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Review

Diabetic macular oedema: evidence-based treatment recommendations for Asian countries

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Abstract

Diabetic macular oedema is the most common cause of diabetic retinopathy-induced vision loss. Efficacy of anti-vascular endothelial growth factor therapy in diabetic macular oedema has been demonstrated in randomized controlled trials. An Asian-specific guideline for diabetic macular oedema treatment is needed as patients in Asia tend to present with far more advanced disease than seen elsewhere in the world. Previous reviews of diabetic macular oedema management lacked a broader assessment of anti-vascular endothelial growth factor treatment choices and newer trials. Recent clinical trial data allow head-to-head comparisons between the different anti-vascular endothelial growth factor agents and treatment regimens. This review aims to summarize the clinical evidence related to various treatment regimens for clinicians, with a focus on anti-vascular endothelial growth factor therapies, and to provide guidance on the treatment of diabetic macular oedema in Asian patients.

Key words: anti-vascular endothelial growth factor, Asia, diabetes mellitus, diabetic macular oedema, evidence-based treatment.

Introduction

Diabetes mellitus (DM) is a significant and growing global health problem.[1] Patients with diabetes are

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at risk of developing a variety of related complications, including diabetic retinopathy (DR), which may negatively affect their quality of life.[2–4] It has been estimated that nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes have DR during the first two decades of disease.[5] In 2012, a meta-analysis of population studies estimated the global prevalence of DR among persons with DM to be 34.6%, which translates to approximately 100 million people globally.[6]

Diabetic macular oedema (DME) is the most common cause of DR-induced vision loss.[7] The global prevalence of DME in persons with DM has been estimated to be 6.8%, with rates estimated to be slightly lower in Asian populations (age-standardized prevalence: 5.0%).[6] This is expected to change with time as more people in Asia develop diabetes, become older and live with longer duration of disease.[8,9]

The primary aetiology of DME is chronic hyperglycaemia, which activates biochemical pathways that lead to inflammation and vascular dysfunction.[7] Vascular endothelial growth factor (VEGF) plays a principal role in this cascade by promoting angiogenesis and damaging the blood–retina barrier by inducing alterations in tight junctions between retinal endothelial cells.[2,10] This leads to the accumulation of fluid in the macula. Although the use of focal/grid laser photocoagulation has been the mainstay of DME treatment for the last 30 years, clinical developments in the 21st century have expanded the treatment landscape to include intraocular administration of anti-VEGF agents and corticosteroids.[11–14]

Anti-VEGF therapy for DME was developed in response to an increased understanding of the role of VEGF in the pathogenesis of DR and the observation of increased VEGF levels in the retina and vitreous of eyes with DR.[15] Thus, intraocular anti-VEGF inhibitors – particularly inhibitors of the VEGF-A isoform – specifically target angiogenesis[16] and reduce microvascular permeability[17] in the eye, resulting in effective resolution of the VEGF-dependent mechanisms that drive DME.[18] Current evidence for anti-VEGF applies to patients with centre-involved DME with at least some degree of visual loss. Inclusion criteria into anti-VEGF trials mostly have visual acuity (VA) cut-offs at 6/9.6–6/12. The International Council of Ophthalmology 2017 guidelines for diabetic eye care recommend a VA cut-off of 6/9 or worse in centre-involved DME to commence anti-VEGF therapy.[19] A recent study has also reported that patients with poorer baseline best-corrected visual acuity (BCVA) experienced greater improvement in BCVA than patients with higher baseline BCVA, but better clinical outcome values can be achieved with early treatment (i.e. before BCVA and central retinal thickness deteriorate).[20] Additionally, suboptimal early BCVA response to DME treatment has been reported to be an indicator for poorer long-term visual outcomes than eyes that have a pronounced early response.[21] Currently, aflibercept, bevacizumab and ranibizumab are the three anti-VEGF treatments often used in clinical practice. Whereas aflibercept and ranibizumab have been approved for use in DME treatment in some Asian countries, bevacizumab is widely prescribed 'off label'.[11]

An Asian-specific guideline for DME treatment is needed for several reasons. First, in many Asian countries, the lack of access to eye specialists, the lack of adequate clinical guidance and low awareness of diabetes, DR and DME limit the optimal management of DR and diabetes-related complications. This is due, in part, to a rapid surge in the incidence of diabetes within Asia over the recent decades, the treatment of which has overwhelmed health-care facilities and resources.[22–24] Other factors influencing treatment decisions include cultural factors, adequate patient interactions, affordability and the national reimbursement criteria. A 2013 assessment of DR in India concluded that, although there was a good level of awareness of evidence-based practice among ophthalmologists, awareness of the DR risk was poor among both patients with diabetes and their primary care providers.[25] A recent review of clinical guidelines for diabetes and DR cited intraocular anti-VEGF pharmacotherapy as the standard of care; however, the expensive and resource-intensive nature of this type of treatment impedes its adoption in Asian countries.[26] Finally, the fear of needles may limit the use of anti-VEGF therapy.[27] These factors frequently place both patients and clinicians under various socio-economic pressures to use fewer injections when treating DME in Asia.

