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ORIGINAL RESEARCH

Twelve-Month Response and Safety of Intravitreal Dexamethasone Implant in Treatment-Naïve and Recalcitrant Diabetic Macular Edema (TREAT-DME Study)

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Purpose: To compare twelve-month visual, anatomical, safety, and inflammation-biomarker outcomes of intravitreal dexamethasone implant (DEX) in treatment-naïve versus recalcitrant center-involving diabetic macular edema (CI-DME) eyes.

Patients and Methods: In this multicenter, retrospective cohort study (January 2022 to December 2024) at two Indian tertiary centers, adults with type 2 diabetes and CI-DME confirmed by optical coherence tomography (OCT) were stratified into treatment-naïve or recalcitrant cohorts. All eyes received a 0.7 mg dexamethasone implant, with pro-re-nata retreatment for recurrent fluid, ≥5-letter best-corrected visual acuity (BCVA) loss, or ≥50 µm central macular thickness (CMT) increase. Visits at baseline and periodic intervals up to 12 months included BCVA, intraocular pressure (IOP), slit-lamp and fundus exams, and OCT quantification of CMT and presence and/or hyperreflective foci (HRF). Safety and adverse event monitoring included IOP elevations, cataract progression, and other ocular adverse events. Statistical analysis used paired and independent tests with $P < 0.05$.

Results: We analyzed 102 eyes (30 naïve, 72 recalcitrant) from 74 patients (mean age 61.7 ± 8.8 years). Mean DEX implants per eye were 1.83 ± 0.73, higher in recalcitrant eyes (1.87 vs 1.73; $P = 0.02$). At 12 months, mean BCVA improved from 0.73 ± 0.26 to 0.62 ± 0.28 logMAR ($P = 0.002$), with no intergroup differences ($P > 0.05$). Mean CMT decreased from 520 ± 144 to 462 ± 192 µm ($P = 0.03$), similarly across cohorts ($P > 0.10$). HRF declined from 58% to 26% ($P < 0.001$). Ocular adverse events included cataract progression in 39% of phakic eyes (26% underwent surgery) and transient IOP elevations >21 mmHg in 9.8%, all managed medically; no glaucoma surgery was required.

Conclusion: In real-world practice, intravitreal DEX implant delivers sustained visual and anatomical benefits in both treatment-naïve and recalcitrant CI-DME eyes. Although cataract progression and transient IOP rises occur, they are predictably manageable. Its extended durability and acceptable safety profile underscore DEX implant as a practical, valuable option across diverse DME populations.

Keywords: dexamethasone implant, diabetic macular edema, real-world

Introduction

Diabetic macular edema (DME) is a common and vision-threatening complication of diabetic retinopathy (DR).[1,2] With over 400 million people globally affected by diabetes, DME has emerged as the leading cause of vision loss among working-age adults with diabetes.[1,2] Meta-analyses estimate that roughly 5–10% of people living with diabetes develop DME during the course of the disease; worldwide prevalence is on the order of 6–7% of people living with diabetes, translating to approximately 20–30 million affected adults.[1,3–5] Vision impairment from DME dramatically reduces patients' quality-of-life, undermining tasks such as reading and driving and imposing substantial socioeconomic burden.

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Indeed, clinical studies have shown that even moderate vision loss from DME correlates with declines in vision-specific quality-of-life scores.[5]

Focal/grid laser was the first effective therapy for DME, but over the past decade intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents (ranibizumab, aflibercept, bevacizumab) have become the standard for center-involving disease, offering superior vision gains and edema reduction.[5–12] Yet many eyes exhibit incomplete fluid resolution despite monthly injections, and this high treatment burden strains patients and clinics.[7,13,14] The heavy treatment burden of frequent injections and clinical visits also strains patients and healthcare systems. Moreover, anti-VEGF therapy addresses predominantly VEGF-driven leakage and may not fully counteract the multifactorial pathophysiology of chronic DME. This chronic DME also has a strong inflammatory component: hyperglycemia and ischemia drive cytokine and adhesion-molecule release, disrupting the blood–retinal barrier (BRB), with optical coherence tomography (OCT) detected hyperreflective foci (HRF) serving as an inflammation biomarker.[15–18] Consequently, intravitreal corticosteroids, which broadly inhibit these pathways, have been investigated, especially in eyes unresponsive to anti-VEGF therapy.[15–18]

The dexamethasone intravitreal implant (DEX; Ozurdex®; Allergan, Inc., Irvine, CA, USA) is a biodegradable device releasing 700 µg dexamethasone over 3–6 months. It consistently outperforms sham treatment in macular-edema trials, with a predictable safety profile: surgery-manageable cataracts and transient, medically controllable intraocular pressure (IOP) spikes.[15–20] Despite strong trial results, optimal real-world use of steroid implants in DME remains unclear, especially for "recalcitrant" cases with chronic inflammatory edema that may benefit when VEGF inhibition falls short.[15–17] Small studies suggest switching refractory eyes to DEX implant improves anatomy and vision, yet most DEX trials focused on treatment-naïve or mixed populations.[15–17] Long-term comparative data between naïve and refractory DME are scarce. Clarifying differences in efficacy, durability, and safety across these groups is essential to inform clinical decision-making.

