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Narrative Review

Management of Refractory Diabetic Macular Edema: A Review Article

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Abstract

Diabetic retinopathy (DR) is a major cause of visual impairment worldwide. Visual reduction in patients with DR is usually related to diabetic macular edema (DME). Today, the intravitreal injection of anti-vascular endothelial growth factors (VEGF) is replacing macular laser photocoagulation as the standard treatment for DME; however, in some patients, incomplete responses to the anti-VEGF injection, defined as refractory DME, may occur. Currently, the sequence of using one treatment option and the timing to switch from one agent to another is not fully understood, and the data from clinical trials on the appropriate approach to manage refractory DME is insufficient. In the current study, a review was conducted to evaluate therapeutic options for the management of refractory DME.

Keywords: Diabetes Mellitus, Macular Edema, Intravitreal Injection, Vascular Endothelial Growth Factor, Vitrectomy

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Introduction

Despite improvement in medical and surgical treatments, diabetic retinopathy (DR) remains one of the major causes of visual reduction in the world.[1-5] The visual reduction in patients with DR is usually related to diabetic macular edema (DME) and/or retinal neovascularization.[5-7] Laser photocoagulation as the gold standard of treatment can maintain or improve visual acuity; however, it may result in a reduction in the visual field, color vision, or in contrast sensitivity impairment.[8-10]

Metabolic changes and inflammatory reactions in diabetic patients can lead to the loss of endothelial tight junctions and result in blood-retinal barrier dysfunction.[7,11] DME is affected by the expression of inflammatory mediators such as vascular growth factor (VEGF), transforming growth factor-β, tumor necrosis factor-α, interleukins, and matrix metalloproteinases.[11-13] Therefore, intravitreal injections of anti-VEGFs may be effective in the treatment of DME, but not all patients respond to this treatment modality. Also, due to multiple and frequent injections, the compliance with treatment is usually low with an elevated risk of ocular or systemic complications.[14]

Corticosteroids can inhibit VEGF formation, prostaglandins, and other inflammatory mediators.[15,16] It has been shown that the intravitreal injection of corticosteroids can reduce macular edema secondary to various ocular diseases.[17,18] In comparison to systemic administration, the intravitreal injection of corticosteroids can deliver the appropriate concentration of drug to the retina despite a reduction in systemic side effects.[16]

Many previous studies have demonstrated that anti-VEGFs have significant effects on the treatment of DME with reductions in macular edema and gains in visual acuity. Today, anti-VEGF agents are replacing laser photocoagulation as the primary gold standard.[19-23] In some patients, optimal DME control was not achieved using anti-VEGFs; this group of patients is defined as persistent or refractory DME. However, there is no general agreement on the definition of refractory DME in the literature. The prevalence of refractory DME is estimated to be around 50%.[19]

In this study, a review was conducted to evaluate therapeutic options in the management of refractory DME.

Anti-VEGF Switching

In the REEF study, Dhoot et al prospectively evaluated the efficacy of 0.5 mg and 2 mg intravitreal ranibizumab injections in the treatment of persistent DME.[24] They defined persistent DME as a central subfield thickness (CST) of more than 300 μm after at least 2 injections of 1.25 mg bevacizumab. In total, 43 patients received 3 monthly intravitreal 0.5 mg ranibizumab injections. After 3 months, cases with residual DME changed to 3 monthly intravitreal 2 mg ranibizumab injections. Dhoot et al found that CST had decreased by 113 μm and 165 μm at months 3 and 6, respectively, and mean visual acuity had increased by 6.4 letters and 8.8 letters at months 3 and 6, respectively. The authors concluded that

the intravitreal injection of 0.5 mg or 2 mg ranibizumab can improve anatomic and visual outcomes in eyes with previous low response or no response to intravitreal bevacizumab. Moreover, increasing the ranibizumab dosage from 0.5 mg to 2 mg can lead to better results in some eyes.

