

Evidence-Based Treatment Modalities in Diabetic Macular Edema

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ÖZ

Diyabetik makula ödemi önemli bir görme kaybı nedenidir. Merkezi tutan diyabetik makula ödeminde fokal/grid laser tedavileri ile görmeye stabilizasyon sağlanırken son yıllarda intravitreal kortikosteroidler ve anti-VEGF tedavileri ile görme artışları elde etmek mümkün olmuştur.

Anahtar Kelimeler: Diyabetik makula ödemi, anti-VEGF, kortikosteroid.

ABSTRACT

Diabetic macular edema is an important cause of visual loss. Previously, the vision could be stabilized with focal/grid laser photocoagulation therapies in diabetic macular edema with central involvement. Recently, it has become possible to attain visual gains with the help of intravitreal corticosteroids and anti-VEGF agents.

Key Words: Diabetic macular edema, anti-VEGF, corticosteroids.

INTRODUCTION

Diabetic macular edema (DME) characterized by edema and thickening in the central macula is an important complication of diabetic retinopathy which can result in permanent loss of vision. In Wisconsin Diabetic Retinopathy Epidemiology study, DME prevalence has been reported as 20.1% in type I diabetics, 25.4% in type II diabetics on insulin therapy and 13.9% in type II diabetics not using insulin (1). In the same study, it was shown that DME prevalence is strongly associated with duration of diabetes mellitus, reporting DME prevalence as 0% and 3% in type 1 and 2 diabetic patients with disease duration less than 5 years and 29% and 20% in those disease duration more than 20 years.¹ In 53% of DME cases left untreated, at least 2-order of visual loss was reported during 2-years follow-up.² DME is the leading cause of visual impairment in DM cases.³ Thus, it is important to treat DME effectively. The primary goal of treatment is to reduce leakage and increased vascular permeability.

In this review, we will discuss control of systemic risk factors and evidence-based DME treatments such as focal

grid laser, anti-VEGF agents and corticosteroids.

Systemic Medical Therapy:

The control of systemic medical status plays an important role in the treatment of DME. Elevated blood glucose and lipid levels, hypertension and renal dysfunction may lead unresponsive DME despite treatment. The importance of systemic risk factors has been established in Diabetes Control and Complications Trial (DCCT), Epidemiology of Diabetes Interventions and Complications (EDIC) and United Kingdom Prospective Diabetes Study (UKPDS).⁴⁻⁶ In the DCCT conducted on 1441 type 1 DM cases between 1982 and 1993, it was shown that strict control of blood glucose decreases risk for proliferative diabetic retinopathy, DME onset and laser therapy. In nine years, DME incidence was 44% in standard treatment group while 27% in intensive treatment group, with estimated risk reduction of 29% .⁴ The EDIC is the extension study of DCCT

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and clinically relevant macular edema (CRME) rate was 16.4% in intensive treatment group between years 17 and 20.⁵ In the UKPDS study on 1148 patients with type 2 DM, strict blood glucose control was associated with significant risk reduction for macular laser requirement while strict blood pressure control with significant risk reduction for at least 3-order visual loss in median 8.4 years of follow-up.^{6,7}

Macular Laser Therapy:

Since ETDRS (Early Treatment of Diabetic Retinopathy Study) published in 1985, laser photocoagulation has long been primary treatment method in DME treatment.⁸ The visual acuity loss was prevented in 50%; however, improvement was detected in only 17% of cases treated. Complications such as central/ paracentral scotoma, loss in color vision, enlargement in laser scars and secondary subretinal neovascular membrane have been reported with this treatment.⁹ Today, focal laser therapy is being used in DME without central involvement.

Anti-VEGF Therapies:

Vascular endothelial growth factor (VEGF) is elevated in hypoxia and hyperglycemia, which is an important factor in the pathogenesis of DME. It was shown that elevated VEGF levels within intraocular fluid is associated to vascular permeability and DME severity.¹⁰ Some phase II and III trials showed recovery in DME and improvement in vision by anti-VEGF therapy and ranibizumab and aflibercept were approved in anti-VEGF therapy. In the literature, there are studies on four agents in DME treatment, including pegaptanib, ranibizumab, bevacizumab (off-label) and aflibercept.

