ORIGINAL ARTICLE

Consensus on managing center-involving diabetic macular edema in Hong Kong: perspective

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Abstract

Diabetic macular edema is a common cause of vision loss in the working-age population, and its prevalence is increasing in Asian countries. Managing diabetic macular edema encompasses effective control of systemic factors and intraocular treatment including anti-vascular endothelial growth factor therapy, corticosteroid implants, and laser photocoagulation. Based on several guidelines and the available evidence, we present consensus on managing diabetic macular edema in Hong Kong to ensure optimal anatomical and visual outcomes. Although anti-vascular endothelial growth factor agents are recommended first-line treatment for patients with diabetic macular edema experiencing vision loss; however, the frequent dosing regimen imposes great clinical and patient burden. Longer-acting anti-vascular endothelial growth factor agents are needed to allow for longer intervals between treatments. As demonstrated in the KITE and KESTREL studies, brolucizumab, an anti-vascular endothelial growth factor A agent, is associated with fewer cases of intraretinal or subretinal fluid than aflibercept, despite fewer injections. Similarly, faricimab, a bispecific antibody targeting both vascular endothelial growth factor A and angiopoietin-2, demonstrated comparable vision gains with longer treatment intervals and larger improvements in anatomical outcome in the YOSEMITE and RHINE trials. Early intensive anti-vascular endothelial growth factor therapy leads to greater improvements in visual acuity and anatomical outcomes. Patients who respond inadequately to anti-vascular endothelial growth factor therapy, as monitored by optical coherence tomography, should switch treatment modality.

Key words: Angiopoietin-2; Intravitreal injections; Laser therapy; Vascular endothelial growth factors; Visual acuity

Introduction

Diabetic macular edema (DME) may cause vision loss.[1] The prevalence of DME in Asian populations (despite being lower than in other populations) is expected to increase as the incidence of diabetes increases.[2] Effective systemic

control, managing comorbidities of diabetes, and ocular treatment are important in DME management.

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents are recommended first-line therapy for patients with center-involving DME,[3-6] but approaches to treatment posology and therapy selection differ.[1] Moreover, these treatments are costly and thus access may be limited for some patients who may in turn develop more advanced forms of the disease.[2]

Anti-VEGF agents (aflibercept, bevacizumab, and ranibizumab) can improve visual acuity in patients with DME.[7] However, these agents have limited potency and durability, necessitating frequent dosing regimens.[8] Patients receiving repeated intravitreal therapy (IVT) injections suffer a heavy medical burden, involving lengthy wait times for outpatient clinics and multiple appointments.[8] Further research into longer-acting anti-VEGF agents is warranted.

Brolucizumab and faricimab are comparably effective to aflibercept, potentially necessitating fewer injections and enabling longer intervals between treatments.[9,10] A group of experts reviewed the recent clinical and real-world data to reach a consensus on the role of current therapeutic agents in managing DME.

Methodology

Eight ophthalmologists from Hong Kong and one from Singapore convened in September 2022 to seek consensus on recommendations for managing DME in Hong Kong based on the published evidence and their clinical experience. Before the meeting, the experts reviewed the literature on diagnosing and managing DME. Three of the experts then developed recommendation statements, which were voted on and discussed at the meeting. Each proposed recommendation was voted on using a five-point Likert scale (accept completely, accept with some reservation, accept with major reservation, reject with reservation, reject completely).[11] No further changes were necessary if ≥80% voted 'accept completely' or 'accept with some reservation'. Recommendations with <80% acceptance threshold were revised and then voted again after the meeting. The wording and/or content of the rejected statements were adjusted (**Table 1**). The approved statements were the expert panel's consensus recommendations for managing DME in Hong Kong. A treatment algorithm relevant to Hong Kong's population was then proposed (**Figure 1**).

