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Editorial

Long-Term Outcome of Approved Pharmacotherapy for Diabetic Macular Edema: A Review of Randomized Controlled Trials in Fluocinolone Acetonide Implants, Dexamethasone Implants, Aflibercept and Ranibizumab

Diabetic macular edema (DME) is a major sight-threatening cause in diabetic patients. The pathophysiology of macular edema involves both the presence of inflammation and angiogenic stimulant regarding vascular endothelial growth factor (VEGF) [1]. Intravitreal injections of anti-VEGF, including ranibizumab [2-8], bevacizuamb [9], pegaptanib [10], aflibercept [11] are proven to be effective for managing DME. Intravitreal injections of corticosteroids, potent anti-inflammatory agents, such as fluocinolone acetonide implants (Retisert) [12], fluocinolone acetonide inserts (Iluvein) [13,14], dexamethasone implants [15,16], and triamcinolone acetonide [2] have been shown to be beneficial to DME. The Food and Drug Administration of US and European Medicines Agency have approved intravitreal injections of fluocinolone acetonide inserts (Iluvein), dexamethasone implants, aflibercept, and ranibizumab for treating DME. Herein the long-term outcome of the randomized controlled studies in these approved pharmacotherapies will be reviewed.

Iluvein™ (Alimera Sciences, Alpharetta, GA, USA) is the intravitreal insert that can slowly release fluocinolone acetonide in low dose (0.2 μg/day). The insert is nonbiodegradable, which can be delivered into the vitreous cavity through a 25-gauge needle. Iluvein showed an anti-edematous effect persisting as long as three years after single injection [14]. The FAME study collected subjects with persistent DME despite at least 1 macular laser treatment. The patients were randomized into 375 eyes receiving fluocinolone acetonide low-dose insert (0.2 μg/day), 393 eyes in high-dose insert (0.5 μg/day), and 185 eyes in sham injections [13]. Significant visual improvement occurred for both doses compared with sham since three weeks following single intravitreal injection. The 2-year results demonstrated that the mean visual gain was 4.4 and 5.4 letters in the low- and high-dose groups, significantly better than 1.7 letters in the sham group. Steroids promote cataract development, which reduces visual acuity. In order to exclude the confounding effect of cataract formation, the authors sub-analyzed visual performance of pseudophakic patients at baseline. A mean increase in 7 letters between baseline and week 6 that remained stable through month 24 in both treatment groups, comparing only 2-letter gain in the sham group. The foveal thickness also showed significant decrease in the treatment group than in the sham group during 2-year follow-up after injections. After month 12, patients with reduced vision or increased retinal thickness from persistent or recurrent DME were allowed to receive repeated injections in the treatment group. Nearly one fifth of the treated patient required two implantations, and below 3% of the treated groups for three or more administrations. Glaucoma and cataract were the major adverse effects after implantation. Glaucoma requiring incisional surgery occurred in 3.7%, 7.6%, and 0.5% of the low-dose, high-dose, and sham groups, respectively. Cataract requiring surgery happened in 74.9%, 84.5%, and 23.1% of the low-dose, high-dose, and sham groups. At three-year outcome, the visual gain remained stable and significant better in two different dosing treatment groups (+5.3 letters) than in the sham injections (+2 letters) [14]. But more adverse reactions were reported: nearly all treated phakic patients developed cataract; the incidence of incisional glaucoma surgery increased to 4.8% in the low-dose group and 8.1% in the high-dose group. Chronic DME was defined as duration of diagnosis more than three years in the study. They found the greater response following Iluvein treatment in patients with chronic DME than in those with non-chronic DME at the end of three-year study [17]. The authors concluded Iluvein would provide an option of treatment for patients with chronic and refractory DME.

