POSITION PAPER

# Optimizing management of diabetic macular edema in Hong Kong: a collaborative position paper

*Neil Bressler,[1] MD, Carmen K.M. Chan,[2,3] MRCP, FRCSEd (Ophth), Ian Y. Wong,[4] FHKAM (Ophthalmology), FRCOphth, Marten Brelen,[2] FRCOphth, PhD, Wai-Man Chan,[2,5] FRCOphth, FRCP, Chi-Kin Ho,[2,6] FRCOphth, FHKAM (Ophthalmology), David Liu,[2,7] FRCOphth, FRCSEd, Timothy Y.Y. Lai,[2,8] MD, FRCOphth*

[1]*Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.*
[2]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China.*
[3]*Hong Kong Eye Hospital, Hong Kong SAR, China.*
[4]*Department of Ophthalmology, The University of Hong Kong, Hong Kong SAR, China.*
[5]*Department of Ophthalmology, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China.*
[6]*Department of Ophthalmology, Tuen Mun Hospital, Hong Kong SAR, China.*
[7]*Dr. David Liu & Partners Eye Center, Hong Kong SAR, China.*
[8]*2010 Eye & Cataract Centre, Hong Kong SAR, China.*

*Correspondence and reprint requests:*
*Dr. Timothy Y.Y. Lai, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, 4/F Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong SAR, China.*
*Email: tyylai@cuhk.edu.hk*

## Abstract

Focal/grid laser photocoagulation therapy has been the mainstay of treatment for diabetic macular edema at least since the 1980s, but the standard of care has changed with the advent of agents that target vascular endothelial growth factor. It is widely agreed that anti–vascular endothelial growth factor agents are the preferred first-line option for patients with fovea-involving diabetic macular edema who are able to access anti–vascular endothelial growth factor therapy. However, dosing protocols for anti–vascular endothelial growth factor agents vary and may not be well understood, including when to consider adding or switching to alternative therapies, such as photocoagulation or corticosteroid treatment. In light of such recently changing treatment approaches, a panel of local retinal specialists and an international expert convened to evaluate the roles of anti–vascular endothelial growth factor agents, corticosteroids and laser therapy in the treatment of diabetic macular edema and to formulate a set of recommendations that aim to optimize diabetic macular edema management in Hong Kong. This document summarizes the panel's recommendations. The key recommendation for the treatment of diabetic macular edema that involves the fovea is that physicians consider adopting an early intensive anti–vascular endothelial growth factor dosing schedule followed by a deferred injection strategy for stability (either resolution of diabetic macular edema or stable diabetic macular edema no longer improving or worsening) after the first 6 months. This protocol has been shown to reduce long-term treatment burden in terms of the number of injections and clinical visits required, while maintaining, on average, excellent outcomes. However, the panel acknowledges that physicians need to consider cost and accessibility restrictions applicable to each patient and to adjust their treatment strategy accordingly.

*Key words: Aflibercept; Diabetic retinopathy; Macular edema; Ranibizumab; Receptors, vascular endothelial growth factor*

## Introduction

Diabetic macular edema (DME) is a leading cause of vision loss, particularly among the working-age population.[1-3] DME arises from glucose-related damage to retinal capillaries.[2] The retinal tissue becomes hypoxic, increasing its expression of vascular endothelial growth factor (VEGF) that induces vascular leakage and neovascularization.[2,3] These leaking capillaries cause the macula to become swollen and thickened, thereby causing blurring of vision or metamorphopsia.[2]

An estimated 11% of patients with diabetes mellitus develop DME. While the overall prevalence of DME among patients with diabetes aged 20 to 79 years is approximately 7.5%, the risk increases over time.[4,5] Given the global diabetes epidemic, it is expected that the number of DME cases in Hong Kong will increase.[2] At present, approximately 10% of the population in Hong Kong aged 20 to 79 years, and 20% of those aged ≥65 years, have diabetes.[6,7] Moreover, a recent study of 174,532 patients with diabetes in Hong Kong revealed a prevalence of diabetic retinopathy of 39%; 9.8% of these patients had sight-threatening diabetic retinopathy, including DME.[8]