DME definition and treatment goals

Statement 1: DME is a multifactorial disease that may require inhibition of multiple pathways for optimal management

Chronic hyperglycemia activates several pathways that contribute to vascular and tissue damage in organs including the eye.[12] DME is a complex and multifactorial condition, characterized by the breakdown of the blood-retinal barrier, which allows fluid and serum macromolecules to accumulate in the intercellular space.[13]

The synergistic effects of several growth factors promote angiogenesis, hyperpermeability, and inflammation in diabetic retinopathy, suggesting that inhibiting a single pathway may not sufficiently control DME. Agents that inhibit pathways other than VEGF alone are needed.[14-18]

Statement 2: Systemic control is an essential treatment goal when managing DME

Poor control of diabetes comorbidities, including hypertension, renal impairment, and hyperlipidemia, may result in a poor prognosis of diabetic retinopathy. Controlling blood glucose levels, blood pressure, and cholesterol levels can slow or stop diabetic maculopathy from progressing.[19]

Statement 3: DME treatment should aim for the best visual outcome with edema improvement while minimizing the treatment burden

Statement 4: Regular optical coherence tomography (OCT) monitoring is recommended to assess treatment response

OCT is widely used to monitor DME and can be used to personalize DME treatment regimens.[20] OCTs can assess anatomical parameters such as macular thickness and the presence of hyperreflective foci or intraretinal and subretinal fluid, enabling identification of patients who can benefit from the treat-and-extend strategy to reduce their treatment burden.[21]

Statement 5: Anti-VEGF treatment is considered ineffective if reduction in central subfield thickness (CST) is <10% after at least three to six injections

Several studies evaluating anti-VEGFs for DME define a limited early response as a ≤10% reduction in CST after three to six injections. A post-hoc analysis of the VISTA and VIVID trials investigated patients with DME who had suboptimal responses at week 12 following 3 monthly aflibercept injections or one laser treatment.[22] Aflibercept significantly improved best-corrected visual acuity (BCVA) by week 100 relative to laser treatment in several eyes with DME.[22] In another study that applied the same indication for limited early response to anti-VEGF agents, aflibercept was superior to bevacizumab and ranibizumab in improving vision outcomes; all three anti-VEGF agents had comparable safety profiles.[23]

Statement 6: Switching therapy is an option for managing patients with refractory DME

Anti-VEGF agents prevent the activation of VEGF receptors on endothelial cells and thus stop vascular endothelial hyperplasia from developing, thereby counteracting DME pathogenesis.[24]

Current guidelines recommend monthly monitoring during the first 6 months of anti-VEGF treatment.[1,4] Monitoring should continue thereafter because worsening visual acuity

Table 1. Voting results on consensus statements on managing center-involving diabetic macular edema (DME) in Hong Kong

Statement	% of ophthalmologists (n=9)*				
	Accept completely	Accept with some reservation	Accept with major reservation	Reject with reservation	Reject completely
1: DME is a multifactorial disease that may require inhibition of multiple pathways for optimal management	100	-	-	-	-
2: Systemic control is an essential treatment goal when managing DME	100	-	-	-	-
3: DME treatment should aim for the best visual outcome with edema improvement while minimizing the treatment burden	100	-	-	-	-
4: Regular optical coherence tomography monitoring is recommended to assess treatment response	75	25	-	-	-
5: Anti-VEGF treatment is considered ineffective if reduction in central subfield thickness is <10% after at least three to six injections	75	25	-	-	-
6: Switching therapy is an option for managing patients with refractory DME	100	-	-	-	-
7: Anti-VEGF agents, with or without ANG-2 inhibition, are recommended first-line treatment for center-involving DME	87.5	12.5	-	-	-
8: A good safety profile should be considered when selecting a first-line intravitreal therapy	100	-	-	-	-
9: Intensive intravitreal therapy during the first year is important to maximize patients' visual improvement and minimize the number of injections in subsequent years	100	-	-	-	-
10: Fixed dose, treat-and-extend, or as-needed regimens may be considered for anti-VEGF agents after the loading dose, based on anatomical and functional assessments	100	-	-	-	-
11: Switching between intravitreal therapy agents could be beneficial for patients with refractory DME	100	-	-	-	-
12: Focal laser treatment is an option for patients with non-center-involving DME/ extrafoveal leaking microaneurysms	100	-	-	-	-
13: Steroid implants can be used as a first-line treatment for pseudophakic patients without a history of glaucoma	75	25	-	-	-
14: Focal laser and grid laser can be a treatment option with or without anti-VEGF therapy or other combination	87.5	12.5	-	-	-
15: Pars plana vitrectomy may be performed in patients with vitreomacular traction or epiretinal membrane	88	13	-	-	-