To address this gap, we conducted a 12-month, multicenter, retrospective cohort study in Indian patients with center-involving DME (CI-DME) to compare the visual, anatomical, and safety outcomes between treatment-naïve and recalcitrant eyes following DEX implant.

Materials and Methods

Design

This multicenter, retrospective cohort study encompassed patient data from January 1, 2022, to December 31, 2024, at two tertiary referral centers in India: the Retina Institute of Bengal (Siliguri) and the Shantilal Shanghvi Eye Institute (Mumbai). Institutional Review Board approval was obtained (Shantilal Shanghvi Foundation Ethics Committee, Mumbai, India; SSEI/IRB/0008/2025), and all procedures conformed to the tenets of the Declaration of Helsinki. Prior to intravitreal therapy, informed written consent was obtained from each participant for both treatment and the subsequent use of de-identified clinical data for research purposes.

Subjects

Inclusion criteria comprised adults (≥18 years) diagnosed with type 2 diabetes mellitus (glycated hemoglobin ≤ 8.0%) and CI-DME confirmed by spectral-domain OCT (SD-OCT). CI-DME was defined as fluid involving the central 1 mm (foveal center on early treatment of diabetic retinopathy scale [ETDRS] grid) on spectral-domain OCT. Two cohorts were defined: treatment-naïve eyes (no anti-VEGF injection also) and recalcitrant eyes (persistent central macular thickness [CMT] > 350 µm or ≤15% reduction over six months despite ≥3 anti-VEGF injections). Eyes with concurrent retinal pathology, media opacities precluding OCT imaging, prior vitreoretinal surgery, or coexisting uveitis/vasculitis were excluded.

Imaging Protocol and Hyperreflective Foci Assessment

Baseline SD-OCT (Cirrus HD-6000; Carl Zeiss Meditec, Dublin, CA, USA) was performed according to standardized scanning protocols. HRF were operationally defined as discrete, well-circumscribed intraretinal particles (20–40 µm

diameter) exhibiting reflectivity equal to or exceeding that of the retinal pigment epithelium band, located between the internal and external limiting membranes. HRF counts were performed on horizontal B-scans at the level of the foveal center, using a standardized region of interest (±500 μm from foveal center, extending from internal limiting membrane to external limiting membrane). All measurements were conducted by a masked grader using Cirrus HD-6000 software with calliper tools, and background adjustments were applied using the device's automated normalization. This standardized approach was applied consistently to all baseline and follow-up scans.

Treatment Administration and Follow-Up

Each eligible eye received a single 0.7 mg DEX implant under strict aseptic conditions in an operating theatre setting. Follow-up visits were scheduled at 1, 3, 6, 9, and 12 months post-implantation. Follow-up visits were considered acceptable within a ±2-week window. With this allowance, no eyes were lost to follow-up and all analyses were conducted on complete cases without the need for data imputation. At each visit, assessments included best-corrected visual acuity (BCVA) measured in ETDRS letters, IOP by Goldmann applanation tonometry, slit-lamp biomicroscopy including cataract evaluation, dilated fundus examination, and SD-OCT for CMT determination. Criteria for re-implantation after month 4 adhered to a pro re nata (PRN) regimen: persistent or recurrent intraretinal/subretinal fluid, BCVA decline ≥5 ETDRS letters, or CMT increase ≥50 μm relative to the previous lowest measurement.

Outcome Measures

The primary efficacy endpoints were mean change in BCVA and CMT from baseline to month 12. Secondary analyses included subgroup comparisons between treatment-naïve and recalcitrant cohorts, monitoring of adverse events (IOP, cataract progression, others), and the proportion of eyes demonstrating HRF resolution.

All adverse events (IOP elevation, cataract progression, other ocular complications) were monitored at each study visit and managed according to standard protocols. IOP elevations >21 mmHg were managed with topical antiglaucoma medications and re-evaluated at follow-up visits; no eyes required treatment discontinuation based on IOP rise alone. Cataract progression was monitored clinically and by LOCS III grading; clinically significant cataracts (vision-limiting) were offered surgery at patient discretion, with continued study participation post-surgery. Severe adverse events requiring DEX discontinuation were predefined as: retinal detachment, endophthalmitis, or sustained glaucoma refractory to medical therapy.

Statistical Analysis

Statistical computations were performed using SPSS 23.0 (IBM Corp., Armonk, NY). Continuous variables are expressed as mean ± standard deviation; categorical data as frequencies and percentages. Within-group temporal changes were analyzed via paired t-tests or Wilcoxon signed-rank tests based on distribution normality. Between-group differences employed independent t-tests or chi-square tests. A two-tailed P-value <0.05 denoted statistical significance.

