

# A Multimodal Approach to Diabetic Macular Edema

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Diabetic macular edema is one of the most common causes of visual acuity impairment in adults. Various treatment modalities are currently used. They include laser therapy, intravitreal or periocular injection of steroid, intravitreal injection of anti-vascular endothelial growth factor, and pars plana vitrectomy. Introduction of newer therapeutic agents, such as ranibizumab and aflibercept has changed the paradigm of treatment approaches for diabetic macular edema. However, traditional treatment methods, such as laser photocoagulation and vitrectomy, are still being used effectively in certain situations. Each treatment modality has its own unique mode of action, and has advantages and disadvantages at the same time. Given multiple mechanisms are involved in the development of diabetic macular edema, a combination treatment approach is often employed rather than using only one of the treatment modalities. In this review, treatment outcomes of each approach are summarized and combination approaches are discussed.

**Key Words:** Aflibercept; Bevacizumab; Dexamethasone; Diabetic Macular Edema; Ranibizumab

## INTRODUCTION

Diabetic macular edema (DME) is one of the leading causes of visual impairment in adults [1]. Various cytokines are involved in the pathogenesis of DME [2-4]. Among these cytokines, vascular endothelial growth factor (VEGF) plays a key role [5-7].

Various treatment modalities such as laser, intravitreal or periocular injection of agents that inhibit these cytokines, and vitrectomy have been used to control macular edema and to restore visual acuity.

Laser treatment has long been a standard treatment for DME since the 1980s [8]. Although grid or focal laser treatment could reduce risk of visual acuity loss, visual acuity improvement could not be expected in most of the cases. Introduction of therapeutic molecules that can be injected into the vitreous cavity opened a new era for the management of DME [9-11], because this new treatment approach could result in visual acuity improvement. With advances in vitrectomy machineries, surgical intervention is still being considered for refractory DME or even as a primary approach.

These treatment modalities can be used as monotherapy, but

more often are used in combination approaches. Since each treatment modality has their unique mode of action, synergistic effect is expected by combining them.

This review aims to summarize major clinical trial results of each treatment modality and discuss possible combination treatment strategies.

## LASER TREATMENT

Focal or grid laser photocoagulation has long been used to treat diabetic macular edema. Efficacy of focal laser photocoagulation has been proven by a landmark study called the Early Treatment of Diabetic Retinopathy Study (ETDRS) [8]. They showed that focal laser photocoagulation for clinically significant diabetic macular edema reduced the risk of visual loss. Modified laser treatment protocol, such as modified the ETDRS laser technique or mild macular grid laser were then suggested [12-14]. In the modified ETDRS technique, both direct and grid laser treatments are applied. Direct laser treatments are placed to all leaking microaneurysms in areas of retinal thickening between 500 and 3,000 microns

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from the foveal center. No laser is applied within 500 microns from the disc. A spot size of 50 microns with duration of 0.05 to 0.1 seconds laser burns is used. A gray to white burn should be evident after the laser application. Grid treatment is applied to all areas of diffuse leakage or nonperfusion within the area of 500 to 3,000 microns from the fovea. A laser spot size of 50 microns and burn duration of 0.05 to 0.1 seconds are used. Barely visible light burns are made. Mild Macular grid photocoagulation is another modification, in which, only a grid pattern laser is applied to the macula within 500 to 3,500 micron from the foveal center. While laser parameters are similar to the modified ETDRS technique, the grid laser is applied to the unthickened retina as well, and no direct treatment to the microaneurysms are applied. Comparative study of these two techniques showed that the mild macular grid technique was less effective at reducing macular edema than the modified ETDRS technique [13]. Even in an era of Anti-VEGF, focal laser treatment for focal macular edema is still effective and a less expensive treatment modality in some patients. Focal laser treatment for microaneurysms detected by indocyanine green angiography (ICGA) has recently been suggested as an alternative technique [15].

## STEROID INTRA/PERIOcular INJECTION

Steroid treatment is useful for the treatment of diabetic macular edema, because it blocks various cytokines, as well as VEGF, that are involved in the pathogenesis [16]. Intravitreal injection of triamcinolone has shown its efficacy in improving vision in patients with refractory DME [9]. Increased intraocular pressure and cataract development were frequently seen as side effects. Dexamethasone intravitreal implant is being used for various type of macular edema including diabetic macular edema [17]. Dexamethasone implant 0.7 mg and 0.35 mg has proven to be effective in improving and maintaining visual acuity for 3 years. About 4 injections were required over 3 years [10].

## ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR (Anti-VEGF)

As anti-VEGF intravitreal injection opened a new era in treating macular degeneration [11,18], it has become the mainstay treatment of diabetic macular edema these days. Since VEGF has been known to play a significant role in the development of diabetic

macular edema [5,6], inhibition of this cytokine may help resolve edema and restore visual acuity. Currently available anti-VEGF agents that are used for intravitreal injection include ranibizumab, aflibercept, and off label use of bevacizumab. Ranibizumab is the first of these agents that was approved for diabetic macular edema. In a pivotal phase III study [19], 44.8% of the ranibizumab treated patients showed visual acuity gain of 15 letters or more, compared to 18.1% in sham treated patients ( $P < 0.0001$ ) at 24 months. Other studies also showed its efficacy in treating diabetic macular edema [20,21].

Aflibercept is another anti-VEGF agent that has been approved for diabetic macular edema. In its pivotal study, both intravitreal injection of 2 mg aflibercept every 4 weeks (2q4 group), and 2 mg aflibercept every 8 weeks after 5 monthly doses (2q8 group) showed superiority over laser controls [22].

Intravitreal bevacizumab injection has been used as an off label treatment approach for diabetic macular edema [23,24]. Recent comparative study of these three agents has shown that all of these three agents were effective in improving vision in eyes with center-involved diabetic macular edema [25]. At worse levels of baseline visual acuity, aflibercept was more effective at improving vision.

## VITRECTOMY

Surgical approaches through pars plana vitrectomy has long been used to treat diabetic macular edema. They were especially known to be effective for DME with tight posterior hyaloid attachment or those associated with epiretinal membrane traction. Although their effectiveness in reducing macular edema and restoring vision has been suggested in multiple publications [26-28], well executed prospective, multicenter clinical trials have not been conducted. Given recent advances in small gauge, less invasive vitrectomy technique, surgical intervention at earlier stages rather than as a last resort has also been suggested.

## COMBINATION THERAPY

Since multiple factors play a role in the development of diabetic macular edema, instead of using only one of the treatment modalities, a combination treatment approach is suggested.

### 1. Anti-VEGF + focal/grid laser

Based on RISE/RIDE [19] RE,AD-2 [21], RESTORE [20], DRCR

network study results [29], anti-VEGF monotherapy has proven to be more effective than laser monotherapy, regardless of combining laser treatment. However, single injection cannot maintain visual acuity gain, repetitive injections are needed. Combining focal/grid laser treatment may reduce need of anti-VEGF injection [21].

### 2. Intravitreal/periocular steroid + focal/grid laser

Although intravitreal steroid injection treatment has shown promising outcomes in restoring vision from diabetic macular edema, repetitive injection can cause cataract and glaucoma [30]. From this reason, long term outcome of combining triamcinolone intravitreal injection to the laser treatment is not satisfactory [31]. In pseudophakic patients, however, combination of steroid intravitreal injection to laser treatment shows equivalent long term treatment outcomes to the anti-VEGF and laser combination [29]. Therefore, combination treatment using steroid intravitreal injection could be a good option for the patients who have already had, or have plans to have a cataract operation. Although adding macular grid laser to steroid intravitreal injection does not bring additional visual acuity gain, it may help to maintain the effect of steroid for longer periods of time and reduce recurrence [32].

### 3. Anti-VEGF + intravitreal/periocular steroid

Although the action mechanism of anti-VEGF and steroid is different, additive effect from combining these two agents is not significant [33].

### 4. Vitrectomy + intravitreal/periocular steroid + laser photocoagulation

Vitrectomy is one of the options for refractory macular edema. Combination of vitrectomy, steroid intravitreal injection and macular laser photocoagulation has shown long term efficacy for refractory diabetic macular edema [34].

## CONCLUSION

For treatment of diabetic macular edema, various treatment modalities can be used. Each treatment method has a different mode of action. Given that multiple factors play roles in the development of diabetic macular edema, monotherapy often has limited treatment outcome in some of the patients. For these patients, rather than using one of these treatment modalities, a tailored approach by combining them would be reasonable.

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