Pegaptanib:

Pegaptanib sodium (Macugen; Eyetech Inc., USA/Pfizer) is a RNA aptamer that binds VEGF 165. In a 2-years study comparing pegatinib (0.3 mg) and sham injections in DME cases with central involvement, by pegatinib injections with 6-weeks interval in the first year and, if indicated thereafter, the rate of at least 10-letters visual acuity gain was found as 36.8% at year 1 and 38.3% at year 2 in pegatinib group and 19% at year 1 and 30% at year 2 in the control group.¹¹ At the end of second year, the mean visual acuity gain was 6.1 letters in the pegatinib group and 1.3 letters in the control group ($p < 0.01$). In the study, less patient in pegatinib group required laser therapy, which was allowed after week 18 (year 1, 23.3 vs. 41.7%; year 2, 25.2% vs. 45%). Today, pegatinib is not used routinely.

Ranibizumab

Ranibizumab (Lucentis; Genentech ABD/Novartis, Switzerland) is a recombinant, humanized anti-VEGF antibody fragment (150 kDa) that inhibits all forms of VEGF-A. It was approved for DME treatment by FDA in 2011 and it also has approval and reimbursement at dose of

0.5 mg for this indication in Turkey.

The READ-1 study, published by Nguyen et al., is one of the preliminary studies about ranibizumab in DME treatment.^{10,12} In the study, 0.5 mg ranibizumab was applied to 10 cases with chronic DME at baseline and on months 1, 2, 4 and 6. On month 7, it was observed that fovea thickness was decreased by 85% compared to baseline with average 12.3 letters gain in best corrected visual acuity. In all time points, the decrease in fovea thickness was correlated to improvement in visual acuity. The injections were well-tolerated without ocular or systemic adverse event. Subsequent multicenter, randomized, phase II and III studies were conducted to demonstrate ranibizumab effectiveness. The RESOLVE study was designed to investigate effects of two different concentration of ranibizumab on reducing macular edema and visual acuity in clinically relevant DME.¹³ Ranibizumab at doses of 0.3 and 0.5 mg were applied as 3 injections per month over one year; and, if indicated according to visual acuity, central macular thickness and safety criteria thereafter, in two groups. At the end of month 12, a significant, sustained improvement was found in visual acuity and central macular thickness with both doses of ranibizumab. Visual acuity gain ≥ 10 and ≥ 15 letters was found to be 3-folds higher in ranibizumab groups compared to sham injection group.

The effectiveness of ranibizumab as monotherapy in DME was also shown in phase III studies, namely RISE and RIDE.^{14,15} In these studies, the patients were assigned to receive 0.3 mg ranibizumab, 0.5 mg ranibizumab or sham injection. Monthly injections were administered to treatment groups over 2 years. After 2 years, 0.5 mg ranibizumab was given to sham injection group. Laser therapy as salvage treatment was allowed by month 3. Ranibizumab exerted its effect by day 7. At the end of year 2, average 8.5-9.9 letters visual acuity gain was detected in ranibizumab groups with less patients requiring laser therapy. Visual outcomes sustained at year 3.

Ranibizumab monotherapy was compared with laser therapy either alone or in combination in READ-2, RESTORE and DRCR-net studies. The READ-2 is a multicenter, randomized phase II study comparing ranibizumab with focal/grid laser therapy either alone or in combination in 126 DME cases.¹⁶ Ranibizumab was given at baseline and on months 1, 3 and 5 while laser therapy was performed at baseline and on month 3.

On month 6, mean visual acuity gain was 7.24 letters in ranibizumab group and 3.8 letters in combination group while visual acuity was reduced by 0.24 letters in laser monotherapy group. The decrease in central macular thickness was greater in ranibizumab group when compared to laser monotherapy group. Although somewhat decrease was observed in macular edema in focal/grid

laser group, there was no correlation with visual acuity gain. After month 6, ranibizumab treatment was maintained in all groups if indicated and, at the end of year 2, visual acuity was increased by 7.7 letters in ranibizumab group, by 6.8 letters in combination group and by 5.8 letters in the group received laser therapy monotherapy during first 6 months.¹⁷ At the end of year 3, additional 3.1 letters improvement was achieved by more injections in ranibizumab group.¹⁸ Although vision did not improve as much as this level in laser groups, edema resolution was observed in more patient and less injection was required. The study revealed that one could start treatment with monthly ranibizumab therapy in DME; followed by injections when indicated and that combination with focal/grid laser therapy could decrease number of injections needed.