Controlling blood glucose levels, as well as comorbidities such as hypertension, are key components of diabetes management, including managing DME, but therapeutic interventions, including focal/grid laser photocoagulation therapy and anti-VEGF therapies also play important roles.[9] Corticosteroids, such as intravitreal triamcinolone acetonide and dexamethasone implants, may also be useful, particularly in pseudophakic eyes, but are not superior to anti-VEGF therapy.[9] Laser therapy reduces the risk of vision loss in DME and has been the mainstay of treatment for DME over the last few decades.[10] However, in recent years a number of clinical trials have clearly shown that vision can be stabilized in most patients, and even improved by 2 or more lines, in approximately half of those treated with anti-VEGF therapy, which has been shown to be superior, on average, to both laser and corticosteroid therapy.[2,11] Accordingly, anti-VEGF therapy is recommended as a first-line treatment option for fovea-involving DME in a number of international guidelines.[9,12,13] At present, there is no consensus regarding the optimal anti-VEGF dosing regimen; some dosing protocols suggest 5 loading doses administered monthly followed by a fixed 8-week dosing schedule; others suggest 3 loading doses administered monthly followed by top-up injections administered on a pro re nata (PRN) basis.[14,15] The Diabetic Retinopathy Clinical Research Network (DRCR.net) has advocated yet a different regimen.[11,16]

Given the wide variety of treatment options and dosing regimens available, physicians may require some guidance to determine the optimal management approach for their patients.

## Methods

The decision to develop this position paper was made by a panel of local retinal specialists and an international expert on retinal and macular disorders. A meeting was convened on 21 March 2016 to formulate a set of recommendations to optimize DME management in Hong Kong. The recommendations were developed following a series of presentations and round-table discussions on the current status of DME therapy, and based on data from key clinical trials and evidence-based best practice approaches. This position paper and the recommendations contained within were reviewed and approved by all participants in May 2017.

## Practice in Hong Kong in 2016

Before discussing recommendations from the panel, a summary was developed to describe ophthalmologists' current use of laser therapy and anti-VEGF therapies in Hong Kong. All participants agreed these were first-line treatments for most patients with DME. Corticosteroids were regarded as a suitable second-line therapy.

Discussion among the panelists indicated that physicians practicing in Hong Kong were administering anti-VEGF therapy according to a schedule of monthly intravitreal injections for 3 months among patients able to access such treatment. Further injections were administered PRN in response to further deterioration without specifically defining 'deterioration'. Laser photocoagulation was usually reserved for special cases where there was clear evidence of leakage from a microaneurysm surrounded by a circinate ring of lipid exudate, or if patients did not respond to, or could not afford, anti-VEGF therapy. Intravitreal corticosteroids were recommended for patients who had fovea-involving DME in eyes with no history of glaucoma or ocular infection that were pseudophakic, or with significant cataracts (for concurrent cataract extraction and intravitreal corticosteroid injection).

Treatment selection in Hong Kong was also influenced by waiting times for consultations, potential delays in receiving treatment and the lack of reimbursement for anti-VEGF therapy. Patients who cannot access anti-VEGF therapy often continue receiving laser therapy.

The evidence supporting the use of currently available pharmacologic treatment options and their use in Hong Kong is reviewed below.

### Anti–vascular endothelial growth factor therapy

#### *Ranibizumab*

The safety and efficacy of anti-VEGF therapy in DME was first established based on studies that compared ranibizumab with sham/laser photocoagulation. Data from the RISE and RIDE studies indicate that vision loss associated with DME may be reversed and clinically significant improvement

in visual acuity is achieved with monthly anti-VEGF therapy over several years.[17] A significantly greater proportion of patients treated with monthly injections of intravitreal ranibizumab 0.3 mg or 0.5 mg achieved a ≥15 Early Treatment Diabetic Retinopathy Study letter gain at 24 months than patients administered sham injections in both trials. These improvements were also associated with reductions in central subfield thickness (CST) on optical coherence tomography (OCT).[17]

Ranibizumab as monotherapy, or in combination with laser therapy, was also superior to laser monotherapy in improving the mean change in best-corrected visual acuity (BCVA) letter score from baseline through 12 months in the RESTORE study.[18] The changes in BCVA from baseline were accompanied by an improvement in OCT CST from baseline.[18] There were no definitive efficacy differences detected between the ranibizumab and combination arms with respect to improvement in BCVA or the number of injections required.[18] The functional and anatomic improvements with ranibizumab were maintained for at least 3 years with patients requiring fewer injections each year.[19]

