Does Dexamethasone implant Combination with Aflibercept monotherapy have an effect on 1-year outcomes in treatment-naive Diabetic Macular Edema with Inflammatory Biomarkers?

Cemal OZSAYGILI (cemalozsaygili@gmail.com)  
University Of Health Sciences, Kayseri City Hospital

Nurettin BAYRAM  
University Of Health Sciences, Ankara Etlik City Hospital

Research Article

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Abstract

Purpose

To compare the anatomical and functional outcomes of the combination of aflibercept and dexamethasone implant (CT) against aflibercept monotherapy (AM) in treatment-naive diabetic macular edema (DME) patients with serous macular detachment and hyperreflective foci.

Methods

This study included 82 eyes of 82 patients with treatment-naive DME who completed the follow-up period of 12 months. All patients had optical coherence tomography (OCT) biomarkers of an inflammatory DME phenotype. Patients were consecutively selected and classified into two groups. The CT group consisted of 39 eyes treated with aflibercept therapy and initially combined with a single-dose dexamethasone implant. The AM group consisted of 43 eyes treated with aflibercept alone. The primary outcome measures of the study were the mean reduction of the central macular thickness (CMT) and total macular volume parameters (TMV) and improvement in best-corrected visual acuity (BCVA).

Results

In both groups, the patient characteristics including age, gender, duration of diabetes, HbA1c levels, phakic percentage, and diabetic retinopathy status were similar (P > 0.05). The mean reduction in CMT and TMV was significantly higher in the CT group compared to the AM group (P < 0.001 and P = 0.002, respectively), while mean letter gains were not significantly higher (P = 0.240) at the end of the study. In the CT group, 8 eyes (20.5%) showed a transient IOP increase, and 18% of patients developed cataract. In subgroup analysis, the mean letter gain in pseudophakic eyes was significantly higher (12.5 in the CT vs. 9.3 in the AM group, P = 0.027).

Conclusion

The CT, where inflammation is prominent, can provide faster recovery. The pseudophakic eyes seem to be the ideal patient group for CT.

INTRODUCTION

Diabetic macular edema (DME), the main cause of severe visual impairment in diabetic retinopathy (DR), is encountered in approximately 7% of all diabetic patients [1]. The antagonist of vascular endothelial growth factor (anti-VEGF) agents or corticosteroids targeting non-VEGF inflammatory pathways are using as pharmacological therapy in the treatment of DME. Clinical studies have shown that approximately 10 to 40% of patients gained 6 to 11 letters in best-corrected visual acuity (BCVA) after 1 year of treatment with anti-VEGF agents [2, 3]. Therefore, they are considered as the first-line treatment in center-involved DME. Nevertheless, most patients still required multiple anti-VEGF injections, and this therapy does not provide a long-term resolution of refractory DME in up to 50% of treated patients [4, 5]. Therefore, alternative treatment options are needed.

The retinal vascular leakage in DME can also develop through non-VEGF-dependent inflammatory pathways, as well as VEGF upregulation, so chronic subclinical inflammation plays an essential role in the pathogenesis [6]. Corticosteroids have anti-inflammatory, antiangiogenic, and anti-permeability effects [7, 8] and may treat DME by reducing prostaglandin synthesis from VEGF-independent inflammatory pathways by inhibiting leukostasis and enhancing the barrier function of vascular endothelial cell tight junctions [8, 9]. Recently, serous macular detachment (SMD) and hyperreflective foci (HRF)
have been proposed as optical coherence tomography (OCT) biomarkers of an inflammatory DME phenotype. Both biomarkers have been associated with higher levels of inflammatory cytokines in the vitreous and aqueous humor samples, which may better respond to intravitreal steroid treatment. In 2014, the FDA approved dexamethasone (DEX) implant for treating DME. The effectiveness of intravitreal 0.7 mg DEX implant (Ozurdex, Allergan, Inc., Irvine, CA) in DME has been demonstrated by BCVA improvement and decreased retinal thickness [10].

In light of these recent insights, targeting multiple pathways may provide synergistic treatment responses in DME. Corticosteroids downregulate VEGF production but do not affect VEGF molecules in the vitreous. Thus, combining anti-VEGF and corticosteroid drugs can greatly suppress vascular permeability by blocking VEGF and the inflammatory cytokines and chemokines involved in DME.

