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INTRAVITREAL DEXAMETHASONE IMPLANT IN EPIRETINAL MEMBRANE-ASSOCIATED DIABETIC MACULAR EDEMA REFRACTORY TO ANTI-VEGF THERAPY: A VISUAL PERFORMANCE AND RETINAL ULTRA-STRUCTURAL ANALYSIS

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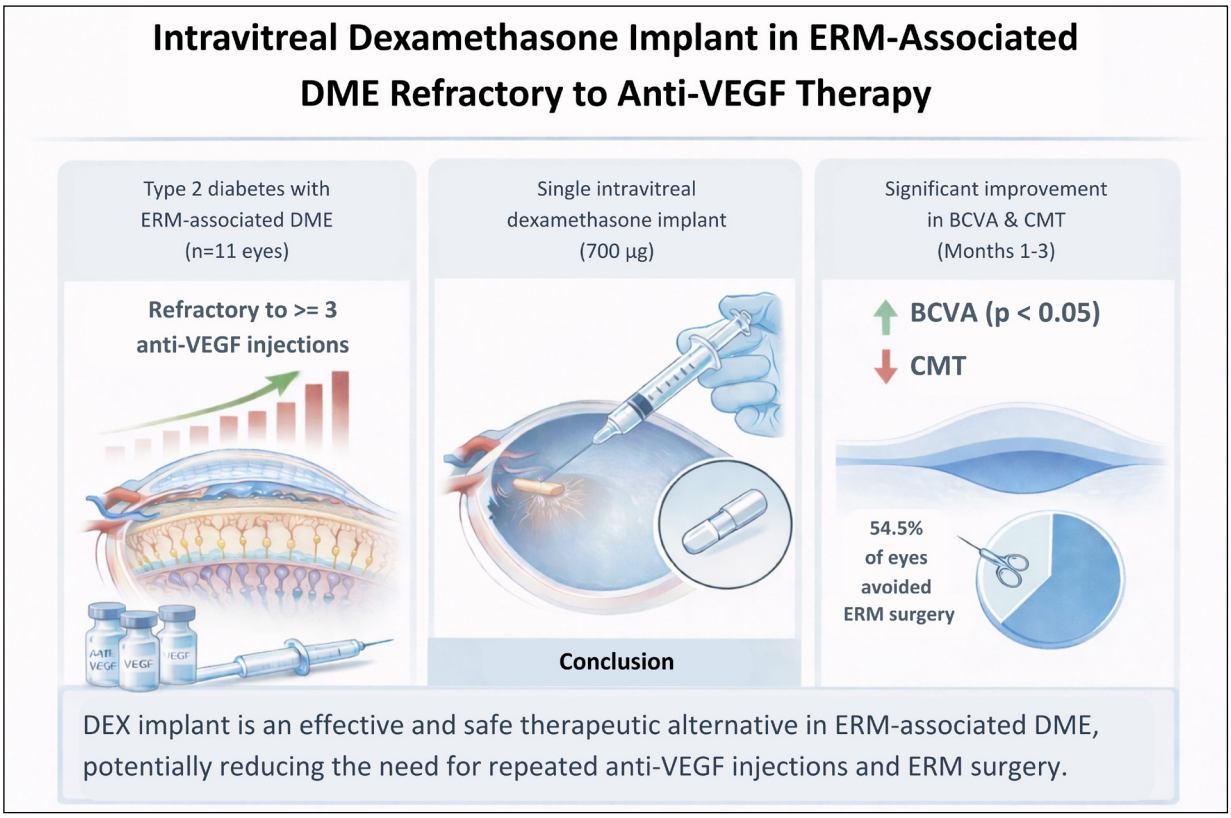
ABSTRACT – *Objective:* The am of the study was to report clinical outcomes of intravitreal dexamethasone (DEX) implant in patients with epiretinal membrane (ERM)-associated diabetic macular edema (DME) unresponsive to intravitreal ranibizumab (IVR).

Materials and Methods: 11 eyes of type 2 diabetes patients >18 years old with ERM-associated DME unresponsive to ≥3 IVR injections were included. Patients with central macular thickness (CMT) >300 µm following a single dose DEX implant between January 2021 and December 2023, suggesting unresponsiveness or poor response, were retrospectively evaluated. A full ophthalmologic examination was performed pre- and first-to-sixth month post-therapy, including measuring best-corrected visual acuity (BCVA), intraocular pressure (IOP), and retinal ultra-structural parameters like CMT, central 1 mm retinal thickness (RT), and central macular volume (CMV).

Results: The mean age was 66.50±5.01 years. BCVA increased considerably in the first two months (p<0.050) compared to pre-therapy. Changes in CMT, RT, and CMV were statistically significant for ≥4 months for CMT, five months for RT, and six months for CMV (p<0.050). Increased BCVA coincided with retinal ultra-structural healing throughout the same period. Most patients had predominantly normal IOPs. Anti-glaucoma medication was initiated in just three patients where IOPs were >25 mmHg.

