Intravitreal Dexamethasone Implant in Patients Who Did Not Complete Anti-VEGF Loading Dose During the COVID-19 Pandemic: a Retrospective Observational Study

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ABSTRACT

Introduction: To compare the functional and anatomic outcomes between eyes in patients with diabetic macular edema (DME) who underwent a complete anti-vascular endothelial growth factor (VEGF) loading dose with aflibercept and those who were switched to dexamethasone intravitreal (DEX) implant after an incomplete anti-VEGF treatment regimen during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: This was a retrospective and comparative study conducted on patients with DME. Main outcome measures were mean change in best corrected visual acuity (BCVA) and central retinal thickness (CRT) from baseline to month 4.

Results: Forty-three eyes (23 eyes in the anti-VEGF group and 20 eyes in the DEX group) were included. Mean BCVA significantly improved from 37.7 ± 25.3 and 35.7 ± 22.0 letters at baseline to 45.4 (23.9) (mean adjusted BCVA improvement 7.6 ± 20.8 letters, $p = 0.033$) and 46.1 ± 26.0 (mean adjusted BCVA improvement 10.6 ± 15.9 letters, $p = 0.049$) at month 4 in the anti-VEGF and DEX groups, respectively, with no significant differences between study groups (mean adjusted BCVA difference 2.8 letters, 95% CI -9.4 to 14.9 letters, $p = 0.648$). There were no statistically significant differences in the proportion of eyes that achieved a BCVA improvement of ≥ 5, ≥ 10, and ≥ 15 letters between groups. CRT was significantly reduced from baseline to month 4 in both DEX (mean adjusted CRT reduction 167.3 ± 148.2 μm, $p = 0.012$) and anti-VEGF groups (mean adjusted CRT reduction 109.9 ± 181.9 μm, $p < 0.001$), with no differences between them (mean adjusted CRT difference 56.1 μm, 95% CI -46.0 to 158.2 μm, $p = 0.273$). Of 20 eyes in the DEX group, 16 (80.0%) and 9 (45.0%) eyes achieved a CRT reduction of $\geq 20\%$ from baseline at 2 months and at 4 months, respectively.

Conclusions: Our results seem to suggest that DEX implant can significantly improve both functional and anatomic clinical outcomes in

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patients who were unable to complete anti-VEGF loading dose during the COVID-19 pandemic.

Keywords: COVID-19; Dexamethasone Intravitreal Implant; Diabetes; Diabetic Macular Edema; Diabetic Retinopathy; Vascular Endothelial Growth Factor Inhibitors

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Key Summary Points

Why carry out this study?

Switching to a sustained released dexamethasone intravitreal (DEX) implant has seemed to be a feasible option in patients with diabetic macular edema who do not adequately respond to intravitreal vascular endothelial growth factor inhibitor (anti-VEGF) injections.

Measures adopted during the coronavirus disease 2019 (COVID-19) pandemic have dramatically disrupted the provision of health care, resulting in deferral of routine ophthalmic procedures.

This study aimed to compare functional and anatomic outcomes in patients with diabetic macular edema who underwent a full anti-VEGF regimen (monthly injection during 5 months) versus those who underwent dexamethasone intravitreal implant after an incomplete anti-VEGF treatment regimen.

What was learned from the study?

DEX implant significantly improved both functional and anatomic outcomes in patients who were unable to complete anti-VEGF loading dose.

DEX implant may be a valuable option for treating patients with DME who have not completed the standard anti-VEGF loading dose regimen.

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetes [1]. DME is a chronic, multifactorial, and sight-threatening condition that critically impacts on the patient's quality of life [2, 3]. Many different treatment options are currently available for DME; among these, intravitreal injections of anti-vascular endothelial growth factor inhibitors (VEGF) are considered the first line of treatment in center-involving DME [4]. However, on the basis of large clinical trial results, only 33–45% of patients with DME on anti-VEGF agents showed three lines or more of visual improvement [4–6], which supports the presence of multiple factors contributing to the pathophysiology of DME [5–7]. Since there is increasing evidence about the role of inflammation in the pathophysiology of DME, corticosteroids have taken an active role in its treatment [7–11].

