

# Intravitreal Bevacizumab for Treatment of Diabetic Macular Oedema

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## Abstract

Diabetic macular oedema (DMO) is a leading cause of vision loss in the working-age population worldwide. Numerous early studies suggest an important role for intravitreal anti-VEGF agents such as bevacizumab in the management of DMO. We reviewed manuscripts that had investigated pharmacokinetic, efficacy, safety, dose and frequency of intravitreal bevacizumab (IVB) injections as well as effect of macular ischaemia, initial macular thickness and optical coherence tomography (OCT) patterns of DMO on the final results of treatment with IVB. In summery literature searches disclosed that almost all studies published up to now provided evidence supporting use of IVB for treatment of either naïve or persistent DMO in short and long term up to 2 years.

## Keywords

Bevacizumab, clinically significant diabetic macular oedema, diabetic retinopathy, macular laser photocoagulation, triamcinolone acetonide

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Diabetic macular oedema (DMO) is the major cause of visual loss in the working-age population worldwide. Based on one study during a period of 10 years the development of DMO occurred in 20.1 % of patients with type 1 diabetes, 25.4 % of type 2 patients requiring insulin and 13.9 % of type 2 patients not requiring insulin.<sup>1</sup> Laser photocoagulation was the only evidence based treatment available for subjects with clinical significant macular oedema, defined by the early treatment diabetic retinopathy study (ETDRS).<sup>2</sup> However the beneficial effect of macular laser photocoagulation (MPC) on DMO was inferred only because it reduce the risk of moderate visual loss by 50 %.<sup>2</sup> For diffuse DMO, MPC has even more limited results, and based on a study, performing modified MPC visual acuity (VA) was increased in only 14.5 % of the eyes.<sup>3</sup> Moreover, diabetic retinopathy clinical research network (DRCR. Net) has recently shown a VA improvement of more than five letters in 51, 47 and 62 % of cases by MPC at 1, 2 and 3 years of follow-up respectively.<sup>4–6</sup>

Destructive nature, adverse effects and suboptimal efficacy of MPC have led to investigators to find alternative treatments. Pharmacotherapy of DMO with intravitreal drugs especially anti-VEGFs such as ranibizumab, bevacizumab and aflibercept have been the focus of the most recent attentions, among them bevacizumab has greatest popularity because of higher availability and lower cost. The off-label use of bevacizumab has been applied to many neovascular diseases of the eye such as age-related macular degeneration, proliferative diabetic retinopathy and other retinovascular disorders such as macular oedema secondary to retinal vein occlusion and diabetic retinopathy.<sup>7–8</sup> The use of intravitreal bevacizumab (IVB) is becoming increasingly more prevalent, however some unresolved issues such as ideal regimen, duration of treatment, combination therapy and long-term safety are unanswered and deserve further investigations. In this review article we have tried to provide some answers for common questions in this regard based on published literature.

## Pathophysiology of Diabetic Macular Oedema

Several physiological mechanisms have been proposed to contribute to the pathogenesis of DMO. The exact mechanisms by which elevated glucose initiates the vascular disruption and results in the ultimate blood retinal barrier (BRB) breakdown in diabetic retinopathy remain poorly defined. There are several hypotheses that contribute to DMO formation including:

1. Increase in hydrostatic pressure that was described by Starling. Similar to congestive heart failure, DMO can be considered as a congestive macular oedema. Based on Starling law hydrostatic and oncotic pressure counteract each other; pressure differences are responsible for the movement of fluid between tissue beds and intravascular spaces. Changes in vessel diameter together with increased hydrostatic pressure can contribute to oedema formation. Furthermore the above mentioned mechanism can increase in shear stress which may cause damage to endothelial cells and cause endothelial decoupling over time.<sup>9–11</sup>
2. Ischaemia secondary to hypoxia can lead to decrease in oxygen tension in retina which results in vasodilation of the retinal vessels that can increase macular oedema by increasing hydrostatic pressure. Increased in oxygen tension may decrease macular oedema by reversing the earlier described mechanism.
3. Hyperglycaemia per se or together with other mechanisms may induce endothelial dysfunction and cause more vascular damage.<sup>12–14</sup>
4. Increased VEGF production: VEGF mediates angiogenesis by promoting endothelial cell migration, proliferation and survival. Amongst the various VEGF family members, VEGF-A, is a critical regulator of ocular angiogenesis and vascular permeability.<sup>15</sup> VEGF can cause rapid post-translational modifications to tight junctions by stimulating occluding phosphorylation and inducing tyrosine phosphorylation of zonula occludence that result in

disruption of tight junction and increase permeability.<sup>16,17</sup> Other mechanisms that VEGF can increase vessels permeability are by inducing a rapid and transient phosphorylation of VE-cadherin, disorganisation of endothelial junction proteins and dissociation of the adherence junction.<sup>18,19</sup>

