Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Comparison of Anatomical and Functional Efficacy of Intravitreal Ranibizumab and Dexamethasone Implant in Refractory Diabetic Macular Edema: A One-Year Prospective Non-Randomized Open-Label Observational Clinical Trial

**Büşra ÇOBAN**

bsr.coban@gmail.com

T.C. İstanbul Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi

**Akın Çakır**

T.C. İstanbul Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi

**Gamze Maden Karataş**

T.C. İstanbul Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi

**Eren Vurgun**

T.C. İstanbul Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi

**Research Article**

**Keywords:** Diabetic macular edema, systemic serum biomarkers, local OCT biomarkers, intravitreal ranibizumab, intravitreal dexamethasone

**Posted Date:** July 29th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-10334333/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** No competing interests reported.

# Abstract

**Purpose**

To compare the anatomical and functional efficacy of an early switch to intravitreal ranibizumab (IVR) or dexamethasone implant (IVD) in eyes with persistent diabetic macular edema (DME) after bevacizumab, and to explore OCT and systemic predictors of treatment response.

**Methods**

This prospective, observational, non-randomized, open-label clinical study included 115 eyes of 80 patients with treatment-naïve, center-involved DME that persisted despite three consecutive monthly intravitreal bevacizumab injections. At month 4, eyes were switched either to IVR (0.5 mg/0.05 mL; 68 eyes) or IVD (0.7 mg; 47 eyes) at the discretion of the treating ophthalmologist. Patients were followed monthly for 12 months on a pro re nata regimen. Best-corrected visual acuity (BCVA, logMAR), central macular thickness (CMT, SD-OCT), intraocular pressure (IOP), OCT biomarkers, and systemic laboratory parameters (including systemic immune-inflammation index, SII) were recorded. Treatment outcomes were systematically evaluated. Predictors of CMT gain and BCVA outcome were analyzed.

**Results**

Baseline CMT was similar between the groups (IVR: 435.80 ± 132.27 μm; IVD: 449.51 ± 104.19 μm). After switching, both groups showed a significant reduction in CMT over time ($p < 0.001$), with comparable final CMT at month 12 (339.14 ± 90.90 μm vs. 369.66 ± 116.57 μm; $p = 0.131$). Dexamethasone produced a significantly greater CMT reduction at month 2 ($p < 0.001$). Baseline BCVA was 0.48 ± 0.38 logMAR in the IVR group and 0.52 ± 0.42 logMAR in the IVD group ($p = 0.453$). Visual acuity remained comparable through months 1, 2, 3, and 6 ($p = 0.088$, 0.087, 0.109, and 0.070, respectively. However, at month 12, a statistically significant difference emerged in favor of IVR, with better visual acuity compared to IVD (0.35 ± 0.37 vs. 0.66 ± 0.49 logMAR; $p = 0.001$). IOP increase was more frequent in the IVD group, with 17% of eyes requiring topical antiglaucoma therapy, but all were controlled medically. Baseline CMT was the only OCT parameter significantly associated with treatment efficacy ($p < 0.01$). Among systemic markers, higher SII was significantly associated with greater early CMT reduction at month 2 in the dexamethasone arm ($p = 0.028$).

**Conclusions**

Both intravitreal ranibizumab and dexamethasone implants resulted in meaningful anatomical improvement in refractory DME. Dexamethasone implants induced a faster early reduction in CMT, whereas ranibizumab achieved more sustained visual gains over 12 months. Elevated SII may help identify patients who are more likely to benefit from an early anatomical response to dexamethasone. These prospective, real-world data support individualized treatment decisions integrating anatomical, functional, and inflammatory profiles.


# INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of blindness among working-age adults in developed countries.[1] Vision impairment associated with DR is primarily caused by diabetic macular edema (DME). [2]. In the pathogenesis of diabetes, chronic hyperglycemia represents the predominant underlying mechanism, driving increased oxidative stress and a sustained inflammatory response. Consequently, this process compromises the integrity of the blood–retinal barrier by inducing endothelial dysfunction and vascular injury mediated by VEGF, TNF, interleukins, and other cytokines. These alterations culminate in progressive retinal ischemia and the development of diabetic macular edema through enhanced microvascular permeability[3] Intravitreal anti-VEGF therapy is currently the first-line and effective treatment for DME.[4] Nevertheless, a considerable proportion of patients show an insufficient response, with persistent edema reported in 32% to 66% of eyes after at least six monthly injections. [5]. This highlights the need for alternative strategies in cases with a suboptimal response to anti-VEGF therapy In recent years, intravitreal corticosteroids have gained prominence as a viable therapeutic option due to their anti-inflammatory, anti-VEGF, and anti-proliferative effects.[6]

To our knowledge, based on a Medline search, only one prospective study has been published comparing intravitreal ranibizumab (IVR) with intravitreal dexamethasone(IVD) for the treatment of DME.[7] We conducted a prospective, open-label, non-randomized observational study to compare visual acuity outcomes and spectral-domain optical coherence tomography (SD-OCT) findings in patients treated with intravitreal ranibizumab versus intravitreal dexamethasone for persistent DME.