As such, focal/grid laser photocoagulation treatment, which has long been the 'gold standard', is still considered the mainstay treatment option for many Asian ophthalmologists. Collectively, these factors mean that patients in Asia tend to present with far more advanced disease than seen elsewhere in the world.[28]

Another area concerning anti-VEGF therapy for DME that requires further clarification is the treatment regimen. One common perception is that, because anti-VEGF therapies have now been used for neovascular age-related macular degeneration (AMD), the principles of treatment applied to AMD may be extrapolated to DME. However, AMD and DME differ vastly in their pathophysiology, clinical presentation, natural history, treatment goals and outcomes.[29,30] Indeed,

data from studies with longer follow-up now suggest that early intensive therapy can stabilize vision and few retreatments are needed from year 3 onwards in many patients.[31,32] Furthermore, the recent release of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T results allows head-to-head comparisons between the different anti-VEGF agents and treatment regimens. This review aims to summarize the clinical evidence related to various treatment regimens for clinicians, with a focus on anti-VEGF therapies, and to provide guidance on the treatment of DME in Asian patients.

METHODS

A literature search of key clinical trials of DME treatments available in MEDLINE was conducted. This provided an update of studies that were published after August 2013, since a previous review that included publications that were published prior to August 2013.[13] The search string used was 'Macular Edema'[Mesh] AND ('Ranibizumab'[Mesh] OR 'aflibercept'[Supplementary Concept] OR 'Bevacizumab'[Mesh] OR 'Adrenal Cortex Hormones'[Pharmacological Action]) AND 'diabetic'[All Fields] AND (Randomized Controlled Trial[ptyp] AND ('2013/09/01'[PDAT]: '2016/12/31'[PDAT])). Preference was given to reports of regional clinical trials, meta-analyses and DME management publications.

Expert opinions from retinal specialists practicing in Singapore, South Korea, Taiwan, Hong Kong, Malaysia, Thailand, Indonesia and the Philippines were collected at round-table discussions held on 29 May 2015 and 4 June 2016. These discussions covered newly released data from several pivotal clinical trials and the development of recommendations for the optimal treatment/management of DME in Asia. To the extent possible, these recommendations take the variation in health-care environments within Asia into account, and the key considerations are discussed. Practical guidance on the clinical management of DME has been proposed based on expert evaluation of current evidence but will be subject to country-specific considerations, such as local regulatory environment, and subject to change as more data become available, especially in Asian patient populations. For the purpose of this article, recommendations mentioning 'Asia' will refer specifically to Singapore, South Korea, Taiwan, Hong Kong, Malaysia, Thailand, Indonesia and the Philippines; however, these recommendations are also generalizable to other countries within Asia.

CONSENSUS RECOMMENDATIONS

Recommendation 1: Anti-VEGF therapy should be given as a first-line treatment for patients with centre-involving DME with central vision loss

Current treatment options for DME are laser, corticosteroid and anti-VEGF therapy. Laser treatment, such as focal and/or grid laser photocoagulation, has long been seen as the 'gold standard' for treatment of DME.[11] Although the exact mechanism by which laser treatment works is unknown, it is believed that the treatment alters fluid flow through the retinal pigment epithelium or induces local changes in cytokine levels.[12,33] The Early Treatment for Diabetic Retinopathy Study (ETDRS) and others have shown that focal/grid laser photocoagulation treatment may maintain BCVA in patients with clinically significant DME and reduce retinal thickness in a proportion of them.[34] However, focal/grid laser photocoagulation treatment does not substantially improve BCVA and is associated with a significant risk of vision loss in the long term due to complications such as scar enlargement and secondary choroidal neovascularization. Anti-VEGF therapy has been shown in numerous trials to be superior to focal/grid laser photocoagulation in achieving gains in BCVA (Table 1).[31,32,35–42] The likelihood of visual loss was reported to be greater in patients with DME who received laser photocoagulation treatment than in those treated with anti-VEGF therapy.[13,31,32,35,36,42] Additionally, the DRCR.net Protocol I study showed no additional benefit on BCVA or injection number between deferred laser and prompt laser.[31,32,42]

Ranibizumab, aflibercept and bevacizumab are the commonly used anti-VEGF therapeutics. In DME, they function by blocking the action of VEGF in the eye to reduce neovascularization and fluid build-up. Ranibizumab is a fragment (48 kDa) of the recombinant humanized monoclonal immunoglobulin G1κ antibody that inhibits all human VEGF-A isoforms.[43] Its efficacy and safety in DME, including a long-term improvement/maintenance of VA, have been established in phase II (RESOLVE and READ-2) and phase III (RESTORE, DRCR.net Protocol I, RISE and RIDE) clinical trials.[13] In the RESTORE study, ranibizumab was given as three initial monthly injections and then *pro re nata* (as needed) if stable VA was not reached. The mean average BCVA change from baseline was +6.1 ETDRS letters with ranibizumab alone to +5.9 ETDRS letters with ranibizumab plus laser and +0.8 ETDRS letters with laser.[38] These gains were maintained during the extension study.[44] The REVEAL study used a protocol similar to that of RESTORE and compared ranibizumab monotherapy