Pericytes loss, increased placental growth factor (PLGF), hepatocyte growth factor I, superoxide, nitric oxide and peroxynitrite and increase in inflammatory mediators such as tumour necrosis factor- $\alpha$ , transforming growth factor- $\beta$ , intercellular adhesion molecule-1 and interleukin-6 all may lead to breakdown of the BRB and can further contribute to macular oedema formation.<sup>20-31</sup> Early in the diabetic retinopathy process, DMO may be driven more by hyperglycaemia and ischaemia induced injuries, whereas other growth factors such as VEGF or PLGF play a greater role once proliferative diabetic retinopathy develops.

## Intraocular Pharmacokinetics of Bevacizumab

Bevacizumab, a recombinant humanised monoclonal immunoglobulin antibody, is an anti-human vascular endothelial growth factor with molecular weight of 149 KD.<sup>32</sup> In rabbits, Bakri and colleagues investigated the pharmacokinetics of 1.25 mg intravitreally injected bevacizumab in both vitreous and aqueous humor and reported elimination half-times of 4.88 days from vitreous and 4.32 days from aqueous.<sup>33</sup> A human study demonstrated that the half-life of bevacizumab in aqueous humor after intravitreal delivery of 1.5 mg was 9.82 days. Bevacizumab concentration peaked on post-injection day 1, with a mean concentration of 33.3  $\mu\text{g/ml}$  and dropped to less than 1  $\mu\text{g/ml}$  at day 51.<sup>34</sup> Another experimental pharmacokinetic study has also demonstrated that IVB concentration above the median inhibition concentration which was determined to be 22 ng/ml would remain for 78 days.<sup>35</sup> An unpublished study by Casky and colleagues showed that half-life of bevacizumab in vitreous of 18 patients after injection of 1.25 mg Bevacizumab was 10 days (IOVS 2007; 48 ARVO E-abstract 4936). Another human study disclosed that elimination half-time of bevacizumab in aqueous after 1.5 mg intravitreal injection was 7.58 days and after 3 mg intravitreal bevacizumab injection was 11.67 days.<sup>36</sup> A study with mathematical model demonstrated that biological activity of intravitreal bevacizumab remained between 27 and 38 days after injection that was somehow similar to ranibizumab.<sup>37</sup> Intra-ocular injections of anti-VEGF agents have systemic absorption and some studies have shown that very low doses of bevacizumab can reach the fellow uninjected eye. It is postulated that bevacizumab enters the eye from the systemic circulation through the anterior route, where it diffuses in the vitreous, rather than entering through the choroidal blood flow. One study investigated changes of serum VEGF concentration after IVB injection in treatment of DMO and reported maximal reduction of serum VEGF was noted on the 7th post-injection day and 28 days later again VEGF level in serum was raised.<sup>38</sup> One experimental study found that concentration of bevacizumab in the vitreous of the rabbits' fellow eye varied incrementally, from 0.35 ng/ml at 1 day to 11.7 ng/ml at 4 weeks while concentration of bevacizumab in the vitreous of injected eye was 400  $\mu\text{g/ml}$  at day 1 and 10  $\mu\text{g/ml}$  at day 30.<sup>33</sup>

## Published Results of Bevacizumab for Diabetic Macular Oedema

Bevacizumab is still an off-label treatment for DMO. Published randomised clinical trials for efficacy of intravitreal bevacizumab for treatment of DMO can be categorised in to two major groups:

1. Intravitreal bevacizumab for treatment of naïve DMO; and
2. Intravitreal bevacizumab for refractory DMO (see *Table 1*).