Abbreviations: ANG-2=angiopoietin-2; DME=diabetic macular edema; VEGF=vascular endothelial growth factor.

* *Consensus was defined as 80% of ophthalmologists selecting 'accept completely' or 'accept with some reservation'. Statements that did not achieve consensus are not included.*

(VA) and CST rebound are common.[1,4] Beyond the first year, intervals between treatments may gradually extend for patients with stable VA and CST.[1,4]

Although 33% to 45% of patients with DME achieve ≥3 lines of visual improvement after intensive anti-VEGF injections,[3-6] some patients do not respond sufficiently. Suboptimal responses can be attributed to other factors involved in DME's pathogenesis that have not been fully addressed, including the upregulated intraocular inflammation cascade.[25] Differences in VEGF gene expression may also be a contributing factor; thus, combining therapies or switching to an anti-VEGF agent with a different mechanism of action is recommended.[26]

Treatment selection: IVT injections (anti-VEGF and anti-VEGF/ANG-2)

Statement 7: Anti-VEGF agents, with or without ANG-2 inhibition, are recommended first-line treatment for center-involving DME

Aflibercept, ranibizumab, and bevacizumab have shown to improve VA after 2 years of treatment.[27] Aflibercept and ranibizumab are the preferred first-line therapies in patients with a baseline BCVA letter score of <69; the addition of off-label bevacizumab is recommended for those with a baseline BCVA of ≥69.[27] Asia-Pacific regional experts agreed on using anti-VEGF agents as the first-line treatment for center-involving DME with vision loss and using