With the coronavirus disease 2019 (COVID-19) outbreak over the last year, the strategies adopted by different governments to reduce the risk of infection spread have dramatically disrupted the provision of health care, resulting in deferral of routine ophthalmic procedures [12, 13]. As a result of the risk of irreversible visual loss, treatment planning and prioritization during the pandemic has become more critical than ever in order to achieve and maintain optimal clinical outcomes in patients with DME [14, 15]. Although we have established specific schedules for patients with DME [16], many patients were unwilling to follow the recommended treatment regimen [16].

Switching from anti-VEGF injections to a sustained released dexamethasone intravitreal (DEX) implant has been shown to provide good functional and anatomic outcomes [17–20]. Thus, because we have encountered many patients with DME who were unable to comply with the anti-VEGF scheduled treatment regimen, we considered DEX implant as an option for treating these patients during the COVID-19 pandemic.

This study aimed to compare functional and anatomic outcomes in patients with DME who

underwent a full anti-VEGF regimen (monthly injection during 5 months) versus those who underwent DEX treatment after an incomplete anti-VEGF treatment regimen.

METHODS

This retrospective comparative study included 20 patients with DME who were unable to receive a complete loading regimen of at least five consecutive anti-VEGF injections because of the COVID-19 pandemic and subsequently underwent treatment with DEX implant from April 2020 to January 2021 and 23 patients with DME treated from January 2016 to February 2020 with five monthly intravitreal injections of aflibercept as a control group, at a tertiary level hospital (University of Magna Graecia, Catanzaro, Italy). This study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee of the University of Magna Graecia, Catanzaro, Italy.

Inclusion criteria were age 18 years or older, diagnosis of type 2 diabetes mellitus, HbA1c $\leq 9\%$ (75 mmol/mol), sufficiently clear ocular media, adequate pupillary dilation, fixation to permit high quality optical coherence tomography (OCT) imaging; macular edema defined clinically and by structural spectral domain (SD)-OCT as the presence of central retinal thickness (CRT) of $\geq 250\,\mu m$ with intra/subretinal fluid and not having received any anti-VEGF treatment before starting the study. Exclusion criteria included concomitant ocular disease that could cause macular edema including choroidal neovascularization, retinal vein occlusion, uveitis and recent intraocular surgery less 6 months prior, and the presence of any retinal disease other than diabetic retinopathy (i.e., hypertensive retinopathy, central serous retinopathy, or macular dystrophies). Both phakic and pseudophakic patients were included in the study. Minimum follow-up was 4 months.

If both eyes were eligible, only one eye (chosen at random) was used for the analysis.

Patients who had been switched from anti-VEGF therapy to DEX implant for any reason other than inability to attend consultation due to COVID restrictions were excluded from the study.

Assessments

Each patient was assessed at baseline (prior to aflibercept injection for the anti-VEGF group and prior to DEX implantation for the DEX group) and 2 and 4 months after both interventions. During each follow-up visit, comprehensive ophthalmologic examination was performed including best corrected visual acuity (BCVA) testing using the standard early treatment diabetic retinopathy study (ETDRS) protocol, slit lamp examination, intraocular pressure (IOP) measurement, and dilated fundus biomicroscopy. Structural SD-OCT (Optovue; Optovue Inc., Fremont, CA, USA) was also performed at every visit. Complications were also assessed in all follow-up visits.

Outcomes

Main outcome measures were change in BCVA and CRT from baseline to month 4.

Secondary outcome measures included incidence of adverse events and proportion of eyes that achieved a CRT reduction of $\geq 20\%$ from baseline to month 4; proportion of eyes achieving a BCVA improvement of ≥ 5, ≥ 10, and ≥ 15 letters; and proportion of eyes losing ≥ 5, ≥ 10, and ≥ 15 letters in BCVA. Anatomic success was defined as a CRT reduction of $\geq 10\%$ from baseline to month 4.