## METHOD

The present study was designed as a prospective, observational, non-randomized, open-label clinical trial and was registered at ClinicalTrials.gov (NCT06179030). The study protocol adhered to the principles of the Declaration of Helsinki and received approval from the institution’s Clinical Research Ethics Committee (Cemil Tascıoglu City Hospital). Written informed consent was obtained from all participants prior to enrollment.

# Study Population

All patients evaluated in the Retina Section of the Department of Ophthalmology at Cemil Tascıoglu City Hospital, who had treatment-naïve center-involved DME in at least one eye between April 2022 and October 2023, were invited to participate.

The inclusion criteria were as follows:

(1) persistent center-involved DME, defined as cases that were treatment-naïve at diagnosis and had received a loading dose of three consecutive monthly intravitreal bevacizumab injections (Avastin®; 1.25 mg/0.05 mL), yet failed to demonstrate an adequate response;

(2) age ≥ 18 years; and

(3) provision of written informed consent.

Weak functional response was defined according to DRCR Retina Network criteria: patients were considered non-responders if they failed to gain ≥ 5 ETDRS letters for baseline VA 20/25–20/32, ≥ 10 letters for baseline VA 20/40–20/63, or ≥ 15 letters for baseline VA 20/80–20/320.

Poor anatomical response was defined as failure to achieve a CMT reduction of ≥ 50 μm, ≥ 100 μm, or ≥ 200 μm on SD-OCT depending on baseline edema severity (mild, moderate, or severe). [8]

Exclusion criteria included:

(1) presence of other vitreoretinal diseases;

(2) media opacities impairing OCT image quality;

(3) ocular surgery within the preceding six months.

A total of 115 eyes from 80 patients were included in the study.

## Treatment Protocol

At the fourth month, patients with persistent DME underwent a switch in intravitreal treatment. In Türkiye, the national reimbursement policy requires patients with diabetic macular edema to complete three consecutive monthly intravitreal bevacizumab injections before alternative intravitreal therapies become eligible for reimbursement. Accordingly, treatment switching in the present study was performed immediately after completion of the mandatory bevacizumab loading phase, representing the earliest feasible switch permitted within the national healthcare system. The selection of the subsequent therapeutic agent was left to the discretion of the attending ophthalmologist during the clinical visit, without predefined criteria. Some patients were switched from anti-VEGF to anti-VEGF therapy and initiated on ranibizumab (Lucentis®; 0.5 mg/0.05 mL), whereas others were switched from anti-VEGF therapy to a steroid regimen with a dexamethasone implant (Ozurdex®; 0.7 mg). The investigators did not intervene in treatment decisions.

The proliferative status of diabetic retinopathy (proliferative vs. non-proliferative) was assessed using fundus fluorescein angiography (FFA) performed during the treatment-naïve phase. Demographic characteristics, including age and sex, as well as systemic comorbidities, were recorded.

Peripheral venous blood samples were obtained from all patients before switching. Laboratory parameters, including complete blood count (hemogram), glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, urea, creatinine, high-sensitivity C-reactive protein (hs-CRP), and lactate dehydrogenase (LDH), were measured and recorded. The systemic immune-inflammation index (SII) was calculated using complete blood count parameters according to the formula: platelet count × neutrophil count / lymphocyte count.

## Follow-up Schedule

Following the switch, all patients were evaluated monthly with standardized ophthalmic examinations, including BCVA measurement and spectral-domain OCT. Subsequent treatments were administered using a pro re nata (PRN) regimen.

Data were collected prospectively over 12 months and analyzed at the following time points for both groups: baseline (treatment-naïve), post-loading phase (pre-switch), and 1, 2, 3, 6, and 12 months post-switch.

## Ophthalmic Examination

Each patient underwent a comprehensive ophthalmologic evaluation at every monthly visit. BCVA was measured using a Snellen chart, and decimal values were converted to logMAR units for analysis. Additional assessments included applanation tonometry, undilated and dilated slit-lamp biomicroscopy, and fundus examination.

## OCT Imaging and Biomarker Assessment

Spectralis SD-OCT (Heidelberg Engineering, Germany) was performed for all patients. CMT was automatically calculated as the mean retinal thickness within the central 1-mm ETDRS subfield. The follow-up mode was used to minimize test–retest variability.

Intraretinal fluid morphology was classified as cystoid or diffuse edema. The following OCT biomarkers were evaluated across the central five B-scans: hyperreflective foci (HRF) (< 30 μm), hard exudates (> 30 μm), subfoveal hard exudates, disorganization of the retinal inner layers (DRIL), external limiting membrane (ELM) disruption, ellipsoid zone (EZ) damage, epiretinal membrane (ERM), and cystoid retinal degeneration (> 600 μm). Hyperreflective foci were categorized as none, mild (0–10), moderate (11–20), or severe (≥ 21). The “pearl necklace sign,” defined as hyperreflective dots surrounding cystoid spaces, was also recorded. All OCT scans and biomarker evaluations were performed by a single ophthalmologist to ensure consistency.