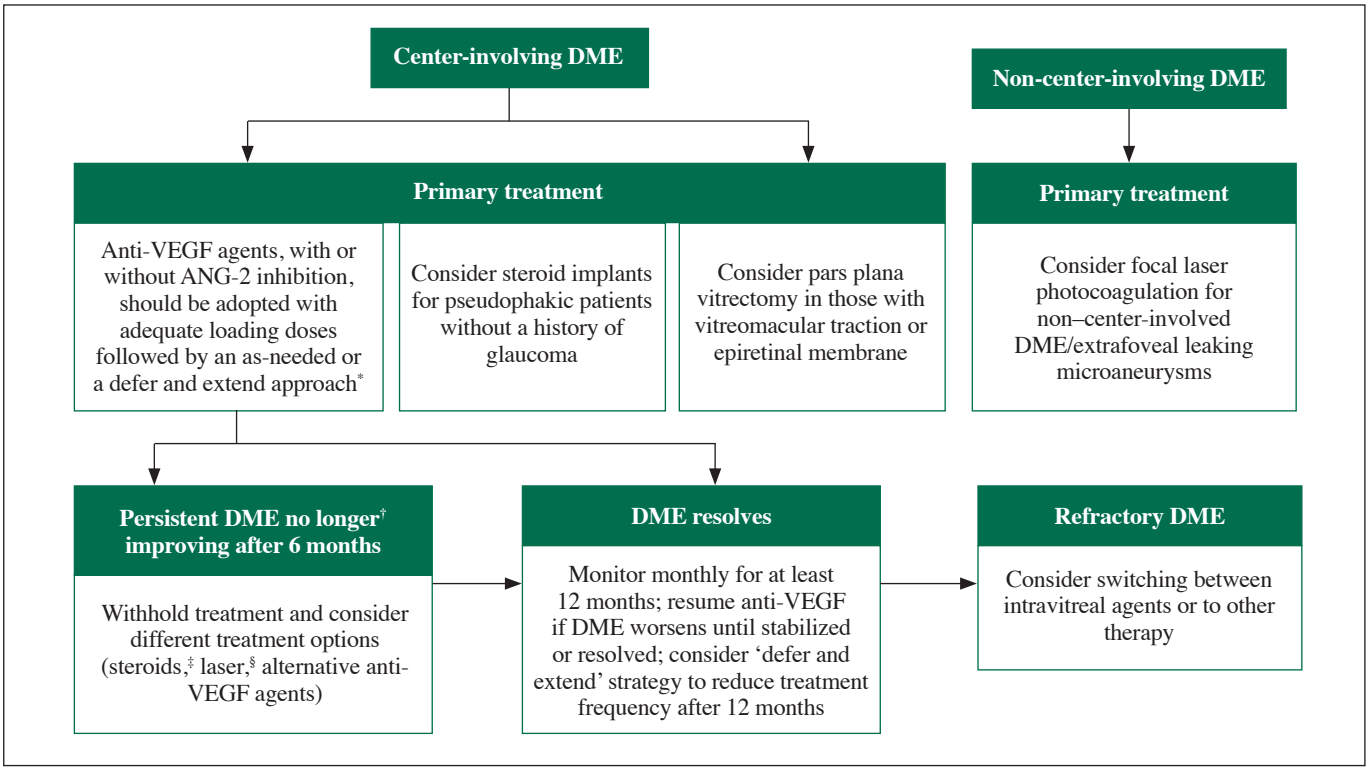

Figure. Suggested treatment algorithm for managing center-involving diabetic macular edema (DME) in Hong Kong

Abbreviations: ANG-2=angiopoietin-2; DME=diabetic macular edema; VEGF=vascular endothelial growth factor

* *An acceptable safety profile should be considered when selecting a first-line intravitreal. Fixed dose, treat-and-extend, or as-needed regimens may be considered for anti-VEGF agents after the loading dose, based on anatomical and functional assessments.*

† *An inadequate response to anti-VEGF treatment is defined as a CST reduction ≤10% after 3 to 6 injections.*

‡ *Steroids may be accompanied by cataract formation and increase in intraocular pressure.*

§ *Focal and grid laser photocoagulation have been associated with a significant long-term risk of vision loss.*

corticosteroids as a secondary treatment.[28] Nonetheless, guidelines on managing DME have not been established, although multiple trials have demonstrated the superiority of anti-VEGF therapy over laser therapy in improving BCVA.

In two randomized phase III trials (VIVID and VISTA), patients with DME received either aflibercept injections every 4 or 8 weeks (after 5 monthly injections) or macular laser photocoagulation therapy. Both regimens of aflibercept were superior to laser therapy in improving mean BCVA at week 148.[29] The efficacy of anti-VEGF agents was also demonstrated in the RISE and RIDE trials, which were randomized phase III sham injection–controlled trials investigating ranibizumab injection in patients with DME.[30] Significantly more patients receiving ranibizumab gained ≥15 letters in BCVA by 24 months.[30] Bevacizumab has shown to effectively treat patients with refractory and treatment-naïve DME, either as a monotherapy or in combination with triamcinolone acetonide or laser photocoagulation.[31-34]

KITE and KESTREL were randomized phase III clinical studies comparing brolucizumab and aflibercept for the treatment of DME.[35] A loading dose of five brolucizumab injections every 6 weeks for the first 24 weeks was followed by a maintenance dose every 8 or 12 weeks depending on disease activity until week 72 (KESTREL) or week 100 (KITE).[35] Despite involving fewer injections, brolucizumab met the primary endpoint (a mean change in BCVA non-inferior to aflibercept).[35] Occurrence of intraretinal fluid or subretinal fibrosis was fewer with brolucizumab than aflibercept.[35] Brolucizumab's safety profile at week 100 was consistent with published data from year 1.[35,36]