The RESTORE is a phase III study investigating effectiveness of ranibizumab monotherapy, ranibizumab plus laser therapy and laser monotherapy in 345 DME cases.¹⁹ Ranibizumab therapy included 3 compulsory injections, followed by individualized on-demand treatment with re-treatment criteria based on monthly control visits and disease stability. At the end of month 12, highest gain by letters was recorded in ranibizumab monotherapy group (6.1 letters in ranibizumab monotherapy, 5.9 letters in combination and 0.8 letters in laser monotherapy groups). Ranibizumab was associated to improved vision in cases with both focal and diffuse edema. Ranibizumab plus laser therapy was not found superior against ranibizumab monotherapy regarding visual acuity gain. Laser monotherapy was found to be inferior against ranibizumab groups regarding both visual acuity gain and reduction in central macular thickness. Ten or 15 letters was observed to be 2- to 3-folds more common in ranibizumab groups compared to laser monotherapy. In the 2-years open-label extension phase where 0.5 mg ranibizumab was also given to patients in laser monotherapy group when needed, mean number of injections was decreased to 6 per year in the first year and to 3 per year in the second year. By on-demand therapy, visual acuity gain in the first year was preserved in ranibizumab groups while visual acuity gain was also achieved in the laser group.^{20,21}

Diabetic Retinopathy Clinical Research Network (DRCR-net) conducted a multicenter, randomized, phase III study to investigate effects of corticosteroid, ranibizumab and laser therapy (Protocol I).^{22,23} Overall, 854 DME eyes with central involvement were randomized to treatment arms: ranibizumab plus early laser therapy, ranibizumab plus delayed laser therapy, laser monotherapy and 4 mg triamcinolone. Based on results on year 1, both early and delayed (≥ 24 weeks) focal/grid laser combined with intravitreal ranibizumab were associated with better outcomes regarding vision and OCT when compared to focal/grid laser alone. Mean number of laser therapy was 2 in ranibizumab plus early laser group while no laser therapy was needed in 72% of eyes in the ranibizumab plus delayed laser group. At year 2, visual acuity gain was preserved in ranibizumab groups. Mean number of injections required was 2 in early laser groups whereas it was 3 in the delayed

laser group. Again, at year 2, the decrease in central macular thickness persisted but progressive increase in vision seen in first year did not continue and vision at the end of first year did not show significant alteration in laser groups. In the second year, there was a significant difference favoring delayed laser therapy regarding visual acuity gain between early and delayed laser arms.²⁴ From original sample, 77% of patients completed 5 years and mean visual acuity gain was 10 letters in ranibizumab plus early laser group, 8 letters in ranibizumab plus delayed laser group, 7 letters in triamcinolone plus early laser group and 5 letters in laser group. When interpreting results, it should be taken into account that latter groups received ranibizumab after year 2.^{25T} The marked reduction in number of injections required over time was one of the important findings in the study. Median number of injections required was 8 in ranibizumab plus early laser, 9 in ranibizumab plus delayed laser groups in first year whereas 2 and 3 in the second year and 1 and 2 in the third year, respectively. On year 5, there was no case requiring injection in these groups.

Ranibizumab was approved for DME management based on outcomes provided by above-mentioned studies. In summary of product characteristics, it is recommended to use treatment monthly and to maintain until reaching maximum visual acuity or achieving stable vision in 3 consecutive control visits.

Bevacizumab:

Bevacizumab (Avastin; Genetech ABD/ Roche Switzerland) is a full-length (149 kDa) recombinant humanized antibody against all VEGF-A isoforms, which is used off-label in ophthalmology. The BOLT (Bevacizumab or Laser Treatment) is a single-center, phase II study comparing 1.25 mg bevacizumab every 6 weeks with laser therapy every 4 months in 80 cases with DME. At the end of year 2, mean visual acuity gain was found to be 8.6 letters in the bevacizumab monotherapy group while visual acuity was decreased by 0.5 letters in the laser group.²⁶ In another randomized, phase III study, bevacizumab monotherapy, laser photocoagulation and bevacizumab plus triamcinolone acetonide were compared. The superiority detected in bevacizumab on month 6 did not persist at the end of study.²⁷

Aflibercept:

Aflibercept or VEGF Trap-Eye (Eylea; Regeneron/Bayer) is a fusion protein of primer regions in VEGF receptor 1 and 2, which blocks all VEGF-A isoforms and placental growth factor. It is approved for DME treatment by FDA in 2015 and it has approval and reimbursement for this indication Turkey.