Results

A total of 102 eyes from 74 patients with DME treated with DEX were included in the analysis, with a mean age of 61.7 ± 8.8 years (range, 41–82 years). Of these, 48 (65%) were males and 26 (35%) were female. The study comprised 30 treatment-naïve eyes (29.4%) and 72 eyes (70.6%) previously treated with anti-VEGF agents. The mean number of previous anti-VEGF injection in the recalcitrant group was 4.47 ± 2.43. The mean number of DEX implants delivered over 12 months was 1.83 ± 0.73 for all eyes, with treatment-naïve eyes receiving a mean of 1.73 ± 0.69 implants and previously treated eyes 1.87 ± 0.75 implants (P = 0.02), indicating a significantly higher reinjection rate in recalcitrant eyes. Table 1 demonstrates the demographic characteristics and treatment profile of the study eyes.

Best-Corrected Visual Acuity Outcomes

At baseline, mean BCVA was 0.73 ± 0.26 logMAR for all eyes, with no significant difference between the naïve and previously treated groups (0.74 ± 0.28 vs 0.73 ± 0.26, P = 0.89). Both groups showed significant visual improvement at each follow-up visit, BCVA showed rapid improvement at 1–2 months (0.54 ± 0.27 logMAR, P < 0.001), followed by

Table 1 Demographic Characteristics and Treatment-Profile of the Study Population

Baseline Variables		Values	
Total number of Eyes		102	
Age (years)	Mean ± SD	61.7 ± 8.8	
Number of Previous Injection Received	Mean ± SD	4.47 ± 2.43	
Number of DEX implants received over 12 months in the entire study cohort	Mean ± SD	1.83 ± 0.73	
Number of DEX implants received over 12 months based on the treatment status	Treatment- Naïve Eyes	1.73 ± 0.69	$P = 0.02$
	Recalcitrant Eyes	1.87 ± 0.75	

Abbreviations: SD, Standard deviation; DEX, Dexamethasone implant.

partial rebound by month 12 (0.62 ± 0.28 logMAR), yet remaining significantly better than baseline ($P = 0.002$). There were no significant differences in BCVA outcomes between naïve and previously treated eyes at any timepoint ($P > 0.05$ throughout) (Tables 2 and 3).

Table 2 Changes in the Best-Corrected Visual Acuity, Central Macular Thickness, and Intraocular Pressure in the Study Cohort

Timepoint	BCVA (logMAR) Mean ± SD	*P*-value	CMT (μm) Mean ± SD	*P*-value	IOP (mmHg) Mean ± SD	*P*-value
Baseline	0.73 ± 0.26	–	520 ± 144	–	13.8 ± 2.6	–
1 month	0.54 ± 0.27	<0.001*	349 ± 134	<0.001*	14.8 ± 2.9	0.012*
2 months	0.52 ± 0.26	<0.001*	318 ± 128	<0.001*	14.7 ± 3.0	0.021*
3 months	0.54 ± 0.27	<0.001*	351 ± 148	<0.001*	14.6 ± 2.9	0.019*
6 months	0.57 ± 0.27	<0.001*	412 ± 184	<0.001*	15.1 ± 3.0	0.006*
9 months	0.60 ± 0.29	0.002*	453 ± 202	0.021*	15.2 ± 3.2	0.004*
12 months	0.62 ± 0.28	0.002*	462 ± 192	0.030*	15.3 ± 3.0	0.007*

Note: *Statistically significant.
Abbreviations: BCVA, Best-corrected visual acuity; CMT, Central macular thickness; IOP, Intraocular pressure.

Table 3 Changes in the Best-Corrected Visual Acuity Based on the Treatment Status of the Study Eyes

Timepoint	BCVA (logMAR) Treatment-Naïve Eyes (Mean ± SD)	Intra-Group *P*-value	BCVA (logMAR) Recalcitrant Eyes (Mean ± SD)	Intra-Group *P*-value	Inter-Group *P*-value
Baseline	0.74 ± 0.28	–	0.73 ± 0.26	–	0.89
1 month	0.56 ± 0.27	0.001*	0.53 ± 0.27	<0.001*	0.61
2 months	0.54 ± 0.26	0.001*	0.51 ± 0.26	<0.001*	0.52
3 months	0.56 ± 0.26	0.002*	0.53 ± 0.27	<0.001*	0.59
6 months	0.59 ± 0.27	0.006*	0.56 ± 0.27	<0.001*	0.47
9 months	0.63 ± 0.29	0.03*	0.59 ± 0.29	0.002*	0.40
12 months	0.65 ± 0.28	0.03*	0.61 ± 0.28	0.001*	0.39

Note: *Statistically significant.
Abbreviation: BCVA, Best-corrected visual acuity.

Central Macular Thickness

Mean CMT at baseline was 520 ± 144 µm (naïve: 546 ± 155 µm; treated: 508 ± 139 µm; $P = 0.12$). Both groups experienced significant CMT reduction following DEX, with the lowest mean values observed at 1–2 months (overall CMT at 2 months: 318 ± 128 µm, $P < 0.001$). At 12 months, mean CMT remained reduced at 462 ± 192 µm (p = 0.03), with no significant intergroup difference at any visit ($P > 0.10$ at all timepoints) (Table 2 and Table 4).

Hyperreflective Foci

HRF were present in 58% of eyes at baseline (70% in naïve, 54% in treated, $P = 0.16$) and significantly decreased to 26% overall at 12 months ($P < 0.001$ compared to baseline), with no statistically significant difference between subgroups at any visit ($P = 0.91$) (Table 5).