In their retrospective multi-center study, Ehrlich et al evaluated the outcomes of intravitreal ranibizumab injections in eyes with refractory DME following an initial minimum of 3 intravitreal bevacizumab injections (DERB study).[25] In total, 202 eyes from 162 patients were included and followed for at least 12 months. A mean of 8.8 ± 4.9 bevacizumab injections were administered before switching to ranibizumab, and a mean of 7.0 ± 2.7 ranibizumab injections were administered in the follow-up period after switching. The median CST decreased significantly from 436 ± 162 μm to 319 ± 113 μm, and the median logMAR visual acuity increased significantly from 0.40 ± 0.48 to 0.38 ± 0.40. This study further showed that a higher CST prior to switching and a higher number of ranibizumab injections after switching were associated with acceptable results. Ultimately, they concluded that switching from bevacizumab to ranibizumab can result in anatomical improvement in many cases with refractory DME and lead to ≥2 lines of visual improvement in 22% of cases. In another retrospective study, Ciulla et al treated 33 eyes with refractory DME following prior treatments (including macular laser, triamcinolone acetonide, bevacizumab or dexamethasone implant) with 0.3 mg intravitreal ranibizumab.[26] After 48 weeks of follow up and a mean of 6 intravitreal ranibizumab injections, the mean CST improved from 384 μm to 335 μm, and the mean best corrected visual acuity (BCVA) improved from 20/110 to 20/90. The authors demonstrated that intravitreal ranibizumab can be effective in the treatment of refractory DME.

Katz et al retrospectively assessed the efficacy of switching to ranibizumab in patients with refractory DME.[27] In their study, 40 eyes of 32 patients with refractory DME who were initially treated with intravitreal bevacizumab were included. They showed that the CST was significantly reduced, but the improvement in visual acuity was not statistically significant following the conversion from bevacizumab to ranibizumab.

In a prospective randomized study, Ehlers et al evaluated the efficacy of intravitreal ranibizumab in the treatment of refractory DME with prior treatment with intravitreal bevacizumab.[28] A total of 27 patients were enrolled in their study and treated with 3 monthly intravitreal ranibizumab injections, after which they were randomized to a treat-and-extend (TAE) regimen (12 eyes) or to monthly injections (15 eyes) over 12 months. In the TAE group, the treatment interval was extended by 2 weeks to a maximum of 12 weeks if the CST was 300 μm or less or if complete intra- or sub-retinal fluid absorption occurred. The mean BCVA increased significantly by 5.3 letters, and the mean CST decreased significantly by 99.6 μm at 12 months. At the final visit, 18.5% of cases had gained 3 lines or more of vision, and 3.7% of cases had lost 3 lines or more. In the TAE group, treated patients gained 8.4 letters and CST decreased by 120.2 μm, while in the monthly injection group, patients gained 2.7 letters and CST decreased by 83.1 μm. The authors demonstrated that switching to ranibizumab in patients with refractory DME to bevacizumab may result in significant anatomic and visual improvement, although TAE and monthly injection protocols resulted in the same outcomes.

In the ROTATE trial, the efficacy of 0.3 mg intravitreal ranibizumab in the treatment of 30 eyes with persistent DME after bevacizumab injection was evaluated.[29] Patients were divided into a sustained group and pro re nata (PRN) group. At month 12, the mean BCVA improvement from baseline was 6.4 letters in the PRN group, 6.7 letters in the sustained group, and 6.5 letters overall. The mean reduction in the CST was 127 μm and 92 μm in the PRN group and sustained group, respectively, and 116 μm overall. Finally, the authors concluded that intravitreal injection of 0.3 mg ranibizumab can improve the anatomic and visual outcomes in patients with refractory DME after bevacizumab injection.

In a study by Lee et al, 62 eyes with persistent DME following at least 3 monthly intravitreal bevacizumab injections were treated with a single intravitreal ranibizumab injection and were followed-up for 1 month,[30] after which, anatomic responses were monitored monthly, and intravitreal ranibizumab was injected on a PRN protocol for 3 months. The mean CST was reduced significantly from 422 μm to 346 μm, and the mean BCVA improved from 20/49 to 20/46, a statistically insignificant result. In 39 eyes (62.9%), anatomic responses were achieved. After 3 months and following the mean of 2.6 intravitreal ranibizumab injections in the non-responder eyes, the mean CST improved significantly (from 492 μm to 317 μm), but the BCVA remained unchanged (from 20/52 to 20/48, $P = 0.066$).