Although there are studies on combination therapy in refractory DME in the literature, to the best of our knowledge, there is no clinical study evaluating the effectiveness of combination therapy in treatment-naive patients. Herein, we compare the 12-month therapeutic outcomes of combination of dexamethasone implant and aflibercept (CT) against aflibercept monotherapy (AM) in patients with treatment-naive DME with SMD and HRF, reflecting inflammation.

**MATERIALS AND METHODS**

**Participants**

This retrospective, interventional, comparative trial was performed at a single site. We reviewed the medical records of the DME patients who underwent aflibercept monotherapy or combined aflibercept plus DEX implant treatment between January 2017 and January 2021. Patients had at least 12-month follow-up medical records and had not been treated before. The protocol of the trial was approved by the local clinical research ethics committee of Health Sciences University Kayseri City Training and Research Hospital (#88408086) and was conducted by the principles of the Declaration of Helsinki. Written informed consent was obtained from patients before the injection procedures.

All patients included in the study had the inflammatory DME phenotype. HRF that spread through the retinal layers and SMD, an indicator of inflammatory etiology, were detected by Spectral Domain OCT (SD-OCT) (Fig. 1a-b). Patients who did not have fundus fluorescein angiography (FFA) records at the beginning of the treatment or with macular ischemia, defined as a foveal avascular zone (FAZ) diameter greater than 500 microns in FFA, were excluded from the study. In their medical records, eyes treated with dexamethasone implant simultaneously with aflibercept treatment or once in 1 week and continued treatment with aflibercept were determined as combined therapy (CT); eyes treated with aflibercept alone were termed aflibercept monotherapy (AM). Only the right eye was selected in patients with both eyes eligible for the study to avoid bias. Patients previously receiving anti-VEGF monotherapy to the fellow eye were also excluded.

The demographic data of the pooled patients collected from the medical records were age, gender, duration of diabetes mellitus (DM), HbA1c levels, and DR status. A comprehensive ophthalmological examination, BCVA, Intraocular pressure (IOP), central macular thickness (CMT), and total macular volume (TMV) were recorded at baseline and each visit of the patients. The BCVA was measured using the ETDRS charts at a distance of 4 m, and CMT was measured from SD-OCT (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany) at the central 1-mm subfield. TMV was calculated automatically from OCT software. Intraocular pressure (IOP) was measured using Goldmann applanation tonometry. A significant elevation in IOP was defined as an increase of more than 5 mmHg, and a marked progression in lens opacity was defined as an increase of more than 2 grades according to Lens Opacities Classification System III [11] compared to the initial examination.

**Treatment protocol**
In the CT group, DEX implant injections were applied in the same session as the aflibercept injections or within 1 week. CT and AM groups received a 3 monthly intravitreal 2 mg aflibercept injection as the loading phase, followed by pro re nata (PRN) treatment based on the required re-treatment protocol. DEX implant injection was performed only once at the beginning of therapy to benefit from the anti-inflammatory effect and to avoid the possibility of cataract development with repeated injections. During follow-up, anti-VEGF re-treatments were performed in the presence of new or persistent cystoid retinal changes, a decrease of 5 ETDRS letters in vision from the best previous measurement and/or an increase in CMT 50 µm or more compared with the previous lowest value on SD-OCT. In addition, the complete resolution of edema was defined as the absence of any fluid at SD-OCT and CMT below 320 um in males and below 305 um in females, respectively. All medical recorded data in the patients’ files were documented by the same retina specialist (CO). OCT evaluations were performed by the other retina specialist (NB), who was masked and did not know which patients were treated with CT or AM.

Since the baseline characteristics were similar but not the same, serial changes of the BCVA, CMT, and TMV were analyzed at follow-up time points. Also, the percentages of patients who gained 10 letters, the percentage of patients with complete edema resolution, the total number of injections administered, the rate of cataract development, and IOP elevation were investigated.

**Statistical Analysis**

Statistical analysis was performed by the Statistical Package for the Social Sciences software (version 24.0; IBM, Chicago, IL). Mean and standard deviation was used for describing the normally distributed quantitative variables, and for non-normally distributed variables, median and range were used. Categorical variables were defined as percentage and frequency. The normality of the distribution was verified by the Shapiro-Wilk test for quantitative variables such as BCVA (letters), TMV (mm³), and CMT (µm). The paired sample t-test was used to compare changes in CMT, TMV, and BCVA within the treatment groups. Serial changes in the BCVA, TMV, and CMT were compared between the CT and AM groups with repeated measures. Chi-square tests or Fisher's exact test was used to compare categorical variables such as the rate of patients with a 10-letter or greater gain and the complete resolution of DME patients. Pearson's correlation coefficients were performed to assess the relation of BCVA with CMT. The null hypothesis was rejected for values of \( p < 0.05 \).