Data Analysis

All statistical analysis was performed using IBM SPSS (version 27.0; IBM, Armonk, New York). For descriptive statistics, number (percentage), mean (standard deviation, SD), mean (95% confidence interval, CI), and median (interquartile range) were used as appropriate.

Data were tested for normal distribution using a Shapiro–Wilk's test.

A Friedman's two-way analysis test was used to assess the changes in BCVA and CRT.

Analysis of covariance (ANCOVA) was used to compare changes in BCVA and CRT between

study groups. The model included "group" as a factor and age, baseline BCVA, and previous laser photocoagulation as covariates. Poisson regression analysis was used to compare the proportion of patients who achieved a specific BCVA gain or loss. Categorical variables were compared using a Fisher's exact or chi-squared test as appropriate.

RESULTS

Forty-three eyes were included, 23 (53.5%) eyes in the anti-VEGF group and 20 (46.5%) eyes in the DEX group. Mean age was 63.6 ± 9.3 and 62.3 ± 7.4 years in the in the anti-VEGF and DEX groups, respectively ($p = 0.617$). Minimum and maximum follow-up were 115 days and 136 days for the DEX group and 113 days and 139 days for the anti-VEGF group.

Table 1 summarizes the main demographic and clinical characteristics of the study population. In the DEX group, mean number of intravitreal anti-VEGF injections was 2.4 ± 0.7. Time between the last anti-VEGF injection and first DEX implant in the switch group was 160.7 ± 102.8 days (range 91.0–218.9 days).

Mean BCVA significantly improved from 37.7 ± 25.3 and 35.7 ± 22.0 letters at baseline to 45.4 (23.9) (mean adjusted BCVA improvement 7.6 ± 20.8 letters, $p = 0.033$) and 46.1 ± 26.0 (mean adjusted BCVA improvement 10.6 ± 15.9 letters, $p = 0.049$) at month 4 in the anti-VEGF and DEX groups, respectively; there were no significant differences between study groups (mean adjusted BCVA difference 2.8 letters, 95% CI -9.4 to 14.9 letters, $p = 0.648$) (Fig. 1).

There were no statistically significant differences in the proportion of eyes that achieved a BCVA improvement of ≥ 5, ≥ 10, and ≥ 15 letters between groups (Fig. 2). Similarly, there were no differences in the proportion of eyes losing ≥ 5, ≥ 10, and ≥ 15 letters (Fig. 2).

In the DEX group, there was a statistically significant reduction in CRT from $583.6 \pm 129.4 \, \mu m$ at baseline to $473.7 \pm 197.0 \, \mu m$ at month 4 (mean adjusted CRT reduction $167.3 \pm 148.2 \, \mu m$, $p = 0.012$). Similarly, CRT was significantly reduced in the anti-VEGF group from $560.1 \pm 83.7 \, \mu m$ at baseline to $392.7 \pm 146.9 \, \mu m$ at month 4 (mean adjusted CRT reduction $109.9 \pm 181.9 \, \mu m$, $p < 0.001$). There were no differences between groups in mean CRT reduction (mean adjusted CRT difference $56.1 \, \mu m$, 95% CI -46.0 to $158.2 \, \mu m$, $p = 0.273$) (Fig. 3).

Of 20 eyes in the DEX group, 16 (80.0%) and 9 (45.0%) eyes achieved a CRT reduction of $\geq 20\%$ from baseline at 2 months and at 4 months, respectively. At month 4, anatomic success was achieved in 12 (60.0%) eyes in the DEX group and 16 (69.6%) in the anti-VEGF group ($p = 0.515$).

Regarding safety, 1 eye (4.3%) developed IOP elevation in the anti-VEGF group and 3 (15.0%) in the DEX group ($p = 0.233$). In all cases topical medications were effective to manage the IOP. Of the 10 phakic eyes at baseline, only 1 (10.0%) eye of a 68-year-old patient in the DEX group developed visually significant lens opacification throughout the follow-up. Additionally, 1 eye (4.3%) in the anti-VEGF group and 2 eyes (10.0%) in the DEX group experienced a BCVA loss of ≥ 15 letters, ($p = 0.482$).