# Statistical Analysis

Statistical analyses were performed to compare anatomical and functional outcomes between the IVR and IVD groups over a one-year follow-up period. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Baseline demographic and clinical characteristics were compared between groups using appropriate parametric or non-parametric tests, depending on data distribution.

Changes in BCVA and CMT over time were evaluated using repeated-measures analysis of variance (ANOVA) to assess within-group changes and between-group differences across follow-up visits. When applicable, post hoc analyses with appropriate corrections were performed to identify time points with significant differences. Parametric tests were used for normally distributed variables, whereas non-parametric alternatives were applied when normality assumptions were not met.

A p value < 0.05 was considered statistically significant. All statistical analyses were conducted using [SPSS version 25; IBM Corp., Armonk, NY, USA].

## RESULTS

# Baseline characteristics

A total of 115 eyes from 80 patients were included in the analysis, with each eye considered an independent case. At baseline, 68 eyes were assigned to the IVR group and 47 eyes to the IVD group. At the 6-month follow-up, 66 eyes in the IVR group and 42 eyes in the IVD group remained under observation. By month 12, 61 eyes in the IVR group and 40 eyes in the IVD group completed the study

The two groups were comparable in terms of demographic and ocular characteristics. The mean age was 63.25 ± 9.51 years in the ranibizumab group and 63.40 ± 9.99 years in the dexamethasone group (p = 0.934). The female-to-male ratio was 35/33 in the ranibizumab group and 20/27 in the dexamethasone group (p = 0.448)

Lens status at baseline was similar between the groups (p = 0.838), with 30.4% of eyes being pseudophakic and 69.6% phakic. No changes in lens status occurred during the 12-month follow-up period. The baseline edema patterns were comparable between the groups (p = 0.512). Likewise, the baseline severity distribution of diabetic retinopathy did not differ significantly between the groups (p = 0.227). (Table 1).

**Table-1**

Comparison of demographic and ocular characteristics between the groups

| **Age (year)** | | **Ranibizumab (n = 68)** | **Deksametazon (n = 47)** | **Intergroup comparison (p value)** |
|---|---|---|---|---|
| | | **63,25 ± 9.51** | **63,40 ± 9,99** | **0,934** |
| Sex (W/M) | | 35/33 | 20/27 | 0,448 |
| Lens status | **Phakic** | 20 | 15 | 0,838 |
| | **Pseudophakic** | 48 | 32 | |
| Diabetic Retinopathy Stage | **Non-proliferative** | 52 | 16 | 0,227 |
| | **Proliferative** | 41 | 6 | |

Comorbidity profiles were similar between the two groups (p = 0.170), as shown in Fig. 1.

Baseline systemic laboratory characteristics were comparable between the two groups and are presented in Table 2.

**Table-2**

Comparison of baseline systemic laboratory parameters between the groups

| HbA1c(%) | Ranibizumab (mean ± SD) | Dexamethasone (mean ± SD) | Intergroup comparison (p value) |
|---|---|---|---|
| | **7,88 ± 1,81** | **7,89 ± 1,51** | **0,772** |
| Erythrocyte Sedimentation Rate (mm/hour) | 18,29 ± 15,31 | 13,45 ± 11,79 | 0,110 |
| Neutrophil-to-Lymphocyte Ratio (NLR) | 2,90 ± 1,12 | 2,68 ± 1,33 | 0,134 |
| SII (Systemic Immune-Inflammation Index) ($10^9$/L) | 834,36 ± 469 | 715,07 ± 526,27 | 0,207 |
| Total cholesterol (mg/dl) | 187,11 ± 41,98 | 183,31 ± 44,57 | 0,647 |
| LDL cholesterol (mg/dl) | 103,94 ± 37,76 | 109,31 ± 41,45 | 0,480 |
| HDL cholesterol (mg/dl) | 45,69 ± 12,04 | 46,06 ± 10,40 | 0,860 |
| Triglycerides (mg/dl) | 182,91 ± 83,20 | 156,46 ± 70,03 | 0,088 |
| Urea (mg/dl) | 45,51 ± 27,33 | 40,85 ± 12,95 | 0,838 |
| Creatinine (mg/dl) | 1,16 ± 0,75 | 1,00 ± 0,36 | 0,912 |
| High-sensitivity C-reactive protein (hs-CRP) (mg/dl) | 6,42 ± 11,30 | 5,41 ± 9,44 | 0,397 |
| Lactate dehydrogenase (LDH) (U/l) | 202,93 ± 46,83 | 214,26 ± 46,87 | 0,325 |

Baseline OCT biomarker distributions were comparable between the IVR and IVD groups (Table 3). No significant intergroup differences were observed in edema type, presence of subretinal fluid, hyperreflective foci grading, hard exudates, subfoveal hard exudates, DRIL, epiretinal membrane, cystoid degeneration, pearl necklace sign, external limiting membrane disruption, or ellipsoid zone disruption ( $p > 0.05$). Overall, OCT structural characteristics were well balanced between treatment groups prior to switching.