**RESULTS**

**Basic Characteristics**

Eighty-two eyes from 82 patients who fulfilled the inclusion criteria and completed the follow-up period of 12 months were included, of which 39 eyes were in the CT and 43 eyes were in the MT injection schedule. Table 1 presents the baseline demographic and clinical characteristics of the enrolled patients. About 43.6% of the patients in the CT group and 48.8% of the patients in the AM group were males (\( P > 0.05 \)), and the mean age of the patients was 54.8 vs. 56.2 in the CT and AM groups, respectively (\( P > 0.05 \)). The median duration of DM was 10.4 vs. 10.1 years in groups, respectively (\( P > 0.05 \)). Mean HbA1c levels were 8.5% vs. 8.1%, and mean diabetic retinopathy (DRP) status (mild to moderate DRP vs. severe DRP) was also similar in both groups (\( P > 0.05 \)). Initially, 58.9% and 51.1% of the patients were phakic in the CT and AM groups, respectively (\( P > 0.05 \)). Baseline CMT values were 617.7µm ± 149.5 vs. 572.6 µm ± 76.7 (\( P > 0.05 \)), TMV values were 12.42±1.68 mm³ vs. 11.61±1.03 mm³ (\( P > 0.05 \)), and BCVA values were 46.3 ± 4.4 vs. 47.6 ± 3.1 ETDRS letters in the CT and AM groups respectively (\( P > 0.05 \)). IOP values were 15.9 mmHg in the CT and 15.6 mmHg in the AM group (\( P > 0.05 \)).
Table 1
Ocular and non-ocular baseline characteristics of patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Combined Therapy, n:39</th>
<th>Monotherapy, n:43</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%) (N)</td>
<td>17 (43.6%)</td>
<td>21 (48.8%)</td>
<td>0.337</td>
</tr>
<tr>
<td>Age (years), mean (SD) (N)</td>
<td>54.8±06</td>
<td>56.2±2.1</td>
<td>0.198</td>
</tr>
<tr>
<td>Duration of diabetes (years), median (IQR) (N)</td>
<td>10.4±2.8</td>
<td>10.1±2.6</td>
<td>0.461</td>
</tr>
<tr>
<td>HbA1c (%), mean (SD) (N)</td>
<td>8.5±0.5</td>
<td>8.1±0.6</td>
<td>0.085</td>
</tr>
<tr>
<td>DRP-status (mild/moderate-severe) (eyes)</td>
<td>24/15</td>
<td>29/14</td>
<td>0.112</td>
</tr>
<tr>
<td>CMT (µm), mean (SD) (N)</td>
<td>617.7±149.5</td>
<td>572.6±76.7</td>
<td>0.061</td>
</tr>
<tr>
<td>TMV (mm³), mean (SD) (N)</td>
<td>12.42±1.68</td>
<td>11.61±1.03</td>
<td>0.063</td>
</tr>
<tr>
<td>BCVA ETDRS letters</td>
<td>46.3±4.4</td>
<td>47.6±3.1</td>
<td>0.089</td>
</tr>
<tr>
<td>Phakic, n (%) (N)</td>
<td>23 (58.9%)</td>
<td>22 (51.1%)</td>
<td>0.246</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>15.9±1.5</td>
<td>15.6±1.4</td>
<td>0.345</td>
</tr>
<tr>
<td>Follow-up time, (months) mean (N)</td>
<td>13.5±2.1</td>
<td>12.2±0.8</td>
<td>0.716</td>
</tr>
</tbody>
</table>

DRP, diabetic retinopathy; CMT, central macular thickness; TMV, total macular volume, BCVA, best-corrected visual acuity; IOP, intraocular pressure