Ashraf et al evaluated the efficacy of early switching from bevacizumab to ranibizumab or aflibercept in a retrospective study.[31] A total of 59 eyes from 45 patients were evaluated; of them, 17 eyes were switched to aflibercept and 42 eyes were switched to ranibizumab. Their results showed significant improvements in BCVA and CST occurring in both groups, although no statistically significant difference in BCVA or CST was observed in the 2 groups. In addition, they found that CST, number of injections, or BCVA before switching affected the response to switching. In a retrospective study, 21 eyes from 19 patients with refractory DME who received 6 (median number) intravitreal injections of bevacizumab or ranibizumab were switched to intravitreal aflibercept injections.[32] After switching, the median number of intravitreal aflibercept injections was 3. The mean central foveal thickness (CFT) following the first injection decreased significantly from 453.52 μm to 362.57 μm, and the mean CFT had decreased significantly to 324.17 μm at the final follow-up visit (median 5 months). The mean logMAR visual acuity improved from 0.42 to 0.39 after the first injection and to 0.37 at the final visit ($P = 0.04$). The authors demonstrated that switching to aflibercept can improve anatomic and visual outcomes in patients with refractory DME.

Rahimy et al evaluated the efficacy of switching to aflibercept in patients with DME unresponsive to ranibizumab and/or bevacizumab.[33] In their retrospective

study, 40 eyes from 37 patients with at least 4 intravitreal ranibizumab or bevacizumab injections before switching and a minimum of 2 aflibercept injections after switching were evaluated. The mean logMAR visual acuity improved from 0.60 (prior to switching) to 0.55 ($P=012$). The mean central macular thickness (CMT) decreased from 459.2 μm (prior to switching) to 348.7 μm ($P<0.0001$). The authors concluded that switching to aflibercept from bevacizumab or ranibizumab in patients with refractory DME may lead to significant improvement in anatomic outcomes, but the improvement in visual acuity was not statistically significant.

In their prospective study, Wood et al treated 14 eyes with refractory DME unresponsive to bevacizumab and/or ranibizumab with an intravitreal injection of 2 mg aflibercept.[34] One month after the single aflibercept injection, anatomic improvement had occurred in 79% of eyes, and the CST had improved from 421 μm to 325 μm ($P<0.0132$); however, improvement in visual acuity was detected in 21% of eyes.

Chen et al prospectively evaluated the visual and anatomic outcomes of 72 eyes with DME refractory to bevacizumab or ranibizumab after switching to intravitreal aflibercept.[35] Three monthly doses of aflibercept were injected intravitreally. With an increase in the CST or visual gain of less than 1 line at 1 month following the conversion to aflibercept compared with before switching, the eye was considered a non-responder to aflibercept. One month following the aflibercept injection, 58.3% of eyes (42 eyes) had responded to switching. The mean BCVA improved from 0.65 logMAR to 0.31 logMAR ($P=0.0008$), and the CST decreased from 438.5 μm to 297.9 μm ($P=0.0004$) in responders.

Bahrami et al evaluated the efficacy of switching to aflibercept in 43 eyes from 43 patients with DME and with CMT >300 μm unresponsive to at least 4 intravitreal bevacizumab injections in the prior 6 months.[36] Five monthly intravitreal aflibercept injections were administered as a loading dose, and then the treatment interval was extended to 8 weeks. The mean number of intravitreal injections before switching was 16.6 during a period of 26.9 months. At month 24, the mean CMT had decreased significantly from 417 μm to 380 μm, and the mean BCVA had improved significantly from 67.8 letters to 71.0 letters. The authors concluded that switching to aflibercept was effective in improving visual and anatomic outcomes in patients with DME unresponsive to bevacizumab.