Conclusions: DEX implant could be a reliable and effective therapeutic alternative for ERM-associated DME resistant to anti-VEGFs, particularly during the first 3 months of treatment, when it appears to be most effective. A single DEX implant can produce a satisfactory and reasonably safe response, and the treatment can be repeated even after the implant's potency has gradually declined. Importantly, improved BCVA and retinal ultra-structure following DEX implant could lessen the need for ERM surgery and multiple intravitreal anti-VEGF injections. If ERM-associated DME persists despite multiple DEX implants, surgery should be considered.

KEYWORDS: Anti-VEGF, Dexamethasone implant, Diabetic macular edema, Epiretinal membrane, Ranibizumab.



Graphical Abstract. A study workflow schematic showing intravitreal dexamethasone implant reliability and efficacy as a therapeutic alternative in epiretinal membrane-associated diabetic macular edema resistant to anti-VEGFs, as well as improvements in visual acuity and retinal ultra-structure, reducing the need for multiple injections and surgery.

INTRODUCTION

Diabetic macular edema (DME), with a global prevalence ranging from 3.15% to 19.96%, is the leading cause of vision loss in diabetic retinopathy (DR)[1]. Aside from the impact of diabetes type, ethnicity, race, and disease duration, DME prevalence varies widely depending on demographics and research approach[2]. Anatomically, DME is associated with a breakdown of the inner blood-retinal barrier, leading to vascular leakage, fluid accumulation, and increased central macular thickness (CMT)[3]. This eventually leads to leukocyte recruitment and adherence to the retinal vascular endothelium, the production of inflammatory factors [including vascular endothelial growth factors (VEGFs), intercellular adhesion molecule-1, tumor necrosis factor-α, and interleukin-6], and changes in endothelial tight junction proteins[4]. Symptomatically, DME can cause decreased vision, reduced color perception, metamorphopsia, and, if persistent, visual loss owing to irreparable retinal damage[3]. As far as DME is concerned, ophthalmologists have had the potential to improve retinal clinico-anatomical outcomes over the last few years, thanks to newer diagnostic and therapeutic strategies, one of which is the use of optical coherence tomography (OCT) biomarkers that affect therapeutic responses.

Typically, DME patients have a high frequency of vitreomacular interface abnormalities (VMIAs). Among them is epiretinal membrane (ERM), which is defined by fibrocellular proliferation on the internal limiting membrane in the macular area. ERM may be idiopathic or secondary to various retinal disorders, with the most common being retinal detachment surgery[5,6]. Besides, diabetes has been identified as a major risk factor for ERM formation[7,8]. There is also a well-established association between ERM and DME[5,6,9], as evidenced by a 7%-16% incidence of VMIAs[10]. However, there has been minimal investigation into whether VMIAs affect the success of newer therapies, particularly intravitreal agents like corticosteroids (CSs) and anti VEGFs[11].

In general, if DME and ERM coexist, surgery for ERM may be preferred. But this should only be undertaken if intravitreal agents fail. Anteroposterior traction may actually suggest the need for vitreoretinal surgery. However, ERM commonly results in tangential traction, and there is no agreement on the benefits of surgery in this matter[1]. Intravitreal agents should therefore be the first-line treatment for ERM-associated DME. In this context, anti-VEGFs are currently regarded as the gold-standard therapy in DME treatment, having been demonstrated to dramatically improve clinical results[12]. As a mat-

ter of fact, both intravitreal ranibizumab (IVR) and dexamethasone (DEX) implants have been shown to improve structural and visual outcomes in ERM-associated DME[13]. Unfortunately, ERM presence may influence anti-VEGF efficacy in DME. In other words, VMIA sufferers may find these agents less effective[14,15]. Though ERM patients are likely to require more frequent injections for inflammation, the existence of ERM-induced retinal traction or a physical barrier may impede drug penetration in ERM-associated DME. This may ultimately lead to unresponsiveness in anti-VEGF efficacy[14,16].

Intravitreal CSs reduce inflammation by inhibiting several inflammatory cytokines, thereby decreasing capillary leakage, inflammatory cell migration, edema, and fibrin deposits[17]. Aside from their therapeutic benefits, CSs can bind to tissues and have a number of effects on cell proliferation, transmembrane transport, and reactive oxygen species activity[18]. Although both DEX and fluocinolone acetonide (FA) implants have been approved for intravitreal injection in DME, the former is more water-soluble due to its reduced lipophilicity, resulting in faster clearance than other intravitreal CSs[19]. As a result, it is not surprising that DEX implant has a lower risk of intraocular complications than triamcinolone acetonide (TA) or FA[20]. Most importantly, the DEX implant was developed first, and the Food and Drug Administration and European Medicines Agency approved its use in DME patients in 2014, based on the MEAD research findings[21]. This implant, which is presently the first option for intravitreal CS therapy[22], is associated with an early anatomic response[13]. Furthermore, contemporary research has focused on certain patient subgroups to identify those who may benefit most from early or first-line DEX therapy, including vitrectomized eyes, pseudophakic eyes, and non-compliant patients[22].