Safety Analysis

Mean IOP increased from 13.8 ± 2.6 mmHg at baseline to 15.3 ± 3.0 mmHg at 12 months ($P = 0.007$). Transient IOP elevations >21 mmHg occurred in 9.8% of eyes, with no eye developing an IOP of >30mmHg or requiring glaucoma

Table 4 Changes in the Central Macular Thickness Based on the Treatment Status of the Study Eyes

Timepoint	CMT (µm) Treatment-Naïve Eyes (Mean ± SD)	Intra-group *P*-value	CMT (µm) Recalcitrant Eyes (Mean ± SD)	Intra-Group *P*-value	Inter-Group *P*-value
Baseline	546 ± 155	–	508 ± 139	–	0.12
1 month	370 ± 135	<0.001*	345 ± 133	<0.001*	0.28
2 months	334 ± 129	<0.001*	314 ± 126	<0.001*	0.20
3 months	368 ± 147	0.001*	345 ± 149	<0.001*	0.24
6 months	442 ± 186	0.01*	400 ± 183	0.002*	0.17
9 months	481 ± 204	0.02*	447 ± 202	0.03*	0.29
12 months	484 ± 194	0.04*	452 ± 191	0.03*	0.33

Note: *Statistically significant.
Abbreviation: CMT, Central macular thickness.

Table 5 Changes in the Proportion of Eyes with Resolution of Hyperreflective Foci in the Study Cohort and the Subgroups

Timepoint	HRF % (Entire Cohort)	*P*-value	HRF % Treatment-Naïve Eyes (Mean ± SD)	Intra-Group *P*-value	HRF % Recalcitrant Eyes (Mean ± SD)	Intra-Group *P*-value	Inter-Group *P*-value
Baseline	58% (59/102)	–	70% (21/30)	–	54% (38/72)	–	0.13
1 month	20% (20/102)	<0.001*	20% (6/30)	<0.001*	19% (14/72)	<0.001*	0.89
2 months	17% (17/102)	<0.001*	17% (5/30)	<0.001*	17% (12/72)	<0.001*	1.00
3 months	18% (18/102)	<0.001*	17% (5/30)	<0.001*	18% (13/72)	<0.001*	0.92
6 months	22% (22/102)	<0.001*	23% (7/30)	<0.001*	24% (17/72)	<0.001*	0.90
9 months	27% (28/102)	<0.001*	27% (8/30)	<0.001*	28% (20/72)	<0.001*	0.91
12 months	26% (27/102)	<0.001*	27% (8/30)	<0.001*	26% (19/72)	<0.001*	0.91

Note: *Statistically significant.
Abbreviation: HRF, Hyperreflective foci.

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surgery. All eyes were managed with topical anti-glaucoma medications. IOP rises were similar between naïve and treated groups ($P = 0.58$) (Table 2 and Table 6).

Although the study cohort had a mean age of 61.7 ± 8.8 years, baseline cataract prevalence was 0% because: (1) all 102 eyes were phakic or pseudophakic at enrollment; (2) among phakic eyes (n = 78 eyes, 76%), lens opacities were minimal at baseline (LOCS III score ≤2 in all cases), consistent with clinically insignificant cataracts; (3) 24 eyes (24%) were pseudophakic at baseline and excluded from cataract progression analysis. During follow-up, 40 phakic eyes developed clinically significant cataract progression by 12 months (53% of 78 phakic eyes), with 16 eyes (21% of 78 phakic eyes) undergoing surgery. Importantly, post-cataract-surgery eyes were retained in the primary efficacy analysis (BCVA, CMT) as cataract surgery typically improves vision (or stabilizes it), providing conservative estimates of DEX benefit. Among the study cohort, cataract progression was observed in 39% at 12 months (naïve: 53%, recalcitrant: 33%; $P = 0.05$), while 26% underwent cataract surgery during follow-up. No significant difference in the rate of cataract progression or surgery was detected between subgroups (Table 7).

No systemic adverse events were reported during the study period.

Figures 1 and 2 are representative cases of the study cohort.

Table 6 Changes in the Intraocular Pressure Based on the Treatment Status of the Study Eyes

Timepoint	IOP (mmHg) Treatment-Naïve Eyes (Mean ± SD)	Intra-group *P*-value	IOP (mmHg) Recalcitrant Eyes (Mean ± SD)	Intra-Group *P*-value	Inter-Group *P*-value
Baseline	13.4 ± 2.7	–	14.0 ± 2.5	–	0.09
1 month	14.7 ± 3.1	0.02*	14.9 ± 2.8	0.01*	0.67
2 months	14.6 ± 3.2	0.04*	14.8 ± 2.9	0.02*	0.60
3 months	14.7 ± 3.0	0.03*	14.5 ± 2.9	0.03*	0.73
6 months	15.4 ± 3.3	0.01*	14.9 ± 3.0	0.01*	0.38
9 months	15.7 ± 3.1	0.01*	15.0 ± 3.3	0.01*	0.21
12 months	15.5 ± 3.2	0.01*	15.2 ± 2.9	0.01*	0.58

Note: *Statistically significant.
Abbreviation: IOP, Intraocular pressure.