**Table-3**

Comparison of baseline local OCT parameters between the groups

| OCT Biomarkers | | Ranibizumab (%) | Dexamethasone (%) | Intergroup comparison (p value) |
|---|---|---|---|---|
| **Edema Type** | Cystoid | 67,6 | 61,7 | P = 0,414 |
| | Diffuse | 32,4 | 38,3 | |
| **Subretinal Fluid (SRF)** | Absent | 70,6 | 61,7 | P = 0,877 |
| | Present | 29,4 | 47,4 | |
| **Hyperreflective Foci (HRF)** | None | 2,9 | 0 | p = 0,665 |
| | Mild (0–10) | 29,4 | 36,2 | |
| | Moderate (11–20) | 19,1 | 21,3 | |
| | Severe (21 and more) | 48,5 | 42,6 | |
| **Hard Exudates** | Absent | 35,3 | 25,5 | P = 0,790 |
| | Present | 64,7 | 74,5 | |
| **Subfoveal Hard Exudate** | Absent | 89,7 | 91,5 | P = 0,790 |
| | Present | 10,3 | 8,5 | |
| **DRILL** | Absent | 97,1 | 100 | P = 0,666 |
| | Present | 2,9 | 0 | |
| **Epiretinal Membrane (ERM)** | Absent | 94,1 | 89,4 | P = 0,167 |
| | Present | 5,9 | 10,9 | |
| **Cystoid Degeneration** | Absent | 67,6 | 66,0 | P = 0,373 |
| | Present | 32,4 | 34,0 | |
| **Pearl Necklace Sign** | Absent | 70,6 | 66,0 | P = 0,728 |
| | Present | 29,4 | 34,0 | |
| **External Limiting Membrane (ELM) Disruption** | Absent | 92,6 | 91,5 | P = 0,946 |
| | Present | 7,4 | 8,5 | |
| **Ellipsoid Zone (EZ) Disruption** | Absent | 86,8 | 80,9 | P = 0,745 |
| | Present | 13,2 | 19,1 | |

# Assessment of Treatment Responses in Patients

In the ranibizumab group, the mean number of injections administered after the switch was 4.52 ± 1.32, whereas in the dexamethasone group it was 2.72 ± 0.90 (P < 0.05).

Initially, the mean CMT in the IVR group was 435.80 ± 132.27 μm before the IVB loading dose, decreasing to 405.96 ± 124.50 μm after three consecutive monthly IVB injections. Similarly, the mean CMT in the IVD group was 449.51 ± 104.19 μm before the IVB loading dose, and 476.12 ± 166.38 μm after the three monthly IVB injections. There was no statistically significant difference in baseline CMT between the two groups (P = 0.568)

Following the switch, both treatment groups demonstrated a statistically significant reduction in mean CMT over time (p < 0.001). At month 12, the final CMT values were comparable between the IVR- and IVD-switched groups (339.14 ± 90.90 μm and 369.66 ± 116.57 μm, respectively; P = 0.131).

When the temporal course of CMT was evaluated, a statistically significant difference in favor of the dexamethasone group was observed at month 2 after the switch, with a greater reduction in central macular thickness compared to the IVR group (p < 0.001) The change in CMT over time was depicted in Fig. 2.

At baseline, the mean BCVA was 0.48 ± 0.38 logMAR in the IVR group and 0.52 ± 0.42 logMAR in the IVD group, with no statistically significant difference between them (p = 0.453). Before switching, the mean BCVA was 0.45 ± 0.39 logMAR in the IVR group and 0.57 ± 0.49 logMAR in the IVD group, with no statistically significant difference between the groups (p = 0.157). During early follow-up, the two groups demonstrated comparable visual trajectories. BCVA comparisons at months 1, 2, 3, and 6 showed no significant intergroup differences (p = 0.088, p = 0.087, p = 0.109, and p = 0.070, respectively). Correspondingly, mean BCVA values remained stable and similar across both groups: IVR versus IVD at month 1 (0.39 ± 0.39 vs. 0.53 ± 0.46 logMAR), month 2 (0.36 ± 0.38 vs. 0.50 ± 0.43 logMAR), month 3 (0.36 ± 0.38 vs. 0.48 ± 0.43 logMAR), and month 6 (0.38 ± 0.39 vs. 0.53 ± 0.46 logMAR).

By month 12, however, the visual outcomes diverged significantly in favor of ranibizumab (p = 0.001). The IVR group maintained a stable improvement, reaching 0.35 ± 0.37 logMAR, whereas BCVA in the IVD group worsened relative to earlier visits, measuring 0.66 ± 0.49 logMAR. Thus, while visual acuity remained comparable between the groups throughout the first 6 months, ranibizumab demonstrated superior functional outcomes at the 12-month visit. The longitudinal changes in BCVA are illustrated in Fig. 3.

