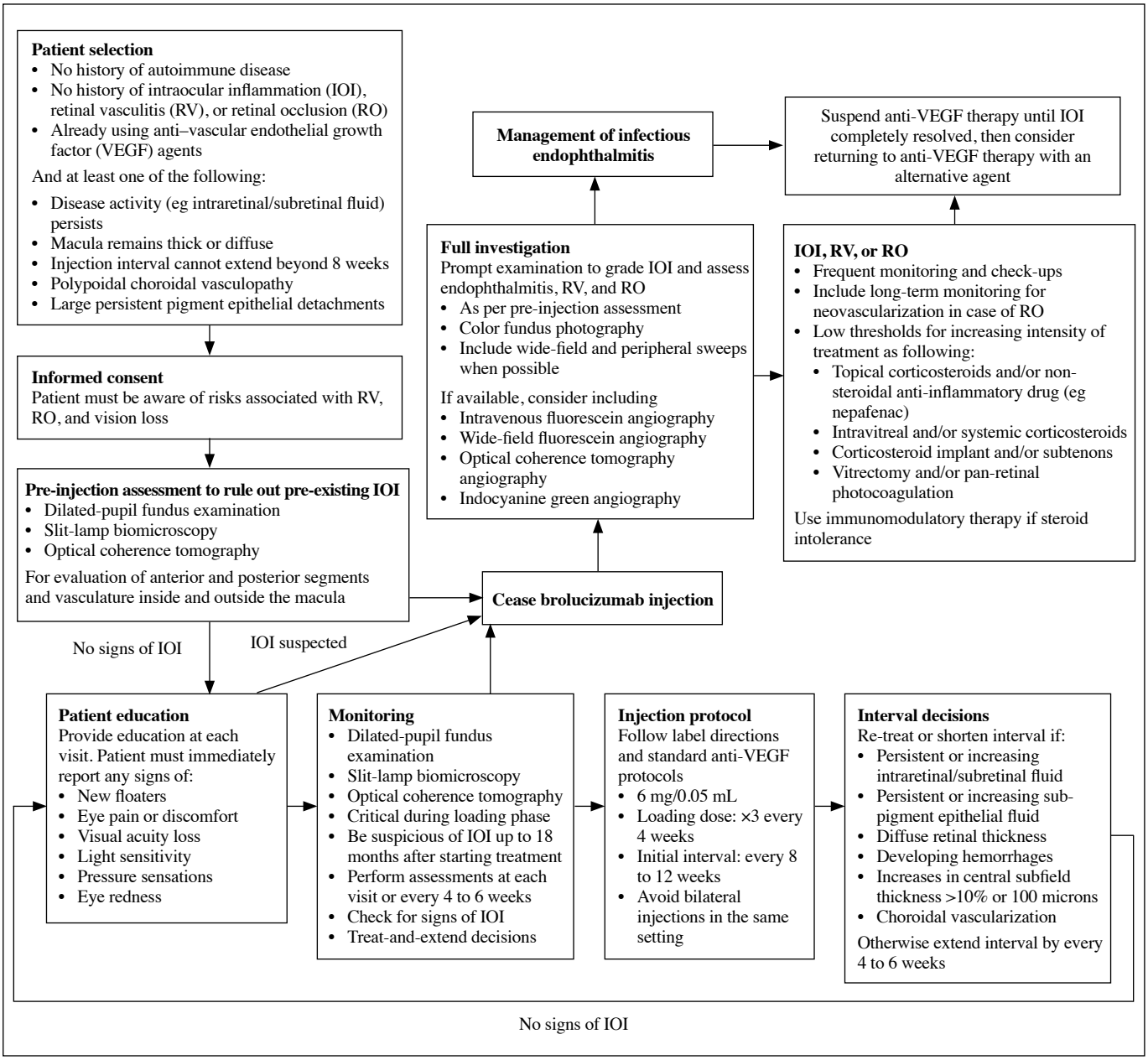


Figure. Proposed management plan for clinical use of brolucizumab[33-35]