The ANG-2 pathway should be targeted for managing DME, as levels of ANG-2 are upregulated in many retinal diseases.[37,38] Faricimab is the first bispecific-antibody intraocular DME agent targeting both ANG-2 and VEGF-A. Simultaneous inhibition may stabilize blood vessels and reduce neovascularization, resulting in improved potency and durability against retinal diseases. Its large molecular size increases its half-life in the vitreous fluid. The modified inactive fragment crystallizable domain reduces systemic exposure and pro-inflammatory responses.[37] Hong Kong clinical experts believe that faricimab may be an effective first-line treatment for DME owing to its long-acting efficacy.

YOSEMITE and RHINE were double-blinded phase III trials in which patients with DME were randomized to receive injections of either faricimab (every 8 weeks or according to personalized treatment intervals) or aflibercept (every 8 weeks).[10] During the loading phase, patients in the faricimab group received injection every 4 weeks until they attained a CST of <325 μm or after week 12.[10] From week 12 onwards, dosing intervals could be maintained, extended, or reduced, depending on responses in CST and BCVA.[10] Over the 56-week treatment period, 62% of patients completed a full dosing cycle of every 12 weeks and maintained or extended to every 16 weeks.[10] The proportion of patients receiving faricimab every 16 weeks increased by 7.2% (YOSEMITE) and 13.5% (RHINE) between weeks 52 and 96.[10] Faricimab elicited greater reductions in CST than aflibercept during 2 years of treatment.[10] RHONE-X, a 4-year follow-up study of YOSEMITE and RHINE, is ongoing.[39] YOSEMITE and RHINE remain the only phase III studies comparing faricimab with aflibercept for the treatment of DME.[10] Additional comparative effectiveness trials in clinical and real-world settings are needed.

The 2022 National Institute for Health and Care Excellence guideline recommends aflibercept, ranibizumab, brolucizumab, or faricimab for adult patients with DME to treat visual impairment and a central retinal thickness of ≥400 μm at the start of treatment.[40-43] However, intraocular inflammation is a potential adverse event of brolucizumab.[40] The Australian Pharmaceutical Benefits Advisory Committee proposed inclusion of brolucizumab and faricimab in the authority-required listing for the treatment of visual impairment in DME.[44,45]

Statement 8: A good safety profile should be considered when selecting a first-line IVT

Large randomized controlled trials have not reported any major safety concerns regarding anti-VEGF agents for DME.[2] However, a meta-analysis of anti-VEGF agents, including aflibercept and ranibizumab, revealed that patients at high risk of atherothrombotic disease who have received these agents for 2 years have a potentially increased risk of mortality and cerebrovascular incidents.[46] The long-term KITE and KESTREL studies also reported new cases of retinal vasculitis after first-line treatment with brolucizumab.[35] Faricimab and aflibercept both demonstrated acceptable, comparable safety profiles in the YOSEMITE and RHINE studies: the exposure-adjusted rates of ocular and non-ocular adverse events were similar between treatment regimens.[10]

Statement 9: Intensive IVT during the first year is important to maximize patients' visual improvement and minimize the number of injections in subsequent years

Statement 10: Fixed dose, treat-and-extend, or as-needed regimens may be considered for anti-VEGF agents after the loading dose, based on anatomical and functional assessments

Early intensive treatment is associated with improved visual outcomes (**Table 2**).[47-49] This approach is supported by the results of the Protocol T trial, which recommends early intensive dosing intervals (every 4 weeks) for the first 6 months.[2] If the patient's condition is stable, the dosing interval can be extended on an as-needed basis at week 24, followed by a monitor-and-extend approach in the second year.[2] After intensive treatment in the first year, fewer anti-VEGF injections were needed in the second year (a median of 5 to 6 injections), compared with the first year (a median of 9 to 10 injections).[7,27]

