REVIEW

State of the art management of diabetic macular edema

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Abstract

Macular edema following diabetic retinopathy is one of the ocular complications associated with diabetes, and it is the leading cause of visual loss in the active young and middle aged population in developed countries. While all patients with diabetes particularly those with diabetic retinopathy are at increased risk of developing eye complications, early detection and timely intervention may prevent or delay loss of visual acuity. Systemic management of diabetes through combined control of blood sugar, hypertension, and hyperlipidemia has remained the most effective method to prevent diabetic retinopathy and its progression. Development of diabetic retinopathy and related complications require, surgical and medical interventions including photocoagulation, vitrectomy, and intravitral drug injection to preserve vision. Considering recently most popular treatment of diabetic macular edema (DME) including intravitreal anti-vascular endothelial growth factor (VEGF) agents, several issues such as ideal regimen, duration of treatment, combination therapy and long -term safety have remained unanswered yet and deserve further investigations. In this review, all the articles that had investigated such treatment modalities for DME as well as pharmacokinetic, efficacy, safety, dose and frequency of intravitreal pharmacologic agents and also the effect of macular ischemia, initial macular thickness and optical coherence tomographic patterns of DME on the final outcomes of treatment with Intravitreal drugs are reviewed. In summary, literature searches reveal that almost all studies that have been published up to now provide some evidence that support the use of intravitreal anti-VEGF agents for treatment of either naïve or persistent DME in short and long term up to two years.

Key words: Intravitreal vascular endothelial growth factor inhibitor agent; Clinically significant diabetic macular edema; Diabetic retinopathy; Macular laser photo-coagulation; Intravitreal steroid

Core tip: There are multiple treatment approaches for diabetic macular edema so in this article we reviewed almost all treatment modalities for diabetic macular edema and efficacy and side effects of them.

INTRODUCTION

Recent published studies have been dramatically modifying the management paradigm of diabetic macular edema (DME). The Recent protocols based on these studies have substituted pharmacotherapy instead of the standard treatment of macular laser photocoagulation for DME. Nowadays, the strategy for treatment of DME is to find some ways for either preventing DME formation or early intervention in a symptomatic stage of diseases to preserve vision. In the past, Laser photocoagulation was the only evidence based standard treatment available for subjects with CSME, defined by the early treatment diabetic retinopathy study (ETDRS)[1]. However, the beneficial effect of macular laser photocoagulation (MPC) on DME was attractive, because it reduced the risk of moderate visual loss by 50% at that area[1]. For diffuse DME, MPC was even less effective and based on one study, applying modified MPC, visual acuity (VA) improvement observed in only 14.5% of the eyes[2]. Moreover, diabetic retinopathy clinical research network (DRCR. Net) has recently shown a VA improvement of more than 5 letters in 51%, 47% and 62% of cases using MPC at 1, 2 and 3 years follow-up, respectively[3,4]. Destructive nature, adverse effects and suboptimal efficacy of MPC have led investigators to find alternative treatments. Pharmacotherapy of DME with systemic and intravitreal drugs especially intravitreal steroids and anti-vascular endothelial growth factor (VEGF) agents such as Pegaptanib, bevacizumab, ranibizumab, and aflibercept have been the focus of the most recent attentions. The use of intravitreal drugs is becoming more popular; however several issues such as optimal medication, length of treatment, combination therapy and long-term safety of agents are still not clear enough and deserve further investigations. The present review article attempts to provide some answers for common questions in this regard on the basis of published literatures.

EPIDEMIOLOGY

DME is the major cause of visual loss in the active young and middle aged patients worldwide. While the risk of DME has been shown to vary with a number of factors including the type of diabetes, disease duration, and insulin dependence, it is expected to grow along with the prevalence of diabetes. Almost 285 million people have diabetes and one fourth of them will finally develop macular edema. The rise in the incidence of diabetes is a major public health concern worldwide and diabetic retinopathy, as the most common microvascular complication of diabetes, may lead to blindness in the working aged population. Based on one study, it has been estimated that one out of 12 Americans with diabetes aged $\geqslant$ 40 has vision threatening retinopathy. The number of people with type 2 diabetes is growing particularly in countries with low socioeconomic conditions. Some epidemiologic studies has shown the association of high incidence of diabetic retinopathy with poor control of hyperglycemia and hypertension, which both are more common in countries with limited access to health care. According to another study, within a 10 year period the chance of developing macular edema was almost 20.1% in patients with type I diabetes, 25.4% of type 2 patients receiving insulin and 13.9% of type 2 patients not receiving insulin. DME may cause severe visual loss if remain untreated, with up to 33% of cases losing 3 lines of vision after 3 years[1,5-9].

PATHOPHYSIOLOGY OF DME

For pathogenesis of DME several physiological mechanisms have been postulated up to know. The exact mechanism by which hyperglycemia initiates the vascular disruption and results in the blood retinal barrier (BRB) breakdown in diabetic retinopathy have remained poorly understood. Several hypotheses are contributed to DME formation including: (1) increase in hydrostatic pressure that was described by Starling. Similar to congestive heart failure, DME can be considered as a congestive macular edema. Based on Starling law, hydrostatic and oncotic pressure counteract each other; the difference between such pressures is responsible for the movement of fluid between tissue beds and intravascular spaces. Changes in vessel diameter along with increased hydrostatic pressure can contribute to edema. Furthermore, the above-mentioned mechanism can increase in shear stress which may damage endothelial cells or may cause endothelial decoupling over time[10-12]; (2) ischemia secondary to hypoxia can lead to a decrease in oxygen tension in retina resulting in vascular dilation and this can increase macular edema by raising hydrostatic pressure. An increase in oxygen tension may reduce macular edema by reversing the aforementioned mechanism[13]; (3) hyperglycemia per se or together with other mechanisms may induce endothelial dysfunction and cause more vascular damage[14,15]. Hyperglycemia disrupts the retinal neurovascular unit through biochemical abnormalities that may damage or induce apoptosis of endothelial cells, pericytes, microglia, and neurons. The effects of intracellular hypoglycemia include free radical induction (oxidative stress), protein kinase C (PKC) activation, advanced glycation end-product formation, and increased hexosamine pathway flux[13]; and (4) increased VEGF production: VEGF mediates angiogenesis through promoting endothelial cell migration and proliferation. Among the various VEGF factors, VEGF-A, is a critical regulator of ocular angiogenesis and vascular permeability[16-20].

All above described aberrations result in hypoxia, ischemia, inflammation, and alteration of the vitreo-retinal interface.

The following factors have also been involved

in the pathogenesis of macular edema formation and breakdown of BRB: increased placental growth factor (PLGF), hepatocyte growth factor l, nitric oxide, peroxynitrite and on the other hand an increase in inflammatory mediators such as tumor necrosis factor-α, transforming growth factor-β, intercellular adhesion molecule-1 and interleukin-6[21-31]. It is important to note all cases of macular edema following diabetic retinopathy can not be accounted for by a single molecular target. Instead, overlapping and interrelated molecular pathways play a role in both initiating vascular damage and prolongation of tissue damage that further increase chronic macular edema.