Ozurdex™ (Pharm Allergan Inc., Irvine California) is the intravitreal implant that can slowly release dexamethasone. The implant consists of a biodegradable copolymer of polylactic-co-glycolic acid containing 0.7-mg dexamethasone, which can be delivered into the vitreous cavity through a 22-gauge needle. The Ozurdex showed an anti-edematous effect as long as four to six months after single injection [15]. The PLACID study, a randomized controlled trial, collected 126 eyes with DME receiving Ozurdex and

macular laser and 127 eyes in sham injections and laser therapy [15]. Maximal response was found one month after the injection with visual improvement in nearly eight letters in the combined treatment group, significantly better than 2.3-letter gain in the laser only group. The central retinal thickness also showed significant decrease in the combined treatment group one month after Ozurdex implantation, than in the laser only group. The effect of Ozurdex diminished six months after the injection. The same response for macular edema was noted after repeated injections of Ozurdex during 12-month follow-up. Decreases in the area of diffuse vascular leakage measured angiographically were significantly larger with Ozurdex plus laser treatment. Over 12 months, cataract progression occurred in nearly one fifth of phakic eyes, and a 10-mmHg intraocular pressure increase from baseline was observed in 15.2% of all patients receiving two injections of Ozurdex. The intraocular pressure increases were usually transient and controlled with medication or observation. No surgery or laser for elevated intraocular pressure was required.

The MEAD study randomly assigned patients with DME to receive Ozurdex 0.7 mg in 351 eyes, Ozurdex 0.35 mg in 347 eyes, and sham injections in 350 eyes for 3-year follow-up [16]. The patient can be retreated if central retinal thickness more than 225μm, but no more often than every six months. Mean number of treatments received over 3 years was 4.1 with Ozurdex 0.7 mg and 4.4 with Ozurdex 0.35 mg. The mean visual gain at year 3 was significantly better in Ozurdex group (+3.5 letters) than in sham group (+2.0 letters). In order to exclude the confounding effect of cataract formation, the authors sub-analyzed visual performance of pseudophakic patients at baseline. A better visual outcome was found in pseudophakic subgroup: A mean increase in nearly 6 letters in the Ozurdex group, significantly superior than only 1 letter in the sham group at the end of 3-year follow-up. Mean average reduction in macular thickness from baseline was greater with Ozurdex treatment group than with sham group. Rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the Ozurdex 0.7 mg, Ozurdex 0.35 mg, and sham groups, respectively. Increases in intraocular pressure were usually controlled with medication or no therapy; only 2 patients (0.6%) in the Ozurdex 0.7 mg group and 1 (0.3%) in the Ozurdex 0.35 mg group required glaucoma incisional surgery.

Aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) is a decoy receptor fusion protein, composed of the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2, which are fused to the Fc domain of human IgG1. Aflibercept can downregulate both VEGF-A and placental growth factor, which are synergistic for pathologic angiogenesis. The VISTA and VIVID studies, two randomized controlled trials, demonstrated the efficacy of intravitreal aflibercept 2 mg over the macular grid laser for 872 patients with center-involving DME for one-year follow-up [11]. The authors initially used monthly injections for five months, then treated ever 4 weeks (2q4) or every 8 weeks (2q8). Mean visual gains from baseline to one year were +12.5 and +10.7 letters in aflibercept 2q4 and 2q8 groups, significantly better than +0.2 letters in laser only group in VISTA. Mean visual gains in VIVID at one year was similar; +10.5 and +10.7 letters in aflibercept 2q4 and 2q8 groups, significantly better than +1.2 letters in laser group in VIVID. Decrease of macular thickness was more prominent in the aflibercept groups than in the laser group, without accompanying serious ocular and systemic adverse events. The visual results at two years from the VISTA trial were announced recently by Bayer Company. Significantly visual gains persisting for two years, were +11.5 and +11.1 letters in aflibercept 2q4 and 2q8 groups, greater than +0.2 letters in laser only group in VISTA.

Ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, and Novartis Pharma AG, Basel, Switzerland) is an antibody fragment with a high binding affinity towards all forms of VEGF-A, which can effectively inhibit intraocular level of VEGF-A. The DRCR.net study included 854 eyes with visual impaired by center-involved DME, who were randomized to receive sham injection or intravitreal triamcinolone 4 mg with prompt macular laser, or intravitreal injections of 0.5-mg ranibizumab with prompt or deferred laser, which meaning laser delayed more than 24 weeks [2]. Ranibizumab was administered every four weeks until no longer improving, but with resumption if worsening. The one-year results demonstrated ranibizumab with prompt or deferred laser resulted in a mean gain of nine letters, significantly better than four letters in the triamcinolone with prompt laser group and three letters in the laser only group. Reduction in mean central subfield thickness was greater in the ranibizumab and triamcinolone group than in the laser only group. The two-year outcome also showed intravitreal ranibizumab with prompt or deferred laser more effective than prompt laser alone for the treatment of DME involving the central macula. After three-year follow-up, the mean visual change was +9.7 letters in the ranibizumab with deferral laser, significantly better than +6.8 letters in the ranibizumab with prompt laser [3]. Although the five-year visual outcome revealed similar visual gains (+7.2 and +9.8 letters) were observed between the ranibizumab with prompt and deferral laser, better visual outcome was detected in the deferral laser (+17 letters) than in the prompt laser (+10 letters) in the subgroup with poor baseline vision [4]. Fewer cumulative ranibizumab injections were required in the ranibizumab with prompt laser group (median 13 injections) than in the ranibizumab with deferral laser group (median 17 injections). All the patients received laser treatment in the ranibizumab group combined with prompt laser, but only approximately half (44%) of the cases having laser in the ranibizumab group combined with deferral laser. After three-year treatment, nearly half (54% in the prompt laser and 45% in the deferral laser) of the eyes enrolled did not require ranibizumab injections. No significant ocular or nonocular safety events were identified in the ranibizumab group except injection-associated endophthalmitis in three eyes (1%) over 5-year period. These facts suggest intravitreal ranibizumab can maintain long-term visual gain up to five years, either combined with prompt, delayed or even no macular laser treatment. The injection frequency can gradually decrease after regular follow-up, and no longer injections needed in nearly half of the patients with fovea-involving DME. Adding macular focal/grid laser at the initiation of intravitreous ranibizumab can successfully reduce the injection number of ranibizumab, possibly through restoration blood-retina-barrier and stimulation of pumping function of retinal pigment epithelium. But laser may own a potentially destructive effect for macula, which limits the visual improvement in the patients with initially poor vision receiving ranibizumab plus immediate laser. The

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DRCR.net study in these patients with DME also found intravitreal ranibizumab reduced risk of diabetic retinopathy progression [18]. Another analysis of one-year data from DRCR.net trial revealed better visual prognosis after ranibizumab for eyes with DME was associated with younger age, less severe diabetic retinopathy, absence of surface wrinkling retinopathy, and prominent reduction of macular thickness [19].

The RESTORE study included 345 patients with visual impaired by DME, who were randomized to receive sham injection with laser, or intravitreal injections of 0.5-mg ranibizumab with laser or not [5]. Three monthly ranibizumab was administered then PRN based on visual acuity stability and disease progression retreatment criteria. Macular laser was given at baseline then PRN according to Early Treatment Diabetic Retinopathy Study guidelines. The one-year results demonstrated ranibizumab alone or combined with laser caused in mean gains of +6.1 and +5.9 letters, significantly superior to laser monotherapy in +0.8-letter visual gain. Reduction in mean central retinal thickness was significantly more in the ranibizumab with or without laser group than in the laser only group. Mean seven ranibizumab injections were required in the ranibizumab with or without laser groups at the first year. All patients were eligible to receive ranibizumab and laser PRN from month 12 to month 36 [6]. At the end of 3 years, visual improvement maintained in the prior ranibizumab only group (+8 letters) and in the prior ranibizumab plus laser group (+6.7 letters). Mean 6.8 injections were needed in the prior ranibizumab only group, and 6 injections in the prior combined treatment group from month 12 to month 36. Approximately 19% to 25% of patients in the ranibizumab with or without laser did not require any ranibizumab injections between month 12 and 36. In the prior laser group, a progressive visual gain for six letters was observed after allowing ranibizumab after month 12. The most frequently reported ocular serious adverse effect over 3 years was cataract (16.3%), the nonocular serious adverse effects were coronary artery disease (3.6%) and cerebrovascular accident (2.4%) in three-year ranibizumab treated patients. The authors concluded ranibizumab can improve and maintain visual acuity and decrease central retinal thickness with a progressively declining number of injections over 3 years.