DISCUSSION

The results of the current paper have shown that DEX implant may be a valuable option for treating patients with DME who have not completed the standard anti-VEGF loading dose regimen.

COVID-19 has posed a global public health threat due to the severity of its contagion and associated morbidity and mortality [16, 17]. In fact, the volume of outpatient and surgical procedures has significantly decreased during the pandemic [12]. In most ophthalmic centers, provision of care was restricted to urgent or emergency cases [21].

Anti-VEGF intravitreal injections are currently considered the standard of care for patients with DME [4]. However, since unintentional treatment interruptions can result in severe adverse visual sequelae [22, 23], evaluation of alternative longer-term therapy is crucial for achieving optimal clinical outcomes among patients with DME [14]. The positive effect of

Table 1 Baseline demographic and clinical characteristics

	Anti-VEGF group ($n = 23$)	DEX group ($n = 20$)	p value[a]
Age, years			
Mean (SD)	63.6 (9.3)	62.3 (7.4)	0.617[c]
Sex, n (%)			
Women	5 (21.7)	7 (35.0)	0.497
Men	18 (78.3)	13 (65.0)	
Number of IVI*, n (%)			
1	0 (0.0)	2 (10.0)	< 0.001[b]
2	0 (0.0)	9 (45.0)	
3	0 (0.0)	9 (45.0)	
5	23 (100.0)	0 (0.0)	
Lens status, n (%)			
Phakic	4 (17.4)	6 (30.0)	0.473
Pseudophakic	19 (82.6)	14 (70.0)	
Preoperative laser, n (%)			
None	13 (56.5)	8 (40.0)	0.478[b]
PRP	4 (17.4)	6 (30.0)	
Macular grid	0 (0.0)	1 (5.0)	
Combined**	6 (26.1)	5 (25.0)	
Presence of IRF, n (%)			
No	6 (26.1)	4 (20.0)	0.728
Yes	17 (73.9)	16 (80.0)	
Presence of SRF			
No	22 (95.7)	16 (80.0)	0.167
Yes	1 (4.3)	4 (20.0)	
PDR, n (%)			
Yes	14 (60.9)	12 (60.0)	1.000
No	9 (39.1)	8 (40.0)	
BCVA***			
Mean (SD)	37.7 (25.3)	35.7 (22.0)	0.785[c]
CRT			

Table 1 continued

	Anti-VEGF group (*n* = 23)	DEX group (*n* = 20)	*p* value[a]
Mean (SD)	560.1 (83.7)	583.6 (129.4)	0.478[c]

VEGF vascular endothelial grow factor, *DEX* intravitreal dexamethasone implant, *SD* standard deviation, *IVI* intravitreal injections, *PRP* pan retinal photocoagulation, *IRF* intraretinal fluid, *SRF* subretinal fluid, *PDR* proliferative diabetic retinopathy, *BCVA* best corrected visual acuity, *CRT* central retinal thickness

*Aflibercept

**PRP + macular grid

***Letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) charts

[a] Fisher exact test

[b] Chi-squared test

[c] *T* test
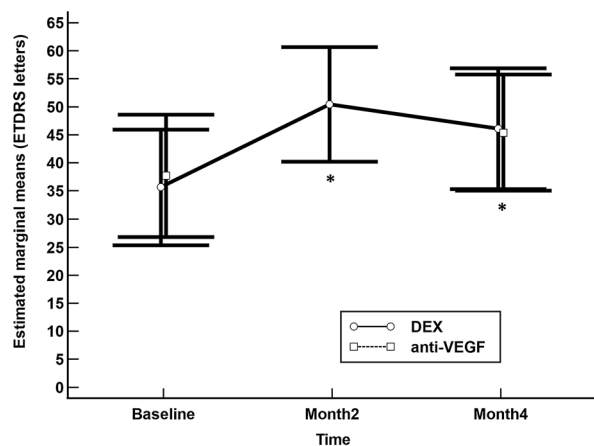
Fig. 1 Mean change in best corrected visual acuity in the anti-VEGF and dexamethasone intravitreal (DEX) implant study groups. The vertical bars represent the 95% confidence interval. Intra-group statistical significance was determined using the Wilcoxon test. Statistical significance between groups was determined using the Mann–Whitney *U* test. No significant differences were found between groups. *$p < 0.05$ in both groups as compared to baseline