SYSTEMIC TREATMENT OF DME

The purpose of systemic treatments in DME is either to reduce the risk of retinopathy development in diabetic patients or to decrease the risk of progression of existing retinopathy or maculopathy to more severe forms. Systemic treatments mostly focus on metabolic and blood pressure control which are modifiable risk factors for DME. Renin-angiotensin system inhibitors and angiotensin converting enzyme blockers like lisinopril, candesartan, enalapril and losartan are treatment modalities which have shown high probability of slowing the progression of retinopathy[32,33]. Lipid lowering agents such as fenofibrate and statins may be useful for treating DME [34-41].

PHARMACOKINETICS OF INTRAVITREAL DRUGS USING FOR DME

Bevacizumab

Bevacizumab, a recombinant humanized monoclonal immunoglobulin antibody, is a VEGF inhibitor agent with molecular weight of 149 KDa. One experimental study has demonstrated that the elimination half-time of bevacizumab was 4.88 d from vitreous and 4.32 d from aqueous after its intravitreal injection in rabbits[42]. The half-life of bevacizumab in aqueous humor and vitreous after intravitreal injection of 1.5 mg were 7.58-9.82 d and 10 d, respectively[43,44]. Another experimental study has also demonstrated that intravitreal bevacizumab (IVB) concentration more than the median inhibition concentration which was determined to be 22 ng/mL would last for about 78 d[45,46]. Intra-ocular injections of anti-VEGF agents have systemic absorption and some studies have shown that small doses of bevacizumab can reach the fellow eye. The concentration of bevacizumab in the vitreous of the rabbits' uninjected eye increased gradually, from 0.35 ng/mL at day 1 to 11.7 ng/mL at week 4 while its concentration in the vitreous of injected eye is 400 μg/mL at day 1 and 10 μg/mL at day 30[42].

Ranibizumab

Ranibizumab is a humanized monoclonal antibody fragment with a molecular weight of 48 KDa and binds

to all isoforms of VEGF-A. Multiple experimental studies have disclosed that vitreous and aqueous elimination half-life was calculated to be 2.88-9 d and 2.84-7.19 d, respectively[47-51]. Another study has demonstrated that after Intravitreal injection of ranibizumab, it was distributed rapidly to the retina (6-24 h), and the concentrations were approximately one third of primary amount in the vitreous and bioavailability to the retina was 50% to 60%[51]. Based on experimental and clinical studies significant biological activity of ranibizumab (0.5 mg) usually persists for 30 d after intravitreal injection[50].

Aflibercept

Aflibercept has a VEGF-Trap activity. It is a fusion protein with high VEGF binding activity and molecular weight of 110 KDa and binds to VEGF-A, VEGF-B and placental growth factor. VEGF Trap has a very high VEGF-binding affinity about 140 times more than that of ranibizumab. A study has demonstrated that aflibercept could be detected in the rabbit's vitreous cavity until day 28 and the average retention time with standard error after correction for radioactive decay was 4.58 ± 0.07 d[52]. One study has revealed that after injection of aflibercept with doses of 0.5, 2 and 4 mg, the intravitreal an anti-VEGF activity similar to ranibizumab at 30 d, would occur at 73, 83 and 87 d, respectively[53].

Pegaptanib

Pegaptanib is a small 28-base RNA aptamer that specifically binds and blocks the 165-amino-acid isoform of VEGF (VEGF165) and, therefore, has no pan-VEGF activity. The available data for systemic pharmacokinetics of pegaptanib refer to measurements after intravenous injection in rhesus monkeys. Its measured elimination half-live was short (9.3 h)[54].

Intravitreal corticosteroids

Corticosteroids reduce the breakdown of the blood-retinal barrier and experimentally have been disclosed to down regulate VEGF production too. Pharmacokinetic of the most popular corticosteroids being used for the treatment of DME is described below.

Triamcinolone acetonide

Triamcinolone acetonide is a potent anti-inflammatory and anti-angiogenic agent. A human study has demonstrated that intravitreal triamcinolone acetonide (TA) retention time was 141.8 ± 39.6 d in patients with retinal vein occlusion and 114.5 ± 59.6 d in patients with macular edema secondary to diabetic retinopathy[55]. Another experimental study has disclosed that half-life of preservative free triamcinolone acetonide in the vitreous, after intravitreal injection of 4, 16, and 4 mg triamcinolone containing preservative, were found to be 24, 39, and 23 d, respectively[56]. The triamcinolone acetonide concentration in serum

after intravitreal high-dose injection did not increase significantly. It's concentration reached from 0 μg/L preinjection to 0.065 ± 0.21 μg/L postinjection[57].

Sustained-release dexamethasone intravitreal implant
Dexamethasone, as one of the potent corticosteroids family, has been demonstrated to suppress inflammation by inhibiting multiple inflammatory cytokines which usually result in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells. OZURDEX® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone. After intravitreal sustained- release dexamethasone injection (0.7 mg), investigators were able to detect it in the retina and vitreous till 6 mo, with peak concentrations during the first 2 mo in one experimental study[58]. Another experimental study has evaluated the dexamethasone pharmacokinetics after sustained-release dexamethasone intravitreal implantation in nonvitrectomized and vitrectomized eyes. Dexamethasone could be detected in both nonvitrectomized and vitrectomized eyes for up to 31 d. There were no statistically significant differences in dexamethasone concentration between nonvitrectomized and vitrectomized eyes at any follow up ($P > 0.05$). The maximum concentrations of dexamethasone in retina of nonvitrectomized eyes was 4110 ng/mL and in retina of vitrectomized eyes was a bit lower (3670 ng/mL)[59].

Fluocinolone acetonide sustained delivery device
Solubility of fluocinolone acetonide is much lower than dexamethasone (almost 1/24). Duration of the effect of intravitreal Retisert implant is about three years. In fluocinolone acetonide sustained delivery device–implanted eyes, the mean levels of drug in the vitreous varied from 0.10 to 20.21 mg/mL within 54 wk. The mean levels did not show statistically significant difference at various time points. Fluocinolone acetonide could not be detected at any follow up in the aqueous of drug device-implanted eyes or in the aqueous or vitreous of fellow eyes that did not contain a device[60].

PUBLISHED RESULTS OF BEVACIZUMAB FOR DME
Bevacizumab is still an off-label treatment for DME. Efficacy of bevacizumab based on published randomized clinical trials can be categorized into two major groups: (1) intravitreal bevacizumab for of naïve DME; and (2) intravitreal bevacizumab for refractory DME (Table 1).