Table 1. Summary of key trials investigating anti-VEGF treatment in DME employing different dosing regimens

	DRCR.net Protocol T[52,53]	BEVORDEX[54,55]	RISE/RIDE[45–47]	VIVID/VISTA[35,36]	RESTORE[37,38]	DRCR.net Protocol I[31,32,42]	REVEAL[41]	BOLT[39,40]
Anti-VEGF arm(s)	Aflibercept 2 mg, bevacizumab 1.25 mg, ranibizumab 0.3 mg	Bevacizumab 1.25 mg	Ranibizumab 0.3 or 0.5 mg	Aflibercept 2q4 or 2q8	Ranibizumab 0.5 mg or ranibizumab 0.5 mg + laser	Ranibizumab 0.5 mg + deferred laser or ranibizumab 0.5 mg + prompt laser	Ranibizumab 0.5 mg or ranibizumab 0.5 mg + laser	Bevacizumab 1.25 mg
Comparator	NA	Dexamethasone	Sham	Laser	Laser	Prompt laser, triamcinolone 4 mg + prompt laser	Laser	Laser
Sample size	660 eyes of 660 patients	88 eyes of 61 patients	759 eyes of 759 patients	872 eyes of 872 patients	345 eyes of 345 patients	854 eyes of 691 patients	396 eyes of 396 patients	80 eyes of 80 patients
Study duration (years)	2	2	3 (sham injection-controlled for 2 years)	2	3 (open-label extension after year 1)	5 (2-year extension after main study)	1	2
Study site(s)	USA	Australia	USA, South America	VIVID: Australia, Europe, Japan; VISTA: USA	Australia, Canada, Europe, Turkey	USA	Asia	UK
Baseline VA characteristics	Mean VA letter score 6/15	Mean BCVA 55.5–56.3 letters across both groups	Majority of patients with VA <6/12 but >16/60	Mean BCVA 59–61 letters across all groups	Mean VA 62–65 letters across all groups	VA 6/9.6 to 6/96	Mean BCVA 58.4–58.8 letters across all groups	Mean BCVA 34–69 letters across both groups
Prior anti-VEGF treatment	None within prior 12 months	No bevacizumab within prior 2 months	None within prior 3 months	VIVID: 6–11% (received more than 3 months prior to trial); VISTA: 41–45% (received more than 3 months prior to trial)	None within prior 3 months	None within prior 4 months	None within prior 3 months	None within prior 3 months
Regimen	Six initial monthly injections + *PRN*	Monthly injections *PRN*	Monthly injections	Five initial monthly injections + 2q4 or 2q8	Three initial monthly injections + *PRN*	Four initial monthly injections + *PRN*	Three initial monthly injections + *PRN*	Three initial 6-weekly injections + *PRN*
Number of anti-VEGF injections[†,‡]	Aflibercept: 13.4 (2 years); bevacizumab: 14.3 (2 years); ranibizumab: 14.1 (2 years)	Bevacizumab: 9.1 (year 1), 4.8 (year 2)	0.3/0.5; RISE: 29.8/28.5 (3 years); RIDE: 28.0/30.4 (3 years)	2q4/2q8; VIVID: 22.6/13.6 (2 years); VISTA: 21.3/13.5 (2 years)	Ranibizumab: 7.0 (1 year); ranibizumab + laser: 6.8 (1 year)	Ranibizumab + prompt laser: 12 (3 years, median); ranibizumab + deferred laser: 15 (3 years, median)	Ranibizumab + laser: 7.0 (1 year); ranibizumab: 7.8 (1 year)	Bevacizumab: 13 (2 years, median)
Change in VA from baseline to the end of the study (letters gained)[†,‡]	Aflibercept: +12.8; bevacizumab: +10.0; ranibizumab: +12.3	Bevacizumab: +9.6; dexamethasone: +6.9	Sham/0.3/0.5; RISE: +2.6/12.5/11.9; RIDE: +2.3/10.9/12.0	Laser/2q4/2q8; VIVID: +0.7/11.4/9.4; VISTA: +0.9/11.5/11.1	Laser: +0.8; ranibizumab + laser: +5.9; ranibizumab: +6.1	Laser: +2[§]; triamcinolone + prompt laser: +0[§]; ranibizumab + prompt laser: +7; ranibizumab + deferred laser: +10	Laser: +1.4; ranibizumab + laser: +5.7; ranibizumab: +5.9	Laser: −0.5; bevacizumab: +8.6

[†]Data reported are from the core studies only. Data from the extension phases, if applicable, are not reported. [‡]Values represent means, unless otherwise indicated. [§]Data are from 2 years instead of 3 years. In the second year of the planned 3-year study, intravitreal ranibizumab plus prompt or deferred laser treatment was observed to be more effective through 2 years than prompt laser treatment alone. Patients originally assigned to prompt laser treatment alone or triamcinolone plus prompt laser treatment were subsequently given the opportunity to switch to intravitreal ranibizumab treatment 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best-corrected visual acuity; DME, diabetic macular oedema; NA, not applicable; *PRN*, *pro re nata* (as needed dosing); VA, visual acuity; VEGF, vascular endothelial growth factor.