Spectral Domain-Optical Coherence Tomography Measurements

TMV and CMT values were significantly decreased ($P<0.001$) in both groups at each visit (Table 2). In the CT group, the mean CMT decreased from 617.7 µm to 292.2 µm ($P<0.001$), and in the AM group decreased from 572.6 µm to 337.2 µm in 12 months ($P<0.001$). In the CT group, the mean TMV decreased from 12.42 mm$^3$ to 8.13 mm$^3$ ($P<0.001$), and in the AM group decreased from 11.61 mm$^3$ to 8.92 mm$^3$ in 12 months (Table 3). In the comparison of the CT and AM groups, the difference in a mean decrease in CMT did not differ significantly in the first month ($P=0.088$), but in the following months, the CT group was significantly superior to the MT group ($P<0.001$) (Table 2). Similarly, concerning the mean change in TMV, the CT group was significantly superior to the AM group during follow-up (Table 3). At the end of 12 months, macular edema was completely resolved in 64% of the eyes in the CT group compared with 44.2% of the eyes in the AM group ($P=0.035$) (Fig. 2a-b).
Table 2
Central macular thickness results and differences between the groups

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<thead>
<tr>
<th></th>
<th>Combined therapy</th>
<th>Monotherapy</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
<td>2 months</td>
<td>3 months</td>
<td>6 months</td>
<td>9 months</td>
<td>12 months</td>
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<tr>
<td>CMT, µm</td>
<td>617.7±149.5</td>
<td>441.8±105.5</td>
<td>326.6±63.9</td>
<td>300.5±67.8</td>
<td>332.7±65.2</td>
<td>313.1±58.5</td>
<td>292.2±51.5</td>
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<td>P-value</td>
<td>&lt; 0.001</td>
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<td>572.6±76.7</td>
<td>453.7±79.8</td>
<td>416.3±74.7</td>
<td>387.4±72.9</td>
<td>410.6±72.1</td>
<td>384±70.3</td>
<td>337.2±59.5</td>
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<td>P-value</td>
<td>&lt; 0.001</td>
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<td>0.061</td>
<td>0.088</td>
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<td>&lt; 0.001</td>
<td>0.011</td>
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</table>
| CMT, central macular thickness

Table 3
Total macular volume results and differences between the groups

<table>
<thead>
<tr>
<th>Total macular volume, mm³</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined therapy</td>
<td>12.42±1.68</td>
<td>11.20±1.13</td>
<td>10.62±1.03</td>
<td>10.12±0.97</td>
<td>9.76±0.92</td>
<td>9.48±0.95</td>
<td>8.13±0.94</td>
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<tr>
<td>P-value (difference</td>
<td>&lt; 0.001</td>
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<tr>
<td>Monotherapy</td>
<td>11.61±1.03</td>
<td>10.77±1.16</td>
<td>10.22±1.16</td>
<td>9.74±1.14</td>
<td>9.42±1.11</td>
<td>9.11±1.11</td>
<td>8.92±1.08</td>
</tr>
<tr>
<td>P-value (difference</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<td>vs. baseline)</td>
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<tr>
<td>P-value (difference</td>
<td>0.063</td>
<td>0.014</td>
<td>0.021</td>
<td>0.004</td>
<td>0.011</td>
<td>0.033</td>
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<td>between groups)</td>
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Visual Acuity Measurements

In both groups, BCVA improved significantly compared to baseline at each visit ($P<0.001$). In the CT group, BCVA increased from 46.3 letters to 57.9 ($P<0.001$), and in the AM group increased from 47.6 letters to 56.9 in 12 months ($P<0.001$) (Table 4). When adjusted for baseline values, the increase in mean BCVA was significantly higher in the CT group in the first 6 months of follow-up but similar in the second 6-month period of the study. At the end of the 12th month, the CT group achieved an average of 11.6 ETDRS letters, while the mean of the AM group was 9.3 letters ($P=0.240$). Additionally, 52% of CT eyes vs. 44.2% of AM eyes experienced 10 or more letters gain in the 12th month ($P=0.432$). When only pseudophakic eyes were evaluated, the mean BCVA improvement was 12.5 ETDRS letters in the CT group and 9.3 letters in the AM group ($P=0.027$). The rate of the gain of 10 or more letters was also found to be higher in the CT group (72.6% vs. 44.4%, $P=0.018$). None of the AM-treated eyes lost more than 10 letters, but 4 of the 39 eyes (10.2%) in the CT eyes did, and all of them were phakic. In the final analysis, it was observed that foveal hard exudates that might affect BCVA were 23.2% in the CT group and 30.7% in the MT group. There was no significant difference between groups in terms of foveal exudate ratios ($P=0.466$).
Table 4
Visual acuity outcomes and differences between the groups