Table 7 Changes in the Proportion of Eyes with Cataract in the Study Cohort and the Subgroups

Timepoint	Presence of Cataract (Entire Cohort)	*P*-value	Presence of Cataract (Mean ± SD)	Intra-Group *P*-value	Presence of Cataract (Mean ± SD)	Intra-Group *P*-value	Inter-Group *P*-value
Baseline	0% (0/102)	–	0% (0/30)	–	0% (0/72)	–	–
1 month	2% (2/102)	0.16	3% (1/30)	0.34	1% (1/72)	0.32	0.88
2 months	6% (6/102)	0.04*	10% (3/30)	0.11	4% (3/72)	0.09	0.32
3 months	10% (10/102)	0.01*	17% (5/30)	0.03	7% (5/72)	0.06	0.27
6 months	24% (25/102)	<0.001*	33% (10/30)	0.001	21% (15/72)	<0.001*	0.18
9 months	30% (31/102)	<0.001*	43% (13/30)	<0.001	25% (18/72)	<0.001*	0.12
12 months	39% (40/102)	<0.001*	53% (16/30)	<0.001*	33% (24/72)	<0.001	0.05

Note: *Statistically significant.

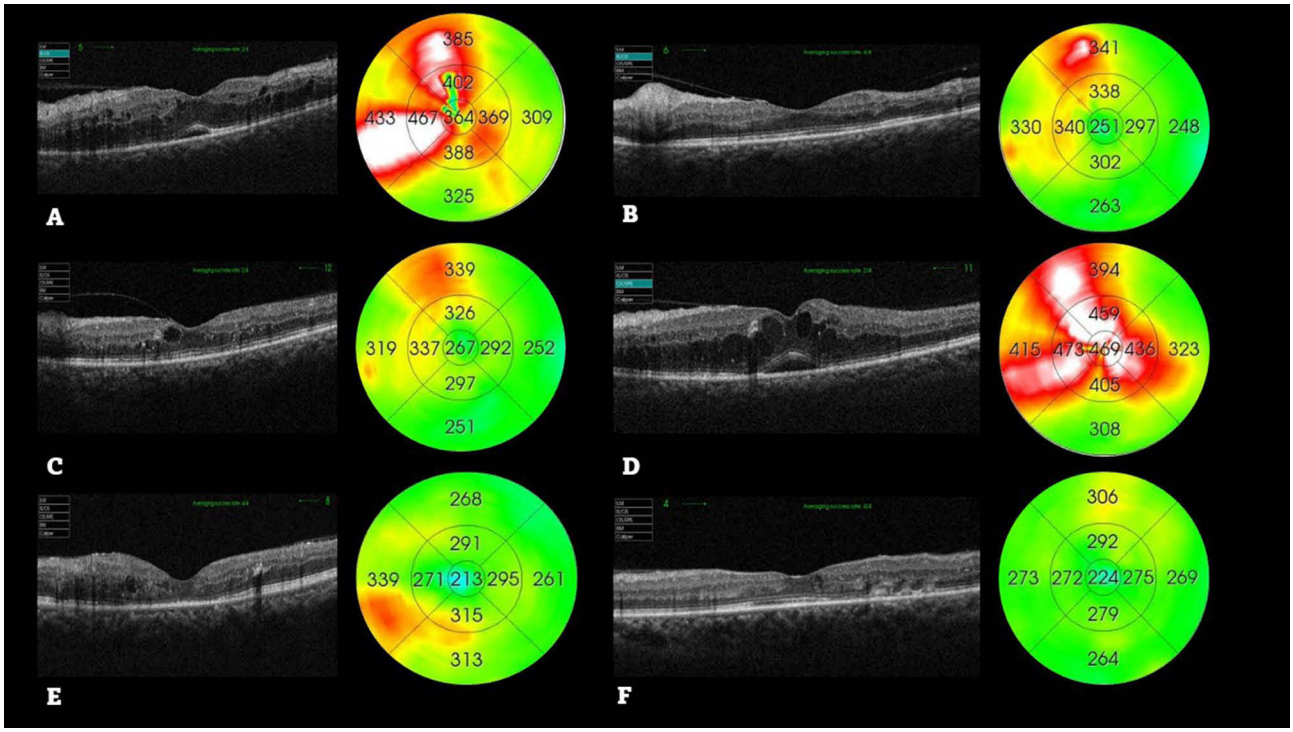

Figure 1 A 54-year-old male with diabetes mellitus and hypertension presented with refractory diabetic macular edema (DME). Baseline spectral-domain optical coherence tomography (SD-OCT) (**A**) demonstrated DME with best-corrected visual acuity (BCVA) of 20/120. Two months after the first intravitreal dexamethasone (DEX) implant, the macula was completely dry and BCVA improved to 20/63 (**B**). At three months, trace cystoid changes reappeared despite further BCVA improvement to 20/40 (**C**). By six months, rebound edema had recurred and BCVA had declined to 20/200, prompting a second DEX injection (**D**). Two months following the second implant (nine months after the first), near-total fluid resolution was achieved with BCVA of 20/63 (**E**), and this anatomical and functional response was sustained at 12 months, with BCVA of 20/40 (**F**).