Intravitreal bevacizumab for treatment of naïve DME
One randomized clinical trial that has been published in 3 separate reports (publications are related to the same study) demonstrated that improvement of VA of the IVB over the combined IVB/IVT and MPC treatment that was observed at month 6 did not sustain for 2 years. The authors concluded that despite better efficacy of IVB over combined IVB/IVT and MPC in short term, the magnitude of its effect lessened over time. Based on that study IVB provided a better visual outcome at 6 mo in comparison to MPC, however any alteration in CMT beyond the six-week time point corresponded to the vision change was not detected. Interestingly no adjunctive effect of IVT could be demonstrated in short and long term[61-63]. DRCR. Network also conducted a randomized clinical trial of the short- term effect of IVB for DME (24 wk) and demonstrated subgroups of cases that had received 1.25 and 2.5 mg bevacizumab at baseline and 6 wk had a larger reduction in CMT at 3 wk and an approximately one line improvement in vision at 12 wk 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 DRCR Network study[64]. One clinical trial has reported that IVB was an effective drug for treatment of DME and adding IVT did not affect the outcomes except for elevating the intraocular pressure (IOP)[65]. Another study has reported that VA and CMT at 12 mo were comparable in eyes that were treated with IVB, IVB/IVT and IVT and no beneficial effect of the combination injection was detected[66].

Intravitreal bevacizumab for refractory DME
Refractory cases of DME are defined as cases who do not response to macular photocoagulation. In one randomized clinical trial, the authors reported that three, 6 wk-interval injections of bevacizumab at had a more beneficial effect on refractory DME. In this study the addition of triamcinolone in the first injection although induced earlier visual improvement; however, it did not cause any significant additive effect during follow-up[67]. More recently Bevacizumab or Laser Therapy study has reported the two years results of comparing intravitreal bevacizumab (1.25 mg) *vs* MPC for the treatment of persistent center-involving CSME in 80 cases. According to this study, the median gain in BCVA was higher for IVB in comparison to MPC (+9 letters for IVB *vs* +2.5 letters for MPC). The median of treatments were 13 for IVB and 4 for MPC groups. Mean central macular thickness (CMT) reduction in 24 mo was slightly greater in IVB group (-146 μm) *vs* the MPC group (-118 μm) but it was not statistically significant[68]. Several other case series have also provided evidence supporting beneficial effect of IVB for persistent DME with the logic that persistence or recurrence of DME after MPC may be attributed to the creation of more VEGF by the ischemic retina, which eventually may raise to persistent or recurrent DME despite MPC[69-71].

In summary, literature searches for present study disclosed that almost all relevant published studies have provided evidences supporting IVB for treatment of either naïve or persistent DME in short and long terms up to two years.

Table 1 Summary of the studies using intravitreal Bevacizumab for treatment of diabetic macular edema

Ref.	Purpose	Study design	Out comes measures	IVB dose	Interval of injection	Naive or refractory/ DME	Duration of study	Number of eyes	Treatment regimen	Results
Soheilian *et al*[61]	IVB or IVB, IVT or MPC	Randomized clinical trial	BCVA, CMT	1.25 mg	-				(1) 1.25 mg IVB; (2) IVB/ IVT/ 1.25 mg IVB and 2 mg IVT; and (3) MPC	Group B and C had a greater reduction in CMT at 3 wk and 1 line better median VA over 12 wk there were no significant differences between group B and C. Combining MPC with IVB resulted in no apparent short term benefit
Soheilian *et al*[62]	IVB or IVB/ IVT or MPC	Randomized clinical trial	BCVA, CMT	1.25 mg	12 wk	Naïve	24 wk	150 eye	(1) 1.25 mg IVB; (2) IVB/ IVT 1.25 mg IVB and 2 mg IVT; and (3) 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 wk. CMT Changes were not significant among the groups in all visits
Soheilian *et al*[63]	the same as above	randomized clinical trial	BCVA, CMT	1.25 mg	12 wk	Naïve	2 yr	150 eyes	The same as above	The significant superiority of VA improvement in the IVB group, which had been noted at month 6, did not sustain thereafter up to 24 mo, 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
DRCR.Net[64]	IVB for DME	Randomized phase 2 clinical trial	CMT, BCVA	1.25 mg 2.5 mg	6 wk	Naive	24 wk	121	(1) Foal MPC12 or (2) 1.25 mg IVB at base line and 6 wk; (3) 2.5 mg IVB6 at baseline and 6 wk or (4) 1.25 mg at baseline; and (5) 1.25 mg IVB at base line and 6 wk + MPC at 3 wk	The significant treatment effect on VA was demonstrated at both 6 and 12 wk in the IVB group and only at 6 wk in the IVB/IVT group. Significant CMT reduction was observed in eyes in the IVB and IVB/ IVT groups only up to 6 wk, however, CMT changes were not significant in the groups
Marey *et al*[65]	IVB or IVB/ IVT for DME	Randomized clinical trial	VA and CMT	1.23 mg		Naïve	12 wk	90	(1) IVB; (2) IVB and IVT (4 mg); and (3) IVT	There was significant improvement in the VA in the three study groups at week 6 and 12. Comparing the visual acuity results at 6 wk 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

Lim *et al*[66]	IVB or IVB/ IVT or IVT	Randomized 3arm clinical trial	BCVA, CMT	1.25 mg	6 wk	Naïve	12 mo	111 eyes	IVB group, two IVB injections with 6 wk intervals; IVB / IVT (2 mg IVT + 1.25 mg IVB); 2 mg IVT	The IVB/ IVT group and IVT group showed better visual acuity and reduced CMT at 6 wk and 3 mo. 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
Ahmadieh *et al*[67]	IVB or IVB/T for refractory DME	Randomized clinical trial (Placebo-Controlled)	CMT BCVA	1.25 mg	6 wk	Refractory	24 wk	115 eyes	(1) three injection of 1.25 mg IVB at 6 wk intervals; (2) IVT (2 mg) followed by two injections of IVB at 6 wk intervals; and (3) sham injection	CMT was reduced significantly in both IVB and IVB/ IVT groups. Significant improvement of BCVA was seen in both IVB and IVB/ IVT groups. No significant differences were detected in the changes of CMT and BCVA between the IVB and IVB/IVT groups
BOLT study[68]	IVB or MPC for DME	Randomized clinical trial	BCVA	1.25 mg	6 wk	Refractory /DME	12 mo	80 eyes	IVB MPC	The mean ETDRS BCVA at 12 mo was 61.3 ± 10.4 in the IVB group and 50.0 ± 16.6 in the MPC group. The IVB group gained a median of 8 ETDRS letters, whereas the MPC group lost a median of 0.5 ETDR letters. At 12 mo, CMT decreased from 507 ± 145 μm at baseline to 378 ± 134 μm ($P < 0.001$) in the IVB group, whereas it decreased to a lesser extent in the MPC group, from 481 ± 121 μm to 413 ±135 μm ($P = 0.02$)

IVB: Intravitreal bevacizumab; IVP: Intravitreal pegaptanib; IVR: Intravitreal ranibizumab; IVT: Intravitreal triamcinolone; IVTL: Intravitreal triamcinolone plus laser; IVVTE: Intravitreal VEGF Trap Eye; DME: Diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness.