# Subgroup Analysis Of BCVA Changes According To Lens Status in The Dexamethasone Group

In a subgroup analysis of the IVD group stratified according to lens status (pseudophakic vs. phakic), no significant difference in baseline BCVA was observed between the two groups prior to the treatment switch. The mean baseline BCVA was comparable, measuring 0.54 logMAR in pseudophakic eyes and 0.58 logMAR in phakic eyes (p = 0.771). At the 12-month follow-up, BCVA remained largely stable in the

pseudophakic group (0.59 logMAR), whereas a slight deterioration was noted in the phakic group (0.68 logMAR). Despite this numerical difference in change-from-baseline BCVA, the intergroup comparison did not reach statistical significance (p = 0.555)

## Safety Analysis

At baseline, no patients with a prior diagnosis of glaucoma were included in the study, and none were using antiglaucomatous medication. There was no significant difference between the groups in terms of baseline intraocular pressure (IOP). During follow-up, evaluation of IOP changes over time showed a significant increase in mean IOP within the dexamethasone group ($p < 0.001$). In this group, 8 out of 47 patients (17%) required initiation of antiglaucomatous therapy. Among these patients, four were managed with a two-agent topical antiglaucoma regimen, while the remaining four required escalation to a three-agent topical antiglaucoma regimen. Despite the rise, all IOP elevations returned to baseline levels by the fourth month, and the increases were effectively controlled with topical IOP-lowering medications.

None of the patients experienced serious complications associated with intravitreal injections, such as retinal detachment, or endophthalmitis.

## Predictors of Anatomical and Functional Treatment Response

To evaluate predictors of treatment response, patient characteristics—including age, sex, baseline laboratory parameters (HbA1c, SII, etc.)—as well as baseline OCT biomarkers were statistically compared with final CMT gain and final visual acuity outcomes. Among the OCT parameters, baseline CMT was the only factor that showed a significant association with treatment efficacy ($p < 0.01$), while no meaningful correlation was observed between other OCT biomarkers and CMT reduction. Similarly, no significant relationships were found between systemic factors (age, sex, HbA1c, SII, and other laboratory values) and either final CMT gain or final visual acuity.

However, because a significant difference in CMT between the treatment groups was observed at month 2 following the switch, a covariance analysis was performed to investigate the variables contributing to this early anatomical response. The analysis revealed that, in addition to the continued effect of the intravitreal agent (dexamethasone vs. ranibizumab), the systemic inflammatory index (SII) had a statistically significant impact on the month-2 CMT gain ($p = 0.028$). Higher SII values were associated with a greater early reduction in CMT in favor of dexamethasone, indicating that elevated SII may serve as a potential predictor of early anatomical response to corticosteroid therapy after switching.

# DISCUSSION

In this prospective clinical study, we evaluated anatomical and functional outcomes following an early switch to intravitreal ranibizumab or dexamethasone implants in eyes with persistent diabetic macular edema after an initial bevacizumab loading phase. To our knowledge, this is the only study in the

literature evaluating an early switch to either ranibizumab or dexamethasone with a one-year follow-up period. Both treatment strategies produced significant reductions in central macular thickness over 12 months, consistent with the established efficacy of anti-VEGF agents and corticosteroids reported in major trials. The anatomical improvements observed in the ranibizumab group align with findings from RESOLVE, READ-2, and RESTORE, all of which demonstrated meaningful reductions in retinal thickness and gradual visual functional gains with anti-VEGF monotherapy. [4,9,10] Our final 12-month CMT values in the IVR group were comparable to those documented in RESTORE and READ-2 after anti-VEGF loading protocols.

A key anatomical distinction in our study was the early superiority of dexamethasone at month 2, where significantly greater CMT reduction was observed compared with ranibizumab. This early response mirrors the rapid anti-edematous effects reported in the BEVORDEX and MEAD trials, underscoring the potent anti-inflammatory and anti-permeability mechanisms of corticosteroid implants. [11,12] Nevertheless, similar to BEVORDEX and MEAD, the pronounced anatomical response in the dexamethasone group did not translate into proportional visual improvement. By month 12, CMT outcomes converged between groups, consistent with the randomized trial by Callanan et al., which demonstrated anatomical non-inferiority between dexamethasone and ranibizumab despite differing treatment frequencies. [13]

Visual outcomes in our study revealed an important divergence between treatment groups. While BCVA remained comparable through month 6, a significant difference emerged by month 12 in favor of ranibizumab. This trajectory parallels long-term findings from the RISE and RIDE trials, in which ranibizumab achieved sustained and clinically meaningful improvements in BCVA. In contrast, visual recovery in the dexamethasone group was limited despite early structural improvement—an observation consistent with the BEVORDEX study, where substantial reductions in central macular thickness did not translate into equivalent functional gains. Several mechanisms may account for this disparity. Cataract progression, a well-recognized adverse effect of dexamethasone implants, likely contributed to the attenuated visual outcomes observed in the steroid group, in line with findings from the MEAD study, where cataract-related vision loss represented a major limiting factor in phakic eyes. Supporting this interpretation, subgroup analysis in our study showed that pseudophakic patients in the intravitreal dexamethasone group largely preserved their visual acuity, whereas a trend toward visual decline was observed in phakic patients. However, this difference did not reach statistical significance, possibly due to the limited sample size in the subgroup analysis and the resulting reduction in statistical power. Additionally, pre-existing disruptions of the external limiting membrane or ellipsoid zone—although not significantly associated with treatment response in our biomarker analysis—may have further constrained the functional recovery potential in steroid-treated eyes.