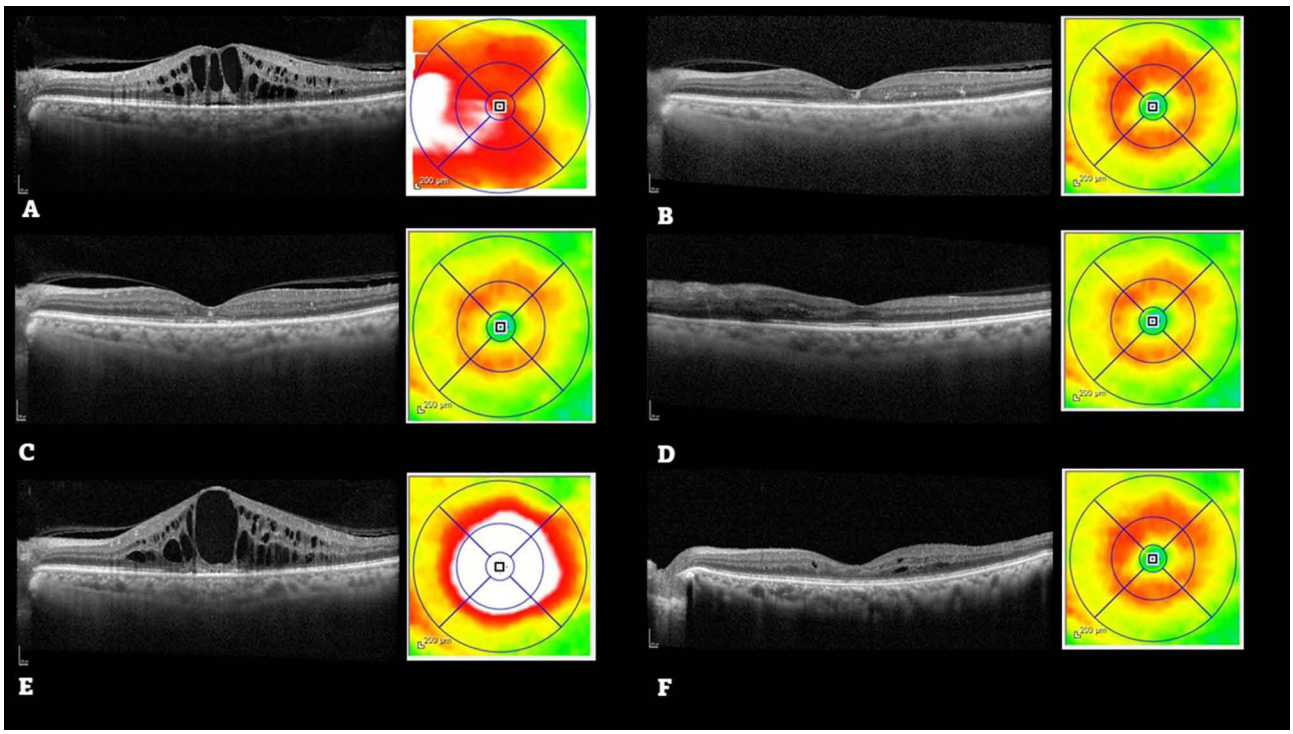

Figure 2 A 62-year-old male with diabetes mellitus, hypertension, and chronic kidney disease (CKD) with treatment-naïve diabetic macular edema, underwent treatment with an intravitreal dexamethasone (DEX) implant. At baseline (**A**), spectral-domain optical coherence tomography (SD-OCT) demonstrated marked cystoid macular edema (CME) with a best-corrected visual acuity (BCVA) of 20/80. Two months after the first DEX implant (**B**), the macula was completely dry and BCVA had improved to 20/40, and this anatomical and functional gain was sustained at three months (**C**) (BCVA 20/32) and at six months (**D**) (BCVA 20/32). At nine months from the initial treatment (**E**), recurrence of macular fluid was noted with a corresponding decline in BCVA to 20/120, prompting administration of a second implant. By 12 months (**F**), near-total fluid resolution was achieved and BCVA had rebounded to 20/40.

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Discussion

Our study evaluated the twelve-month efficacy and safety of intravitreal DEX implants in a cohort of patients with CI-DME, divided into two groups: treatment-naïve and recalcitrant DME eyes. Both groups showed significant visual and anatomical improvement with a favorable safety profile, confirming the utility of DEX in DME management. While both treatment-naïve and recalcitrant eyes experienced significant improvement in BCVA and CMT, recalcitrant eyes required a higher number of reimplants,[4,5] aligning with the hypothesis that chronic edema may necessitate more frequent treatment.