PUBLISHED RESULTS OF RANIBIZUMAB FOR DME

There are multiple clinical trials (READ-2, REVEAL, RESTORE, RESOLVE, RIDE, RISE and DRCR.net) that have investigated the effect of intravitreal ranibizumab for the treatment of DME. In such comparison studies the efficacy of intravitreal ranibizumab with macular photocoagulation or the combination of intravitreal ranibizumab and MPC (READ-2, RESTORE and REVEAL) was evaluated. Some other studies have compared the response of DME to intravitreal ranibizumab with sham group (RESOLVE, RIDEand RISE). Furthermore, DRCR. net has compared the effect of intravitreal ranibizumab and prompt laser with deferred laser treatment for DME.

READ-2 was the first large RCT (*n* = 126) which made a comparison between ranibizumab (0.5 mg) alone, ranibizumab combined with laser and laser alone. In a period of 6 mo, BCVA improved dramatically in ranibizumab group compared with laser alone. Adding laser to ranibizumab did not provide further BCVA gain at 6 mo. In this study with two years follow up disclosed that use of ranibizumab caused more benefits for patients with DME. Furthermore, when ranibizumab was combined with focal or grid laser treatments, the residual edema and frequency of injections were decreased as well[72,73]. In two similar studies REVEAL study (*n* = 396) and RESTORE study (*n* = 345)] in 12 and 24 mo follow up, the same results as READ-2 study was achieved[74,75]. In RESOLVE study 151 cases were randomly assigned to two doses of ranibizumab (0.3 and 0.5 mg) and sham injection. This study disclosed that the maximum improvement of best corrected visual acuity (BCVA) at one year was obtained in 0.3 mg group (11.8 letter gain) comparing to the 0.5 mg group (8.8 letter gain) or sham injection (1.4 letter loss)[76]. In other two similar studies in terms of the design (RISE and RIDE) 0.3 and 0.5 mg of ranibizumab with sham injection were compared. In the RISE study, a better visual outcome ($\geq$ 15 letters gain) was observed in the 0.3 mg group at two years, However in the RIDE study a better outcome was reported in the 0.5 mg group. In both of these studies a rapid sustainable VA improvement was reported and risk of loosing visual acuity decreased[77]. In another

clinical trial DRCR.net, compared ranibizumab (0.5 mg) plus prompt laser (3-10 d after ranibizumab injection) and deferred laser ($\geq$ 24 wk after ranibizumab) with sham injection plus prompt laser, and with triamcinolone plus prompt laser. In this study both groups that had received ranibizumab had a better VA improvement than triamcinolone or laser alone groups within 12 mo. Two-year results were similar to 1-year results. Three-year results of this study, however, suggested that focal/grid laser treatment shortly after intravitreal ranibizumab led to no better, and possibly even worse vision outcomes than deferring laser treatment ($\geq$ 24 wk) in eyes with center involving DME[78,79]. One recent published study compared intravitreal bevacizumab with ranibizumab in DME cases and reported that both of these agents had similar effects on macular thickness reduction through one year follow up although the average injection number was greater in the bevacizumab group[80] (Table 2).

PUBLISHED RESULTS OF PEGAPTANIB FOR DME

Two studies have evaluated pegaptanib for the treatment of DME and both have compared it with sham injection. Macugen Diabetic Retinopathy Study group in a clinical trial including 172 cases compared 0.3, 1 and 3 mg of intravitreal pegaptanib with sham injection. This study demonstrated that in 36 wk pegaptanib had better VA outcomes. The treatment groups showed more decrease in central retinal thickness and they also required less additional therapy with photocoagulation at follow-up. In this study 0.3 mg was the most efficacious dose[81,82]. Another study including 260 cases compared pegaptanib (0.3 mg) and sham injection and were able to show a better VA improvement in the pegaptanib group within 24 mo. However, there was no significant difference in the proportion of patients with $\geq$ 10 letter improvement[83] (Table 3).

PUBLISHED RESULTS OF AFLIBERCEPT FOR DME

The effect of Aflibercept (AFL) on macular edema secondary to diabetic retinopathy has been evaluated in three clinical trials. DaVinci study included 219 cases, Which were randomized to the following schedules: 0.5 mg every 4 wk, 2 mg every 4 wk, 2 mg monthly for 3 mo, then every 8 wk, and 2 mg monthly for 3 mo followed by treatment as required and these groups were compared with laser treatment alone. All aflibercept groups had a statistically better BCVA and CMT change than the laser group at 6 mo. The most effective regimen that caused better VA improvement and CMT reduction was 2 mg every 4 wk; however, the difference between the groups was not significant. All aflibercept groups showed a significantly better BCVA

compared to laser at 12 mo[84,85].

In VIVID and VISTA studies patients were randomized to 2 mg Intravitreal AFL every 4 wk (2q4) plus sham laser and 2 mg Intravitreal AFL every 8 wk (2q8) following 5 initial monthly doses plus sham laser and macular laser treatment plus sham treatment. In VIVID-DME, BCVA in intravitreal AFL treated eyes was improved by +10.5 letters (2q4) and +10.7 letters (2q8) from baseline up to week 52, compared to an increase of only +1.2 letters for laser only ($P < 0.0001$ for both intravitreal AFL arms compared to laser). In VISTA-DME, BCVA was improved by +12.5 letters (2q4) and +10.7 letters (2q8) compared to the stable result of +0.2 letters in the laser group ($P < 0.0001$). (Unpublished data, presented only at EURETINA, September 2013) (Table 4).

PUBLISHED RESULTS OF INTRAVITREAL CORTICOSTEROIDS FOR DME

Intravitreal triamcinolone

Multiple studies have evaluated the efficacy of intravitreal triamcinolone on naïve or refractory DME. Some of these studies compared the efficacy of intravitreal triamcinolone alone with laser alone whereas some others compared the efficacy of intravitreal triamcinolone alone, combined intravitreal triamcinolone and laser with laser alone. The results of intravitreal triamcinolone alone compared to sham injection have been reported by some investigators. The effect of intravitreal triamcinolone either alone or combined with anti-VEGF agents has been assessed by some other researchers too.

Overall, three doses of triamcinolone acetonide 1, 4 and 8 mg have been assessed in different reports. DRCR.net group evaluated 1 and 4 mg intravitreal triamcinolone in comparison to laser alone. This study disclosed that laser therapy caused a better VA improvement within 24 mo[86]. In two other published reports 4 mg intravitreal triamcinolone injection was compared with laser alone. However no significant BCVA improvement was reported in both groups at 6 and 12 mo[87,88]. The effect of triamcinolone on persistent cases of DME has been evaluated in two studies with different results. The efficacy of 4 mg of triamcinolone comparing with sham injection was assessed and disclosed that mean BCVA improved more significantly in intravitreal triamcinolone injection group up to 24 mo; furthermore, five-year results of the same study confirmed earlier results[89]. Conversely the second study has compared frequent intravitreal triamcinolone injection with the conventional laser therapy for refractory macular edema secondary to diabetic retinopathy, but no further benefits of intravitreal triamcinolone injection was observed[88].