(n = 133) with ranibizumab plus laser (n = 132) and laser alone (n = 131) in Asian patients over a 12-month period.[41] The mean BCVA change with ranibizumab as monotherapy or combined with laser was superior to that with laser alone (+5.9 and +5.7 letters, respectively, *vs* +1.4 letters). The RISE and RIDE trials both compared 0.3 mg ranibizumab every 4 weeks (q4w) with 0.5 mg ranibizumab q4w and sham (with rescue laser).[45,46] At 24 months, mean BCVA gains were similar across the four groups: RISE 0.3 mg (+12.5 letters; n = 125), RISE 0.5 mg (+11.9 letters; n = 124), RIDE 0.3 mg (+10.9 letters; n = 125) and RIDE 0.5 mg (+12.0 letters; n = 127).[45] At 36 months, mean BCVA gains for sham, 0.3 mg ranibizumab and 0.5 mg ranibizumab were +4.7, +10.6 and +11.4 letters, respectively, in RIDE and +4.3, +14.2 and +11.0 letters, respectively, in RISE.[47] Although some authors suggest that the 0.5 mg dose of ranibizumab might have been more efficacious than the 0.3 mg dose, this has not been supported by clinical trials. The difference in mean BCVA change from baseline to 2 years between the 0.3 and 0.5 mg doses was 0.6 letters in RISE and 1.1 in RIDE.[47,48]

Aflibercept is a fully human recombinant fusion protein that inhibits both VEGF-A and VEGF-B isoforms as well as placental growth factors 1 and 2 and galectin-1.[43,49] The phase II Da Vinci study (n = 221)[50] and phase III VIVID (n = 406) and VISTA (n = 466) studies[35] have established the superiority of aflibercept over laser therapy. In the VIVID and VISTA studies, patients were randomized to receive aflibercept 2 mg q4w (2q4) or 2 mg every 8 weeks (2q8) after five initial monthly doses or laser therapy. Significant BCVA gains were evident with aflibercept 2q4 and 2q8 compared with laser in both the VIVID (+10.5/10.7 letters *vs* +1.2 letters, respectively; $P < 0.0001$) and VISTA (+12.5/10.7 letters *vs* +0.2 letters, respectively; $P < 0.0001$) studies after 52 weeks of treatment.[35] After 100 weeks of treatment, VA gains with aflibercept 2q4 and 2q8 remained greater that those with laser in both the VIVID (+11.4/9.4 letters *vs* +0.7, respectively; $P < 0.0001$) and VISTA (+11.5/11.1 *vs* +0.9, respectively; $P < 0.0001$) studies.[36] These visual improvements were maintained at week 148, and similar overall efficacy was observed in the aflibercept 2q4 and 2q8 groups.[51] From week 100, participants in the laser arm of the VIVID and VISTA trials were permitted to receive aflibercept; however, they did not achieve the same kind of vision improvements observed in the aflibercept 2q4 and 2q8 treatment arms.

Bevacizumab is a full-size (149 kDa) humanized recombinant monoclonal immunoglobulin G antibody that inhibits all isoforms of VEGF-A.[43] In the phase II BOLT study (n = 80), 1.25 mg bevacizumab every 6 weeks resulted in a median gain of +8 ETDRS letters compared with a median loss of −0.5 ETDRS letters in the laser group (P = 0.0002) at 12 months.[39] At 24 months, the bevacizumab arm gained a median of +9 ETDRS letters *versus* +2.5 letters with laser (P = 0.005), with a mean gain of +8.6 letters for bevacizumab *versus* a mean loss of −0.5 letters with laser.[40]

