Expert opinion on Brolucizumab-related intraocular inflammation and proposed workflow

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Background

Brolucizumab is the latest addition to the anti-vascular endothelial growth factor (VEGF) treatment armamentarium indicated for neovascular age-related macular degeneration (nAMD) and has been commercially available in Malaysia since October 2020.

In the HAWK and HARRIER trials, brolucizumab 6mg demonstrated non-inferior visual acuity gains and superior anatomic outcomes versus aflibercept 2mg at week 48.[1,2] Approximately 50% of brolucizumab-treated eyes were prolonged to every 12 weeks injection intervals after the loading dose up to week 48[1]. The trial demonstrated that brolucizumab provides effective disease control with potential for reduced treatment burden.[1,2]

In terms of safety, a higher incidence of intraocular inflammation (IOI) events was associated with brolucizumab 6mg compared to aflibercept 2mg.[1,2,3] The Novartis-commissioned external Safety Review Committee (SRC) conducted a post hoc unmasked analysis of images from cases in HAWK and HARRIER reported as having IOI by investigators. Of the 1088 study eyes treated with brolucizumab in HAWK and HARRIER, the SRC reported IOI of any form in 50 eyes (4.6%). Of the 50 eyes, 36 eyes (3.3%) had concomitant retinal vasculitis, of which 23 (2.1%) had concomitant retinal vascular occlusion.[4] The overall rate of moderate to severe vision loss (≥ 15 ETDRS letters) in the HAWK & HARRIER trial was comparable between brolucizumab (7.4%) and aflibercept (7.7%) despite the higher incidence of these IOI events.[4]

While further examination of the possible root cause, patient characterization as well as mitigation and management strategies for these adverse events continue, it is important that recommendations are developed to inform and guide ophthalmologist should these IOI events occur after treatment with brolucizumab and other anti-VEGFs. A working group comprising 7 medical retina and uveitis specialists reviewed the available scientific literature and local adverse events reports to deliberate on the management of these IOI events. This article presents the guidance on patient selection, evaluation as well as potential treatment strategies for these IOI events. It is important to note that these recommendations are primarily based on the authors' expert opinion and should be considered as a guidance rather than a formal protocol or guideline. The working group also acknowledges that practice, facilities, and available therapies vary between regions and centers. Thus, clinicians should choose the most appropriate from what is available to them.

Patient profile and practice

Data from IRIS registry and Komodo database of patients receiving brolucizumab therapy for nAMD revealed that eyes with a history of IOI or retinal vascular occlusion were at greater risk of developing brolucizumab-related IOI events.[5,6] This working group is of the view that Brolucizumab should be avoided in patients with underlying uveitis or IOI. There was also a slight female preponderance for IOI but this is not viewed as a contraindication.[5,6] Several anecdotal reports suggest an association of IOI events with underlying systemic autoimmune disease; however this remains inconclusive.

Although the HAWK & HARRIER trials demonstrated the efficacy and safety of brolucizumab in treatment-naive patients, it is the opinion of this working group to be cautious when using brolucizumab as a first-line agent. There is increasing real world publications demonstrating the efficacy and safety of brolucizumab in patients switched from other anti-VEGFs. In patients exhibiting suboptimal response or resistance to existing anti-VEGF, brolucizumab can be recommended as a treatment option.

This working group also cautions against the practice of bilateral injections. Clinicians are reminded that the clinical benefits and risks of brolucizumab apply to each treated eye and each injection.[7] In patients with only one seeing eye or a precious eye, the use of brolucizumab should take into consideration previous response to other anti-VEGFs and should be used cautiously.

All patients planned for brolucizumab injections should be counseled on the benefits and risks of treatment with informed consent in place. It is important to ensure the patient is aware of the symptoms of IOI events and understands the urgency of prompt presentation for treatment. The treating center's personnel responsible for receiving patients' calls must also be informed to avoid delayed management.