In a retrospective study, 49 eyes from 34 patients with DME refractory to bevacizumab were treated with intravitreal aflibercept injection.[37] All patients had at least 3 intravitreal bevacizumab injections before switching to aflibercept, and all patients were followed-up for at least 3 months after switching. The mean visual acuity improved from 0.55 logMAR to 0.46 logMAR ($P=0.038$), and the mean CMT decreased from 437 μm to 349 μm ($P<0.001$). In 24% of eyes (12 eyes), macular edema was absorbed after the conversion to aflibercept. The authors found that the improvement in visual acuity and CMT was superior in eyes with poorer initial visual acuity prior to conversion compared to eyes with initial visual acuity better than 0.4 logMAR.

Demircan et al compared the outcomes in eyes with refractory DME who received intravitreal aflibercept following prior unresponsive intravitreal ranibizumab injections with eyes who continued with intravitreal ranibizumab injections.[38] In this retrospective study, 43 eyes with a CMT ≥350 μm who received at least 3 monthly intravitreal ranibizumab injections and were then treated with either ranibizumab or aflibercept with a PRN regimen were included. This study showed that the CMT decreased significantly from baseline in both groups with switching to aflibercept or continued with ranibizumab. The mean changes in the CMT were 188.6 μm in the switching group and 60.3 μm in the continued ranibizumab group ($P=0.003$). The results showed that, despite the anatomical benefits of switching to aflibercept, there were no visual benefits.

Corticosteroids

Corticosteroids reduce the production and release of VEGF, suppress pro-inflammatory cytokines and prostaglandins, reduce leukocytes migration, suppress the release of ICAM-1, enhance the barrier function of vascular endothelial cell tight junctions, and probably have a neuroprotective effect on the retina.[39-44] Because of the known side-effects of corticosteroids, including glaucoma and cataract progression, they are not used as a first-line option in the management of DME. Usually, they are considered as the second-line modality, especially in DME refractory to anti-VEGF agents.[45] Corticosteroids that are used for DME management include triamcinolone acetonide, fluocinolone acetonide insert, and dexamethasone implant.

Kim et al evaluated the efficacy of posterior sub-tenon triamcinolone acetonide injection in the treatment of DME unresponsive to bevacizumab.[46] A total of 40 eyes from 34 patients with DME and CST>300 μm who experienced an increase in the CST following 1 or 2 intravitreal bevacizumab injections or no decrease following 3 or more intravitreal injections were enrolled in this retrospective study. Posterior sub-tenon injections of 20 mg triamcinolone acetonide were administered. At month 6, the mean CST decreased from 476 μm to 427 μm ($P<0.001$), and the mean BCVA improved from 0.56 to 0.48 logMAR ($P=0.133$). The mean intraocular pressure was 15.50 mm Hg at baseline and 15.56 mm Hg at month 6.

Shoeibi et al reported the results of adding 2 mg triamcinolone acetonide to intravitreal bevacizumab for the treatment of refractory DME.[47] They defined refractory DME as persistent macular edema after laser photocoagulation. The authors randomized 115 eyes from 101 patients into 3 study groups: the intravitreal bevacizumab group (41 eyes) that received 3 intravitreal injections of 1.25 mg bevacizumab at 6-week intervals, the combined intravitreal bevacizumab and triamcinolone acetonide group (37 eyes) that received 2 mg of intravitreal triamcinolone acetonide combined with the first intravitreal bevacizumab injection, and the sham injection group. CMT was reduced significantly in the intravitreal bevacizumab group, but the reduction was not

statistically significant in the combined bevacizumab and triamcinolone acetonide group. Also, visual improvement was not statistically significant in any of the groups. The authors concluded that intravitreal bevacizumab injections have beneficial effects for the management of refractory DME, but adding triamcinolone acetonide offers no additional benefits.