The current corticosteroid treatment options for DME are dexamethasone, fluocinolone acetonide (FA) and triamcinolone acetonide (TA). They function by inhibiting inflammatory mediators and strengthening tight junctions in the endothelial basement membrane to limit permeability and leakage, which cause macular oedema.[56] The MEAD study examined the safety and efficacy of 0.7 mg *versus* 0.35 mg dexamethasone intravitreal implant (DEX-implant; Ozurdex, Allergan plc Clonshaugh Business and Technology Park Coolock, Dublin, D17 E400, Ireland) in the treatment of patients with DME.[57] Patients received a low mean number of treatments over 3 years (4.1, 4.4 and 3.3 injections with DEX-implant 0.7 mg, DEX-implant 0.35 mg and sham, respectively).[45–47] Although a significant improvement was observed in the percentage of patients with a ≥15-letter improvement in BCVA from baseline to the end of the study, the rates of cataract-related adverse events in phakic eyes were also higher than in the sham group (DEX-implant 0.7 mg, 67.9%; DEX-implant 0.35 mg, 64.1%; sham, 20.4%).[57] The OZDRY study compared the effectiveness and safety of 5-monthly fixed dosing with *pro re nata* dexamethasone (Ozurdex) treatment in patients with refractory DME. Based on a per protocol analysis, a 5-monthly fixed dosing of dexamethasone was non-inferior to optical coherence tomography (OCT)-guided *pro re nata* therapy at 12 months (mean BCVA change: +1.48 ± 14.8 *vs* −0.17 ± 13.1, respectively; P = 0.02).[58] More recently, the OZLASE study examined the safety and clinical efficacy of combined repeated dexamethasone (Ozurdex) and macular laser therapy (MLT) compared with MLT monotherapy. Despite a significant decrease in central subfield thickness, there was no significant difference in the visual outcomes of the two treatment arms at 56 weeks (combination arm, −0.3 ± 11.4 ETDRS letters; MLT monotherapy, +0.4 ± 9.6 ETDRS letters).[59] Cataract development or progression is likely in phakic eyes treated with DEX-implant, but cataract removal is uneventful and is followed by a clinically relevant improvement in vision compared with sham treatment. Prompt diagnosis and cataract extraction are needed for optimal visual outcomes with DEX-implant.

The Fluocinolone Acetonide for Diabetic Macular Edema study, which evaluated the long-term safety and efficacy of intravitreal inserts releasing 0.2 (low dose) and 0.5 μg/day (high dose) FA in patients with

DME, reported improvements in VA with FA implants compared with sham implants.[60,61] However, a number of corticosteroid-related side effects occurred, and nearly all patients with phakic eyes developed cataracts.

In the DRCR.net Protocol I study,[31,32,42] TA and prompt laser treatment was compared with ranibizumab and either deferred or prompt laser treatment. Compared with sham injection plus prompt laser, the TA plus prompt laser group had a mean decrease in BCVA from baseline to 2 years (−1.6 letters; 95% confidence interval: −6.6 to +3.3 letters; $P < 0.001$).[42] However, a subgroup analysis of patients who were pseudophakic at baseline showed that BCVA gain following TA and prompt laser was still observed and may have been as equally effective as ranibizumab. This finding spurred the development of dexamethasone and FA implants.[56]

The BEVORDEX study compared bevacizumab with DEX-implant.[55] The results indicate that, although no significant difference was observed in the proportion of eyes with a 10-letter gain in BCVA between bevacizumab and DEX-implant, the latter group had more cases of visual loss – mainly in eyes that were phakic at baseline.[55] Eyes that were randomized to receive bevacizumab had a mean of 9.1 ± 3.1 injections compared with eyes randomized to receive DEX-implant, which received a mean of 2.8 ± 0.9 injections.[55]

Overall, the data suggest that steroid therapy for DME may require fewer treatments than anti-VEGF therapy, but the risk of steroid-induced ocular hypertension and cataract formation remains an issue.[56] Corticosteroids may be more relevant to the treatment of chronic DME, particularly in patients with pseudophakic eyes, because the condition is speculated to be driven more by inflammatory cytokines than by VEGF.[56]

On the basis of the data reviewed, we recommend that anti-VEGF therapy be given as a first-line treatment for patients with centre-involving DME with vision loss (Table 2). Intravitreal corticosteroid treatment may be considered as a first-line therapy in select cases, such as pseudophakic or postvitrectomy eyes, or if the patient is at high risk of thromboembolic events.

Recommendation 2: Choice of anti-VEGF agent depends on baseline VA

The DRCR.net Protocol T study was a head-to-head comparison of the three anti-VEGF therapies for DME.[52,53] The mean number of injections administered over 2 years was similar for all three anti-VEGF treatments: 13.4 (aflibercept), 14.3 (bevacizumab) and 14.1 (ranibizumab). At 12 months, the mean BCVA gain was +13.3 letters with aflibercept, +9.7 letters with bevacizumab and +11.2 letters with ranibizumab ($P < 0.001$ for aflibercept *vs* bevacizumab, $P = 0.003$ for aflibercept *vs* ranibizumab and $P = 0.21$ for ranibizumab *vs* bevacizumab). Central subfield thickness decreased, on average (±SD), with aflibercept (169 ± 138 μm), bevacizumab (101 ± 121 μm) and ranibizumab (147 ± 134 μm).[52] At 2 years, the mean BCVA gain was +12.8 letters with aflibercept, +10.0 letters with bevacizumab and +12.3 letters with ranibizumab ($P = 0.02$ for aflibercept *vs* bevacizumab, $P = 0.47$ for aflibercept *vs* ranibizumab and $P = 0.11$ for ranibizumab *vs* bevacizumab). Central subfield thickness decreased, on average (±SD), with aflibercept (171 ± 141 μm), bevacizumab (126 ± 143 μm) and ranibizumab (149 ± 141 μm).[53]