The DRCR.net Protocol I study provided further long-term data over 5 years that ranibizumab combined with prompt or deferred (≥24 weeks) focal/grid laser could improve visual acuity compared with the standard treatment for DME of laser alone.[11] Nonetheless, these outcomes only required monthly treatment for the first 6 months with one exception, if the OCT CST was not thickened abnormally or the visual acuity was 20/20 or better at 2 consecutive injections following at least 4 injections. This latter circumstance was the exception rather than the rule, so essentially, most eyes received 6 initial monthly injections. After 6 months, ranibizumab was continued only if there was improvement of OCT CST of at least 10%, or of visual acuity of at least 5 letters, compared with the last 2 consecutive injections. Otherwise, injections were withheld, even if there was persistent but stable DME. Once injections were withheld, if DME CST or visual acuity worsened, injections were resumed. Focal/grid laser was added in persistent but stable DME after 6 monthly injections if there were treatable lesions and at least 4 months had passed since any prior laser treatment. If the condition is stable without injections after 1 year, follow-up could be extended to at least every 2 months and if remaining stable, extended to every 4 months. This approach resulted in sustained visual acuity gains through 5 years with only about 40% requiring any focal/grid laser, usually only once or twice, and with a decreasing number of injections and visits in years 2, 3, 4 and 5.[20]

***Aflibercept***

Intravitreal aflibercept 2 mg significantly improved vision outcomes and reduced rates of severe vision loss compared with laser monotherapy in the VIVID and VISTA studies.[21] Patients were randomized to monthly intravitreal injections of aflibercept 2 mg for 5 months plus further injections administered on a monthly or bimonthly basis or laser photocoagulation.[21] Both studies also showed that aflibercept achieved superior functional and anatomic outcomes to laser therapy.[21]

The DRCR.net Protocol T study showed that aflibercept 2 mg, bevacizumab 1.25 mg and ranibizumab 0.3 mg generally have comparable efficacy, on average, in patients with mild vision loss (20/32 to 20/40) related to DME. Aflibercept, however, was more effective in improving vision in patients with lower baseline levels of visual acuity at 1 year (baseline letter score <69, equivalent to 20/50 or worse), and compared with bevacizumab at 2 years, following the same regimen as described for Protocol I, at 1 year, with 2 exceptions. First, injections within the first 6 months could be withheld only if both the OCT CST were not thickened and the visual acuity was 20/20 or better; this occurred typically in <5% of the participants in any treatment group. Second, if the OCT CST thickened, or visual acuity worsened, after withholding injections after 6 months, resumption of injections was required rather than recommended.[16] The superiority of aflibercept observed after 1 year contributed to the superiority of aflibercept over bevacizumab or ranibizumab when assessed over 2 years using a post-hoc analysis of the area under the curve for a mean change in visual acuity from baseline.[22,23] At the 2-year time-point itself, aflibercept was superior to bevacizumab, but not ranibizumab across clinically relevant secondary outcomes, including improvement of at least 15 letters from baseline.[22]

## Intravitreal steroids

***Dexamethasone implant***

Intravitreal steroid therapy may have both anti-angiogenic and anti-inflammatory activity. The efficacy and safety of steroid therapy for DME was confirmed in the MEAD study in which significantly more dexamethasone-treated patients (0.70 mg intravitreal implant or 0.35 mg intravitreal implant) achieved a BCVA of ≥15 letters at 3 years compared with those who received the sham implant.[24] Moreover, fewer patients who received dexamethasone 0.70 mg experienced a ≥15 letter loss in BCVA compared with patients receiving a sham implant.[24] There was substantial loss to follow-up, however, and it is unknown how these outcomes would compare with focal/grid laser instead of no (sham) treatment in an intent-to-treat analysis over 3 years.[24] During the second year of treatment, dexamethasone was also associated with an increased risk of cataracts. This may have correlated with reduced treatment efficacy, even after the cataracts were removed, if permanent visual acuity loss occurred in some eyes either from exacerbation of DME or post-surgical cystoid macular edema, or both, following cataract surgery in the setting of DME.[24,25]

Furthermore, a comparable proportion of patients with DME achieved a BCVA improvement of ≥10 letters in a head-to-head comparison of a dexamethasone implant (0.7 mg PRN; maximum of once every 16 weeks) with anti-VEGF therapy

(bevacizumab 1.25 mg PRN; maximum of once every 4 weeks) in the BEVORDEX study, although vision loss of ≥10 letters was more common among the dexamethasone-treated eyes, mainly because of cataracts.[26] Despite this, dexamethasone implants might be considered a first-line therapy in vitrectomized DME eyes that frequently fail to respond to anti-VEGF therapy.[27,28]

