Outcomes of Dexamethasone Implant Treatment in Patients with Diabetic Macula Edema Anatomically Unresponsive to Intravitreal Bevacizumab Treatment: Early Switch to Dexamethasone Study

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ABSTRACT

Purpose: To evaluate the anatomical and visual outcomes of switching to intravitreal dexamethasone implant (IVD) in patients with diabetic macula edema unresponsive to 3 monthly consecutive intravitreal bevacizumab (IVB).

Methods: This retrospective study included patients with diabetic macular edema (DME) who showed anatomically poor response to 3 consecutive IVB injections and were switched to IVD treatment in early period. In the study population best-corrected visual acuity (BCVA), and central retinal thickness (CRT) were recorded at baseline, and on months 3, 6, 9, and 12.

Results: Overall, 27 eyes of 24 patients were included in our study. The mean age was 61.5 ± 9.5 years. The mean BCVA at baseline was 0.70 ± 0.21 LogMAR while the mean BCVA after 3 consecutive IVB injections was 0.69 ± 0.19 LogMAR. (p:0.83). The mean BCVA was 0.52 ± 0.21 LogMAR, 0.39 ± 0.22 LogMAR and 0.45 ± 0.27 LogMAR at 6, 9 and 12 months, respectively. (p=0.013, p=0.002, p<0.001). A statistically significant difference was observed for the mean BCVA at 6, 9 and 12 months compared to the mean BCVA at baseline and 3 months. The CMT was 522 ± 142 µm and decreased to 499 ± 152 µm at 3 months without statistical significance (p=0.51). After switching IVD, The mean CMT was 285 ± 40 µm, 278 ± 116 µm and 328 ± 172 µm at 6, 9 and 12 months, respectively (p<0.001, p<0.001, p<0.001).

Conclusions: Better visual and anatomical results can be obtained with an early switch to IVD treatment in poorly responding DME.

Keywords: Dexamethasone, Bevacizumab, Diabetic macula edema.

INTRODUCTION

Diabetic macular edema (DME) is the most common cause of impaired vision in patients with diabetic retinopathy (DR) worldwide.[1,2] The DME manifests with macular thickening as a result of disrupted blood-retina barrier and increased permeability. The primary factor underlying disruption of blood-retina barrier is vascular endothelial growth factor (VGEF). Although the VGEF is the most significant factor in DME development, it has been proposed that chronic inflammatory process driven by other inflammatory cytokines such as interleukin-1,6 (IL-1,6) and tumor necrosis factor-a (TNF-a) also plays role in the pathogenesis.[3,4] Focal laser photocoagulation previously used in the treatment of DME has been replaced by intravitreal anti-VGEF agents and sustained-release dexamethasone implant which are shown to provide better visual and anatomic outcomes.[5-7] The inhibition of VGEF that plays critical role in vascular permeability is important, shifting initial treatment towards anti-VGEF agents including aflibercept, ranibizumab and off-label bevacizumab. The efficacy of anti-VGEF agents has been proven in several studies.[8-12]

Bevacizumab is a humanized monoclonal antibody that inhibits all isoforms of VGEF-A. In many studies, it was shown that intravitreal bevacizumab (IVB) is effective in the treatment of DME patients.[6,10,13] Given that inflammatory cytokines such as IL-1,6 and TNF-a are involved in the DME pathogenesis, there may be poor response in some

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DME patients despite regular IVB injections.[14] In such case, it may be considered to switch to alternative treatment such as sustained-release dexamethasone implant (DEX implant 0.7 mg; Ozurdex; Allergan, Inc, Irvine, CA) since anti-VGEF agents inhibits only VGEF while dexamethasone implant blocks VGEF gene expression and prevents release of other inflammatory cytokines. In addition, it ensures stabilization of tight-junctions between impaired endothelial cells.[15,16]

In this study, we aimed to effects of early switch to intravitreal dexamethasone implant (IVDI) on anatomical and visual outcomes in treatment-naïve DME patients with poor anatomic response to 3 monthly consecutive intravitreal bevacizumab (IVB injection).

