Review Article

An updated review of long-term outcomes from randomized controlled trials in approved pharmaceuticals for diabetic macular edema

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Abstract: Diabetic macular edema (DME) is a major sight-threatening cause in diabetic patients. We review the long-term outcome of four approved pharmacotherapy for treating DME, including intravitreal injections of corticosteroids (dexamethasone implants and fluocinolone acetonide inserts) and anti-vascular endothelial growth factor (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. Anti-VEGF agents result in low incidence of severe ocular or systemic adverse effects, but glaucoma and cataract should be aware after intravitreal corticosteroids. Prompt treatment with these agents can lead to a better outcome.

Keywords: Intravitreal injection; aflibercept; ranibizumab; dexamethasone implant; fluocinolone acetonide implant; diabetic macular edema (DME)

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Introduction

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 (17) 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 (not less than 1 year follow-up) of the randomized controlled studies in these approved pharmacotherapies will be reviewed.

Ranibizumab

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 4 weeks until no longer improving, but with resumption if worsening. The 1-year results demonstrated ranibizumab with prompt or deferred laser resulted in a mean gain of 9 letters, significantly better than 4 letters in the triamcinolone with prompt laser group and 3 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 2-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 3-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 5-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 3-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 5 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 DRCR.net study in these patients with DME also found intravitreal ranibizumab reduced risk of diabetic retinopathy progression (18). Another analysis of 1-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 1-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. The patients receiving ranibizumab monotherapy or combination therapy subjectively reported more improvement in far and near visual quality than those undergoing laser monotherapy (20). 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 six 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 3-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 2-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. Monthly intravitreal ranibizumab resulted in significantly greater reduction of hard exudate area compared with sham (21). In contrast to the rapid effects of ranibizumab on macular edema, changes in hard exudate area were more gradual. 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) (7). 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-letter 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 six patients (1.2%) and four patients (0.8%), respectively. The authors concluded monthly ranibizumab injections can maintain visual and anatomical benefit 1 week till 3 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 (22) and 3-year (23) results of RISE and RIDE trials, the authors demonstrated ranibizumab can both improve diabetic retinopathy severity and prevent worsening, compared with sham group. Although uncommon, the development of proliferative diabetic retinopathy still occurs in a small percentage of ranibizumab-treated eyes, which may be related to the presence of macular nonperfusion (23). Retinal nonperfusion area on fluorescein angiograms was retrospectively analyzed in RISE and RIDE studies (24). The percentage of patients who showed an increase in retinal nonperfusion from baseline over 2 years in all three 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. The two trials demonstrated that ranibizumab treatment for DME likely improved patient-reported vision-related function outcomes compared with sham, using 25-item National Eye Institute Visual Function Questionnaire (25). After reviewing association between baseline profiles and 2-year outcomes, these two studies found sham-treated patients with renal disease, submacular fluid, or severe cystic edema were likely to have a poor visual outcome in the absence of treatment but respond well when administered monthly injections of ranibizumab (26). This suggests that aggressive, sustained suppression of VEGF can overcome these poor prognostic features. Ranibizumab-treated patients with good baseline visual acuity were likely to have better final visual results (more than 20/40). Poor baseline visual acuity, presence of submacular fluid, young age, and short diabetes duration can predict more visual gain (more than +15 letters) in ranibizumab-treated eyes.

The LUCIDATE study compared the functional and structural effects of ranibizumab versus macular laser therapy in 33 diabetic eyes with center-involving macular edema (27). Subjects were randomized either three loading doses of ranibizumab then retreatment every 4 weeks

as required; or macular laser at baseline, repeated as required every 12 weeks. The 1-year results demonstrated ranibizumab-treated eyes gained 6.0 letters, better than laser groups with 0.9 letters lost. Ranibizumab therapy also improved tritan and protan color contrast thresholds, retinal sensitivity examined by microperimetry, and electrophysiologic function tested by pattern, full-field, and multifocal electroretinogram. Better retinal thickness reduction was seen in ranibizumab therapy than in the laser group. There was no evidence of progressive macular ischemia with ranibizumab therapy.

The READ-2 study included 126 patients with DME. Subjects were randomized to receive 0.5 mg of ranibizumab at baseline and months 1, 3, and 5, focal/grid laser photocoagulation at baseline and month 3 if needed, or a combination of 0.5 mg of ranibizumab and focal/grid laser at baseline and month 3 (28). The 6-month results revealed the mean visual gain was significantly greater in ranibizumab monotherapy (+7.24 letters), compared with laser treatment (–0.43 letters), and combination therapy (+3.80 letters) was not statistically different from ranibizumab or laser monotherapy. After 6 months, all treatments were administered in PRN regimen, and laser group was allowed for ranibizumab treatment. At the end of year 3, the mean visual gains were greater in ranibizumab (+10.3 letters) and combination therapy (+8.9 letters), than in laser group (+1.4 letters) (29). After analyzing the 2-year results in the READ-2 study, the authors found poor baseline visual acuity (less than 20/125), foveal atrophy, and persistent edema were associated with poor visual outcome (less than 20/100) (30).