Because previous studies have shown that presenting vision is a key determinant of visual outcomes, the Protocol T study design included prespecified subgroup analyses stratified by baseline vision. When the initial vision loss was mild (BCVA: 6/9.6 to 6/12), the mean BCVA improvement was similar for aflibercept, bevacizumab and ranibizumab (+8.0, +7.5 and +8.3 letters at 12 months[52] and +7.8, +6.8 and +8.6 letters at 2 years,[53] respectively). When the initial vision loss was moderate to severe (BCVA: 6/15 to 6/96), the mean BCVA improvement was significantly greater with aflibercept (+18.9 letters) than with bevacizumab (+11.8 letters; $P < 0.001$) or ranibizumab (+14.2 letters; $P = 0.003$) at 1 year[52] and with bevacizumab at 2 years (+18.3 *vs* +13.3 letters; $P = 0.02$), although the BCVA improvement with aflibercept was not significantly different from that with ranibizumab at 2 years (18.1 *vs* 16.1 letters, respectively; $P = 0.18$).[53] No significant differences in adverse events were observed between the three anti-VEGF treatment arms; however, a post-hoc analysis reported a higher rate of cardiovascular events in the ranibizumab group.[53] It remains to be determined if this is an accurate observation as there are inconsistencies in the current totality of evidence for ranibizumab.[53] A separate post-hoc analysis reported that for eyes with an initial VA of 6/15 or worse, the mean (SD) letter change in VA over 2 years (area under curve) was +17.1 ± 9.7 letters for aflibercept, +12.1 ± 9.4 letters for bevacizumab and +13.6 ± 8.5 letters with ranibizumab.[62] VA improvement was greater with aflibercept than with bevacizumab ($P < 0.001$) or ranibizumab ($P = 0.009$).

We thus recommend that the choice of anti-VEGF agent depends on baseline VA (Table 2). In patients with poor BCVA (worse than 6/12), aflibercept may lead to a more rapid VA improvement than ranibizumab (0.3 mg) over 1 year, although the difference was not significantly different by year 2 of the DRCR.net Protocol T study.[53] In patients with

better BCVA (better than 20/40), bevacizumab – with its associated cost savings – could be a prudent choice. However, because of limited screening and lack of reimbursed health care in Asia, it is believed that most patients only present when there is significant visual loss. Thus, the significance of consideration regarding baseline VA is particularly relevant.[7]

Similarly, many patients present with DME and coexisting proliferative diabetic retinopathy (PDR).[63] The 2-year DRCR.net Protocol S study results demonstrate non-inferiority of ranibizumab to panretinal photocoagulation (PRP) in terms of VA outcomes in patients with PDR (+2.8 mean VA letter improvement with 0.5 mg ranibizumab *vs* +0.2 letters with PRP; $P < 0.001$ for non-inferiority), including patients with DME.[64] Patients with DME and PDR experienced less improvement in vision when ranibizumab was administered with PRP (+3.6 letters with ranibizumab and PRP *vs* +8.0 letters with ranibizumab; adjusted difference, +3.4 letters, $P = 0.08$). These findings indicate that ranibizumab monotherapy may be considered as initial therapy particularly in patients presenting with DME and PDR.

Recommendation 3: Early intensive anti-VEGF therapy is important for patients in Asia

Results from the DRCR.net Protocol I,[31,32,42] Protocol T[52,53] and VIVD/VISTA[51] studies demonstrated the importance of early intensive treatment ('Treat proactively and intensively as early as possible'), especially within the first 6 to 12 months. Early intensive treatment with at least five to six initial monthly doses, totalling to as many as eight to nine injections in year 1, may be required to achieve good results in patients with DME; the number of injections can be decreased in subsequent years.

Our recommendation is that early intensive therapy is important for patients in Asia (Table 2). The expert panel acknowledges that, although the principle of early intensive therapy was agreed upon, implementation of this principle may be subject to local contexts/constraints (Table 2). Injection frequency in real-world clinical practice is often governed by the cost of treatment, because treatment of DME is not reimbursed in several Asian countries. As a result, the number of anti-VEGF injections currently administered by clinics in Asia is widely considered to be lower than that used in clinical trials (generally 7–13 in the first year).

Notwithstanding these 'real-world' constraints, it remains imperative that physicians understand and convey the importance of early intensive treatment to their patients. Furthermore, it is unclear whether sporadic, irregular treatment with anti-VEGF can achieve the outcomes described with more intensive therapy and whether reduced treatment burden in later years described in the DRCR.net Protocol I study can be achieved without the initial phase of intensive therapy.