In DME, effectiveness of VEGF Trap-Eye was first shown in a pilot study including 5 cases.²⁸

In a multicenter, randomized, phase II study (The Da VINCI study) comparing different doses and regimens of drug with laser photocoagulation, 9.7-12 letters visual acuity gain was achieved in aflibercept groups while visual acuity was decreased by 1.3 letters in laser group at the end of year 1.^{29,30} In the multicenter, phase III studies (The VIDIV and The VISTA studies) including aflibercept arm (2 mg aflibercept every 4 weeks over 5 months; and 2 mg aflibercept every 8 weeks thereafter) and laser arms, it was revealed that marked improvement could be achieved by aflibercept treatment in 52 weeks (aflibercept, +12.5 letters vs. laser, +0.2 letters) and that treatment every 8 weeks after month 5 was as effective as monthly treatment.³¹ The result on week 100 also showed that significant effect of on vision persisted in aflibercept arm (mean visual acuity gain: +11.5 vs. +0.9 letters and +11.4 vs. +0.7 letters in VISTA)³² It was seen that visual acuity gain sustained on week 148 (VIVID: +11.7 / +1.6, VISTA: +10.5 / +1.4).³³

Which Anti-VEGF?

In the literature, in randomized-controlled series which compared ranibizumab with bevacizumab in 60 eyes, it was reported that the mean visual acuity gain was 13 letters by average 7.67 ranibizumab injections and 11 letters by average 9.84 bevacizumab injections at the end of week 48. The proportions of eyes with 10 letters and 15 letters visual acuity gain were comparable in both groups.³⁴ A head-to-head comparison of aflibercept, bevacizumab and ranibizumab was performed by DRRCR-net (Protocol T).^{35,36}

In the study including 660 diabetic cases, aflibercept (2 mg), bevacizumab (1.25 mg) and ranibizumab (0.3 mg) were given every 4 weeks in first year and if indicated in control visit (every 4-6 weeks) thereafter; the protocol allowed focal or grid laser therapy after month 6. At the end of first year, marked improvement was achieved in vision by all agents with similar number of injections. In first year, mean visual acuity gain was 13.3 letters by aflibercept, 11.2 letters by ranibizumab and 9.7 letters by bevacizumab. At year 2, it was 12.8 letters by aflibercept, 12.3 letters by ranibizumab and 10 letters by bevacizumab. In first year, aflibercept achieved significantly higher visual acuity gain in cases with visual acuity $\leq 20/50$ when compared to other agents (18.9 letters in aflibercept, 14.2 letters in ranibizumab and 11.8 letters in bevacizumab); however, the difference between aflibercept and ranibizumab did not persist at the end of second year (18.1 in aflibercept, 16.1 letters in ranibizumab and 13.1 letters in bevacizumab). It was found that the decrease in central subfield thickness was significantly higher by aflibercept when compared to those achieved by other agents in the first year (mean decrease: 169 μ by aflibercept, 147 μ by ranibizumab and 101 μ by bevacizumab). In the second year, aflibercept remained to be superior against bevacizumab but there was no significant difference when compared to ranibizumab (mean decrease 171 μ by aflibercept, 149 μ by ranibizumab and 126 μ by bevacizumab).

Corticosteroids:

As corticosteroids target inflammatory processes in the pathogenesis, they have been used in DME treatment over 2 decades³⁷ These agents stabilize blood-retina barrier by inhibiting pro-inflammatory cytokine production and VEGF expression. Corticosteroids also reduce expression of intracellular adhesion molecule (ICAMs), stabilizing endothelial tight-junctions and decreasing vascular permeability.³⁸

Triamcinolone acetonide

The Protocol B study by DRRCR.net group showed that intravitreal triamcinolone acetonide monotherapy was not as effective as focal/grid laser therapy in DME cases with vision loss. In 2-years Protocol B study including 693 cases, the visual acuity change of +1 \pm 17 letters in laser group was found to be significantly higher than those in both 1 mg and 4 mg triamcinolone groups.³⁹ In the study, steroid-related complications such as IOP elevation or cataract formation was commonly observed. In the above-mentioned Protocol I study, the visual acuity gain by corticosteroids was similar to pseudophakia subgroup although it did not improve as much as cases underwent RBZ.²² Triamcinolone acetonide is used off-label in DME treatment.