Safety outcomes were consistent with previous corticosteroid studies. As in MEAD and BEVORDEX, IOP elevation occurred more frequently in the dexamethasone group, with 17% of patients requiring topical antiglaucoma therapy. All IOP elevations were controlled medically without surgical intervention. No cases of endophthalmitis or retinal detachment occurred in either group.

A notable finding of our study was the influence of systemic inflammation on treatment response. Higher SII values were associated with greater early CMT reduction after dexamethasone, suggesting that systemic inflammatory burden may modulate responsiveness to corticosteroid therapy. This observation supports emerging evidence indicating that systemic inflammatory markers may help guide treatment selection in refractory DME. Our findings emphasize that both anatomical response and functional recovery depend not only on the pharmacologic mechanism of the chosen agent but also on patient-specific factors, including inflammatory burden and phakic status.

An important strength of the present study is its prospective design, which allows for systematic follow-up, standardized data collection, and timely evaluation of treatment response. Unlike retrospective analyses, a prospective approach minimizes missing data, reduces selection bias, and provides a more reliable temporal assessment of anatomical and functional changes following a treatment switch. Furthermore, because the study was conducted under routine clinical conditions rather than in a highly controlled trial environment, it offers valuable real-world evidence on the comparative performance of ranibizumab and dexamethasone implants in everyday practice. Real-life data are particularly important in DME, where patient adherence, variability in disease chronicity, and heterogeneous treatment histories often differ substantially from those observed in large randomized controlled trials. Therefore, our findings may be more generalizable to routine clinical decision-making. Therefore, our findings provide practical insights that complement the controlled data obtained from clinical trials and may be more generalizable to routine clinical decision-making.

In conclusion, both ranibizumab and dexamethasone implants offer meaningful anatomical benefit in refractory DME; however, their functional profiles differ over time. Ranibizumab demonstrated superior long-term visual outcomes, whereas dexamethasone provided faster early anatomical recovery, particularly in patients with elevated systemic inflammation. These results underscore the importance of individualized treatment selection and support ongoing investigation into inflammation-guided therapeutic strategies for DME.

## Declarations

Funding:

No funding was received for this study.

Conflict of Interest:

The authors declare no conflicts of interest related to this work.

Ethical Approval:

This study was approved by the Institutional Clinical Research Ethics Committee of Cemil Taşçıoğlu City Hospital and conducted in accordance with the Declaration of Helsinki. (Approval Number: 48670771-514.99.10014)

Clinical Trial Registration:

ClinicalTrials.gov Identifier: NCT06179030

# References


1. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology*. Dec 1984;91(12):1464-74. doi:10.1016/s0161-6420(84)34102-1
2. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. Mar 2012;35(3):556-64. doi:10.2337/dc11-1909
3. Goldberg RB. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. *J Clin Endocrinol Metab*. Sep 2009;94(9):3171-82. doi:10.1210/jc.2008-2534
4. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. Apr 2012;119(4):789-801. doi:10.1016/j.ophtha.2011.12.039
5. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology*. Jun 2016;123(6):1351-9. doi:10.1016/j.ophtha.2016.02.022
6. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. Oct 2014;121(10):1904-14. doi:10.1016/j.ophtha.2014.04.024
7. Mishra SK, Sinha S, Chauhan R, Kumar A. Intravitreal Dexamethasone Implant versus Intravitreal Ranibizumab Injection for Treatment of Non-Proliferative Diabetic Macular Edema: A Prospective, Randomized and Blinded Trial. *Curr Drug Deliv*. 2021;18(6):825-832. doi:10.2174/1567201817666201202093637
8. Sun JK, Beaulieu WT, Melia M, et al. Defining "Strong" Versus "Weak" Response to Antivascular Endothelial Growth Factor Treatment for Center-Involved Diabetic Macular Edema. *Retina*. Apr 1 2023;43(4):616-623. doi:10.1097/IAE.0000000000003730
9. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. Apr 2011;118(4):615-25. doi:10.1016/j.ophtha.2011.01.031
10. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology*. Nov 2010;117(11):2146-51. doi:10.1016/j.ophtha.2010.08.016
11. Augustin AJ, Kuppermann BD, Lanzetta P, et al. Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. *BMC Ophthalmol*. Oct 30 2015;15:150. doi:10.1186/s12886-015-0148-2