The current study aimed to report the clinical outcomes of intravitreal DEX implant (Ozurdex®, Allergan, Inc., Irvine, CA, USA), particularly in patients with ERM-associated DME who are unresponsive to anti-VEGF therapy. Furthermore, the study aimed to determine the percentage of patients in this category who avoided ERM surgery as a result of the treatment.

MATERIALS AND METHODS

Study design and setting

This retrospective, monocentric, observational study included 11 eyes from 11 patients with type 2 diabetes and ERM-associated DME who were unresponsive to at least 3 doses of IVR therapy. The medical records of treatment-naive DME patients with ERM who were followed up at Ege University Faculty of Medicine Department of Ophthalmology between January 2021, and December 2023 were evaluated. Patients with ERM-associated DME diagnostic codes were chosen from the hospital database. Failure to respond to anti-VEGF therapy was defined as a reduction in CMT of less than 100 µm after at least three consecutive injections, together with persistent intraretinal cystic changes or macular edema with a CMT ≥300 µm on OCT, and a lack of visual improvement (defined as a gain of fewer than one line on the Snellen visual acuity chart)[23]. This retrospective observational study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Ege University (protocol code: 24-9.1T/43, approval date: 19 September 2024). The study was based on the analysis of routinely collected clinical data. Informed consent for the use of clinical data for research purposes was obtained from all patients during routine clinical care. Moreover, this study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in order to increase methodological transparency and clarity in observational research reporting[24].

Participant selection

Patients over 18 years old who were refractory to at least three consecutive monthly IVR injections and had one intravitreal DEX implant were analyzed. The eligibility criteria included clinically significant DME on funduscopy validated by fundus fluorescein angiography, established DME and ERM on OCT, and CMT ≥300 µm on OCT. Given the significance of systemic regulation in the development and treatment of DME, recent HbA1c values between 6.5-7%, which were associated with regulated blood sugar, were also among the eligibility criteria.

Patients with the following characteristics were ineligible for the study: (a) other VMIAs besides ERM, (b) a loss of vision from causes other than ERM-associated DME, (c) a history of any ocular trauma and/or surgery within the last six months, (d) prior pan-retinal or focal laser photocoagulation (within three months)[6], (e) a history of glaucoma, steroid-induced ocular hypertension, ocular inflammatory diseases (e.g. uveitis), retinal comorbidities (including ischemic maculopathy), (f) aphakic eyes with a ruptured or missing posterior lens capsule and eyes with an anterior chamber intraocular lens, and (g) poor quality OCT scans possibly due to lenticulo-corneal pathologies. Additionally, those with retinal ultra-structural abnormalities, such as retinal pigment epithelium atrophy, patterned hard exudative plaques, or sub-retinal fibrosis, were not analyzed.

Ophthalmologic examination

A comprehensive ophthalmologic examination was performed before and at 1, 2, 3, 4, 5, and 6 months after intravitreal DEX implant therapy. This included best-corrected visual acuity (BCVA) in Logarithm of the Minimum Angle of Resolution (logMAR), average of three intraocular pressure (IOP) measurements (mmHg) (Goldmann; Haag-Streit AG, Köniz, Switzerland), and slit-lamp biomicroscopy (HaagStreit, Bern, Switzerland) before and after cycloplegia with tropicamide 1% and phenylephrine 10%. Also, fundus fluorescein angiography was performed in all patients to rule out any potential macular ischemia.

Retinal ultra-structural measurement

All scanning procedures were done using Spectralis HRA-OCT with a volumetric 512 × 49-scan (Heidelberg Engineering, Germany) under standard settings by a single trained ophthalmic technician. One senior ophthalmologist, who was masked to the patients' information, reviewed the OCT images. DME was described as retinal thickening and fluid collection in cystic areas, primarily in the outer plexiform and inner nuclear layers[25]. OCT analyses used an overlay of the ETDRS sub-fields, and the following retinal ultra-structural parameters were automatically calculated by the instrument's software: CMT, central 1 mm retinal thickness (RT), and central macular volume (CMV).

ERM assessment

ERM grading was conducted by a senior retinal specialist (SN) using a 30° by 25° macular volume scan on a Spectralis HRA-OCT, following the staging system defined by Govetto et al[26]. Another senior retina specialist (FA) reviewed the cases before finalizing the grading. ERM presented as prominent, irregular, and hyper-reflective lines positioned on or above the inner retinal surface, frequently with abnormalities of the underlying retina, with hypo-reflective areas between the ERM and the inner retinal surface. Because all patients had previously received at least three IVR injections and had chronic DME – both factors that may influence ERM development and retinal layer architecture – ERM classification was not considered reliable. Except for grade 1, all grades 2, 3, and 4 of the ERM classification exhibit foveal depression. In chronic ERM-associated DME, foveal depression disappears, concealing other stage findings. In this setting, staging the ERM would not be particularly efficient; hence, no further staging was performed.