MATERIAL AND METHOD

We retrospectively reviewed medical records of treatment-naïve DME patients who showed inadequate response to 3 monthly IVB injections and were switched to intravitreal dexamethasone implant treatment between February, 2019 and January, 2020 in our clinic.

All patients gave informed consent. The study protocol was approved by Scientific Research Committee. The patients with macular ischemia on fluorescein angiography (FA), those with vitreoretinal interface disorder on optical coherence tomography (OCT), those underwent panretinal photocoagulation due to retinal ischemia and neovascularization within prior 6 months and those with follow-up <12 months were excluded.

Age, gender as well as BCVA and central macular thickness (CMT) at baseline and on months 3, 6, 9 and 12 were recorded for all patients.

In all visits, a thorough ophthalmological examination including BCVA using projector-based vision chart (4 meter), intraocular pressure (IOP) measurement using applanation tonometry, slit-lamp biomicroscopy and dilated fundus examination were performed. In all patients, OCT (Nidek RS-3000 Advance Capture SRD-OCT, Japan), color fundus imaging and FA (Kowa VX-10i, Kowa Company, Japan HRA-2) were performed before treatment. All examinations and evaluations other than FA were repeated monthly. The FA was repeated if needed by clinician. The CMT was defined as mean thickness of neurosensory retina in a central field (1mm in diameter) in automated manner by OCT mapping software. The diagnosis of DME was made based on clinical findings, OCT, color fundus image and FA. The patients with CMT>300 µm were considered as DME. The patients initially received 3 consecutive monthly IVB injection and were re-evaluated after loading dose. The <100 µm reduction or increase in CMT and/or absence of foveal pitting were defined as criteria for poor response. The DME patients with poor anatomic response was switched to dexamethasone implant. The criterion for re-treatment with dexamethasone implant was >150µm CMT increase compared to lowest value measured after first dexamethasone injection.

Intravitreal Injection Technique

Preparation to intravitreal injection was performed using a standard procedure in all eyes. Briefly, following local administration of propacaine to conjunctival sac in a semi-sterile manner, periorbital region was cleansed using 10% povidone iodine; then, 5% povidone iodine was applied to conjunctival sac. After awaiting 3 minutes, conjunctival sac was washed using sterile saline. Thereafter, the face was covered using a sterile drape and eyelids were opened using a speculum. Bevacizumab (Altuzan; F.Hoffmann-La Roche Ltd. Grenzacherstrasse 124 CH-4070 Basel, Switzerland) was injected using a 30 gauge needle while dexamethasone implant was injected using a 22 gauge prefilled injector at a point 4 mm away from limbus in phakic patients and 3.5 mm away from limbus in pseudophakic patients. After intravitreal injection, prophylactic ofloxacin (5x1, for 1 week) was prescribed to patients.

Statistical analysis

All statistical analyses were performed using SPSS version 20.0. Visual acuity measurements were converted to LogMAR units for statistical purposes. Normal distribution was assessed using Shapiro-Wilk test ($p>0.05$). Descriptive statistics are expressed as minimum, maximum and mean ± standard deviation. Paired-sample t test was used to compare dependent groups. A p value <0.05 was considered as statistically significant.

FINDINGS

Overall, the study included 27 eyes of 24 patients (11 women, 13 men). The mean age was 61.5 ± 9.5 years. Mean follow-up was 15±2 months. Table 1 summarizes demographic and baseline clinical characteristics of the patients.