## Intravitreal Bevacizumab for Treatment of Naïve Diabetic Macular Oedema

The results of one randomised clinical trial has been published in three separate reports (publications are related to the same study) and disclosed that in terms of VA improvement the significant superiority of the IVB over the combined IVB/IVT and MPC treatment that had been observed at month 6 did not sustain up to 24 months. The authors concluded that although IVB treatment may be a better choice than IVB/IVT and MPC in short term, the magnitude of beneficial effect of IVB diminished over time. In that study IVB yielded a better visual outcome at 6 months compared with MPC however a change in CMT beyond the 6-week time point that corresponded to the vision change was not detected. Interestingly no adjunctive effect of IVT could be demonstrated in short and long term.<sup>39-41</sup> The DRCR Network also conducted a randomised clinical trial of the short term effect of IVB for DMO (24 weeks) and demonstrated subgroups of cases that had received 1.25 and 2.5 mg bevacizumab at baseline and six weeks, had a larger reduction in CMT at three weeks and an approximately one line improvement in vision at 12 weeks when compared to a group that were treated by MPC alone at baseline. The combination of IVB and MPC had no short-term benefit in the DRCR Network study.<sup>42</sup> One other clinical trial reported that IVB was an effective drug for treatment of DMO however adding IVT did not affect the outcomes measures except for elevating the intraocular pressure (IOP).<sup>43</sup> Another study reported that VA and CMT at 12 months were comparable in eyes that were treated with IVB, IVB/IVT and IVT and no beneficial effect of the combination injection was detected.<sup>44</sup>

## Intravitreal Bevacizumab for Refractory Diabetic Macular Oedema

Eyes with clinically significant macular oedema unresponsive to previous MPC, consider as refractory DMO. In one placebo-controlled randomised clinical trial the authors reported three consecutive intravitreal injection of bevacizumab at 6-week intervals had beneficial effect on refractory DMO in terms of CMT reduction and VA improvement. In this study addition of triamcinolone in the first injection seemed to induce earlier visual improvement; however, it did not show any significant additive effect later during follow-up.<sup>45</sup>

More recently the Bevacizumab or Laser Therapy (BOLT) study reported 2 years results comparing intravitreal bevacizumab 1.25 mg versus MPC for treatment of persistent centre-involving CSME in 80 cases. According to this study median gain in BCVA was superior for IVB compared with MPC (+9 letters for IVB versus +2.5 letters for MPC). The median number of treatments over 24 months was 13 for IVB and 4 for MPC. Mean CMT reduction was slightly greater in IVB group at 24 months (-146  $\mu\text{m}$ ) versus the MPC group (-118  $\mu\text{m}$ ) but it was not statistically significant.<sup>46</sup> Several other case series studies have also provided evidence supporting beneficial effect of IVB for persistent DMO with the logic that persistence or recurrence of DMO after MPC may be attributed to the production of VEGF by the residual ischaemic retina, which may result in persistent or recurrent DMO despite MPC.<sup>47-49</sup>

In summary, literature searches conducted in this study disclosed that almost all studies published up to now provided evidence supporting use of IVB for treatment of either naïve or persistent DMO in short and long term up to 2 years.