Evaluation of suspected IOI & treatment strategies

During each patient visit, clinicians must conduct a dilated fundus examination for evidence of IOI. As some patients with IOI may be asymptomatic, this is especially important to detect mild IOI. Clinicians are reminded not to ignore mild inflammation. Colour fundus photography, preferably wide-field, is recommended to assist with the detection of IOI.

As the clinical manifestations of IOI may overlap with infectious endophthalmitis, it is important to differentiate between the two early to ensure appropriate management. Infectious endophthalmitis typically develops within 1 week of intravitreal injection whereas IOI events associated with brolucizumab typically presents within 1 to 3 weeks of intravitreal injection.

If in doubt, a steroid challenge may be helpful. The steroid challenge involves instilling topical corticosteroids (i.e. dexamethasone 0.1% or prednisolone acetate 1%) at frequent intervals with regular review. Clinicians may instill topical corticosteroids every 15 minute for 2 hours then review the patient. This can be followed by instillation every 30 minutes for 2 hours and review followed by hourly instillation for 2 hours and so on until the decision is

made. During the steroid challenge, IOI events should begin to improve whereas infectious endophthalmitis would worsen. Features that suggest worsening of the clinical condition and likely indicate infectious endophthalmitis include increasing pain, lid swelling, increasing fibrin, flare and cells which may become less mobile as well as the development or worsening of a hypopyon.

Once a diagnosis of IOI is confirmed, clinicians should appropriately classify the IOI according to its severity and location – anterior uveitis, intermediate and posterior uveitis, retinal vasculitis or retinal vascular occlusive events. As retinal vasculitis and retinal vascular occlusive events have been reported to occur in the presence of IOI, it is important to proactively seek clinical features that would indicate these conditions.[4,8,9] If there is evidence of posterior segment involvement, fundus fluorescein angiography (FFA), with peripheral sweeps if available, is recommended to better identify retinal vasculitis and vascular occlusion. Upon diagnosis of IOI, brolucizumab therapy should be discontinued. Clinicians are reminded that brolucizumab is contraindicated in active IOI.[3] Depending on the severity, clinicians may initiate corticosteroids to treat the inflammation and taper therapy as inflammation improves.

Anterior uveitis

Patients with anterior uveitis may present with redness, floaters and pain for more than 2 days' duration. Reduced vision and photophobia may also be reported by some patients. Examination findings include ciliary injection, cells in the anterior chamber and/ or anterior vitreous as well as keratic precipitates. Optical coherence tomography (OCT) may reveal hyperreflective dots in the vitreous.

Anterior uveitis should be managed with early intensive topical corticosteroids. Patients should be closely monitored and may be seen within 24-48 hours to evaluate response and assess need for therapy escalation. Close monitoring should continue and corticosteroid therapy tapered over a 4-6 week period.

Intermediate and posterior uveitis

Patients with intermediate or posterior uveitis would typically report similar symptoms as anterior uveitis. Posterior involvement may be ascertained by examination findings that include a predominance of vitreous cells, vitritis or haze. FFA, if available, may be particularly useful when inflammation obscures retinal details and would help visualize the retinal vasculature to exclude vasculitis and vascular occlusion. FFA may reveal vascular leakage and/ or optic nerve head leakage or hyperfluorescence.

With posterior involvement, oral corticosteroids at 0.5mg/kg/day should be initiated. Clinicians may consider regional steroids or intravitreal (IVT) steroid implant while intensive topical corticosteroids can be given as an adjunct. Patients should be monitored to assess need for escalation of therapy and treatment should be tapered over a 4-6 week period.

Retinal vasculitis

In addition to features of IOI, retinal vasculitis may present with scotoma. Examination findings include vascular sheathing and may involve arteries and/or veins and can be central and/or peripheral. FFA, if available, would allow for a thorough assessment and typical findings include delayed vascular filling, hyperfluorescence and staining of the vessel wall, and late fluorescein leakage from the optic nerve head.

Patients should be initiated on oral corticosteroids at 0.5-1mg/kg/day and clinicians may consider intravenous (IV) administration (ie. methylprednisolone) if the disease is severe or sight-threatening. Clinicians may also consider adjunctive use of intensive topical corticosteroids or supplement with regional corticosteroids or IVT corticosteroid implant. It is important to carefully monitor these patients to identify occlusive complications and medication may be tapered over a 4-6 week period according to patient response.