switching to DEX implant in eyes with persistent DME unresponsive to anti-VEGF therapy has been previously reported [17–20]. Switching to DEX implant has also been shown to result in better anatomical outcomes over those of continued anti-VEGF therapy [24–26]. In the current study, the indication for switching was not

due to lack of efficacy, but rather the patient's inability to comply with a routine monthly anti-VEGF therapy.

Although, when comparing to those eyes that underwent the standard anti-VEGF therapeutic regimen, switching to DEX implant did not lead better BCVA improvement or CRT reduction, it is noteworthy that one DEX implant significantly improved both functional and anatomic clinical outcomes in those eyes that did not complete anti-VEGF loading dose.
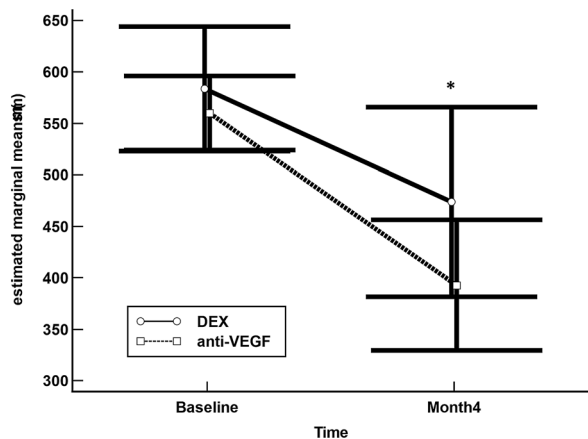
In the DEX group median BCVA improvement between pre- and post-anti-VEGF therapy was not statistically significant (Hodges–Lehmann median difference 5.0 letters, 95% CI − 0.6 to 9.5 letters, $p = 0.097$). Nevertheless, there was significant reduction in CRT after anti-VEGF injections (Hodges–Lehmann median difference 117.3 μm, 95% CI 44.0 to 191.0 μm, $p = 0.002$).

Moreover, after adjustment for age, previous laser, and baseline BCVA, mean BCVA improvement was greater in those eyes that were switched to DEX than in those who underwent anti-VEGF loading dose (mean difference 1.99 letters, 95% CI − 8.85 to 12.83), although such a difference was not statistically significant ($p = 0.712$). However, the power to detect significant differences with the observed values was 7%. Similarly, after adjustment for age, previous laser, and baseline CRT, there were no significant differences in mean CRT
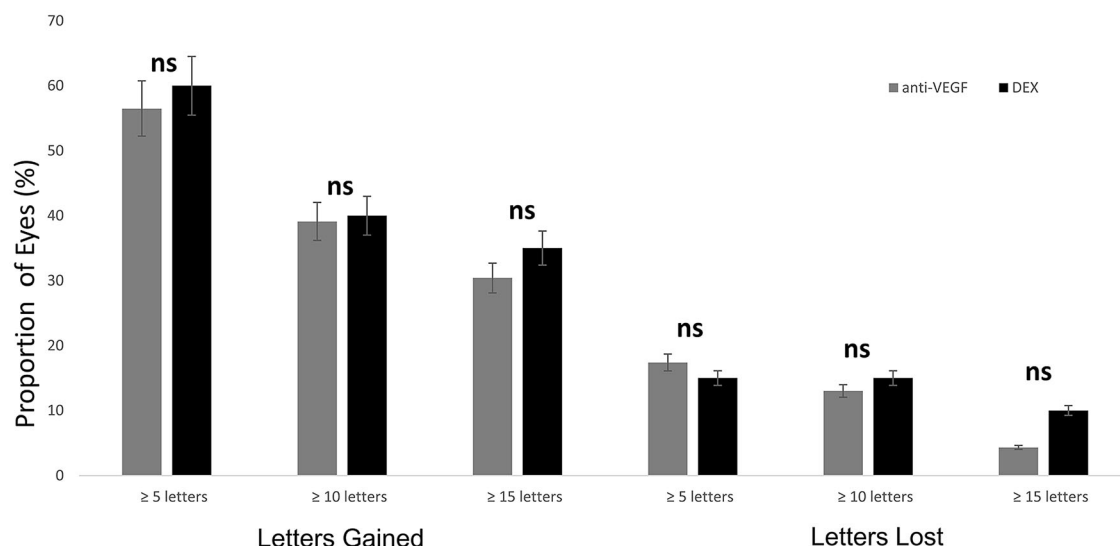
Fig. 2 Comparison in the proportion of eyes achieving a best corrected visual acuity (BCVA) improvement of ≥ 5, ≥ 10, and ≥ 15 letters and a BCVA loss of ≥ 5, ≥ 10, and ≥ 15 letters in the dexamethasone intravitreal (DEX) implant and anti-VEGF groups. ns No significant difference