Intravitreal DEX implant therapy

One ophthalmic surgeon (SN) used a customized, single-use 22-gauge applicator to inject a 700 µg slow-release DEX implant into the vitreous cavity, 3.5- or 4-mm posterior to the corneoscleral limbus, in a sterile operating room setting under topical anesthesia. A topical moxifloxacin 0.5% was then prescribed four times per day for a week.

Outcome measures

The key clinico-anatomical outcome variables were mean BCVA and CMT at baseline and at 1 and 6 months after therapy. Other outcome variables included the study of additional retinal ultrastructural layers investigated using SD-OCT. Moreover, intravitreal DEX-induced adverse effects, including anterior chamber inflammation, lens opacity, ocular discomfort, keratitis, and vitreous opacity, were rigorously monitored, as were surgery-related complications, such as endophthalmitis, conjunctival hemorrhage, and systemic drug effects.

Statistical analysis

The SAS Institute's StatView program was used to perform the analysis. For statistical analysis, Snellen BCVA was converted to logMAR. The data was assessed for compliance and found to be consistent with the normal distribution. Patients' baseline demographic characteristics are presented as mean ± standard deviation (SD), range, or percentage, as appropriate. Moreover, the data were analyzed using repeated-measures analysis of variance, followed by Fisher's Protected Least Significant Difference post-hoc test with adjustment for multiple comparisons. The significance level was set at a p-value of <0.050.

RESULTS

Demographic and clinical characteristics

The mean age of the patients was 66.5 ± 5.0 years; 8 patients (72.7%) were female, and 3 (27.3%) were male. Significant DME persisted in these patients for more than six months, despite IVR therapy with a median injection number of 4.70 (3-10). Diabetes lasted an average of 18.70±6.14 years, and DME for 39.70±19.10 months. Four eyes were pseudo-phakic (36.40%), with seven being phakic (63.60%). Seven (63.60%) eyes had pan-retinal photocoagulation performed more than three months before intravitreal DEX implant therapy.

Pre-therapy and first-, third-, and sixth-month post-therapy IOPs were 15.30 (12-20), 15.30 (11-19), 16.70 (10-25), and 16.10 (13-19) mmHg, respectively. Topical anti-glaucoma therapy was initiated when IOP was over 25 mmHg, which occurred in only three (27.20%) eyes (IOP: 26-30 mmHg). Six (54.50%) eyes did not require ERM surgery, as smooth foveal contours and retinal thickness within normal limits were observed. Besides, no cataract surgery was required in any eye, and no additional drug- and/or surgery-related complications, such as endophthalmitis or rhegmatogenous retinal detachment, were noted.

Best-corrected visual acuity

Following intravitreal DEX implant therapy, there was a substantial increase in BCVA during the first 2 months (p<0.050) compared with pre-therapy, with no significant change thereafter (p>0.050) (Table I, Figure 1A).

Retinal ultra-structural analysis

Pre-therapy CMT, RT, and CMV values were 548.90±136.44 µm, 511.27±129.85 µm, and 11.79±2.60 mm^3, respectively. Fluctuations in these retinal ultrastructural parameters after DEX implant therapy are displayed in Figure 1B, C, D, exhibiting variance from the first to sixth post-therapy months. SD-OCT analysis showed significant changes in CMT, RT, and CMV for at least 4 months for CMT, 5 months for RT, and 6 months for CMV (p<0.050) (Table II). Furthermore, Figure 2 depicts a representative set of OCT images from one of the study patients, illustrating the baseline and post-therapy retinal ultrastructural status, corroborating the findings presented in Table II. Overall, increased BCVA coincided with retinal ultra-structural healing throughout the same time period, only to return to pre-therapy levels in the later months.

Table I. Changes in best-corrected visual acuity following intravitreal dexamethasone implant therapy in epiretinal membrane-associated diabetic macular edema patients (n=11 eyes).

Duration months)	BCVA (LogMAR, mean±standard deviation)	p-value
Pre-therapy	0.88±0.24	-
1st	0.72±0.21	**0.001**
2nd	0.78±0.20	**0.040**
3rd	0.86±0.22	0.730
4th	0.89±0.21	0.850
5th	0.88±0.22	1.000
6th	0.88±0.22	1.000

BCVA=Best-corrected distant visual acuity, logMAR=Logarithm of the Minimum Angle of Resolution, n=Number of patients (eyes). p-values less than 0.05 were considered statistically significant and are highlighted in bold.