12. Fraser-Bell S, Lim LL, Campain A, et al. Bevacizumab or Dexamethasone Implants for DME: 2-year Results (The BEVORDEX Study). *Ophthalmology*. Jun 2016;123(6):1399-401. doi:10.1016/j.ophtha.2015.12.012
13. Callanan DG, Loewenstein A, Patel SS, et al. A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol*. Mar 2017;255(3):463-473. doi:10.1007/s00417-016-3472-1

# Figures

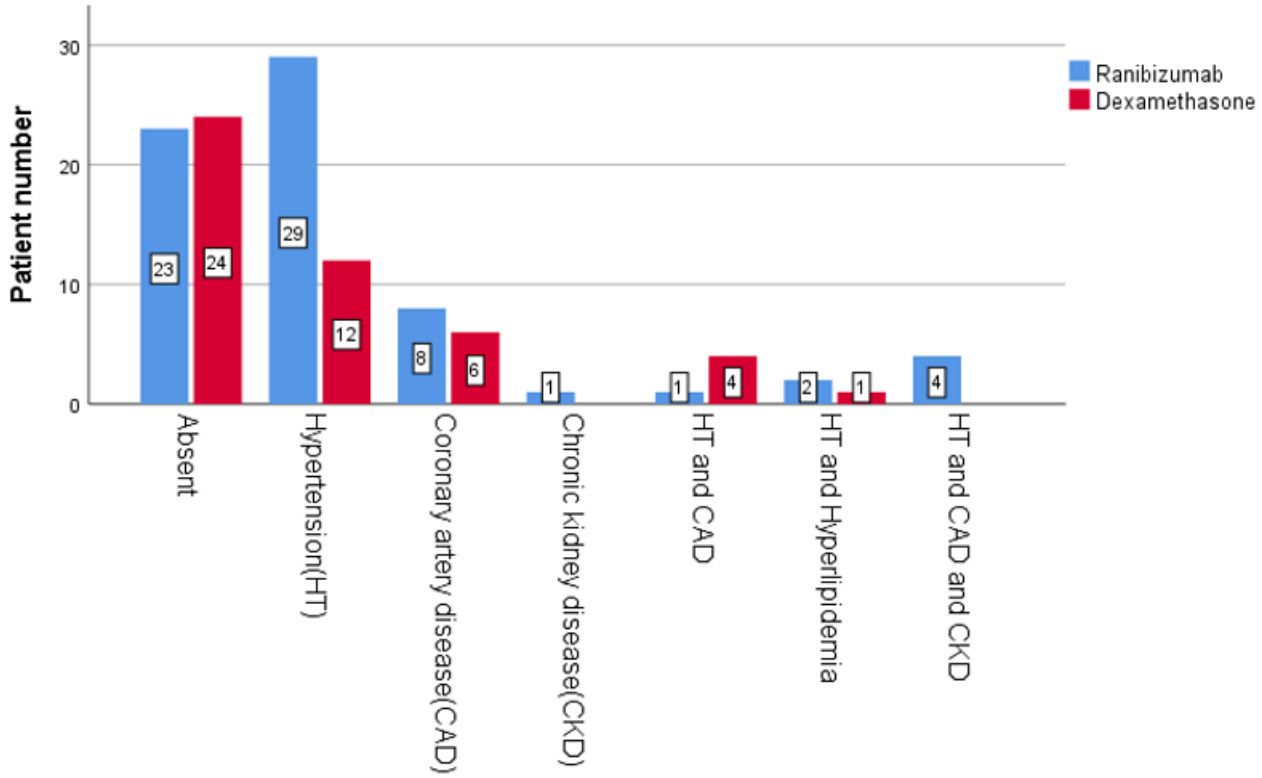