Fig. 3 Mean change in best corrected visual acuity in the anti-VEGF and dexamethasone intravitreal (DEX) implant study groups. The vertical bars represent the 95% confidence interval. Intra-group statistical significance was determined using the Wilcoxon test. Statistical significance between groups was determined using the Mann–Whitney U test. No significant differences were found between groups. $^{*}p < 0.05$ in both groups as compared to baseline

our study was underpowered to detect such a difference (24%).

Regarding safety, there were no unexpected adverse events and there were no differences between groups in either incidence of ocular hypertension or cataract/lens opacification or loss of BCVA.

According to the European Society of Retina Specialists (EURETINA) guidelines [4], anti-VEGF treatment should be initiated early on with monthly injections, and in those patients who experience positive anatomic and/or functional outcomes, continuing with monthly injections until visual acuity and/or OCT stability is reached. This raises the question of whether anti-VEGF treatment can be continued or should it be restarted? In any case, this would require monthly visits, which during the pandemic would not be possible. Therefore, having a therapeutic alternative, like DEX implant, which provides good anatomical and functional outcomes in both treatment naïve and anti-VEGF refractory patients with DME may be considered as a valuable alternative [12, 20, 27].

The most important limitations of the current study are its retrospective design and small sample size. Selection bias and confounding factors are inherent to retrospective studies;

reduction between DEX and anti-VEGF groups (mean difference 62.0, 95% CI − 39.6 to 163.6, $p = 0.224$); however, as happened with BCVA,

nevertheless, strict inclusion/exclusion criteria aimed to minimized such issues. Additionally, our small sample size also limits the power of the analysis. In fact, with the observed pooled standard deviation and the number of eyes included in each group, the power to detect a mean BCVA improvement of 5 ETDRS letters or a CRT reduction of 25 μm between DEX and anti-VEGF groups, with an alpha error of 0.05 in a bilateral contrast, would be 14% and 8%, respectively. Therefore, further investigations with a larger number of recruited patients would be needed. It should be mentioned that our study did not evaluate the role of OCT biomarkers, which may provide valuable information about the predictive capacity of DEX response. Different OCT biomarkers, such as disorganization of retinal inner layers [28] or ellipsoid zone integrity [29, 30], may predict anatomic and functional outcomes after treatment with DEX implants. This information may be extremely useful, particularly in these times, when the pandemic limits our consultation capacity and it is crucial for optimizing our resources.

CONCLUSIONS

Despite these limitations, the results of our study suggested that DEX implant significantly improved both anatomic and functional outcomes in patients who were unable to receive a complete anti-VEGF therapeutic regime during the COVID-19 pandemic.

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