Mean BCVA was 0.70±0.21 LogMAR at baseline while

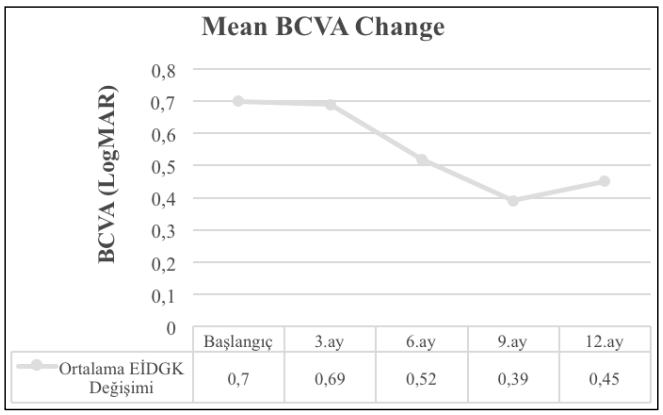
Table 1: *Demographic and baseline clinical characteristics of patients*

Age, years (Mean ± SD)	**61.5 ± 9.5**
Gender,(Female/Male)	11/13
DM duration, years (Mean ± SD))	14.2 ± 5.1
Baseline BCVA (Mean ± SD LogMAR,)	0.70 ± 0.21
Baseline CMT (Mean± SD µm)	522 ± 142

it was 0.69 ± 0.19 LogMAR after 3 consecutive IVB injections (p:0.83). The mean BCVA was 0.52 ± 0.21 LogMAR, 0.39 ± 0.22 LogMAR and 0.45 ± 0.27 LogMAR at 6, 9 and 12 months, respectively. A significant increase was detected in mean BCVA on months 6, 9 and 12 when compared to BCVA at baseline and after 3 consecutive monthly IVB injection (p=0.013; p=0.002; p=0.001). Figure 1 shows mean BCVA change over time.

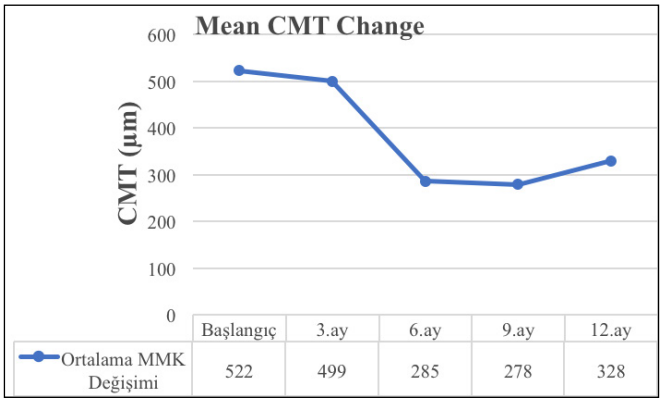
The CMT was 522 ± 142 µm before treatment while it was 499 ± 152 µm after 3 monthly consecutive IVB injections, indicating no significant difference (p=0.51). After switch to IVD, the mean CMT was 285 ± 40 µm, 278 ± 116 µm and 328 ± 172 µm on 6, 9 and 12 months, respectively. It was found that mean CMTs on months 6, 9 and 12 were significantly decreased when compared to those at baseline and on month 3 after IVB injection (p<0,001; p<0,001; p<0,001). Figure 2 shows changes in mean CMT thickness over time.

Mean number of dexamethasone implant injections was 1.9±0.7; overall 128 injection was performed without complication (endophthalmitis, retinal detachment etc.).



Graphic 1: *Mean BCVA (LogMAR) change over time in patients*

BCVA: Best-corrected visual acuity



Graphic 2: *Mean CMT change over time in patients*

CMT: Central macular thickness

DISCUSSION

Today, intravitreal pharmacotherapy has come forefront in the treatment of diabetic macular edema (DME). In recent years, high-quality clinical trials have shown that anti-VGEFs such as ranibizumab, aflibercept and bevacizumab are effective agents in the treatment of DME. In last decade, anti-VGEF agents were commonly adopted as first-line treatment in DME.[8-10,17] Given the adverse effects such as cataract formation and elevated IOP, it is considered as second-line treatment in DME patients.[18] Although efficacy of anti-VGEF agents have been proven, some patients show poor anatomic and visual response to treatment. In such patients, inflammatory cytokines other than VGEF may have more prominent role in the pathogenesis. For instance, inadequate response was observed in considerable number of patients despite fixed monthly injections in pivotal study of ranibizumab.[9] In the sub-analyses of DRCR.net Protocol I study, it was shown that BCVA change after 3 doses of monthly intravitreal ranibizumab (IVR) injection had strong predictive value for outcomes at years 1 and 3 after treatment and that the outcome on month was similar to those at years 1 and 3 in DME patients. Again, in the same study, it was shown that, among patients showing inadequate response on month 3, 15% demonstrated better response when IVR treatment was continued.[19] Thus, switching to dexamethasone can be reasonable in case of early unresponsiveness.