The RESOLVE study included 151 patients with center-involving DME, who were randomized to receive sham injection, or intravitreal injections of either 0.3- or 0.5-mg ranibizumab (31). Three monthly ranibizumab was administered then PRN based on disease activity and dose-doubling was permitted after month 1. The 1-year results demonstrated ranibizumab caused in mean gains of +10.3 letters, significantly superior to sham in –0.4-letter visual loss. Reduction in mean central retinal thickness was significantly more in the ranibizumab group (–194.2 μm) than in sham group (–48.4 μm).

The other approved pharmaceuticals except ranibizumab

Fluocinolone acetonide inserts

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 3 years after single injection (14). The FAME study collected subjects with persistent DME despite at least one 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 3 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 patients 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 3-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 3 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 3-year study (32). The authors concluded Iluvein would provide an option of treatment for patients

with chronic and refractory DME.

Dexamethasone implant

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 4 to 6 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 1 month after the injection with visual improvement in nearly 8 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 1 month after Ozurdex implantation, than in the laser only group. The effect of Ozurdex diminished 6 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 225 μm, but no more often than every 6 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 two patients (0.6%) in the Ozurdex 0.7 mg group and one (0.3%) in the Ozurdex 0.35 mg group required glaucoma incisional surgery.

The BEVORDEX study reported the 12-month results of the first head-to-head randomized comparison of intravitreal Ozurdex every 4 months and bevacizumab every 4 weeks for 88 eyes with center-involving DME (33). The proportion of visual improvement more than 10 letters was comparable between eyes treated with bevacizumab (40%) and Ozurdex-treated eyes (41%). None of the bevacizumab eyes lost 10 letters or more, whereas 11% of Ozurdex eyes did, mostly because of cataract. Mean central macular thickness decreased significantly less for bevacizumab eyes (−122 μm) than Ozurdex eyes (−187 μm). Bevacizumab-treated eyes received more injections compared with Ozurdex-treated eyes. Ozurdex achieved similar visual improvement compared with bevacizumab for DME, with superior anatomic outcomes, fewer injections, but inducing cataract in more patients.

A recently published 12-month study randomly assigned 40 eyes with DME incompletely responding to multiple anti-VEGF injections into two groups (34). One group received combination therapy, including intravitreal bevacizumab at baseline, and subsequent Ozurdex at months 1, 5, and 9. The other group underwent monthly bevacizumab monotherapy in PRN regiment. Mean visual gain in combined therapy was +5.4 letters, similar to bevacizumab monotherapy in +4.9 letters. Mean macular thickness reduction was more prominent in combined therapy (−45 μm) than in bevacizumab monotherapy (−30 μm). The Ozurdex combined with bevacizumab owned superior ability in improving macular morphology in eyes with refractory DME comparing with bevacizumab monotherapy, although visual acuity changes are not greater to bevacizumab monotherapy.

Aflibercept

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 1-year follow-up (11). The authors initially used monthly injections for 5 months, then treated ever 4 weeks (2q4) or every 8 weeks (2q8). Mean visual gains from baseline to 1 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 1 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 2 years from the VISTA trial were announced recently by Bayer Company. Significantly visual gains persisting for 2 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.

Recently, head-to-head comparison of three anti-VEGF agents for DME was published (35). The randomized controlled study included 660 eyes with center-involved DME, who were randomized to receive intravitreal 2-mg aflibercept, 1.25 mg bevacizumab, or 0.3-mg ranibizumab. The injections were administered every 4 weeks until no longer improving, but with resumption if worsening. The 1-year results demonstrated all three anti-VEGFs improving vision in diabetic eyes with macular edema. When the baseline visual loss was mild (visual acuity from 69 to 78 letters), visual gains were similar between aflibercept group (mean +8.0 letters) and ranibizumab group (mean +8.3 letters). At worse levels of initial visual acuity (less than 69 letters), aflibercept was more effective at improving vision (mean +18.9 letters) than ranibizumab (mean +14.2 letters). There were no significant differences among the study groups in the rates of serious adverse events or major cardiovascular events.

Conclusions

There are four approved pharmacotherapies for treating DME, 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. Subjective visual quality, microperimetric retinal sensitivity, color contrast thresholds, and electrophysiologic function all improved following ranibizumab treatment. Prompt treatment with these agents can lead to a better outcome. 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 has effective duration as long as 3 years, and single Ozurdex for 4 to 6 months. 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. Better visual prognosis after ranibizumab treatment for eyes with DME was associated with younger age, short diabetes duration, less severe diabetic retinopathy, absence of surface wrinkling retinopathy, presence of submacular fluid, and prominent reduction of macular thickness. Regarding head-to-head comparison of different pharmaceuticals, Ozurdex achieved similar visual improvement compared with bevacizumab for DME, with superior anatomic outcomes, fewer injections, but inducing cataract in more patients. When diabetic patients present with worse visual acuity owing to macular edema, aflibercept has better performance than ranibizumab.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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