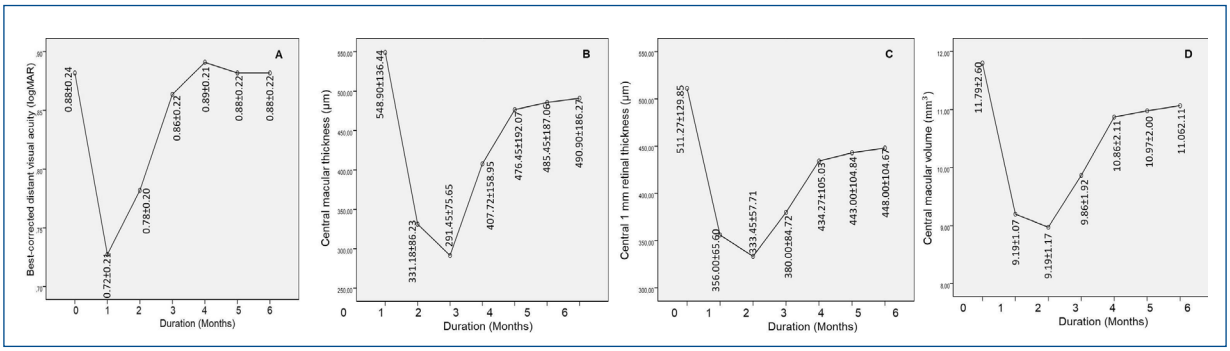


Figure 1. Representative graphic displaying the effect of intravitreal dexamethasone implant therapy before and after therapy on best-corrected visual acuity fluctuation (**A**), retinal ultrastructural parameters (**B**, **C**, **D**) in epiretinal membrane-associated diabetic macular edema patients refractory to intravitreal therapy. Intravitreal dexamethasone implant appeared to be substantially related with a rise in best-corrected visual acuity, notably within the first three months, which occurred concomitant with retinal ultrastructural recovery, only to return to pre-therapy values in subsequent months.

Table II. Results of retinal ultra-structural analysis using Spectral domain optical coherence tomography following a single dose intravitreal dexamethasone implant therapy in epiretinal membrane-associated diabetic macular edema patients (*n*=11 eyes).

Duration (months) and parameters (mean±standard deviation)		*p*-value
Central macular thickness (µm)		
Pre-therapy	548.90±136.44	-
1st	331.18±86.23	**0.003**
2nd	291.45±75.65	**0.000**
3rd	407.72±158.95	**0.005**
4th	476.45±192.07	**0.040**
5th	485.45±187.06	0.060
6th	490.90±186.27	0.090
Central 1 mm retinal thickness (µm)		
Pre-therapy	511.27±129.85	-
1st	356.00±65.60	**0.004**
2nd	333.45±57.71	**0.001**
3rd	380.00±84.72	**0.004**
4th	434.27±105.03	**0.010**
5th	443.00±104.84	**0.030**
6th	448.00±104.67	**0.090**
Central macular volume (mm^3)		
Pre-therapy	11.79±2.60	-
1st	9.19±1.07	**0.060**
2nd	8.97±1.17	**0.004**
3rd	9.86±1.92	**0.005**
4th	10.86±2.11	**0.021**
5th	10.97±2.00	**0.050**
6th	11.06±2.11	**0.052**

n=Number of patients (eyes), µm=Micrometer, mm^3=Cubic millimeter, *p*-values less than 0.05 were considered statistically significant and are highlighted in bold.

DISCUSSION

Briefly, the current study reports the six-month clinico-anatomical outcomes of ERM-associated DME patients treated with a single intravitreal DEX implant. All patients were refractory to at least three consecutive monthly intravitreal IVR injections, with substantial DME persisting for more than six months despite treatment. BCVA and retinal ultra-structural layer assessments were compared before and after therapy. Intravitreal DEX implant was strongly associated with an increase in BCVA, particularly during the first 3 months. This improvement occurred concurrently with retinal ultrastructural repair but returned to pre-therapy levels in the subsequent months. This condition indicated that the intravitreal DEX implant's maximum effectiveness is likely to be reached within the first three months, after which its therapeutic efficacy gradually diminishes[27]. However, this effect was more noticeable in retinal ultra-structure than in BCVA, implying that CMT evaluation alone cannot reliably forecast the visual prognosis. Certainly, neuro-retinal abnormalities, such as lesions in the photoreceptor layer, cysts, exudates, or reduced function of the Müller cells, could conceivably explain this divergence[28].

The current study was consistent with earlier reports indicating that the anti-inflammatory effect of DEX implant is immediate and could be associated with positive results during the first week of therapy[29-31]. As a matter of fact, decreased levels of intravitreal DEX could explain the gradual decrease in efficacy over time. Plus, the chronic nature of the disease is likely to reduce the implant's efficacy[32].

Unlike anti-VEGFs, which directly inhibit VEGF signaling, DEX reduces capillary permeability and the development of secondary macular edema in diverse etiologies[33]. As mentioned earlier, DEX also inhibits leukocyte mobility, reduces the production of VEGF, prostaglandins, and other pro-inflammatory cytokines[33,34], and promotes the barrier function of vascular tight junctions[35]. This appears to be primarily because the route