A Hong Kong panel recommended initiating anti-VEGF injections monthly for the first 6 months, except for (<5% of) patients who have a VA of 20/20 or better and a normal OCT-detected CST after two consecutive injections.[1]

Given the practical challenges of early intensive treatment, less frequent dosing may be beneficial following the loading phase.[2] Longer dosing intervals may translate to fewer physician visits, thereby reducing the treatment burden without compromising effectiveness.[7,27] For example, efficacy is comparable between every 4 weeks and every 8 weeks aflibercept administration. In the RISE and RIDE trials, ranibizumab was associated with vision improvements after 1 or 3 years of treatment, and the improvements were sustained at the 4.5-year follow-up, with a significantly reduced treatment frequency.[50]

Statement 11: Switching between IVT agents could be beneficial for patients with refractory DME

Refractory DME is often defined as a central retinal thickness of >300 μm or a <10% reduction in CST after

Table 2. Improvements in visual acuity and treatment frequency in the first year

Study	Year	Anti-vascular endothelial growth factor agent	Mean No. of injections in the first year	Mean improvement in best-corrected visual acuity after 1 year, No. of letters
Protocol I[47]	2010	Ranibizumab + prompt laser	8	9.0
Protocol I[47]	2010	Ranibizumab + deferred laser	9	9.0
RISE and RIDE[48]	2012	Ranibizumab	10.9	11.1
VIVID and VISTA[49]	2014	Aflibercept	12	11.6

at least three to six anti-VEGF injections.[26] Approximately 40% of patients are deemed to have refractory DME after 2 years of monthly intravitreal ranibizumab treatment.[51] Patients with refractory disease could benefit from intravitreal corticosteroids, focal/grid laser therapy, or an alternative anti-VEGF agent.[51] In a large prospective study, BCVA significantly improved 3 to 6 months after switching from intravitreal bevacizumab to intravitreal ranibizumab, and the improvements were sustained throughout the first year of treatment.[26] Switching from intravitreal aflibercept to intravitreal bevacizumab or intravitreal ranibizumab (because of a poor response) improved CST.[26] In patients who responded poorly to intravitreal aflibercept, more patients who switched to intravitreal faricimab achieved a central macular thickness of <300 μm without any OCT-detected retinal edema at 4 months, compared with those who stayed on intravitreal aflibercept (37.5% vs 3.7%, p=0.001).[52] Moreover, an almost four-fold increase in VA gain (≥2 lines) occurred among patients who switched to intravitreal faricimab, compared with those who continued on intravitreal aflibercept.[52]

Statement 12: Focal laser treatment is an option for patients with non-center-involving DME and/or extrafoveal leaking microaneurysms

Focal macular laser photocoagulation significantly improved early treatment diabetic retinopathy study (ETDRS) letter scores at 12 months in patients with non-center-involving DME and leakage from microaneurysms, compared with patients who did not undergo any treatment.[53]

Statement 13: Steroid implants can be used as first-line treatment for pseudophakic patients without a history of glaucoma

Despite frequent anti-VEGF treatment, numerous patients with DME cannot achieve a dry macula. Intravitreal dexamethasone implants allow a sustained release of the agent from a single procedure, preventing fluctuation in drug levels and encouraging compliance.[54,55] In patients who responded inadequately to ranibizumab, the addition of a dexamethasone implant led to a greater reduction in mean CST after 24 weeks of treatment but did not significantly improve VA.[56] VA responses varied across lens status; pseudophakic eyes may benefit from combined treatment but phakic eyes may have limited response.[56]

Statement 14: Focal laser and grid laser can be a treatment option with or without anti-VEGF therapy or other combination

In a multicenter trial of 115 eyes with center-involving DME, 47% of patients who received focal or grid laser photocoagulation experienced a ≥10% reduction in CST at week 16.[57] 26 eyes were evaluable at week 32. From weeks 16 to 32, 42% of eyes had an additional ≥10% reduction in CST, accompanied by improvements in VA letter score of ≥5 letters.[57]