Retinal vascular occlusion

Retinal vascular occlusion should be considered an ocular emergency. Patients may present with sudden vision loss which may be central or peripheral depending upon the area of vessel involvement. Features of arterial occlusions are typically cotton wool spots, retinal whitening, cherry red spot if acute, box-carring, optic disc oedema and macular oedema. Signs of venous occlusions include intraretinal hemorrhages and irregular venous caliber. Apart from posterior vitreous cells, OCT may also reveal evidence of macular thickening or oedema. FFA findings include vascular leakage, absence of vascular filling, capillary fall out as well as hyperfluorescence of the optic nerve head. ICGA may demonstrate evidence of choroidal ischemia such as patchy choroidal filling defects.

Treatment includes urgent IV corticosteroids followed by oral corticosteroids at 1mg/kg/day. Clinicians may consider supplementing with regional corticosteroids or IVT steroid implant and giving topical corticosteroids as an adjunct.

Close monitoring is required to evaluate response and clinicians should consider referral to a uveitis specialist if inflammation persists despite treatment. Persistent and severe cases may be evaluated for pars planar vitrectomy. Early panretinal photocoagulation should be offered if neovascularization develops and considered prophylactically in extensive peripheral ischemia before new vessels develop.

Additional considerations and referral

Referral to a uveitis specialist is recommended if in doubt or when IOI persists or worsens despite treatment. Resumption of anti-VEGF treatment would depend on nAMD disease activity and should ideally occur after resolution of the inflammatory event. At this time, the working group does not recommend reinitiating brolucizumab in patients who experience an IOI event.

Conclusions

The spectrum of IOI, retinal vasculitis or retinal vascular occlusion following intravitreal brolucizumab injection is uncommon yet can have serious consequences. These recommendations highlight the importance of early diagnosis, prompt and timely treatment of IOI. Intensive therapy and frequent monitoring is needed to minimize the risk of progression of these events. The proposed workflow is prepared to facilitate a consistent management approach in dealing with IOI following intravitreal brolucizumab injections in patients with neovascular age-related macular degeneration.

References:

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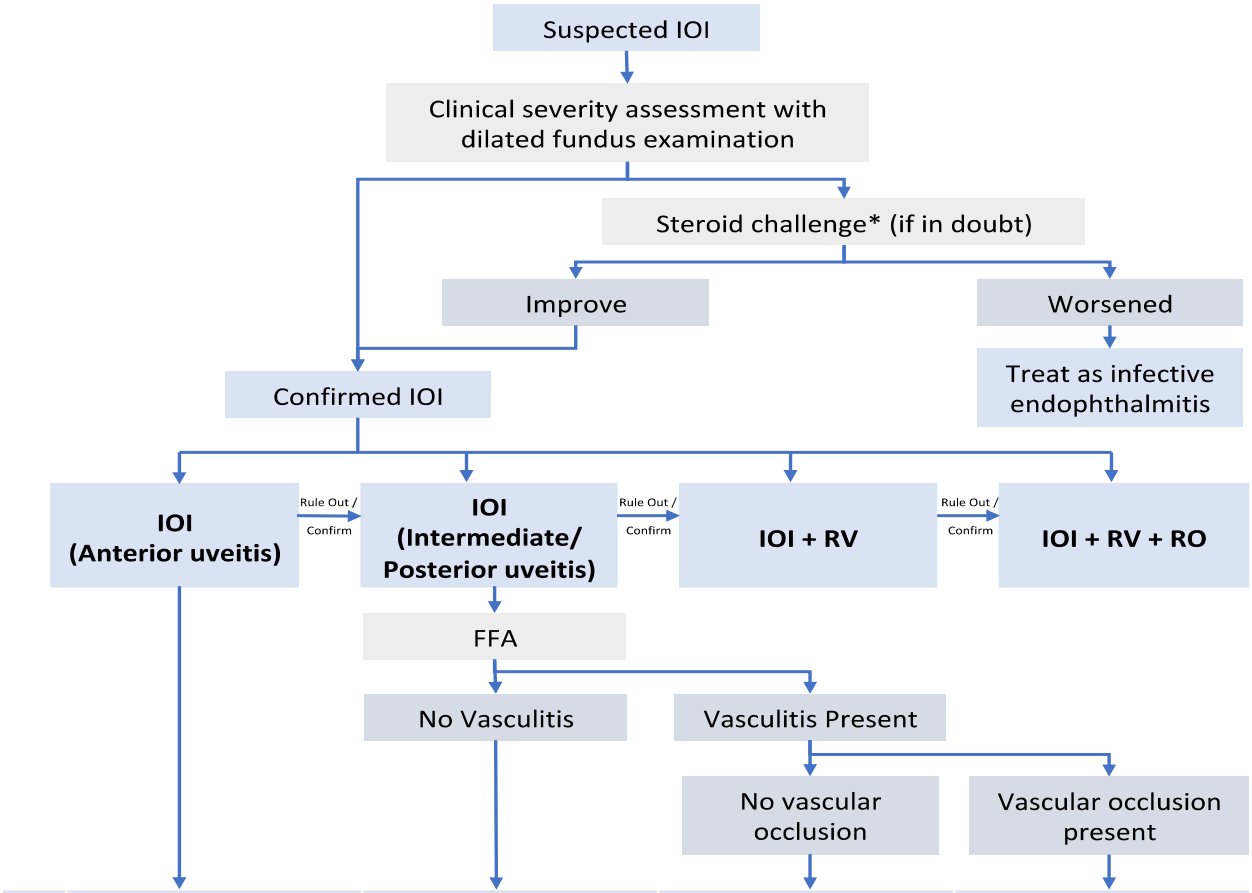
Disclaimer

The working group acknowledged that the mentioned brolucizumab-related IOI and its proposed management were correct at the time of writing of this paper.

Proposed Management for Intraocular Inflammation



	IOI (Anterior uveitis)	IOI (Intermediate/ Posterior uveitis)	IOI + RV	IOI + RV + RO
Treatment	• Early intensive topical steroids & • Close monitoring within 24-48 hrs to assess need for oral or regional steroids	• Systemic steroids (0.5mg/kg/day) • Consider regional steroids or IVT steroid implant • Intensive topical steroids (adjunct) • Close monitoring to assess need for intensification of steroid therapy	• Assess severity of RV • Systemic steroids (0.5-1mg/kg/day) • Consider IV steroids (ie.methylprednisolone) if severe or sight-threatening • Consider regional steroids or IVT steroid implant • Intensive topical steroids (adjunct)	• Ocular emergency • Urgent IV steroids (ie.methylprednisolone) followed by oral steroids - 1mg/kg/day • Consider regional steroids or IVT steroid implant • Intensive topical steroids (adjunct) • Consider PPV in persistent and severe cases
Follow up	• Close monitoring and tapering of medication over 4-6 weeks	• Close monitoring and tapering of medication over 4-6 weeks	• Close monitoring and tapering of medication over 4-6 weeks	• Close monitoring and tapering of medication over 4-6 weeks* • Early PRP if develop neovascularization
Discontinue brolucizumab				

*** Steroid challenge**

Instill topical steroids only (e.g. Maxidex/ Predforte):
- q15mins for 2H ----review;
- q30mins for 2H ----review;
- q1hourly --- review every 2h until decision made

Symptoms & Signs of worsening:
- increasing pain
- lid swelling
- increasing fibrin, flare & cells which may become less mobile
- hypopyon present or worsening

FFA, fundus fluorescein angiography; IOI, intraocular inflammation; IV, intravenous; IVT, intravitreal;
PPV, pars planar vitrectomy; PRP, panretinal photocoagulation; RV, retinal vasculitis; RO, retinal vascular occlusion

Figure1: Proposed workflow in managing Intraocular inflammation (IOI) following intravitreal Brolucizumab injection for neovascularization age-related macular degeneration patients