<table>
<thead>
<tr>
<th>Visual acuity, ETDRS Letters</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
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<tr>
<td><strong>Combined therapy</strong></td>
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<td>p-value (difference vs. baseline)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<tr>
<td><strong>Monotherapy</strong></td>
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<td>p-value (difference vs. baseline)</td>
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</tr>
<tr>
<td>p-value (difference between groups)</td>
<td>0.089</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.170</td>
<td>0.240</td>
</tr>
</tbody>
</table>

Variables and Safety Related to Treatment

There was no statistically significant difference between both groups in terms of the number of injections (7.1 in the CT vs. 7.4 in the AM, \( P = 0.072 \)) at the end of the 12th month. Cataract development/progression and IOP increase were ocular adverse events (AEs) reported in this study. Regarding ocular AEs, 8 eyes (20.5\%) with CT showed a transient IOP increase greater than 5 mm Hg above baseline, and one of the eyes (2.3\%) with AM (\( P = 0.015 \)). Eyes with elevated IOP were treated successfully with topical IOP-lowering medications, and no eye needed glaucoma surgery. Other treatment-related side effects were cataract development in 18\% of patients in the CT group (\( P = 0.001 \)), and 8\% of patients in this group lost 10 or more letters from progression in lens opacity but were not observed in any of the eyes of the AM group. In both groups, there were no treatment-related cases of lens injury, retinal detachment, significant vitreous hemorrhage, or endophthalmitis.

DISCUSSION

The ideal treatment option for DME should improve vision, restore morphological alterations, reduce treatment burden, and be well tolerated by the patients. Several non-surgical treatment options exist, including intravitreal anti-VEGF and steroid therapies for DME treatment. Intravitreal aflibercept has been known to show promise in cases with center-involved DME [12]. In VIVID and VISTA studies, it has been shown to have a significant superiority of aflibercept to laser treatment in anatomic and functional aspects.

Although anti-VEGFs have proven to be effective in treating DME, even in patients who receive multiple injections, only 50 to 75\% of a completely dry macula can be achieved [13]. It has been shown that non-VEGF-dependent chronic subclinical inflammation has an important role in the modulation of endothelial tight junction proteins and leads to DME formation by destroying the outer-retinal barrier [7, 14]. Various inflammatory cytokines (IL-8, IL-6, ICAM-1, MCP - 1, etc.) are up-regulated in eyes with DME and found to be correlated with an increase in retinal vascular permeability [15–18].

DEX implant is the most commonly used steroid agent in routine clinical practice and provides anatomic and functional success in eyes with DME [19, 20]. The MEAD study reported significant visual gain compared to sham at 3 years [10]. Gillies et al. reported that the DEX implant was as efficacious as bevacizumab with a very low ocular risk profile [21]. However, to date, we have not been aware of studies that have combined DEX implant with anti-VEGF therapy for DME in treatment-naive cases with inflammatory biomarkers. Lin et al. compared the combination of DEX implant and aflibercept with aflibercept treatment. In their study, it was observed that the patients had previously received treatment (the eyes had previously received anti-VEGF injection and/or laser treatment) and also the 6-months follow-up period was shorter compared to our study [22]. This stands out as one of the superior aspects of our study. Therefore, we investigated whether combining a DEX implant with aflibercept in treatment-naive DME patients is advantageous over a 12 month period.
Significant increases in cytokine levels have been shown, and intraocular cytokine concentrations were reported to correlate with CMT in DME [23]. Although it is known that VEGF plays an important role in DME formation, VEGF levels usually do not correlate with baseline CMT when DME is complicated by SMD [24]. DME cases with subretinal fluid and HRF are thought to be caused by proinflammatory cytokines, at least as VEGF. Steroids can treat DME with a dual effect by regulating blood flow with a vasoconstrictor effect and controlling chronic inflammation. As mentioned before, IL-6, IL-8, VEGF, MCP-1, ICAM-1, and Angiotensin II are elevated [15, 23, 25] in intraocular fluids of DME patients, and anti-VEGF treatments are known not to suppress all the inflammatory cytokines and chemokines [17, 18]. According to recent studies, targeting only VEGF or VEGF-independent pathways in isolation might not adequately inhibit the increased permeability associated with DME. In some cases, a combined approach may be required, and steroids with anti-VEGF agents may have complementary effects in reducing retinal vascular permeability.