The comparison of the results of intravitreal triamcinolone with anti-VEGF agents have been described earlier.

Table 2 Summary of the studies using intravitreal Ranibizumab for treatment of diabetic macular edema										
Name of study	Purpose	Study design	Outcomes measures	IVR dose	Interval of injection	Naïve or refractory /DME	Duration of study	Number of eyes	Treatment regimen	Results
READ-2 study[73]	IVR for DME	3-arm RCT	BCVA and CMT	0.5 mg	1 and 2 mo	Naïve or refractory	2 yr	126	Group 1 (IVR, n = 42 eyes) injections of 0.5 mg ranibizumab at baseline, 1, 3 and 5 mo Group 2 (L, n = 42 eyes) focal/ grid laser at baseline and 3 mo if CMT ⩾ 250 μm Group 3 (IVRL, n = 42 eyes) IV injections of 0.5 mg ranibizumab at baseline and 3 mo, followed by focal/grid laser treatment 1 wk later	BCVA changes (letters) P value IVR +7.24 0.0003 *vs* L L -0.43 IVRL +3.80 CMT changes (μm) IVR -106.3 All < 0.01 *vs* baseline L -82.8 IVRL -117.2
RESTORE study[74]	IVR for DME	3-arm RCT	BCVA and CMT	0.5 mg	1 mo	Naïve or refractory	1 yr	345	Group 1 (IVR, n = 116 eyes) IV ranibizumab plus sham laser Group 2 (IVRL, n = 118 eyes) 0.5 mg IV ranibizumab plus active laser Group 3 (L, n = 111 eyes) laser treatment plus sham injections	BCVA changes (letters) P value IVR +6.1 SD6.43 < 0.0001 IVRL +5.9 SD7.92 < 0.0001 L +0.8 SD8.56 CMT changes (μm) P value IVR -118.7 < 0.0002 IVRL -128.3 < 0.0001 L -61.3
REVEAL study[75]	IVR for DME	3-arm RCT	BCVA and CMT	0.5 mg	1 mo	NR	1 yr	396	Group 1 (IVR 0.5 mg + sham laser, n = 133) day 1, month 1, 2 and pro-renata thereafter based on BCVA Group 2 (IVR 0.5 mg + active laser, n = 132) day 1, month 1, 2 and pro-renata thereafter based on BCVA Group 3 (sham injection + active laser, n = 131)	BCVA (letters) and CRT(μm) changes: P value IVR + sham laser +6.6; -148.0 < 0.0001 IVR +laser +6.4; −163.8 < 0.0001 Laser + sham +1.8; -57.1
RESOLVE study[76]	IVR for DME	3-arm RCT	BCVA and CMT	0.3 and 0.5 mg	1 mo	Naïve and refractory	1 yr	151	Group 1 (IVR 0.3, n = 51 eyes) 0.3 mg (0.05 mL) IV ranibizumab, 3 monthly injections Group 2 (IVR 0.5, n = 51 eyes) 0.5 mg IV (0.05 mL) ranibizumab, 3 monthly injections Group 3 (C, n = 49 eyes) sham	BCVA changes P value IVR 0.3 +11.8 SD6.6 < 0.0001 *vs* C IVR0.5 +8.8 SD11.0 < 0.0001 *vs* C C -1.4 SD14.2 CMT (μm) P value IVR0.3 -200.7 SD122.2 < 0.0001 *vs* C IVR0.5 -187.6 SD147.8 < 0.0001 *vs* C C -48.4 SD153.4
RISE study[77]	IVR for DME	3-arm RCT	BCVA and CMT	0.3 and 0.5 mg	1 mo	Naïve or refractory	2 yr	377	Group 1 (IVR 0.3 mg, n = 125 eyes) Group 2 (IVR 0.5 mg, n = 125 eyes) Group 3 (C, n = 127 eyes): sham injection	BCVA changes (letters): P value IVR0.3 +12.5 < 0.0001 IVR0.5 +11.9 < 0.0001 C +2.6 CFT (μm): IVR0.3 -250.6 < 0.0001 IVR0.5 -253.1 < 0.0001 C -133.4
RIDE study[77]	IVR for DME	3-arm RCT	BCVA and CMT	0.3 and 0.5 mg	1 mo	Naïve or refractory	2 yr	382	Group 1 (IVR 0.3 mg, n = 125 eyes) Group 2 (IVR 0.5 mg, n = 127 eyes) Group 3 (C, n = 130 eyes): sham injection	BCVA (letters) and CMT (μm): P value IVR0.3 +10.9, -259.8 < 0.0001 IVR0.5 +12.0, -270.7 < 0.0001 C +2.3, -125.8

DME: Diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness. IVR: Intravitreal ranibizumab.

Table 3 Summary of the studies using intravitreal Pegaptanib for treatment of diabetic macular edema

Ref.	Purpose	Study design	Out comes measures	IVP dose	Interval of injection	Naive or refractory /DME	Duration of study	Number of eyes	Treatment regimen	Results
Cunningham *et al*[81]	IVP for DME	RCT	BCVA and CMT	0.3, 1 and 3 mg	1 mo	Naive	36 wk	172	Group 1 (IVP0.3, *n* = 44 eyes) 0.3 mg IV pegaptanib (90 μL) [median 5 injections (range 1-6)] Group 2 (IVP1, *n* = 44 eyes) mg IV pegaptanib (90 μL) [median 6 injections (range 3–6))] Group 3 (IVP3, *n* = 42 eyes) 3 mg IV pegaptanib (90 μL) (median 6 injections (range 1-6) Group 4 (C, *n* = 42 eyes): sham injection	BCVA changes (letters) *P* value IVP0.3 +4.7 0.04 IVP1 +4.7 0.05 IVP3 +1.1 NS C -0.4 CMT changes (μm,) IVP0.3 -68.0 0.02 IVP1 -22.7 NS IVP3 -5.3 NS C +3.7
Sultan *et al*[83]	IVP for DME	RCT	BCVA and CMT	0.3 mg	6 wk	Naive	2 yr	260	Group 1 (IVP, *n* = 133 eyes): 0.3 mg IV pegaptanib Group 2 (C, *n* = 127 eyes) sham injection	BCVA changes (letters) *P* value IVP +5.2 < 0.05 C +1.2 CMT (OCT): Decrease in CMT IVP ≥ 25%: 31.7% NS ≥ 50%: 14.6% NS C ≥ 25%: 23.7% ≥ 50%: 11.9%

DME: Diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness; IVP: Intravitreal pegaptanib.