**Table 1: Published Results of Intravitreal Bevacizumab for Diabetic Macular Oedema**

Author, year	Purpose	Study design	Outcomes measures	IVB Dose	Interval of injections	Naive or refractory / DMO	Duration of study	Number of eyes	Treatment regimen	Results
DRCR:Net 2007	IVB for DMO	Randomized phase 2 clinical trial	CMT, BCVA	1.25 mg 2.5 mg	6 weeks	Naive	24 weeks	121	A) foal MPC B) 1.25 mg IVB at base line and 6 weeks C) 2.5 mg IVB at baseline and 6 weeks D) 1.25 mg at baseline E) 1.25 mg IVB at base line and 6 weeks + MPC at 3 weeks	Group B and C had a greater reduction in CMT at 3 weeks and 1 line better median VA over 12 weeks. There were no significant differences between group B and C. Combining MPC with IVB resulted in no apparent short term benefit
Soheilian 2007	IVB or IVB, IVT or MPC for DMO	Randomized clinical trial	BCVA, CMT	1.25 mg	-	Naive	12 weeks	103	A) 1.25 mg IVB B) IVB/ IVT/ 1.25 mg IVB and 2 mg IVT C) MPC	The significant treatment effect on VA was demonstrated at both 6 and 12 weeks in the IVB group and only at 6 weeks in the IVB/IVT group. Significant CMT reduction was observed in eyes in the IVB and IVB/ IVT groups only up to 6 weeks , however, CMT changes were not significant in the groups .
Soheilian 2009	IVB or IVB, IVT or MPC for DMO	Randomized clinical trial	BCVA, CMT	1.25 mg	12 weeks	Naive	24 weeks	150 eye	A) 1.25 mg IVB B) IVB/IVT 1.25 mg IVB and 2 mg IVT C) MPC	The significant treatment effect on VA was demonstrated in the IVB group at all follow-up visits and in the IVB/ IVT group at 6 and 12 weeks. CMT Changes were not significant among the groups in all visits.
Soheilian 2012	The same as above	Randomized clinical trial	BCVA, CMT	1.25 mg	12 weeks	Naive	2 years	150 eyes	A) 1.25 mg IVB B) IVB/ IVT 1.25 mg IVB and 2 mg IVT C) MPC	The significant superiority of VA improvement in the IVB group, which had been noted at month 6, did not sustain thereafter up to 24 months, and the difference among the groups was not significant at all visits. The reduction of CMT was more in the IVB group in relation to the other two treatment groups however , the difference among the groups was not significant at any of the follow- up visits.
Lin 2012	IVB or IVB/ IVT or IVT for DMO	Randomized three-arm clinical trial	BCVA, CMT	1.25 mg	6 weeks	Naive	12 months	111 eyes	A) IVB group, two IVB injections with 6 weeks intervals B) IVB / IVT (2 mg IVT + 1.25 mg IVB) C) 2 mg IVT	The IVB/ IVT group and IVT group showed better visual acuity and reduced CMT at 6 weeks and 3 months. However, no significant difference in VA and CMT was observed between 3 groups. No significant differences in VA or CMT were observed between the IVB/ IVT and IVT group during the follow- up.
Sobaa 2012	IVB or IVT or MPC for DMO	Matched group- study	BCVA	1.25 mg	6 weeks	Naive	12 months	126 eyes	A) IVB 1.25 mg B) IVT 4 mg C) MPC	6) Rates of VA stabilization (within $\pm 0.2$ logMAR of baseline) were not different between the groups. Higher rates of anatomical and functional success , however , were evident in IVB and IVT groups within 6 months of treatment.
LAM 2009	1.25 mg or 2.5 mg IVB for DMO	randomized clinical trial	BCVA and CMT	1.25 mg 2.25 mg	Three monthly injections	Diffuse Naive and refractory DMO	6 months	52 eyes	A) 1.25 mg IVB B) 2.5 mg IVB	No significant difference in BCVA was observed between the two groups at any time point. Significant improvements of mean logMAR BCVA between baseline and 6 month were seen (improved 0.63 to 0.59 in the 1.25 mg group and 0.6 to 0.47 in the 2.5 mg group). Significant CMT reduction was observed in both groups at all follow – up visits. (P <0.013)