The RISE and RIDE trials included 377 and 382 patients with vision impaired by DME respectively, who were randomized to receive sham injection or monthly 0.3-mg or 0.5-mg ranibizumab treatment over 24-month period [7]. Macular laser was eligible after month 3 if needed. Ranibizumab treatment led to rapid vision improvements, with statistically significant changes versus sham observed as early as 7 days after the first injection. The two-year results demonstrated 0.3 or 0.5-mg ranibizumab administration resulted in mean visual gains of +10 to +12 letters, significantly superior to sham injections in +2 to +3-letter visual improvement. More reduction in mean central foveal thickness was observed in the ranibizumab group than in the sham group. Ranibizumab-treated patients underwent significantly fewer macular laser procedures (0.3 to 0.8 procedures) than sham-treated cases (1.6 to 1.8 procedures). In the third year, 0.3 or 0.5-mg ranibizumab monthly injections continue in prior ranibizumab-treated patients, and sham patients were eligible to cross over to monthly 0.5-mg ranibizumab treatment [8]. At month 36, visual outcome maintained in the prior ranibizumab group with +10 to +14-letter gains from baseline, still superior than prior sham group with +4 to +5-letters visual gains. The incidence of serious adverse events, such as myocardial infarction and stroke, potentially related to systemic VEGF inhibition was as high as 19.7% and 16.8% in patients who received 0.5-mg and 0.3-mg ranibizumab. The ocular serious adverse events in the ranibizumab-treated groups included injection-related endophthalmitis or traumatic cataract over the 36-month treatment period in 6 patients (1.2%) and 4 patients (0.8%), respectively. The authors concluded monthly ranibizumab injections can maintain visual and anatomical benefit one week till three years after treatment in patients with DME. Delayed ranibizumab treatment for DME is associated with a significantly lower extent of improvements in vision than early intervention. Ocular and systemic safety should be addressed after frequent injections of ranibizumab. The efficacy is equivalent between the 0.3-mg and 0.5-mg doses, but the use of 0.3 mg may reduce risks potentially related to systemic VEGF suppression. This may be particularly appropriate in the management of DME because not only 40% to 50% of patients with DME have bilateral disease requiring contemporaneous treatment, but also diabetic patients have an underlying increased risk of mortality and cardiovascular disease. In light of these considerations, the Food and Drug Administration of US approved use of 0.3-mg ranibizumab for DME. Following review of 2-year results of RISE and RIDE trials, they found diabetic retinopathy was less likely to worsen and more likely to improve in patients with DME treated by ranibizumab [7,20]. Retinal nonperfusion area on fluorescein angiograms was retrospectively analyzed in RISE and RIDE studies [21]. The percentage of patients who showed an increase in retinal nonperfusion from baseline over two years in all 3 groups, but at a faster rate in the sham group, resulting in statistically significant differences for ranibizumab (0.5 mg in 16.1% and 0.3 mg in 15.5%) and sham (37.6%). They concluded monthly injections of ranibizumab can slow, but not completely prevent, retinal capillary closure in patients with DME.

In summary, there are four approved pharmacotherapies for treating diabetic macular edema, including intravitreal injections of corticosteroids (dexamethasone implants and fluocinolone acetonide inserts) and anti-VEGF (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular focal/grid laser treatment. There are severe adverse effects in ocular part (injection-related endophthalmitis and traumatic cataract) and nonocular part (arterial thromboembolic events) reported in studies associated with anti-VEGF for DME despite in low incidence. Intraocular pressure elevation and cataract aggravation should be addressed after intravitreal corticosteroids. Single intravitreal Iluvein had effective duration as long as three years, and single Ozurdex for four to six months. Iluvein is useful for patients with chronic and refractory DME owing to its long and persistent anti-edematous effect. Intravitreal anti-VEGF requires initially monthly or frequent administrations, then gradually decreasing number of injections or even stopping the treatment after long-term follow-up. Ranibizumab reduces not only macular edema, but also the risk of diabetic retinopathy progression and retinal ischemia aggravation. Prompt treatment with these agents can lead to a better outcome.

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Conflict of Interest

No author has a financial or proprietary interest in any material or method mentioned. The study was not supported by any grants.

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