Dexamethasone

Some implants have been developed for intravitreal use of corticosteroids. The dexamethasone implant (Ozurdex®, Allergan, Inc., Irvine, CA, USA) is biosoluble material, releasing its content into vitreous over 3 months.⁴⁰ The effectiveness of dexamethasone implant was first shown in phase II study on 171 cases with persistent DME by comparing 350 μ g and 700 μ g implants with sham group. After single implant, at least 2-order improvement in visual acuity was observed by 30% in 700 μ g implant group, by 19% in 350 μ g implant group and by 23% in sham group at month 6.⁴¹ In 700 μ g implant group, central macular thickness was also decreased significantly. The subsequent PLACID study showed marked improvement in visual acuity by laser plus dexamethasone implant.⁴² The MEAD is a phase III study on 1048 patients, which comprises a milestone in defining role of dexamethasone implant in DME management.⁴³ In the study, at least 3-order improvement was achieved in 22% of cases underwent 4.1 implant (0.7 mg) applications per year in average vs. 12% of cases in sham group, indicating a significant difference ($p < 0.018$). Cataract formation was observed in 59.2% of cases in implant group while glaucoma surgery was warranted in 0.6%. The dexamethasone implant was approved for DME by FDA in 2014. It has approval and reimbursement for this indication in Turkey.

The BEVORDEX study was conducted on 88 cases to compare bevacizumab injection every 4 weeks with dexamethasone implant every 16 weeks.⁴⁴ On month 12, at least 10 letters improvement was achieved

in 40% of cases underwent bevacizumab injection (8.6 injection in average) and 41% of cases underwent dexamethasone implant (2.7 implants in average). More prominent reduction was observed in central subfield thickness by dexamethasone implant (-187 μ vs. -122 μ). No significant difference was observed in visual acuity gain on month 24.⁴⁵

The MAGGIORE study compared outcomes of 0.7 mg dexamethasone implant applied at baseline and on months 5 and 10 with 0.5 mg ranibizumab given when indicated in DME management.⁴⁶ At the end of month 12, mean visual acuity gain was 4.3 letters in dexamethasone implant group and 7.6 letters in ranibizumab group. The central macular subfield thickness was decreased by 173.9 μ in dexamethasone implant group and by 163.5 μ in ranibizumab group.

Fluocinolon acetonide:

A novel corticosteroid implant investigated in DME treatment contains 0.19 mg fluocinolon acetonide (Ilu- vien, Alimera Sciences), releasing drug over 36 months. It is not a biosoluble agent and currently not available in Turkey. Its effectiveness was shown in FAME study including 953 patients⁴⁷ At year 2, at least 3-order improvement in vision was significantly higher when compared to sham group. In subgroup analysis, at least 3-order improvement rate was higher in chronic DME (>3 years) (34% and 22.3, respectively).⁴⁸ The major adverse effects include cataract formation and glaucoma and the drug was approved in cases without IOP elevation by FDA.

Safety:

It is important to use safe therapeutic modalities in DM that is associated with potential systemic complications. In previous studies, it was shown that intravitreal anti-VGEF therapy is safe and tolerable in DME. No considerable systemic adverse event was observed. In corticosteroids, cataract formation and IOP elevations is commonly observed by prolonged use. It is important to use licensed agents targeting intraocular pressure in medico-legal perspective.

Expert Panel Recommendations:

In the shed of these studies, The European Society of Retina Specialists (EURETINA) published a guideline for DME management in 2017.⁴⁹ In the guideline, anti-VGEF agents are recommended as first-line therapy in DME management, however, it is emphasized that dexamethasone implant can be preferred as first choice in patients at risk for cardiovascular problems, those unable to attend for frequent injections and pseudophakic cases.

CONCLUSION

Intravitreal agents enable us to aim improvement vision in DME management. However, optimal treatment interval or treatment regimen has not been established yet.

Further assessment of long-term results of studies is needed to establish long-term effectiveness and safety in DME management which is known to be a chronic process.

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