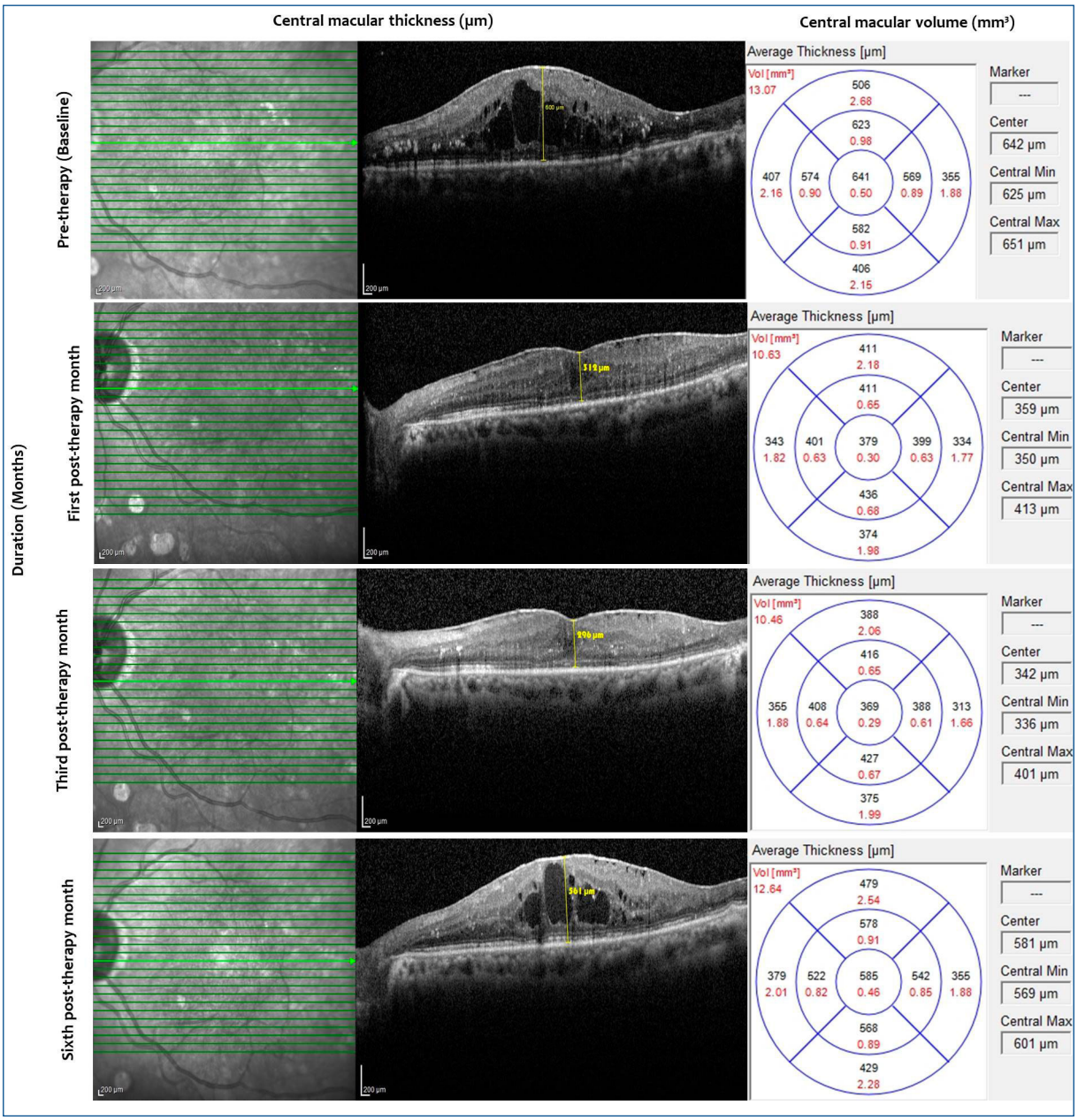


Figure 2. Representative spectral-domain optical coherence tomography image of a patient with epiretinal membrane-associated diabetic macular edema refractory to intravitreal therapy who received one intravitreal dexamethasone implant therapy. The right and left columns show significant changes in the retinal ultra-structure, particularly in central macular thickness and volume (outlined in red), before and after therapy, respectively (p<0.050), indicating that this implant with a three-month efficacy period may lengthen the time between doses while improving patient compliance.

of DEX implant administration is critical to its efficacy. Indeed, a direct intravitreal DEX implant injection allows for attaining the desired drug concentration directly at the site of the disease, reducing systemic adverse effects[34]. In the current study, 54.50% of eyes having intravitreal DEX implant therapy had a smooth foveal contour and normal retinal thickness, hence avoiding ERM surgery. This improved clinical-anatomical outcomes in ERM-associated DME patients refractory to IVR therapy suggests that inflammatory mediators, rather than VEGF, may play an increasingly important role in disease progression. Given the involvement of inflammatory mediators in these patients, it may be reasonable to switch anti-VEGF treatment to DEX (as an alternative or adjuvant therapy)[36] in chronic DME. This may be crucial, particularly in ERM-associated DME, which often does not respond to repeated intravitreal anti-VEGFs. This is mostly because DEX not only regulates blood flow through vasoconstriction but also mediates chronic inflammation, suggesting that it may have a two-fold effect in managing these patients[37].