Azad et al enrolled 60 patients with refractory DME into their prospective study.[48] They defined refractory DME as persistent DME with CMT>250 μm after at least 2 sessions of laser photocoagulation. Patients were randomized into 3 groups: group 1 included patients treated with 1.25 mg intravitreal bevacizumab, group 2 included patients treated with 4 mg intravitreal triamcinolone acetonide, and group 3 included patients who underwent macular laser photocoagulation. At month 6, the BCVA had improved significantly from 20/160 to 20/80 in group 1 and from 20/125 to 20/63 in group 2. The CMT reduction from baseline was statistically significant in both groups 1 and 2. The BCVA improvement (from 20/100 to 20/80) was not statistically significant in group 3. At the 6-month follow-up, the mean CMT had increased from 358 μm to 398 μm in the eyes in group 3. Four eyes in group 1 and 10 eyes in group 2 showed cataract progression, and 6 eyes in group 2 required cataract extraction. Moreover, 10 eyes in group 2 showed intraocular pressure elevation from baseline; however, no eyes required surgical treatment. Ultimately, this study showed that both intravitreal bevacizumab and intravitreal triamcinolone acetonide may be effective in the management of refractory DME; however, intravitreal triamcinolone acetonide may lead to cataract progression or intraocular pressure elevation.

Chan et al evaluated the efficacy of triple therapy including 70 mg sub-tenon triamcinolone acetonide, 1.25 mg intravitreal bevacizumab, and macular laser photocoagulation for the treatment of refractory DME.[49] They included 29 eyes of 29 patients to the triple therapy group and compared them with 18 eyes from 18 patients who were treated with macular laser photocoagulation alone. At month 12, CMT had decreased significantly from 441 μm to 298 μm in the triple therapy group, but changes in BCVA were not statistically significant. In the laser photocoagulation group, no significant changes in CMT or BCVA had occurred.

In September 2014, dexamethasone implant (Ozurdex) was approved by the USFDA for the management of DME. Unsal et al evaluated the efficacy of the Ozurdex implant in the treatment of refractory DME defined as CMT ≥300 μm after at least 3 intravitreal bevacizumab or ranibizumab injections.[50] They included 46 eyes from 46 patients in this retrospective study and found that BCVA improved significantly in the first 4 months after the Ozurdex implantation; however, no significant changes were detected after 4 months. Moreover, CMT decreased significantly after 3 months, but no statistically significant changes were observed after 3 months. The authors concluded that the Ozurdex implant may be effective in the treatment of refractory DME; however, anatomical and visual improvement occurred in the first 3 months following treatment, and frequent injections may be required.

Pacella et al reported the long-term results of Ozurdex implantation in patients with refractory DME.[51] A 700-μg Ozurdex was implanted in 32 patients; the results showed that visual acuity increased significantly at 1, 3, 4, 9, and 15 months after treatment, but at 6, 12, and 18 months, visual acuity tended to return to initial values. The authors concluded that the intravitreal dexamethasone implant can improve the CMT and BCVA in patients with refractory DME. In another prospective study, the efficacy of the 700-μg Ozurdex implant in the treatment of refractory DME was evaluated.[52] In total, 40 eyes with refractory DME and 36 eyes with treatment-naïve DME were included. After treatment with the Ozurdex implant, BCVA improved significantly in both refractory and treatment-naïve groups; however, the improvement in BCVA was significantly better in the treatment-naïve eyes. The reduction in CMT was significant and similar in both groups.

In their retrospective study, Iglicki et al evaluated the efficacy of Ozurdex implant in the treatment of refractory DME and compared it with treatment-naïve DME cases.[53] After 24 months, BCVA had improved significantly in both groups, while vision gain was significantly better in the treatment-naïve eyes. At 24 months, CST was reduced significantly in both groups.

Maturi et al evaluated 40 eyes with refractory DME and BCVA between 20/32 and 20/320 and CST>20 μm.[54] The patients were randomized to receive a combination of bevacizumab plus Ozurdex implant or to receive bevacizumab alone. In the combination therapy group, an intravitreal bevacizumab injection was administered at baseline and Ozurdex was implanted at months 1, 5, and 9; in the bevacizumab monotherapy group, intravitreal bevacizumab was injected if needed (PRN). The mean BCVA changes at month 12 were similar in both groups ($P=0.75$); however, the mean reduction in CST was significantly greater in the combination therapy group ($P=0.03$). In addition, in the combination therapy group, 3 fewer bevacizumab injections were administered.