***Intravitreal triamcinolone acetonide***

Intravitreal triamcinolone acetonide combined with prompt laser therapy was superior to laser therapy alone in a subgroup of patients with pseudophakic eyes. The response was comparable with ranibizumab in these patients through the 2-year follow-up visit,[11] but not at 5 years.[29] Also, 45% of eyes in the corticosteroid group had adverse events related to intraocular pressure compared with approximately 10% in the focal/grid laser group or anti-VEGF groups.[30]

## Optimizing management of diabetic macular edema: latest evidence from DRCR.net studies

The most recent data from studies conducted by the DRCR.net, a collaborative multicenter network involving more than 400 physicians throughout the United States, indicate that initiating treatment with monthly injections of anti-VEGF therapy over the first 6 months (with one exception as described above that occurred in fewer than 5% of patients) with a median of 3 additional treatments administered during the following 6 months, and a median of 5 treatments in the second year, accompanied by subsequent laser therapy for any persistent DME with treatable lesions, maximizes clinical outcomes for patients with DME.[16]

### Treating patients with persistent macular thickening

The DRCR.net Protocol I study showed that approximately 40% of patients with DME display persistent macular thickening after 6 months of anti-VEGF therapy.[31] For patients with persistent DME, a treatment protocol of as-needed anti-VEGF injections from month 6 to month 12 with deferred laser and monthly follow-up, and as-needed anti-VEGF injections after 12 months with follow-up extended to every 2 to 4 months, based on CST or visual acuity, may be adopted as a standard treatment.[31]

Data collected after 3 years of follow-up of patients being administered this protocol indicated that abnormal thickening had resolved in 60% of patients, and vision improved (>10 letters gain) in 43%, after a similar number of injections in patients without persistent macular thickening.[31] Moreover substantial (≥2 line) vision loss was uncommon despite chronic persistent DME after initiating anti-VEGF treatment.[31] While it remains unknown how these eyes would have fared with other regimens, including anti-VEGF injections every month or every 2 months, or switching between anti-VEGF agents or to other regimens such as corticosteroids, the results with the DRCR.net regimen and no switching suggest a high likelihood of successful outcomes and represent a high bar for any alternative regimen to achieve.

### Long-term management of diabetic macular edema with anti–vascular endothelial growth factor and laser therapy

In the DRCR.net Protocol I study, patients received anti-VEGF therapy every 4 weeks until no further improvement were observed (with resumption, if worsening) and either prompt or deferred (≥24 weeks) focal/grid laser treatments.[11,20] After the first year of the study, there was a substantial decrease in the frequency of injections in all patients.[20] In year 4, only half of the study population treated required at least one injection and by year 5, more than half of the patient population did not require any injections.[20] Vision improvements achieved with anti-VEGF and laser therapy in the first year were maintained through year 5, despite the reduced need for subsequent intravitreal anti-VEGF injection.[20,32] Visual acuity among patients who received prompt laser therapy was no better (and in some cases, even worse) than that among patients who received deferred therapy.[20,32]

Analyses performed after 2 years of follow-up in the DRCR.net Protocol T study revealed that visual acuity improvements were maintained with all 3 anti-VEGF agents (aflibercept, ranibizumab and bevacizumab), but greater improvements were observed in those whose vision was worse at baseline.[22] In particular, over 2 years of treatment, aflibercept appeared to offer a greater benefit (area under the curve) than the other anti-VEGF therapies in patients with a baseline visual acuity of 20/50 or worse.[23] Similar to the DRCR.net Protocol I study, patients only received frequent anti-VEGF injections in the first year with a median of 9 to 10 injections; this was reduced by around half to a median of 5 to 6 injections during year 2 with the DRCR.net treatment regimen for DME.[22]

## Position statements and recommendations from the collaborative expert panel

- An optimal DME management regimen should be initiated using monthly anti-VEGF injections for the first 6 months to achieve maximum visual acuity improvement. One exception might be if the case was 'perfect' after 2 consecutive injections, including both visual acuity of 20/20 or better and an OCT CST that appeared normal, recognizing that such exceptions might occur in approximately 5% of patients being treated.
- Patients should be monitored on a monthly basis after the first 6 months of treatment through 1 year as worsening of visual acuity from DME, or worsening of DME CST, often occurs; then incremental increases in treatment intervals can be employed starting at 1 year, first to every 2 months, then every 4 months, unless worsening warrants resumption of anti-VEGF injections with monthly follow-up until stable again. This strategy aims to identify the longest possible treatment-free

interval for each patient, potentially extending the interval between anti-VEGF treatments and improving patient compliance.