As demonstrated in protocol I, laser treatment in combination with anti-VEGF agents may benefit patients with center-involving DME. At 2 years, ranibizumab plus either prompt or deferred laser treatment led to the highest proportion of patients achieving ≥10 improvements in VA letters, compared with triamcinolone plus prompt laser and sham plus prompt laser (45% to 50% vs 35% vs 25%).[58]

Although panretinal photocoagulation is the mainstay treatment against severe vision loss in proliferative diabetic retinopathy, there is a risk of retina damage, exacerbating DME.[59] Ranibizumab is non-inferior to panretinal photocoagulation in improving VA after 2 years of treatment and could be an alternative treatment for proliferative diabetic retinopathy for ≤2 years.[59]

Statement 15: Pars plana vitrectomy may be performed in patients with vitreomacular traction or epiretinal membrane

Patients with vitreomacular traction tend to respond poorly to anti-VEGF therapy, compared with those without.[60] Meta-analyses have suggested that pars plana vitrectomy is not superior to other treatment modalities for DME without tractional elements.[61] Therefore, pars plana vitrectomy may be beneficial as a primary treatment for eyes with vitreomacular traction. Pars plana vitrectomy may also benefit patients with concomitant DME and epiretinal membrane, as the presence of epiretinal membrane at baseline is considered a predictor of poor response to anti-VEGF therapy.[62,63] In a retrospective study of 58 patients with DME, up to 22.4% of patients exhibited epiretinal membrane without vitreous traction at baseline.[64] Among 19 eyes with concomitant DME and epiretinal membrane, pars plana vitrectomy in combination with epiretinal membrane and internal limiting membrane peeling was effective in improving BCVA and central macular thickness, compared with the preoperative status.[65]

Conclusions

Frequent intraocular injections are barriers to effectively managing DME. Therefore, longer-acting agents are needed. Faricimab, an anti-VEGF agent that targets two pathways (VEGF-A and ANG-2), has demonstrated long-acting efficacy. Brolucizumab, a humanized single-chain variable antibody fragment, has demonstrated long-acting efficacy of up to 16 weeks, allowing longer intervals between treatments. We encourage physicians to include brolucizumab and faricimab in clinical practice for long-term cost savings by reducing the number of visits. However, brolucizumab should be a second-line treatment owing to concerns about retinal vasculitis in the first-line treatment.

Based on clinical response, intervals between treatments can be extended after the loading doses to reduce the treatment burden. Physicians should assess patients' responses to treatment through regular OCT of the macula in the first year. For refractory DME or poor response to anti-VEGF treatment, physicians should consider switching intravitreal anti-VEGF agents. Additionally, switching to steroid therapy or a combination with laser therapy may be beneficial.

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 of multiple relevant clinical trials, including those mentioned in the article supported by Roche, Bayer, Novartis, Allergan, Ripple, Amgen, Oculis SA, and Chengdu Kanghong Pharm; he has received consulting fees and honoraria from Bayer, Novartis, and Roche. GC has received grant support or contracts from Boehringer Ingelheim and Novartis as well as consulting fees and honoraria from Bayer, Roche, and Zeiss; she was a participant in a board meeting with Boehringer Ingelheim and had a leadership role for a board meeting with Bayer; she has also received stocks from Amirvax. DN has received an honorarium from Roche. TL has received grant support or contracts from Chengdu Kanghong Biotechnology, Novartis, and Roche as well as honoraria from Alcon, Bayer, Boehringer Ingelheim, Novartis, Roche, and Oculis. All authors report no other conflicts of interest.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. However, financial support was provided by Roche (Hong Kong) Ltd. in relation to the consensus meeting held in support of this manuscript. The funder had no role in the study design or interpretation and was not involved in the manuscript preparation other than providing funds for medical writing.

Data availability

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

Acknowledgements

Medical writing assistance was provided by MIMS (Hong Kong) Ltd. and complied with Good Publication Practice 4 ethical guidelines (DeTora LM et al. Ann Intern Med 2022;175:1298-1304).

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