Table 4 Summary of the study using intravitreal Aflibercept for treatment of diabetic macular edema

Name of study	Purpose	Study design	Out comes measures	IVA Dose	Interval of injection	Naive or refractory /DME	Duration of study	Number of eyes	Treatment regimen	Results
DA VINCI[84,85]	IVVTE for DME	RCT	IVA for DME	0.5 and 2 mg	1 and 2 mo	Naïve or refractory	1 yr	221	Group 1 (IVVTE1, *n* = 44 eyes): IVVTE, 0.5 mg every 4 wk Group 2 (IVVTE2, *n* = 44 eyes): IVVTE, 2 mg every 4 wk Group 3 (IVVTE3, *n* = 42 eyes): IVVTE, 2 mg for 3 initial mo then every 8 wk Group 4 (IVVTE4, *n* = 45 eyes): IVVTE, 2 mg for 3 initial months then as needed Group 5 (L, *n* = 44 eyes): laser photocoagulation Laser modified ETDRS protocol	BCVA changes (letters) *P* value IVVTE1 +8.6 0.005 IVVTE2 +11.4 < 0.0001 IVVTE3 +8.5 0.008 IVVTE4 +10.3 0.0004 L +2.5 CMT(μm) IVVTE1 -144.6 0.0002 IVVTE2 -194.5 < 0.0001 IVVTE3 -127.3 0.007 IVVTE4 -153.3 < 0.0001 L -67.9

DME: Diabetic macular edema; IVTL: Intravitreal triamcinolone plus laser; IVVTE: Intravitreal VEGF Trap Eye; IVA: Intravitral aflibercept.

Intravitreal fluocinolone implants

The efficacy of fluocinolone implant for treatment of DME has been evaluated in two clinical trials. In one of them (FAME study) 0.2 and 0.5 μg per day of fluocinolone was compared with sham injection in patients that were treated with laser. After two years, both doses showed a significant improvement in vision[90]. In the other study 0.59 mg of fluocinolone was compared with laser or no treatment. Significant improvement in VA was observed in the implant group during 9, 18, and 24 mo in comparison with the standard care group. Flucinolone implant group had a significantly higher proportion of eyes showing no evidence of increase in CMT at 6 mo, 1 year, and 2

Table 5 Summary of the studies using intravitreal steroid for treatment of diabetic macular edema

Agent	Number of patients	Total dose (daily release	Duration	Main outcomes
IVTA[86]	693	4 mg TA (Trivaris and triesence) (unknown)	Approximately 3 mo	Less favorable results *vs* photocoagulation at 24 and 36 mo
Fluocinolone acetonide implant (ILUVIEN)[90]	956	180 μg (0.5 μg or 0.2 μg/d)	Up to 3 yr	Generally favorable outcomes at 36 mo
Fluocinolone acetonide implant (retisert)[91]	197	500 μg FA (0.59 μg/d)	2.5 yr	Effective DME therapy at 36 mo, however
				high risks of cataract and glaucoma
Dexamethasone drug delivery system (ozurdex)[92]	171	750 μg dexamethasone (estimated approximately 6.25 μg/d)	Approximately 4 mo	Generally favorable outcomes at 90 d

DME: Diabetic macular edema; IV: Intravitreal; IVTA: Intravitreal triamcinolone; TA: Triamcinolone; FA: Fluocinolone acetonide.

years. The effect of flucinolone implant has persisted up to 30 mo according to these studies[91].

Intravitreal dexamethasone implants

Several clinical trials have shown the efficacy of intravitreal dexamethasone implant for the treatment of DME. In most of published studies use of 0.7 mg of the drug showed a significantly higher proportion of letter gain compared to no treatment group. However lower doses (0.35 mg) of dexamethasone implant did not show statistically significant improvement compared with observation. With further follow up (6 mo), no significant difference between both dexamethasone groups and no treatment group was observed[92]. In the second study, comparison was made between dexamethasone plus laser with laser alone. A better improvement of vision was reported in the dexamethasone plus laser group at 9 mo, However no significant difference between groups during 12 mo of follow up was detected[93] (Table 5).

INTRAVITREAL AND TOPICAL NSAIDS

Pivotal role of prostaglandins in formation of cystoids macular edema after cataract surgery has yielded that the use of NSAIDs, true inhibition of biosynthesis of prostaglandins, for treatment of DME. Many investigators have reported that immune reaction plays some roles in retinal vascular diseases such as DME. In addition to their role as inflammatory mediator, prostaglandins induce angiogenesis. Increase in prostaglandin E2 (PGE2), the major prostaglandin in the retina has been found in various pathologic conditions such as DME. One study demonstrated that PGE2 induces VEGF[94-96]. Topical nepafenac as a prodrug is a non-selective COX inhibitor and hydrolyze into amfenac by uveal tissue and retina. This agent can penetrate into the posterior segment and causes inhibition of some morphologic changes like leukostasis, apoptosis and degeneration of retinal capillary endothelial cells[97,98]. Two small case series showed topical nepafenac significantly decreased CMT and caused an improvement in VA in cases with DME[99,100]. Several studies demonstrated that topical NSAID may prevent cystoids macular edema (CME) after cataract surgery

in cases with diabetes mellitus[101,102].

Two small case series in patients with refractory DME diabetic macular edema refractory to photocoagulation who received two different dosages (500 and 3000 μg) of intravitreal ketorolac, demonstrated a significant VA improvement with no meaningful decrease in macular thickness[103,104]. In one recent study[105] the efficacy of intravitreal diclofenac (500 μg/0.1 mL) with bevacizumab was compared in cases of naïve DME. They reported that in both groups visual acuity significantly improved and visual acuity in patients who received intravitreal diclofenac injection was better than patients who received intravitreal injection of bevacizumab up to 12 wk. However, this functional improvement was noticed without a reduction in macular thickness[105].

SAFETY OF USING INTRAVITREAL AGENTS

Serious ocular adverse effects of intraocular injections may include uveitis, endophthalmitis and retinal detachment. According to the available literatures, intravitreal bevacizumab injections for DME seem not to result in more sever ocular side effects than other treatments, however longer follow-up is still awaitening. The patients with DME are usually younger than patients with senile macular degeneration (AMD) and as a result, they may develop more cataract and glaucoma with multiple intravitreal injections. There are several studies that provide data on the systemic safety of intravitreal VEGF inhibitors. It should be noted that many of the published studies are not valid enough to detect significant differences among study groups with respect to low frequency adverse events. In the CATT study, the rates of serious systemic adverse effects such as CNS stroke, death and heart infarction were almost equal in cases who received either intravitreal bevacizumab or ranibizumab. The rate of severe systemic adverse events and hospitalizations were higher in bevacizumab-treated cases (24.1%) than those who had received ranibizumab (19%)[106]. However, on the basis of currently available literature, such greater systemic risks have not been reported