slit-lamp biomicroscopy, dilated fundoscopy, and optical coherence tomography should be performed at every visit before injection or at regular intervals of 4 to 6 weeks.[35] Signs of IOI, retinal vasculitis, and retinal occlusion at any stage should be managed with prompt and intensive treatment.[33,34] Patients must be educated about symptoms such as floaters, pain, pressure sensations, light sensitivity, and decreased VA to be reported to physicians.[34] Education must be provided at each visit, and immediate reporting must be stressed. Any reports of suspicious symptoms should be examined immediately, and brolucizumab should be halted at any sign of IOI. Optical coherence tomography can be used to monitor disease activity and inform decisions on injection intervals. An injection interval of 12 to 16 weeks should be targeted, although stability at every 8 weeks is acceptable. Decision to extend interval should be supported by the absence of signs of recurring disease activity.

Diagnosis and treatment of intraocular inflammation, retinal vasculitis, and retinal occlusion

Guidelines for diagnosis and treatment of adverse events have been reported.[33,34] Differential diagnosis of infectious endophthalmitis must be ruled out, as it requires a different treatment course (intravitreal antibiotics). Infectious endophthalmitis typically has a more acute onset of symptoms such as hypopyon arising within 1 week of injection, compared with subacute symptoms that tend to arise about 3 weeks after injection and lack hypopyon. Patients should

be evaluated for underlying systemic or infectious diseases that may cause IOI such as giant cell arteritis and collagen vascular diseases. Optical coherence tomography and wide-field or peripheral-field fluorescein angiography should be used for diagnosing. The diagnosis of retinal vasculitis should be confirmed by evaluation of vessel involvement. Treatment regimen should follow a gradient of intensive corticosteroids based on the severity of IOI and/or vascular involvement. Immunomodulating therapy, vitrectomy, and pan-retinal photocoagulation are alternative treatment options, especially for steroid-intolerant patients. If there is no vascular involvement and the IOI is mild, intensive topical corticosteroids can be used. Close monitoring and gradual tapering of dosage can be considered if conditions improve. Patients who fail to respond or worsen should be offered systemic and/or intravitreal corticosteroids. For retinal vasculitis, retinal occlusion, and moderate-to-severe IOI, immediate systemic and intravitreal corticosteroids supplemented with topical corticosteroids should be used. Other adjunctive therapies include corticosteroid implants and/or subtenon steroid injections.

Conclusion

IRF and SRF are pathological features of nAMD, and their resolution is the key to achieve good BCVA outcomes and to extend treatment intervals. However, unresolved IRF/SRF and non-adherence to the treatment schedule may result in vision loss. Moreover, the high frequency of injections burdens healthcare providers and patients. Brolucizumab (6 mg) is effective to improve vision, resolve IRF/SRF, and extend treatment intervals to ≥12 weeks. Brolucizumab has a well-tolerated safety profile. Its rate of vision loss is comparable to that of aflibercept. A safe and effective management plan should involve proper patient selection, regular monitoring (especially in the first 18 months of therapy), and prompt intensive treatment of adverse events.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

NF is a principal investigator in partnerships with Alcon, Allergan, Bayer, Chengdu Kanghong Pharm, Novartis, and Roche, and has received honoraria and research grant from them. RW has received honoraria from Bayer, Novartis, and Roche. WCL has received research grant and honoraria from Alcon and Bayer and honoraria from Allergan and Novartis. TYYL has received honoraria and grant support from Allergan, Bayer, Boehringer Ingelheim, Chengdu Kanghong Biotech, Novartis, and Roche. RK has received grant and financial support from Alimera, Allergan, Bayer, Chengdu Kanghong, Novartis, and Roche. All other authors have received honoraria from Novartis. As editors of the journal, AKHK, WCL, and TYYL were not involved in the peer review process.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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