Literally, DEX is one of the most effective anti-inflammatory CSs. It has a six-fold greater effect than intravitreal TA, which is commonly used to treat secondary retinal edema and is delivered as lipophilic crystals produced in the vitreous over several months. However, this type of TA deposit, supplied at doses of 1.2 and 4 mg in a single injection, does not provide a consistent drug level in the vitreous chamber. This also raises the possibility of adverse effects like IOP elevation and cataract formation and/or progression[38]. Furthermore, while both DEX and FA implants have been approved for intravitreal injection in DME, the latter has distinct pharmacokinetics. Its current formulation releases 0.2 µg of FA per day and maintains a steady-state concentration for 36 months. Yet, peak functional and anatomical effectiveness is attained more slowly, typically 6 months after injection[39]. While the FA implant lasts far longer than the DEX implant, potentially reducing the number of visits and treatments needed, it seems to be more prone to ocular hypertension and cataract formation and/or progression[40]. Importantly, the FA implant was approved for DME patients who had previously received a DEX implant, provided their IOP did not increase significantly[41].

Despite the initial immediate gain in BCVA, the current study revealed that there was a non-significant decrease from pre-therapy levels in the following months. These findings suggest that intravitreal DEX implant therapy at least stabilizes BCVA, which might otherwise deteriorate in the absence of this treatment. Essentially, a biodegradable [poly(lactic-co-glycolic acid) (PLGA)] implant has dual-phase pharmacokinetics, initially releasing a burst of DEX to achieve a rapidly therapeutic concentration followed by a lower steady daily release of DEX in the vitreous chamber for up to four months following a single injection[27]. This technique, as used in the current study, allows DEX implant to produce greater therapeutic effects while lowering the risk of undesirable effects associated with frequent injections or high drug concentration shortly after administration[42,43]. Certainly, individual patient reactions may account for variances in BCVA outcomes following DEX implant therapy.

The current study corroborated prior reports indicating that DEX implant efficacy persisted at least six months despite a steady decrease[29,31]. This condition could be explained by reduced drug release rather than deterioration in diabetes regulation, given that a strict eligibility criterion of HbA1c levels between 6.5-7%, implying regulated blood sugar, was imposed during the follow-up period. Plus, ERM-associated DME patients typically have persistent inflammation throughout their lives[37].

Actually, if ERM-associated DME lasts longer and the response to IVR therapy is diminished, the likelihood of repeated injection rises dramatically[44-46]. Hence, a DEX implant with an effectiveness period of at least 3 months might increase the interval between injections and improve patient compliance[44,46]. Besides, as previously noted, current evidence suggests that combining intravitreal DEX implant with other therapeutic approaches could lead to significant retinal ultra-structural improvements, particularly in these patients[29,47,48].

Moreover, intravitreal DEX implant therapy has a favorable ocular safety profile, which could be explained by the delayed release of a low preservative-free DEX dose (0.7 mg) into the vitreous chamber[27]. More importantly, no serious adverse effects have been reported with even repeated intravitreal DEX implants[42,49,50]. Correspondingly, the current study revealed no significant medical or surgical issues, such as endophthalmitis or rhegmatogenous retinal detachment. Also, none of the eyes required cataract surgery. Only 27.20% of eyes with post-therapy IOPs ranging from 26-30 mmHg elevation, which was generally transient and successfully treated with a topical anti-glaucoma medication, a result that could have therapeutic importance[22]. Interestingly, intravitreal CSs have a specific affinity for lens and trabecular meshwork cells, which could explain the high prevalence of worsening cataract and IOP elevation reported in other studies[20,51]. It has been shown that DEX, in particular, may interfere with critical processes regulating lens cell homeostasis, migration, and differentiation[52]. DEX has also been demonstrated to increase the stiffness of trabecular meshwork cells *in vitro* through stimulating the overexpression of contractile proteins and the formation of extracellular matrix[53]. Furthermore, the accumulation of DEX molecules in the trabecular meshwork can produce an increase in intraocular volume as well as precipitation blockage, both of which contribute to IOP rise[20,51].

As previously indicated, in addition to ERM-associated DME, which frequently responds poorly to anti-VEGFs after the loading dose, DEX implant may be used as a primary treatment or as a substitute for anti-VEGFs in various conditions. It may be useful in treating DME with serous retinal detachment, as this condition has been linked to elevated levels of inflammatory cytokines[54]. Large, empty cysts observed on OCT are often associated with more advanced chronic phases of the disease, in which case a DEX implant might be regarded as the first-line treatment[39,55,56]. DME patients with a significant total volume may be candidates for DEX implant as first-line treatment[57]. When hyperreflective dots are identified on OCT, they appear to suggest a common inflammatory