In another study, Maturi et al evaluated 129 eyes from 116 patients with refractory DME who had previously received at least 3 intravitreal anti-VEGF injections.[55] The patients were randomized to receive the 700-μg Ozurdex implant (65 eyes: combination therapy group) or sham injections (64 eyes: ranibizumab group) in addition to 0.3 mg intravitreal ranibizumab injections every 4 weeks in both treatment groups. At 24 weeks, the mean BCVA improvement was similar in both treatment groups ($P=0.73$), and the mean reduction in CST was significantly greater in the combination therapy group ($P<0.001$). In the combination therapy group, intraocular pressure elevation occurred in 29% of eyes. The authors concluded that the addition of an intravitreal Ozurdex implant to the intravitreal ranibizumab injection does not improve visual acuity more than ranibizumab monotherapy in patients with refractory DME.

In a recent retrospective, multicenter study, Busch et al compared the outcomes of continued anti-VEGF therapy with Ozurdex implant in eyes with refractory DME.[56] Patients who had a visual gain of ≤5 letters or ≤20% CST reduction after 3 monthly intravitreal anti-VEGF injections were included

and randomized to receive continued anti-VEGF therapy or an Ozurdex implant. Totally, 110 eyes from 105 patients were enrolled in this study. At 12 months, the mean improvement in visual acuity and the mean reduction in CST were significantly greater in the Ozurdex implant group ($P=0.004$ and $P=0.024$, respectively). In addition, this study showed that a visual gain ≥10 letters was more likely to happen in the Ozurdex implant group ($P=0.24$).

Fluocinolone acetonide intravitreal implant (Iluvien) is another sustained-release intravitreal steroid that has been evaluated for the treatment of refractory DME. The Iluvien implant contains 190 µg of fluocinolone acetonide and releases 0.2 µg a day up to 36 months.[57] In a retrospective study, 15 eyes from 10 patients with refractory DME following either intravitreal anti-VEGF injection and/or intravitreal steroid injection (triamcinolone acetonide or Ozurdex implant) were included and treated with Iluvien implants.[58] Compared to baseline, BCVA improved in 11 eyes (73.3%), remained unchanged in 2 eyes (13.3%), and decreased in 2 eyes (13.3%). Intraocular pressure elevation occurred in 2 eyes, one of which required cyclocryotherapy. Ultimately, the authors concluded that intravitreal Iluvien implant was an effective therapeutic option for patients with refractory DME.

In their prospective study, Massin et al evaluated the efficacy of Iluvien implant in refractory DME cases with inadequate responses to laser therapy (group 1) or laser and anti-VEGF therapy (group 2).[59] A total of 16 eyes were included and treated with intravitreal Iluvien implant. At month 12 after Iluvien implantation, the mean visual gain and the mean CMT reduction were 5.6 letters and 299 µm in group 1 and 0.9 letters and 251 µm in group 2, respectively.

Elaraoud et al treated 22 eyes with refractory DME using intravitreal Iluvien implant.[60] After 3 months, the mean reduction in CMT and the mean visual acuity gain were 148 µm and 6.4 letters, respectively. Overall, in 18 eyes (68.2%), CMT was improved, and 15 of them also had improved visual acuity. No reduction in CMT was seen in 4 of the 22 included eyes. In another study, Elaraoud et al reported the 6 months and 12 months results of bilateral Iluvien implantation for bilateral refractory DME.[61] At the final visit, visual acuity had improved in 9 of the 10 included eyes. The mean CMT had reduced significantly from 645.3 µm to 287.4 µm, and the mean visual acuity had improved significantly from 44.5 letters to 55 letters. This study demonstrated that bilateral Iluvien implantation may be effective in the treatment of eyes with bilateral refractory DME.