To date, several prospective, controlled studies have been conducted to examine the effects of combining two pharmacological treatments (anti-VEGF and corticosteroids), intravitreal bevacizumab and triamcinolone in the treatment of DME [26]. Soheilean et al. reported that combination therapies improved BCVA earlier than bevacizumab monotherapy with a lower re-treatment rate [27]. In another comparative trial, patients receiving a bevacizumab/triamcinolone combination achieved better 6-week improvement in BCVA, but with a 24-week follow-up, changes in both BCVA and CMT were the same as in bevacizumab monotherapy [28]. The combination of DEX implant and ranibizumab has been shown to reduce in vitro retinal endothelial cell permeability more than both agents [29]. Additionally, relatively long-term effects and the durable action of DEX implant facilitate the combination with anti-VEGF [30]. The combination of anti-VEGF (afiblercept or ranibizumab) and DEX implant at the beginning of treatment may result in a faster BCVA recovery, a longer remission in DME, and a permanent modulation of relapse than that achieved with anti-VEGF monotherapy. Potentially, if such a combination works, the frequency of intravitreal anti-VEGF injections may be reduced. Hernández-Bel et al. compared the results of sequential DEX implant and afiblercept therapy in treatment-naive DME patients [31]. Afiblercept treatment was started 16 weeks after the DEX implant in the sequential group, and the other group was followed up with afiblercept monotherapy. The differences in visual gain and decreased CMT between the two groups were not statistically significant, but the number of injections was reported to be lower in the sequential group (6 vs. 9 injections). As mentioned before, Lin et al. compared two treatment regimens in a group of previously treated patients without treatment initiation and mentioned the advantages of combination therapy in their 6-month results [22]. However, we have not encountered a study examining whether adding the DEX implant to afiblercept therapy in treatment-naive patients at the beginning of the treatment will provide a clinical advantage.

To enhance therapeutic effects and benefit from the anti-inflammatory properties in the early period, we combined DEX implant and afiblercept at the beginning of the treatment. We observed an additive effect in terms of BCVA improvement, CMT, and TMV reduction. The mean change of BCVA, CMT, and TMV is more reliable and reasonable in comparing efficacy. The decrease in CMT was statistically significant in both groups compared to the baseline ($p<0.0001$). The decrease in CMT and TMV, indicators of anatomical improvement, were significantly higher in the CT group than the AM group during follow-up. In addition, at the end of 1 year, the rate of the edema-free eyes (CMT below 320 um and 305 um in males and females, respectively) was significantly higher in the CT group (64% vs. 44.2%, $p=0.035$). The superiority of the anatomical improvement was also observed in functional recovery in the first 6 months in the CT group. In the second 6 months of the study, no significant difference was found in BCVA improvement due to possibly increased lens opacity. When subgroup analysis was performed, we observed that improvement in BCVA in pseudophakic eyes was more prominent than in phakic eyes. The mean BCVA improvement in the CT group was 12.5, in the AM group was 9.3 letters ($p=0.027$), and the rate of gaining 10 or more letters in the CT group was also higher in the pseudophakic eyes (72.6% vs. 44.4%, $p=0.018$). Functional effects were evident earlier, and the VA improvement time was shorter in the CT group with a slightly lower mean number of injections (7.1 vs. 7.4, $p=0.072$).

CT aimed to prevent photoreceptor damage with the help of a rapid decrease in CMT. Ozdemir et al. reported a dramatic anatomical improvement in SMD after intravitreal triamcinolone (IVTA) injection [32]. Pelosini et al. showed a linear
relationship between anatomical improvement and BCVA, considering that irreversible damage to retinal structures was minimal in treatment-naive patients [33]. The visual prognosis is related to the integrity of the OCT’s IS/OS and ELM lines, suggesting that photoreceptor integrity may be the best predictor of BCVA [34, 35]. In the present study, external retinal structures were intact in most of the study eyes due to the evaluation of treatment-naive patients, and Pearson correlation showed a relationship between BCVA and CMT parameters (r=−0.304, p = 0.002). We think this is due to the absence or minimal photoreceptor degeneration in naive patients, as opposed to refractory eyes.