Table 1: Continued

BOLT Study 2012	IVB or MPC for DMO	randomized clinical trial	BCVA	1.25 mg	6 weeks	Refractory / DMO	24 months	80 eyes	A) MPC B) IVB 1.25 mg at baseline, 6 and 12 weeks, then as needed	Mean gain in BCVA at 24 months: (A) +2.5 letters;(B) +9 letters (p=0.005). Mean change in CMT at 24 months: (A) -118 µm; (B) -146 µm
PACORES 2009	IVB (1.25 mg or 2.5 mg) For DMO	Retrospective interventional comparative case series	BCVA	1.25 mg and 2.5 mg	6 weeks	Diffuse Naïve DMO	24 months	139 eyes	A) IVB 1.25 mg B) IVB 2.5 mg	In the 1.25 mg group at 1 month, BCVA improved from 20/150 to 20/107 (P<0.0001). The mean BCVA at 24 months was 20/75 (P<0.0001). Similar results were observed in the 2.5 mg group. (20/168 to 20/118 (P= 0.02) at 1 month and to 20/114 at 24 months (P<0.0001)). In the 1.25 mg IVB The CMT decreased from 466.5±145.2 µm at baseline to 332±129.6µm at 1 month and 286±81.5 µm at 24 months (P<0.0001) Similar results were obtained in the 2.5 mg group
Marey MH 2011	IVB or IVB/ IVT for DMO	Randomized clinical trial	VA and CMT	1.25 mg		Naïve	12 weeks	90	A) IVB B) IVB and IVT (4mg) C) IVT	There was significant improvement in the VA in the three study groups at weeks 6 and 12. Comparing the visual acuity results at 6 weeks between the 3 study groups there was no significant difference and also between each pair of the three study groups ; however at week 12 , there was high significant difference (P= 0.004) and between each pair there was high significant difference between IVT and IVB/ IVT groups (P= 0.001) , significant difference between groups IVT and IVB and no significant difference between group IVB/ IVT and IVB. Comparing the CMT showed the same results.
Soluiman 2010	IVB or IVB+ MPC or MPC for DMO	Randomized clinical trial	BCVA, CMT, FA leakage	1.25 mg		Naïve	6 months	62 eyes	A) IVB B) IVB and MPC C) MPC	At 1 month the improvement in CMT was better than baseline in all groups, yet only significant in the IVB group (P<0.05) and the combined group (P<0.05). At 3 and 6 months the mean CMT reduction was significant only in combined group. At month 1 VA improvement was significant in IVB and combined group, at month 3 VA improvements was significant in combined group and at month 6 there was no significant improvement in the BCVA in all groups.
Ahmadieh 2008	IVB or IVB /T for refractory DMO	randomized clinical trial (Placebo- Controlled)	CMT BCVA	1.25 mg	6 weeks	Refractory	24 weeks	115 eyes	A) three injection of 1.25 mg IVB at 6 weeks intervals B) IVT (2 mg) followed by two injections of IVB at 6 weeks intervals C) sham injection	CMT was reduced significantly in both the IVB and IVB/ IVT groups. Significant improvement of BCVA was seen in both the IVB and IVB/ IVT groups. No significant differences were detected in the changes of CMT and BCVA between the IVB and IVB / IVT groups.

BCVA = best corrected visual acuity; CMT = central macular thickness; DMO = diabetic macular oedema; IVB = intravitreal bevacizumab; IVT = intravitreal triamcinolone; MPC = macular photocoagulation.

## Safety of Bevacizumab

Serious ocular adverse effects of intraocular injection include uveitis, endophthalmitis and retinal detachment. From the literature available to date, there seems to be no greater ocular risks to patients with DMO who had received intravitreal bevacizumab injections than other subgroup of patients, but long-term follow up is needed. Patients with DMO typically are younger than patients with age-related macular degeneration (AMD) and therefore may be at greater risk of cataract progression and IOP elevation after repeated injections. There are some studies that provide data on the systemic safety of intravitreal bevacizumab injection particularly for the treatment of neovascular AMD. It should be noted that many of the published studies are not powered to detect significant differences among study groups with respect to low frequency adverse events. In the Comparison of Age Related Macular Degeneration Trial (CATT) the rates of serious systemic adverse effects (death, myocardial infarction, stroke) were similar for patients receiving either bevacizumab or ranibizumab. Rates of death and arteriothrombotic events were similar for both drugs ( $p>0.6$ ). The proportion of patients with one or more systemic serious adverse events, primary hospitalisations was higher among bevacizumab-treated patients than ranibizumab-treated patients (24.1 versus 19 %,  $p=0.04$ ).<sup>50</sup> Overall from the literature available today, there seems to be no greater systemic risks to DMO patients who are receiving intravitreal bevacizumab.

## Macular Ischaemia and Intravitreal Bevacizumab

Circulation disturbance in the retina and choriocapillaries after intravitreal bevacizumab injection has been a controversial subject in the literature. As bevacizumab is a non-selective VEGF inhibitor, by blocking all isoforms of VEGF, the drug can potentially down regulate activity of essential VEGF isoforms and disturb normal physiological functions of VEGF and eventually interfere with normal retinal and choriocapillaris circulation. Some studies reported that macular ischaemic zone after intravitreal bevacizumab injection was increased.<sup>51,52</sup> One study reported that macular ischaemia had a negative impact on functional and anatomical outcomes 3 months after IVB injections in patients with DMO.<sup>53</sup> On the contrary, the Bolt study reported that the macular perfusion 4 months after IVB injection was not deteriorated.<sup>54</sup> Some other studies justified VA improvement without CMT reduction associated with bevacizumab in cases of DMO may be related to increased macular perfusion rather than leakage reduction and or fluid resorption.<sup>39,41</sup> In conclusion possible harmful effect of bevacizumab on macular perfusion needs to be further clarified.