Recommendation 4: For the subsequent treatment phase, fixed dosing or individualised dosing – based on VA and OCT – should/can be considered, based on local context and recognizing heterogeneity and response

All the clinical trials that used fixed-dosing regimens (RIDE/RISE and VIVID/VISTA) have reported BCVA gains to be maintained for up to 3 years/100 weeks.[35,36,45–47] At 3 years, the RIDE/RISE studies reported an average change in BCVA from baseline of +4.7/4.3 letters (sham), +10.6/14.2 letters (0.3 mg ranibizumab) and +11.4/11.0 letters (0.5 mg ranibizumab).[47] At week 100 in the VIVID/VISTA studies, the mean BCVA gains from baseline were +0.7/0.9 letters (laser control), +11.4/11.5 letters (aflibercept 2q4) and +9.4/11.1 letters (aflibercept 2q8).[36] Mean BCVA gains from baseline to week 148 were +1.6/1.4 letters (VIVID/VISTA, laser control), +10.3/10.4 letters (VIVID/VISTA, aflibercept 2q4) and +11.7/10.5 (VIVID/VISTA, aflibercept 2q8).[51] Aflibercept 2q8 demonstrated efficacy similar to that of aflibercept 2q4, so fewer injections would potentially translate into fewer physician visits and thus a decrease in the number of treatments and in the associated economic burden for patients, caregivers, physicians and health-care systems overall.[35,36] The DRCR.net Protocols I and T used a regimen that treats until no further change (in which some residual fluid may be tolerated) and reported good long-term outcomes with significantly fewer retreatments and monitoring visits in later years. Following the protocol, the results show that even in patients with persistent macular oedema after week 24 of treatment, substantial loss of VA was uncommon through 3 years, even when centre-involved DME chronically persists.[65] Thus, this approach offers an alternative to fixed dosing. In patients with suboptimal response to anti-VEGF therapy, combined laser plus steroid treatment is an option that could be considered as a second-line therapy. In the DRCR.net Protocol T study, at least one laser photocoagulation treatment was performed between 24 and 48 weeks in 37% of aflibercept-treated eyes ($n = 208$), 56% of bevacizumab-treated eyes ($n = 206$) and 46% of ranibizumab-treated eyes ($n = 206$).[52]

Further points to consider include differentiating real 'treatment resistance' from inadequately treated cases. Results from Protocol T suggest that the

Table 2. Recommendations for DME treatment with anti-VEGF in Asia

Recommendation	Asian perspective	Supporting data
Anti-VEGF therapy should be given as a first-line treatment for patients with centre-involving DME with vision loss	• The three anti-VEGF agents that are widely used (aflibercept, bevacizumab and ranibizumab) are superior for vision improvement to laser for treatment of centre-involving DME • Anti-VEGF agents improve vision compared with natural history or focal laser coagulation for treatment of centre-involving DME • Intravitreal corticosteroid treatment may be considered as a first-line therapy in certain conditions, such as pseudophakic or postvitrectomy eyes, or if the patient is at high risk of thromboembolic events	BOLT,[39,40] DRCR.net Protocol I,[31,32,42] RESTORE,[37,38] REVEAL,[41] VIVID/VISTA[35,36]
Choice of anti-VEGF agent depends on baseline VA	• The baseline vision of patients should be considered when selecting the appropriate anti-VEGF for treatment • In patients with worse VA (worse than 6/12), aflibercept may result in a more rapid VA improvement than ranibizumab (0.3 mg) over 1 year, although this difference was not statistically significant in year 2 of the DRCR.net Protocol T study • In patients with better VA (6/12 or better), aflibercept, ranibizumab and bevacizumab are equally effective	DRCR.net Protocol T,[52,53] RESTORE,[37,38] RISE/RIDE,[45,47] VIVID/VISTA[35,36]
Early intensive therapy is important for patients in Asia	• The principle of early intensive therapy was agreed on, but implementation may be subject to local resource constraints • Early intensive treatment with at least five to six initial monthly doses, totalling to as many as eight to nine injections in year 1, may be required to achieve good results in patients with DME and to reduce treatment burden in subsequent years • In RISE/RIDE, patients receiving sham injections who switched to active treatment did not achieve improvements at month 36 that were comparable with those in patients originally randomized to ranibizumab • DRCR.net Protocol I and DRCR.net Protocol T confirm the rationale for early intensive treatment ('Treat proactively and intensively as early as possible') with six initial monthly injections and up to nine injections in year 1; injection numbers can then be reduced in the subsequent years	DRCR.net Protocol I,[31,32,42] DRCR.net Protocol T,[52,53] RESTORE extension,[37] RISE/RIDE,[45–47] VIVID/VISTA[35,36,51]
For the subsequent treatment phase, fixed dosing or individualised dosing – based on VA and OCT – should/can be considered based on local context and recognizing heterogeneity and response	• Aflibercept 2q8 demonstrated efficacy similar to that of aflibercept 2q4; thus, fewer injections would translate into fewer physician visits, reducing treatment burden for patients, caregivers, physicians and health-care systems overall • At the 4.5-year follow-up in the RISE/RIDE trials, the vision gains achieved after 1 or 3 years of monthly ranibizumab treatment were sustained by a much reduced treatment frequency; some patients required no additional treatment • Laser + steroid treatment is still an option in patients with suboptimal response to anti-VEGF therapy • Data suggest that a substantial proportion of patients with DME eventually benefit from continued anti-VEGF treatment over several years and should not be labelled as non-responders prematurely.	DRCR.net Protocol T,[52,53] RISE/RIDE,[46] VIVID/VISTA[35,36]
For non-centre-involving DME, focal/grid laser treatment continues to play an important role in preventing moderate vision loss	• No cases of non-centre-involving DME were included in pivotal randomized controlled trials of anti-VEGF therapy • Cases of non-centre-involving DME may be observed until there is progression to central involvement • Focal/grid laser photocoagulation treatment to leaking microaneurysms may be considered if thickening is threatening the fovea	International Council of Ophthalmology[19]