At the end of the study, the proportion of patients who received more than 10 ETDRS letters was similar (52% vs. 44.2%, p = 0.432); however, when the pseudophakic eyes were evaluated only, it was found to be significantly higher in the CT group. Despite a single DEX implant, the effect of lens opacification on vision in the CT group was found to be significant after 6 months of study. In the study of Maturi et al., an average of 2.1 DEX implant injection was applied. An increase in IOP (28.5% vs. 5.3%) and progression of cataracts (42.8% vs. 0) were found to be significantly higher in the combined treatment group compared to the continued bevacizumab group [36]. In the Bevordex study, 11% of the patients in the DEX implant group lost ≥ 10 letters, but none of the patients in the bevacizumab group was observed [21]. In our study, 10.2% of the eyes in the CT group lost more than 10 letters with one DEX implant. Increases in IOP can usually be controlled by medication and do not require surgical treatment. In fact, in this study, 20.5% of the eyes developed an increase in IOP but all of them were managed with topical medication. Also, in most of the patients, an IOP increase was observed during the 8th week when the maximum efficacy of the DEX implant was observed. For this reason, we recommend IOP control between 4–8 weeks after implantation.

The present study did not observe treatment-related unexpected AEs and arterial thromboembolic events. The rates of adverse events among intraocular corticosteroids differ and were less observed with DEX implant than with triamcinolone acetonide or fluocinolone implant [37]. It should be well known that steroid-associated cataracts usually occur in the second year after commencing intravitreal steroid therapy. In the present study, cataracts developed in 9 eyes, but we would like to mention the short follow-up period of 12 months. Also, the lower rate of increase in IOP and development of cataracts compared to the literature may be due to the possibility of a single DEX implant application. If our study had a longer follow-up period, it could have resulted in a higher rate of cataract development as in the 3-year follow-up MEAD study (29.8%) [10].

Some studies have shown that patient characteristics such as age, control of diabetes, and HbA1c levels may affect the response to drugs used to treat DME [38, 39]. Therefore, baseline and individual systemic factors must be considered when comparing the efficacy of various DME treatment protocols. When the systemic characteristics of the patients were considered, there was no difference between the two groups in terms of age, duration of diabetes, HbA1c values, and DR status. Therefore, the positive effect of this combination cannot be attributed to changes in health status.

Another fact that we think increases the importance of our study is that, as of January 2019, according to local regulations in Social Security Institution in Turkey, for diabetic macular edema, at least 3 doses of bevacizumab should be administered to patients before any other drugs such as aflibercept, dexamethasone implant or ranibizumab are reimbursed. In other words, under current conditions, it is not possible for us to apply aflibercept treatment in a treatment-naive patient or to combine aflibercept treatment with a DEX implant. Therefore, we think that the 12-month follow-up results of this patient group are important.

However, some limitations need to be considered. Inflammation has been suggested to play a role in the pathogenesis of DME, but no specific biomarker is directly associated yet. It would be more helpful to compare with electrophysiological tests whether the rapid resolution of macular edema by adding an anti-inflammatory agent has advantages over the functions of retinal cells. Also, although the eyes with DEX implant applied during the same session with aflibercept or within a week in their medical records are determined as a CT group, to mention a true anti-VEGF + steroid combination, the DEX implant would have to be repeated every 3 months or at a predetermined fixed interval. However, it has been
determined that a single steroid implant applied in the early period helps anatomical success and functional success, especially in pseudophakic eyes may shed light on future prospective studies. Further prospective studies with longer follow-ups and larger sample sizes are needed to better understand which patients can benefit most from patients with DME in early CT both functionally and morphologically.

In conclusion, DME management is still complex, and patients may need multiple treatment approaches to biomarkers in the OCT image. Each DME form should be properly classified and treated specifically. CT can play an essential role in the complex management of DME. This study demonstrates that CT provides superiority in drying the macula in the early DME treatment; whether these findings can be translated clinically regarding BCVA improvement needs support in future studies.

Declarations

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References


Figures
Figure 1

**a-b:** Hyperreflective foci and serous macular detachment detected by Spectral Domain Optic Coherence Tomography (SD-OCT). Baseline vs. final SD-OCT of the eye in the combined treatment group.
Figure 2

a-b: Hyperreflective foci and serous macular detachment detected by Spectral Domain Optic Coherence Tomography (SD-OCT). Baseline vs. final SD-OCT of the eye in the Aflibercept monotherapy group.