In the literature, there are many study showing efficacy of dexamethasone implant in patients refractory to anti-VGEF therapy. In a meta-analysis including 15 studies, Khan et al. found that BCVA was improved by 4-lines on month 6 after switch to dexamethasone implant therapy in patients with poor response to consecutive anti-VGEF injections.[20] In a study on 30 eyes with poor response to 3 consecutive monthly IVB injections, Totan et al. reported that mean BCVA was improved from 0.56 Logmar to 0.44 LogMAR after dexamethasone implant injection and that there was significant decrease in CMT.[14] In a prospective study including 16 eyes with poor response to at least 3 IVB injections, Lazic et al. reported BCVA improvement from 0.29 at baseline to 0.39 on month 3.[21] In agreement with above-mentioned studies, BCVA was improved from 0.69 LogMAR to 0.45 LogMAR after switch to dexamethasone in our patients with poor response to IVB therapy.

In the literature, there are also studies investigating switch to dexamethasone therapy in case of poor response to other anti-VGEF agents in DME patients in addition to those on dexamethasone switch in patients with poor response to IVB.[22,14] In a study, Demir et al. evaluated early and delayed switch to dexamethasone implant in patients with

poor response to 3 and 6 consecutive IVR injections and reported significant visual and anatomic outcome in both groups although outcomes were numerically better in early switch group.[22] In a retrospective study by International Retina Work Group, anti-VGEF injection was continued in some of the patients with inadequate response to 3-to-4 anti-VGEF injection while remaining patients were switched to dexamethasone implant. Better visual and anatomic outcomes were achieved in dexamethasone switch group.[23] Nalcaci et al. reported that mean BCVA was improved from 1.04 to 0.86 LogMAR after a single dexamethasone implant injection in patients with inadequate response to multiple anti-VGEF injections and that CMT remained lower over 6 months when compared to baseline.[24]

In diabetic macular edema, failure to restore impaired vision and anatomy in timely and effective manner can cause irreversible photoreceptor damage. In a study by Demircan et al., the patients with poor response to 3 consecutive IVR injections were assigned into two groups: the patients continued IVR injections in one group and patients switched to aflibercept in the other group. Anatomic improvement was observed in aflibercept group but no change was recorded in BCVA. Authors attributed this finding to irreversible damage in photoreceptors due to prolonged DME.[25] In addition to hypothesis proposed by authors, one may propose that switch among agents from same groups is not as effective as switch to an agent from different group. In recent years, assessment of treatment response is an intensively discussed topic in DME patients. Significant anatomic and visual gain can be achieved by timely and effective treatment changes in patients with inadequate response at early stage. As shown in our study, early switch to dexamethasone implant therapy provided significant visual gain in the group with inadequate response to anti-VGEF agent. The visual acuity was improved from 0.69 LogMAR on month 3 to 0.45 LogMAR on month 12, implying mean VA gain of 2.4 LogMAR (corresponding to 12 letters).

Our study has some limitations including retrospective design, small sample size and anatomic and visual outcomes at short-term. In addition, it is also limited by lack of assessments for OCT parameters such as ellipsoid zone defect, external limiting membrane defect, serous macular detachment and hyper-reflective spots in DME patients with poor response to IVB therapy. On the other hand, we believe that our study may have important contribution to treatment approaches in DME as it showed effects of early dexamethasone implant injections in patients with inadequate response to an anti-VGEF agent which is intensively used in Turkey.

In conclusion, dexamethasone implant can provide significant visual and anatomic gain if given early in patients with diabetic macular edema with poor response to anti-VGEF agents.

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