Comparative analysis with published trials highlights concordance as well as context-specific differences. In the MEAD study (3-year, sham treatment controlled), 22% of eyes gained ≥15 letters with 0.7 mg DEX versus 12% with sham treatment,[20] and mean CMT reduced by ~112 µm on DEX compared to ~42 µm on sham treatment ($P < 0.001$).[20] In our series, mean logMAR BCVA improved roughly by 0.10–0.12 (≈5–6 letters) and CMT by ≈58 µm overall, reflecting these trial outcomes in a real-world setting. Notably, the rise in BCVA was sustained; 12-month BCVA remained significantly better than baseline in both cohorts. In the DEX vs laser trial from China/Philippines, Wei et al[21] found that 5-monthly DEX produced significantly better BCVA (mean +4.3 letters) and central retinal thickness (CRT) reduction (–209 µm) than laser. Our overall BCVA and CMT reductions are smaller than those randomised clinical trials' (RCTs') maximal changes, likely due to the more heterogeneous real-world population and less frequent implants (mean ~1.8 implants over 12 months vs 2 in Wei's protocol). Real-world cohorts report similar trends: the LOUVRE-3 study of largely pre-treated DME (mean 1.4 implants over 8.3 months) found a peak BCVA gain of only +3.6 letters,[22] yet 68% of eyes achieved OCT fluid resolution at least once. The Swiss cohort by Turgut et al[23] also confirmed anatomical gains (mean CST –157 µm) and stable vision after switching refractory eyes to DEX. In a similar multicenter real-life study, Chhablani J et al[24] reported mean logMAR gains from 0.58 to 0.44 (naïve) and 0.65 to 0.48 (refractory), mirroring our findings. Likewise, Castro-Navarro V et al[25] observed equivalent CMT reduction in naïve and refractory eyes, albeit slightly higher letter gains in the naïve subgroup. In summary, our results affirm that intravitreal DEX implants are effective at 12 months irrespective of prior treatment history, echoing both RCTs and observational reports (MEAD, PLACID) that all patient types can benefit from steroid therapy.[20,23]

In our study, HRF were present in 58% at baseline and fell to 26% at year 1, indicating inflammation subsidence. This accords with Rübsam A et al's OCT study,[26] where DEX implants led to a significant HF reduction whereas anti-VEGF did not. In short, our cohort's outcomes are generally consistent with the literature; DEX implants produce robust edema resolution and moderate BCVA gains even in real-world settings,[17,26] albeit somewhat less dramatic than in tightly controlled RCTs.

The efficacy of DEX in chronic DME reflects its broad anti-inflammatory actions. Corticosteroids inhibit a spectrum of cytokines, adhesion molecules, and growth factors implicated in DME pathogenesis. Preclinical studies demonstrate that intravitreal dexamethasone sharply reduces leukostasis and BRB breakdown: in diabetic rat eyes, a single dexamethasone injection cut retinal leukocyte accumulation by ~32% and vascular leakage by ~61%, accompanied by a 70% drop in retinal ICAM-1 expression.[27] At the molecular level, steroids downregulate VEGF and its receptor, interleukin-6, ICAM-1, and other inflammatory mediators.[22–24] This restores endothelial tight junctions and strengthens Müller glial barriers, countering both fluid leakage and "gliosis" that drives edema. The clinical correlate is that steroid-sensitive biomarkers improve: our finding of a marked decrease in HRF (often considered inflammatory cell aggregates) after DEX is in line with the notion that DEX targets the cytokine-driven component of DME. Indeed, Rübsam et al[26] proposed that small HF represent inflammatory cells, which dissipate more with steroids than anti-VEGF. Thus, mechanistically DEX acts "upstream" by broadly quelling inflammation, explaining its particular potency in eyes where chronic cytokines (IL-6, TNF-α, etc.), not just VEGF, are elevated.[22–25] It bears emphasis that this mode of action complements anti-VEGF: anti-VEGF monotherapy cannot fully suppress the pro-inflammatory milieu driving chronic DME. DEX implants thereby address a different arm of the disease pathway (stabilizing BRB integrity and reducing edema through non-VEGF routes).[22–27]

The clinical advantages of the DEX implant emerge clearly from durability and burden perspectives. In our patients, the mean reinjection rate was only ~1.8 per year (1.73 in naïve, 1.87 in recalcitrant eyes). This is far lower than typical

anti-VEGF regimens (often monthly or bi-monthly implants). For example, Turgut et al[26] reported that DEX use halved the annual anti-VEGF burden: pre-DEX patients averaged 6.4 injections/year, which fell to 1.6 after adding DEX ($P < 0.001$). Such reduction in visit frequency is particularly critical in resource-limited settings. In India and similar regions, frequent clinic visits impose severe socio-economic strain. A study from Bhutan noted factors such as limited vitreoretinal units, economic, and geographic constraints as limiting factors in optimal management of retinal patients.[28] A recent Indian study showed that long travel distances and low income significantly reduced follow-up adherence in DR care.[29] By contrast, DEX's 3–4 month effect means fewer visits, potentially improving adherence in this population. Moreover, the gradual steroid release produces steadier anatomical control, minimizing the fluid "saw-tooth" effect seen with intermittent anti-VEGF peaks. Clinically, this translates into meaningful quality-of-life gains; patients face fewer needle procedures and appointments, reducing anxiety and costs. Such practical benefits underscore why DEX is a valuable option, especially when anti-VEGF alone is inadequate or impractical. In a nutshell, DEX implants combine potent edema control with extended durability, making them critical tools to alleviate the heavy treatment burden of chronic DME.