## Initial Macular Thickness, Patterns of Diabetic Macular Oedema and Response to Bevacizumab

The introduction of OCT allowed for objective morphometric evaluation of DMO. In addition OCT produces cross-sectional images of the retina that have been found to correlate well with retinal histology as demonstrated by light microscopy.

Four patterns of structural changes in DMO have been defined; sponge-like retinal swelling, cystoid macular oedema (CME), serous retinal detachment (SRD) and tractional retinal detachment (TRD).<sup>55-57</sup> Initial CMT is an important factor in decision making for treatment of DMO. It has been shown that foveal thickening more than 180  $\mu\text{m}$  by OCT may be the earliest detectable sign of macular thickening and it may be an indicator for a closer follow up of patients with diabetes.<sup>58</sup>

One study has found that a retinal thickening in DMO of 60 % above the normal value has a 50 % probability for reversal of thickening with MPC, whereas thickening of more than 130 % has a less than 2.5 % probability.<sup>59</sup> One study demonstrated that in cases of DMO with CMT of more than 300  $\mu\text{m}$  had the worst response to MPC.<sup>60</sup> In another recently published report it was demonstrated that in short term (up to 6 weeks) eyes with various initial CMT showed a better VA improvement to IVB than MPC. This better response to IVB persisted only in the eyes with initial CMT of  $\geq 350 \mu\text{m}$  up to 36 weeks.<sup>61</sup> One study evaluated the effect of different treatment modalities on morphological variants of DMO and they reported that only beneficial effect of MPC was on sponge like DMO.<sup>62</sup> Some studies reported that the effectiveness of IVB on diffuse DMO was dependent on the OCT pattern; it was more effective on sponge like pattern rather than those associated with CME and SRD.<sup>63,64</sup> It is important to note that visual acuity changes are not always parallel to CMT changes in eyes with DMO. Factors such as duration, extent and severity of macular oedema, presence of foveal hard exudate as well as macular ischaemia could have confounding effect.

## Prophylactic Intravitreal Bevacizumab for Diabetic Macular Oedema in Association with Cataract surgery

Progression of DMO and formation of CME are common complications after cataract surgery in the presence of diabetic retinopathy.<sup>65-67</sup> The pathogenesis of these complications may be related to the changes and rise in the concentration of VEGF in response to surgical trauma and inflammation.<sup>29</sup> One study investigated CME following cataract surgery in patients with diabetic retinopathy and they reported that 6 % of the controls and 12 % of diabetic eyes developed a clinical CME up to 6 weeks. In this report increased frequency of macular changes with both FA and OCT was reported. However changes on OCT or FA were often seen without obvious effect on VA. In this study the final visual outcome in eyes with mild to moderate retinopathy, without previous macular oedema was reported to be as good as in normal eyes at 6 months.<sup>68</sup>

One small randomised clinical trial tried to determine the role of IVB injection at the time of cataract surgery on post-operative increase of retinal thickness in patients with pre-existing moderate or severe non-proliferative diabetic retinopathy and CMT of less than 200  $\mu\text{m}$ . They reported that one month after surgery their control group (not receiving IVB) showed a significant increase in CMT, whereas the bevacizumab group did not show any change. However after 6 months no significant differences in CMT and post-operative visual acuity between two groups could be detected.<sup>69</sup>

Management of established DMO in the presence of cataract is even more important because in some diabetic patients with DMO, effective MPC may not be performed because of co-existing cataract. Even uneventful cataract surgery has been proven to exacerbate DMO in such patients therefore the management of these cases may be more difficult if they undergo phacoemulsification alone. In one retrospective study the results of phacoemulsification with combined IVB and IVT injection in patients with DMO and cataract was evaluated and the authors reported that phacoemulsification with combined IVB and IVT provided a decrease in CMT with some gain in VA at 3 months.<sup>70</sup>

In conclusion, the prophylactic role of IVB on development of DMO and even CME during cataract surgery is still not clarified and needs to be proven in larger studies with longer follow up. For established DMO in the presence of cataract, however combination of IVB and

phacoemulsification seems to be logical even in the absence of large supportive studies.