in DME patients yet. Another concern for treatment of DME by anti-VEGF agents is possible development of retinal atrophy, for which literature is still deficient. However recent sub analysis of the CATT study has evaluated more than 1000 patients with wet AMD to determine the risk factors for geographic atrophy (GA). Subjects had no visible GA at enrollment. Within two years treatment with either ranibizumab or bevacizumab, GA was developed in 18.3%. Risk factors for GA development comprised poor visual acuity, retinal angiomatous proliferation, foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab. The authors recommend that patients be informed about the possible development of GA as a result of monthly anti-VEGF injection, particularly Ranibizumab in AMD cases[107]. Therefore, it can be concluded that in a similar fashion patients with DME may also be prone to development of retinal atrophy, considering their need for further intravitreal injections. This hypothesis needs to be proven by larger studies with long term follow up[108] because it is not still clear that development of GA in CATT study was due to progress in natural course of AMD alone or use of VEGF inhibitor agent. Furthermore cataract formation and increased IOP are common side effects of intravitreal corticosteroid injections and risk of interventional procedures, such as cataract surgery, laser trabeculoplasty, and incisional glaucoma surgery, increase with use of such agents. Outcomes of one clinical trial of IVTA plus laser *vs* laser treatment alone have demonstrated that 61% of patients with DME who had received IVTA required cataract removal *vs* 0% of patients receiving laser therapy alone after two years. Cataract progression was observed in approximately 43% of patients implanted with Retisert (fluocinolone) after one year follow up. Cataract removal was required in 91% of phakic eyes and 33.8% required surgery for ocular hypertention within four years. In the FAME study on phakic population, cataract surgery was performed in 80% of the 0.2 μg per day FAc group, 87% of the 0.5 μg per day FAc group, and 27% of the sham group[89,91,109]. FAME study reported that the percentages of patients who required incisional glaucoma surgery were 8.1% in 0.5 μg per day FAc group and 4.8% in 0.2 μg per day FAc group[109].

Endophthalmitis after intravitreal injections although rare, is a potentially vision-threatening complication and one recent study have estimated this risk to be about one in every 3000 injections or less. Additionally this study reported that bevacizumab, which was prepared by a compounding pharmacy, was associated with greater risks of developing contamination[110].

VITRECTOMY

Some pathologic vitreous changes has been involved as a cause of DME by several mechanical and physiological mechanisms, including macular traction and concentrating of vasopermeable factors in the macular area[111]. A recent published study by DRCR.net evaluated visual and anatomical outcomes of pars plana vitrectomy (PPV) without concomitant cataract surgery for DME in eyes with moderate vision loss and vitreomacular traction. According to this report although CMT was decreased in most of their cases, however visual acuity did not change and the results disclosed that gain of VA $\geqslant$ 10 letters was obtained in 38%, while 22% developed worsening of vision at 6 mo. Another report of DRCR.net interestingly demonstrated that achieving better visual outcomes observed on those cases who had a worse initial visual acuity and also in eyes which epiretinal membrane was removed[112,113]. Anyway, the results of vitrectomy in patients with DME without vitromacular traction are controversial; some studies have demonstrated that vitrectomy with or without ILM removal did not improve vision in DME cases without evident vitreoretinal traction[114,115]. But some other studies have demonstrated that vitreoretinal surgery with or without removal of internal limiting membrane had a beneficial effect in eyes with diffuse non-tractional DME[116,117]. The follower of this idea believes that by vitrectomy, oxygenation of the macula improves and on the other hand the clearance of vasopermeable factors such as VEGFs increases.

LASER

ETDRS disclosed that MPC (focal or grid) can lead to reduction of visual loss in at least 50% of cases. The efficacy of MPC may be attributed to closure of disturbed microaneurysms, although its real mechanism of effect is still unknown[118,119]. It has been hypothesized that by reduction of O2 demand following MPC, some autoregulation mechanisms cause a decrease in blood flow of retina and this eventually reduces edema[120,121]. Few biological studies suggested that the absorption of edema may be due to some changes in the biochemical processes inside the RPE cells[122-127]. Reduction of DME following grid MPC is a support hypothesis for indirect effect of MPC on macular edema[2,128-130]. In one published report two technique of MPC were compared: (1) modified-ETDRS (mETDRS); and (2) mild macular grid (MMG). In the latter technique small mild burns were placed in the whole area of macula, with or without edema, and also microaneurysms were not treated directly. After 1 year follow up, the MMG technique was shown to be less effective than mETDRS technique in reduction of CMT, although visual outcomes in both treatment groups was almost the same[131]. Interestingly one of the most important DRCR.net studies also confirmed the long term better effect of MPC in comparison to intravitreal triamcinolone injection for the treatment of DME. Based on this study short term (6 mo) effect of IVT was better than MPC. However long term effect of MPC was much better and an improvement of more than 5

letter was reported in 62% of caeses after 36 mo follow up[4,86,132]. Subthreshold laser photocoagulation using micropulse laser has recently been the focus of most recent attention for treatment of DME with variable and controversial results. Using this kind of laser may cause little or even no damage to the surrounding retina[132-134]. However future larger randomized studies should prove the result of these preliminary studies.

In conclusion, despite the enthusiasm for using several new pharmacologic agents for DME, laser photocoagulation still remains the gold standard for care of DME cases especially those with focal, non-center involving macular edema.

PROPHYLACTIC TREATMENT FOR DME IN ASSOCIATION WITH CATARACT SURGERY

Progression of DME and development of cystoid changes (CME) are very common after phacoemulsification and also other techniques of cataract removal in cases with diabetic retinopathy[135-137]. Increase in VEGF production following surgical trauma and induction of inflammation may be a cause for formation of CME[29]. Based on one report 6% of the controls and 12% of diabetic eyes developed CME, clinically up to 6 wk after cataract surgery. In this study, eyes with mild to moderate NPDR, and no macular edema was reported to be as good as normal eyes during 6 mo in terms of VA improvement[138]. One study has demonstrated that prophylactic post-operative ketorolac 0.4% may reduce the frequency and severity of macular edema in diabetic eyes after cataract surgery.

One small clinical trial assessed the role of intravitreal bevacizumab injection during cataract surgery in post-operative increase of CMT in cases with moderate or severe NPDR and CMT of less than 200 μm. This report showed that 4 wk after cataract surgery, their controls had a higher macular thickness in comparison to bevacizumab injected group. However, after 6 mo no major differences in CMT and post-operative visual acuity between two groups could be detected[139].

The management of established DME in the presence of cataract is even more important because in some diabetic patients with DME, performing MPC is not possible because of the presence of cataract. All types of cataract surgery even without any complication may worsen DME in such patients; therefore the management of these cases may be more challenging if they undergo phacoemulsification alone. In one retrospective study, the authors reported that phacoemulsification with combined IVB and IVT injection in patients with DME and cataract provided a decrease in CMT along with some gain in VA at 3 mo[140]. In cases with DME and concurrent cataract, some small case series have demonstrated that phacoemulsification and bevacizumab injection at the end of surgery may be helpful and provide some gain in vision. However, no significant change in postoperative CMT, was reported in one study that ranibizumab had been injected simultaneous with cataract surgery. Based on this report, the improvement in vision was due to cataract removal without important change in macular edema[141].

In conclusion, the prophylactic role of anti-VEGF therapy on development of DME and even CME in diabetic cases during cataract surgery is still not clarified and needs to be proven in larger studies with longer follow up. For established DME in the presence of cataract, however, the combination of IVB and phacoemulsification seems to be logical even in the absence of large supportive studies.