Because of the increased clearance of a single injection of intravitreal anti-VEGF in vitrectomized eyes, anti-VEGFs may be less effective in the treatment of DME in vitrectomized eyes; slow-release agents such as the Ozurdex implant or Iluvien implant may be more effective.[62-64] Kumar et al treated 2 vitrectomized eyes with refractory DME using Iluvien implants and showed that DME was completely resolved up to 1 year.[65] In a retrospective study, the efficacy of intravitreal implants for refractory DME in vitrectomized and non-vitrectomized eyes was compared.[66] In total, 24 vitrectomized eyes (group 1) and 19 non-vitrectomized eyes (group 2) were enrolled in this study, treated with Iluvien implants, and followed-up for a mean of 8.5 months. At the final visit, the mean improvement in BCVA was 16.9 and 8.2 letters in group 1 and group 2, respectively. A gain of 15 letters or more occurred in 37.5% of eyes in group 1 and 36.8% of eyes in group 2. The mean reduction in CST was 217.7 µm in group 1 and 155.6 µm in group 2. At the final visit, there were no significant differences between the eyes in group 1 and group 2 regarding BCVA and CST changes.

Surgery

Pars plana vitrectomy (PPV) with or without internal limiting membrane (ILM) peeling has been used for the treatment of refractory DME. In a prospective study, 28 eyes with refractory DME to previous anti-VEGF therapy and with CMT ≥300 µm were treated with 23-gauge PPV and ILM peeling,[67] after which, 0.3 to 0.5 ml of balanced salt solution (BSS) was injected into the sub-retinal space using a 38-gauge cannula to detach the fovea. The mean CMT decreased from 496 µm to 274 µm, and the mean BCVA in decimal form improved significantly from 0.2 to 0.4. The author concluded that PPV with ILM peeling and with the foveal detachment technique can be effective in the management of refractory DME cases.

Ghassemi et al evaluated the effectiveness of PPV with membranectomy and ILM peeling in the treatment of eyes with refractory DME and non-tractional epiretinal membrane.[68] All patients were treated before surgery with at least 2 intravitreal bevacizumab injections and 1 intravitreal triamcinolone acetonide injection. In all, 12 eyes from 11 patients were evaluated and followed-up for a mean period of 14.5 months. The mean CMT decreased significantly from 559 µm to 354 µm ($P=0.001$); however, the improvement in BCVA was not statistically significant (from 0.84 to 0.72 logMAR, $P=0.967$). This study showed that despite the reduction in CMT, PPV with membranectomy and ILM peeling cannot significantly improve the BCVA in eyes with refractory DME and non-tractional epiretinal membrane.

Conclusions

Previous studies have shown that the chronicity of macular edema leads to poor visual outcomes. Thus, in cases with incomplete response to one therapeutic option, a change in therapeutic modality should be considered soon to achieve macular edema resolution and better final visual results. Today, the sequence of using one treatment option and the timing to switch from one agent to another is not fully understood, and the data from clinical trials regarding the appropriate approach to the management of refractory DME is insufficient. Adequate patient education and systemic control of hyperglycemia, hyperlipidemia, and hypertension are valuable in the management of refractory DSME.[69]

In cases with refractory DME following intravitreal bevacizumab or ranibizumab injection, switching to aflibercept may result in favorable outcomes in some cases; however, if adequate responses were not achieved after 3 intravitreal aflibercept injections, intravitreal Ozurdex implant may be a practical choice, especially in patients with severe DME and

in pseudophakic eyes. Intravitreal anti-VEGFs can be used to supplement the effects of intravitreal Ozurdex implantation, and at the end of the Ozurdex's life (3-4 months), a repeat implant may be used. The treatment of focal leaks using macular laser photocoagulation based on fluorescein angiography may be an effective adjuvant option. Intravitreal Iluvien implantation can be used as an alternative modality with a longer duration of action compared with Ozurdex. In cases of intravitreal corticosteroid usage, the intraocular pressure should be monitored regularly. PPV may be used early in eyes with vitreomacular traction or after resistance to other treatment modalities in eyes without traction; however, PPV may result in an anatomical improvement without significant visual improvement. Ultimately, DME may persist in some cases despite full treatment. Further studies are required to achieve alternative options in persistent DME eyes.

Conflict of Interest Disclosures

The author declares that he has no conflicts of interest.

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