## Bevacizumab Dosage and Frequency of Injections for Diabetic Macular Oedema

One of the unresolved issues in using IVB for treatment of DMO is its optimal dosage and frequency of injections. Some studies suggested use of higher dosage of IVB to achieve a better visual and anatomical outcomes but studies that compared the efficacy of 1.25 mg with 2.5 mg IVB for DMO have shown that no significant difference in terms of BCVA and OCT was observed between IVB at doses of 1.25 mg or 2.5 mg.<sup>71,72</sup>

The frequency of IVB injections for DMO is another controversial subject. The effectiveness of intravitreal bevacizumab injection has been reported to last 6, 8 and 12 weeks.<sup>39-48</sup> In the DRCR Network and BOLT study, a pre-scheduled repeated IVB injections were performed at baseline, 6 and 12 week time point. Subsequent injections were guided by an OCT-based re-treatment protocol.<sup>42-46</sup> In the another study a baseline IVB injection performed and re-treated injections performed on an as-needed bases rather than a pre-scheduled injections.<sup>39-41</sup> The logic for longer interval of IVB injection were decreasing complications in a chronic longstanding diseases like DMO and the fact that IVB concentration above the median inhibition concentration (22 ng/mL) remained for 78 days in vitreous and also to prevent retinal atrophy caused by blocking the neuroprotective cytokines and to protect neurons from acute and chronic injuries.<sup>35,73-75</sup>

Overall it seems higher doses of IVB (>1.25 mg) and routine pre-scheduled repeated injections may not be appropriate in DMO for all cases and decision for re-treatment should be individualised in each patient, although under-treatment with longer interval of injections may occur.

## Conclusion

Literature review suggests an important potential role for pharmacotherapy including anti-VEGF agents in the treatment of DMO. The purpose of this review article was addressing the role of intravitreal injection of bevacizumab alone or in combination with intravitreal corticosteroid in comparison to standard treatment including laser macular photocoagulation for treatment of DMO. Moreover safety, dose, frequency,

and pharmacokinetic of intravitreal bevacizumab as well as the effect of initial macular thickness and OCT pattern of DMO on response based on published literature was evaluated. It has been demonstrated that IVB injection is effective in the treatment of primary and persistent DMO in short and long term up to 2 years. Most of the studies reported no further beneficial additive effect of intravitreal triamcinolone on DMO. Intravitreal dosage of bevacizumab for treatment of DMO was 1.25 mg, however treatment algorithm was different in different studies. While some studies preferred a pre-scheduled strategy of monthly or 6 weeks injections, some others treated their cases on an as-needed basis. Although it has been shown that with the use of intravitreal bevacizumab VA improvement are not always parallel to CMT reduction, most of these studies have disclosed that repeated IVB injections are needed to maintain stable CMT and VA in such patients. The emerging popularity of bevacizumab is also raising concerns about safety but most studies reported intravitreal bevacizumab injection has not significant systemic and local side effects.

The relative cost of bevacizumab and other anti-VEGF agents has been another concern. A comparison in cost of these agents shows that wholesale prices of the medications range from US\$1,950 per dose for ranibizumab, US\$1,850 per dose for VEGF-Trap eye and \$995 per dose for pegaptanib, to less than US\$50 per dose for bevacizumab. That is why the use of bevacizumab is becoming increasingly more prevalent.<sup>76,77</sup>

Future studies should evaluate the role of combined intravitreal bevacizumab with non-steroidal anti-inflammatory drugs (NSAIDs) as well as supplemental inspired oxygen to treat hypoxia for the treatment of DMO.<sup>78,80</sup> Furthermore researches need to investigate new molecular targets to prevent or delay the progression of DMO and develop novel strategies for sustained intraocular delivery of anti-VEGF agents to reduce the burden, cost and risk of injections.

## Description of Evidence

Literature search last were conducted in December 2012 in PubMed with no date restriction and limited to studies published in English. The search strategy used the terms 'diabetic macular edema', 'bevacizumab', 'avastin', 'safety of intravitreal bevacizumab', 'pattern of diabetic macular edema', 'macular ischemia' and 'dose and frequency of intravitreal bevacizumab'. ■

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