state, making DEX implant the ideal therapy for DME[58]. Disorganization of the retinal inner layers[59] and the outer retinal layer[60] are major predictive variables in DME patients. Nonetheless, adequately evaluating the retinal layers to predict the disease progression at baseline may be difficult. In this context, the DEX implant's fast anatomic response may aid in the accurate assessment of outer retinal layer status[61]. Moreover, DEX implant may be recommended as the first-line treatment in patients with high-risk cardiovascular disease (as in the initial three months after a heart attack/stroke), poor compliance with anti-VEGF treatment regimen, a history of vitrectomy, as well as in non-proliferative diabetic retinopathy patients scheduled to undergo cataract surgery or in pseudophakia[62]. Overall, DEX implant offers advantages in DME patients with a strong inflammatory component because it has a more potent anti-inflammatory effect than anti-VEGFs. Patients having DEX implant therapy, however, should receive sufficient counseling regarding possible negative consequences[63]. Furthermore, DEX implant therapy may be contraindicated in several conditions. This includes active/suspected ocular/periocular infection, progressive/uncompensated glaucoma requiring more than 3 molecules, posterior capsular disruption (except YAG capsulotomy), aphakic eyes, and hypersensitivity to DEX implant[64].

Indeed, the current study provides evidence supporting the use of a DEX implant in ERM-associated DME patients unresponsive to IVR therapy.

Limitations

Our data interpretations have certain limitations. The study's retrospective, non-randomized aspect may be deemed a limitation. However, the study's reliability improves because its eligibility standards were exceedingly precise. Having a relatively small cohort and an uncontrolled design makes it difficult to draw definitive conclusions, ultimately restricting generalizability. Furthermore, because this study was conducted at an academic facility, the patient sample may have been biased by referral patterns or access to specialist treatment, introducing an element of selection bias. Regardless of potential bias, the study demonstrated that a DEX implant was effective in patients with ERM-associated DME unresponsive to intravitreal anti-VEGFs, as well as the potential to avoid vitreoretinal surgery and/or several monthly intravitreal anti-VEGF injections. Also, considering a relatively short follow-up duration, the study's conclusions should be interpreted cautiously, as longer-term follow-up data are lacking. Despite this, it is widely acknowledged that the coexistence of DME and ERM is rare[65]. Moreover, the majority of patients are referred for surgery after an unsatisfactory response to intravitreal anti-VEGF agents or DEX implants, resulting in a shorter follow-up duration[13]. Additionally, the current study deliberately eliminated additional VMIAs, particularly those causing antero-posterior traction, in which surgery might be preferable to intravitreal agents. Given that the current study patients had already received at least three IVR injections, as well as the fact that there was a chronic DME condition, both of which could impact the natural formation of the ERM and the general layout of the intra-retinal layers, no further ERM classification was performed. Surprisingly, repeated DEX injections do not appear to cause major side effects[27,51,66]. DEX implant is also less likely to cause cataracts and glaucoma than other steroids[27]. Moreover, better anatomic outcomes have been reported in patients receiving repeated DEX implant therapy compared with those retreated with bevacizumab or TA[67,68]. Surely, large-scale, long-term research would be worthwhile for studying and thoroughly untangling the pharmacokinetics and therapeutic effects of DEX implants in the treatment of ERM-associated DME patients.

CONCLUSIONS

Intravitreal DEX implant appears to be a reliable and effective therapeutic option, particularly for patients with ERM-associated DME unresponsive to anti-VEGFs. A single intravitreal DEX implant is associated with a favorable, reasonably safe outcome. Luckily, the procedure can be repeated exactly the same way, even after the implant's potency fades over time. However, in young phakic patients, vigilance should be exercised due to the likelihood of cataract formation and IOP increase during any injection. Although the first three months of treatment appear to be the most effective, it is unclear whether increased retinal thickness is driven by ERM or DME. Improved BCVA and retinal ultrastructure after DEX implant therapy may significantly reduce the need for ERM surgery, while also providing prognostic insights for potential candidates for such surgery. This might also reduce the necessity for multiple intravitreal anti-VEGF injections, which may carry medical or surgical risks, potentially leading to decreased patient adherence. If ERM-associated DME persists despite multiple DEX implants, surgical therapy should be considered. Further short- and long-term prospective research could help determine the therapeutic efficacy of DEX implants and develop treatment guidelines for ERM-associated DME.

Conflicts of Interest
The authors declare no conflicts of interest.

Authors' Contributions
SN and HHG developed the concept of the study, contributed to writing the article, and supervised the project. SN, HHG, CA, and FA contributed to the writing of the article, data collection, interpretation, and analysis. SN, KS, CA, and FA collaborated in initial data collection and contribution to the first draft. SN, KS, and HHG contributed to writing the article and also supervised the Project. SN and HHG contributed to the drafting and essential revision of the manuscript for relevant intellectual content, and to the endorsement of the final version. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Ege University (protocol code 24-9.1T/43, on 19/09/2024).

Informed Consent
Informed consent was obtained from all subjects at the time of enrollment to allow the use of their clinical data for research purposes.

Data Availability
The data supporting our study findings are available from the corresponding author upon reasonable request.

AI Disclosure
The graphical abstract was generated using an AI-based image generation tool. The authors reviewed, edited, and approved the final version and take full responsibility for its content.

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