2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; DME, diabetic macular oedema; OCT, optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor.

maximal response of DME to bevacizumab requires an average of 10 injections over a year. Optimal response was achieved after lesser than four injections in fewer than 2% of patients.[52,53] Even in the group with suboptimal responses, long-term results from Protocol I indicate that continued treatment according to protocol, even in patients with persistent macular oedema at month 6, resulted in a further response in 20%, 45% and 60% of patients at 1, 2 and 3 years, respectively.[65] These results suggest that a substantial proportion of patients with DME eventually benefit from continued anti-VEGF treatment over several years and should not be labelled as non-responders prematurely. Finally, there is currently no evidence from clinical trials to support a switch in anti-VEGF agent, although some case series may suggest improved response in some 'refractory cases'.[66–68]

We thus recommend for the subsequent treatment phase that fixed dosing or individualised dosing, based on VA and OCT, should/can be considered based on local context and recognizing heterogeneity and response (Table 2). Off-label use of bevacizumab to maximize treatment benefit, especially in countries where health-care costs are not reimbursed, should be at the discretion of the clinicians. In addition, deferred focal laser (from month 6 onwards) may be considered as an adjunctive treatment.

Recommendation 5: For non-centre-involving DME, focal/grid laser treatment continues to play an important role in preventing moderate vision loss

To date, no pivotal randomized controlled trials of anti-VEGF therapies have included patients with non-centre-involving DME. We thus recommend that, for non-centre-involving DME, focal/grid laser treatment will continue to play a role in preventing moderate vision loss. This is in alignment with International Council of Ophthalmology guidelines for diabetic eye care, which recommend observation until progression to centre-involving DME or considering focal/grid laser photocoagulation treatment if retinal thickening threatens the fovea.[19]

SAFETY

To date, none of the randomized controlled trials discussed here have reported any significant safety concerns. However, it should be noted that a recent meta-analysis of anti-VEGF treatments for DME revealed a possible increased risk of death and potential cerebrovascular accidents in high-risk patients with DME who received 2 years of monthly anti-VEGF treatment.[69] In addition, the DRCR.net Protocol T study reported an unexpected number of cardiovascular events in the ranibizumab arm, which were incongruent with the event rates reported in previous ranibizumab studies. Although it remains to be seen if this was a true result, the authors recommended that continued vigilance is warranted.[53] As such, it is important to consider the total exposure to anti-VEGF agents when treating patients, particularly those at high risk of vascular disease. There is also concern about the risk of birth defects arising from anti-VEGF treatment during pregnancy. Polizzi and Mahajan[70] propose that such intravitreal anti-VEGF treatments can be given during pregnancy, but only when the potential benefit to the mother outweighs the risk to the foetus.

In the DRCR.net Protocol T study, bevacizumab was purchased and repackaged into single-use vials by a central pharmacy, so there were fewer concerns regarding the risk of infection.[52] Thus, the safety data regarding endophthalmitis reported in DRCR.net studies may not be applicable to settings without a compounding pharmacy service.

CONCLUSIONS

There have been significant advances in the understanding of treatment for DME. However, DME management remains suboptimal in many patients with diabetes, particularly in Asia, because of the factors discussed in this article. The recommendations presented here, based on expert evaluation and current evidence, aim to help guide the optimal choice of treatment and regimen for DME in Asia.

To the extent possible, anti-VEGF treatments should be given to patients with DME as a first-line treatment. In cases in which treatment options are severely limited, focal/grid laser photocoagulation treatment should be undertaken to reduce/prevent disease progression at the very least.

DME is a preventable disease, and there is a need to optimize control of systemic factors, including hyperglycaemia, hyperlipidaemia and blood pressure. Collaborative efforts are required from clinicians, regulatory bodies and pharmaceutical companies to ensure that all patients requiring treatment are receiving the most appropriate course of therapy.

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COMPETING/CONFLICTS OF INTEREST:

None.

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