INITIAL MACULAR THICKNESS, PATTERNS OF DME AND RESPONSE TO TREATMENT

The development and progression of Ocular coherence tomography (OCT) technology has provided precise measurement and assessment of retinal layers in DME.

Changes in retinal layers in DME has been classified into four types: (1) spongy like retinal swelling; (2) CME; (3) subretinal fluid accumulation; and (4) retinal detachment due to vitreomacular traction[142-144]. CMT findings and parameters are important factors in making decision and selection of type of treatment in DME. It has been shown that foveal thickening more than 180 μm by OCT may be the earliest detectable sign of DME[58]. One study showed that MPC has a 50% chance to decrease CMT in cases with more than 60% increase in CMT in relation to normal value, while increasing CMT of more than 130% has the probability of less than 2.5% for such a decrease in CMT[145]. One study has demonstrated that in cases of DME with CMT of more than 300 μm had the worst response to MPC[146]. In another recently published report, it has been demonstrated that in short term (up to 6 wk) the eyes with various initial CMT showed a better VA improvement by IVB than MPC. This better response to IVB persisted only in the eyes with initial CMT of ≥ 350 μm up to 36 wk[147]. One study has evaluated the effect of different treatment modalities on morphological variants of DME and they have reported that the only beneficial effect of MPC was on spongy like DME[148]. Some studies have reported that the effectiveness of IVB on diffuse DME was dependent on the OCT pattern; it was more effective on spongy like patterns than those associated with CME and SRD[149,150]. Furthermore VA and CMT changes are not always parallel in DME and other factors like duration, amount and degree of edema, existence of hard exudate as well as macular ischemia could have confounding effects.

COST OF TREATMENT

The relative cost of bevacizumab and other anti-VEGF

agents has been another concern in clinical practice. A comparison between the costs of these agents has shown that wholesale prices of the medications range from $1950 per dose for ranibizumab, $1850 per dose for VEGF-Trap eye, and $995 per dose for pegaptanib, to less than $50 per dose for bevacizumab. Recently with availability of intravitreal corticosteroid implants, the cost of treatment is even growing higher. That is why the use of bevacizumab is increasingly becoming more popular and more acceptable throughout the world especially among uninsured patients and in developing countries[151,152]. One cost-benefit analyses study has been reported that multiple modalities for treatment of DME did not show significant changes in terms of cost benefit ratio. The following situations have been reported: (1) For DME cases with VA < 20/200, intravitreal triamcinolone caused a better benefit in comparison to MPC; (2) in pseudophakic cases with DME treatment by VEGF inhibitors was as equally effective as laser combined with IVT; (3) DME cases with VA of > 20/32 got more benefit by laser; and (4) use of aflibercept yielded an almost similar visual results in comparison to other treatment options. In conclusion with achieving similar results, choose of cheaper treatment option can yield 40% to 88% money saving[153].

OTHER TREATMENTS UNDER STUDY AND ONGOING TRIALS

Currently, several studies are evaluating the comparative efficacy of different other pharmacologic agents based on different molecular targets to prevent or delay the progression of DME and their results are still pending. Here, some of the most salient of these studies are breifely mentioned: comparing ranibizumab and bevacizumab, evaluation of two regimen for intravitreal ranibizumab, "treat and extend" and "PRN", using VEGF Trap (aflibercept) in VIVID and VISTA trials, comparing combined intravitreal Fasudil and Bevacizumab with intravitreal Bevacizumab alone[154,155]. There is a noticeable study conducting by DRCR.net through which the safety and efficacy of 3 VEGF inhibitors (ranibizumab, bevacizumab and aflibercept) are comparing.

FUTURE HORIZON

Therapeutic resistance is a major conflict for both patients and physicians. There are different types of resistance. The effect of therapy might be temporary thus retreatment is required. Therapeutic resistance is influenced by multiple factors, related to the patients, disease itself, time of therapeutic intervention, patient's comorbidities and other medications in use.

Diabetes induces inflammatory proteins that persist at elevated levels despite normoglycaemia. Retinal inflammation in diabetes is most likely driven by retinal glial cells and these cells release proinflammatory and neurotoxic substances such as tumor necrosis factor-α when they are activated[156]. Once the inflammatory cascade is activated, anti-VEGF therapies may not be effective. Anti-VEGF agents are useful at early stages when simple mechanisms are inducing edema, but in advanced stages corticosteroids affect a large number of pathways and seem to be more effective. In FAME study, it has been shown that only in patients with prolonged disease, the greatest potential for improvement by intravitreal Flucinolone was observed[109]. Future studies should focus on other recently diagnosed physiologic and biologic targets involved in inflammatory response in patients with diabetes.

SUMMARY AND PRACTICAL GUIDELINE FOR MANAGEMENT OF DIABETIC MACULAR EDEMA

For 30 years, MPC has been the mainstay of treatment for DME. Nevertheless, owing to substantial advances in understanding of DME mechanisms, the management of such cases has been dramatically changed. Recent clinical trials suggest that anti-VEGF therapy should be the first choice of treatment in cases with the center involving DME and visual acuity of 20/30 or less[157]. For cases with non-center involving DME macular photocoagulation is still the standard treatment. Current evidence is largely based on studies on ranibizumab and bevacizumab, although regarding aflibercept, additional data are forthcoming. Bevacizumab or ranibizumab injection should be administered on a monthly basis for at least 3 visits and then as needed depending on the visual acuity stability and OCT findings during follow-up[157]. One most recent published randomized clinical trial on 660 cases compared 2 mg aflibercept with bevacizumab 1.25 mg and ranibizumab 0.3 mg. After one year follow up it was concluded that all three agents improved vision but the relative effect depended on baseline visual acuity. In cases with mild initial visual acuity loss no significant difference among the study groups could be detected. However in cases with worse initial visual acuity aflibercept was more effective for improvement of vision. No significant difference in the rates of serious adverse events between the groups was reported[158]. For cases in which the response to anti-VEGF treatment is unsatisfactory, ETDRS laser treatment should be administered after 6 mo[157]. In cases of DME with peripheral capillary non-perfused area, targeted laser photocoagulation of the involved area has been recommended even in the absence of proliferative changes. For advanced non-responding cases to anti-VEGF agents, intravitreal corticosteroid implants can be tried out. When vitreomacular traction is detected by spectral domain OCT, vitrectomy is indicated; such cases may also benefit from adjunctive intravitreal anti-

VEGF and corticosteroid therapy too[157].

DESCRIPTION OF EVIDENCE

Literature search was conducted in September 2013 in PubMed and Scholar Google with no date restriction and was limited to studies published only in English. The search strategy used the terms including diabetic macular edema, the treatment of diabetic macular edema, systemic therapy for diabetic macular edema, intravitreal bevacizumab, ranibizumab, aflibercept, pegaptanib, triamcinolone, dexamethasone, fluocinolone, NSAIDs for the treatment of DME, the safety of intravitreal drugs, pattern of diabetic macular edema, macular ischemia, and the dose and frequency of intravitreal drug injections.

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