The ocular safety profile of intravitreal dexamethasone implants has been generally favorable in prior studies,[20,23] and our findings are consistent with this trend. Steroid-related side effects were common but manageable. By 12 months, 39% of phakic eyes showed cataract progression, with 26% undergoing surgery (no difference between naïve and refractory), aligning with MEAD data.[20] Cataract removal restored vision reliably, making this a predictable, counselable trade-off. IOP elevations were modest: mean IOP rose from 13.8 to 15.3 mmHg ($P = 0.007$), 9.8% of eyes had transient IOP >21 mmHg, all controlled with topical drops, and none required surgery. These results mirror large trials, underscoring that while steroid-induced ocular hypertension is common, it is usually mild and controllable.[20,26] When balanced against anti-VEGF's heavier injection burden and systemic risks, DEX's predictable safety profile makes it a viable option, especially in pseudophakic patients or those unresponsive to VEGF blockade.

The importance of real-world data is clear.[30,31] Unlike RCTs with strict eligibility, our retrospective multicenter cohort reflects the heterogeneity of everyday practice: patients had varying DR severity, co-morbidities, and prior treatments. This external validity is a strength. We saw the influences of socioeconomic and logistic factors on care, factors seldom captured in trials. For instance, limited travel means some patients delay returning, effectively lengthening DEX retreatment intervals. Our multicenter design in urban and semi-urban Indian settings also enhances generalizability across diverse clinical environments. However, retrospective design limits causal inference and may under-report mild events. The sample size (102 eyes) provides reasonable power for main outcomes but is smaller than pooled RCT populations, and the follow-up (12 months) may not capture late adverse events (eg late cataract progression or glaucoma). Unlike parallel RCTs, there was no control group; comparisons to anti-VEGF outcomes must be indirect. Nonetheless, our study design closely mirrors real clinical decision-making, complementing the RCT evidence.

Key limitations include the retrospective nature, lack of a comparator arm, and lack of randomization, which allow potential selection bias (for example, physicians may have preferentially offered DEX to eyes they deemed steroid-responsive). We also lacked a formal patient-reported outcome assessment, such as quality-of-life surveys, which could have quantified the functional impact of fewer visits and improved vision. Also, as with many real-world studies, the timing of repeat DEX implants varied among patients, and treatment administered closer to the end of the follow-up period may have had some influence on the measured outcomes. This variability should be considered when interpreting the results. On the other hand, strengths of our study are its multicenter composition, reflecting two large referral centers, and its inclusive definition of "recalcitrant" DME requiring prior anti-VEGF failure. This allowed robust subgroup comparisons. We meticulously quantified OCT biomarkers (HRF), providing novel insights on inflammation. The thorough safety monitoring (IOP and cataract grading at each visit) lends confidence to our safety conclusions. Finally, the study's conduct in a developing-country context adds valuable data for regions where DME management faces additional socioeconomic constraints.

Looking ahead, several avenues warrant exploration. Combination therapies, such as alternating anti-VEGF and steroid implants, may offer synergistic benefits by targeting multiple pathways; preliminary studies (and our own practice) suggest this strategy can reduce anti-VEGF frequency while maintaining efficacy.[23] Personalized medicine approaches could also refine therapy: for instance, baseline levels of intraocular cytokines or systemic inflammatory

markers might predict which patients will respond to steroids. Biomarker-driven protocols (such as OCT indicators of inflammation, eg HRF or subretinal fluid) deserve study. Head-to-head trials of DEX vs anti-VEGF in defined subgroups (for example, an RCT in pseudophakic DME eyes) could clarify ideal first-line roles. New sustained-release drugs on the horizon (longer-acting steroids, bispecific antibodies) may further change the landscape. In short, our findings call for continued research into optimized regimens: perhaps fixed-interval DEX schedules for refractory cases, or trials of early switch to steroid when VEGF alone fails. Given the chronic nature of DME, strategies to minimize end-organ damage (neuroretina loss) via early inflammation control are also promising areas of investigation.

Conclusion

In summary, the DEX implant provided significant anatomical and visual improvements in both treatment-naïve and previously treated DME eyes over 12 months, complementing RCT evidence. This effectiveness came with a manageable safety profile, cataract progression that is amenable to surgery and mostly mild IOP elevation treatable with drops. Importantly, DEX offered a lasting effect with relatively few implants, a crucial advantage in settings where frequent visits are difficult. While these findings reinforce the potential role of intravitreal corticosteroids for CI-DME, particularly when anti-VEGF monotherapy yields suboptimal response, they should be interpreted within the context of real-world observational evidence. Future prospective studies should investigate combination therapies, biomarker-guided treatment, and head-to-head comparisons to refine the role of DEX implant in the armamentarium.

Disclosure

J.S.: Attached to Shantilal Shanghvi Foundation (SSF) (not relevant to the work under consideration).

The authors declare that they have no competing interests.

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