- Addition of focal/grid laser photocoagulation may be considered in patients who have persistent, stable edema despite anti-VEGF injections after 6 months, provided there are lesions to treat and treatment is no more than every 4 months.
- Switching to other agents may be considered in patients with persistent macular thickening and deteriorating vision after initiating anti-VEGF therapy for 12 months and after using laser therapy after 6 months for persistent DME, recognizing that without switching, excellent results, per the DRCR.net outcomes, may still be achieved. It is unknown if such switching results in as good or better outcomes than not switching.
- A defer-and-extend approach (e.g. treatment regimens used in DRCR.net Protocols I and T) may be considered after 12 months to maintain vision and reduce subsequent injection burden, although evidence to support this approach is currently lacking.
- DME and choroidal neovascular ('wet') age-related macular degeneration should be considered differently; regimens proven beneficial for DME may not apply to choroidal neovascular age-related macular degeneration.

The treatment algorithm suggested by the collaborative expert panel is shown in the **Figure**.

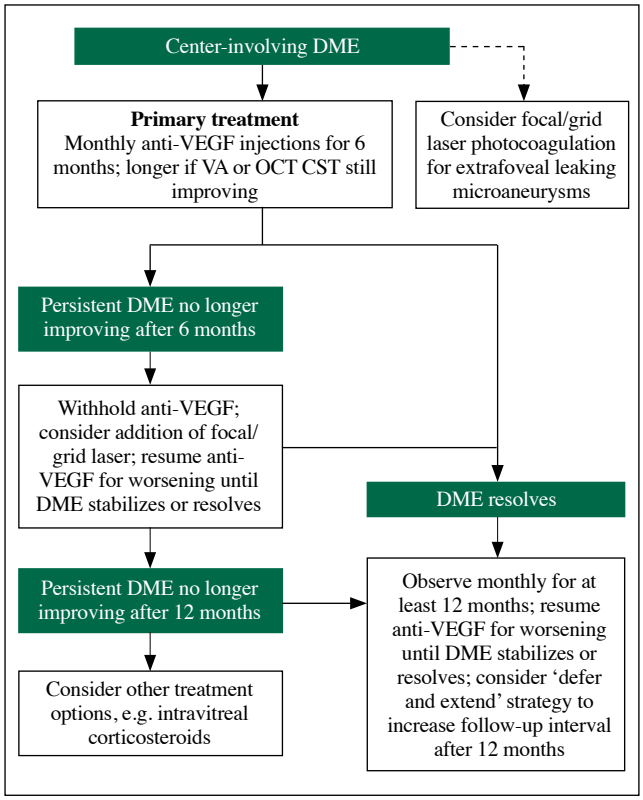


**Figure. Suggested treatment algorithm for center-involving DME.***

*Abbreviations: DME = diabetic macular edema; OCT CST = central subfield thickness on optical coherence tomography; VA = visual acuity; VEGF = vascular endothelial growth factor.*

** Presumes no limitations on treatment resources.*

## Conclusion

Anti-VEGF therapy has led to a paradigm shift in the treatment of DME and offers a superior first-line therapy to laser photocoagulation. Recent data suggest that current practice in Hong Kong, as performed in 2016, may not be optimal because the majority of patients with DME who are treated with anti-VEGF therapies receive suboptimal loading-dose injections. The panel recommends that patients who have access to anti-VEGF treatment attempt to maximize their vision improvement through more intensive anti-VEGF loading-dose injections at treatment initiation, for example, starting with 6-monthly injections unless it becomes 'perfect' following 2 consecutive injections. While this may initially appear to increase the treatment cost, it may be the most cost-effective approach in the long term. Patients who receive this number of initial loading-dose injections generally require fewer subsequent injections due to improved long-term vision stability. A deferred injection approach, when indicated per the DRCR.net treatment regimen, can also be adopted after the first 6 months of anti-VEGF treatment, reducing the number of injections and clinic visits required in subsequent years. This strategy may be particularly useful for patients in Hong Kong given the long waiting times and high volume of patients who require treatment. However, regular visual acuity and OCT monitoring is still required. Ultimately, physicians need to consider each patient on an individual basis and adjust their approach based on the patient's visual acuity at baseline, possible co-existing medical conditions that affect their vision and their ability to access treatment.

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## Declaration

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