**Figure 1**

Distribution of baseline comorbidities between the groups

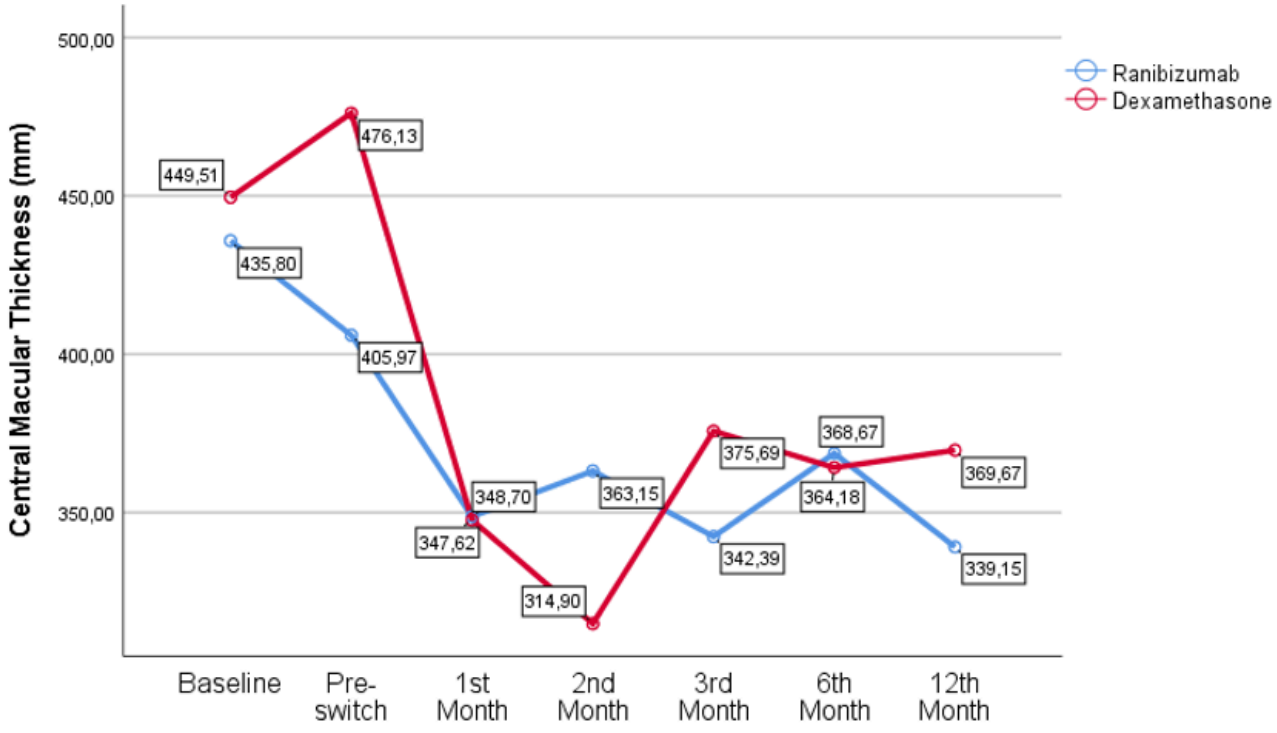



**Figure 2**

Longitudinal changes in central macular thickness in the IVR and IVD groups during 12 months of follow-up

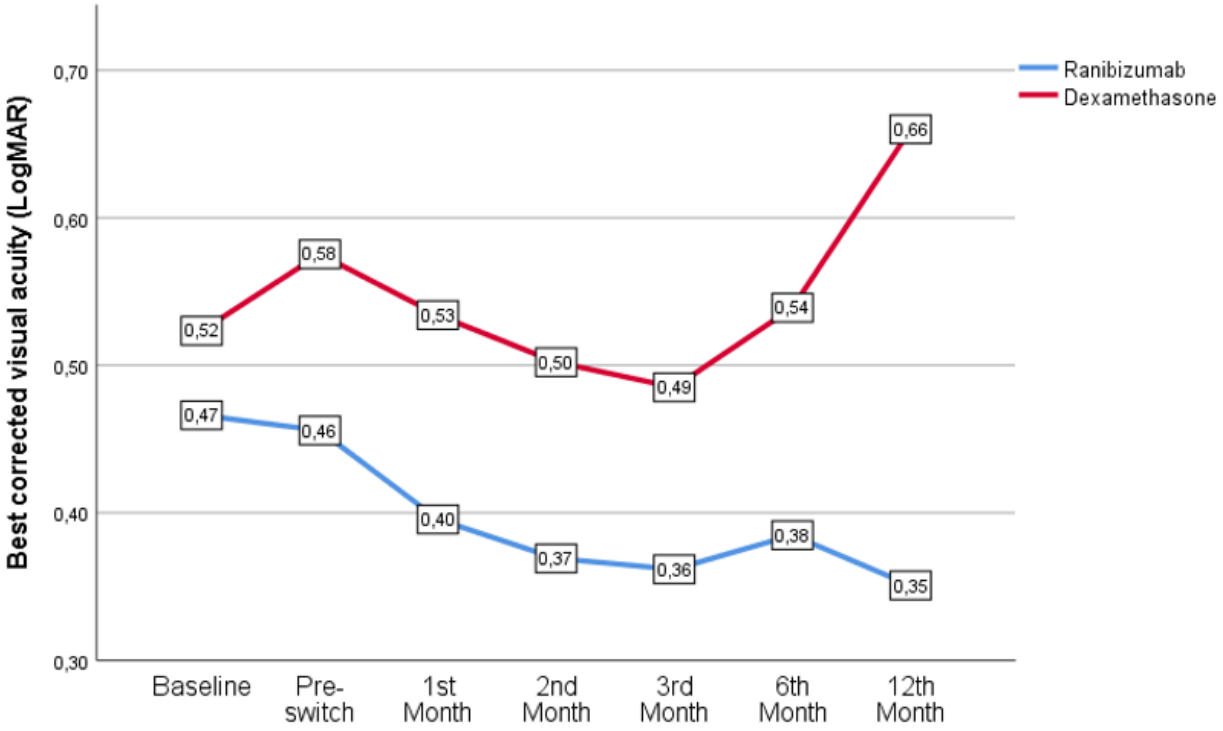



**Figure 3**

Longitudinal changes in best corrected visual acuity in the IVR and IVD groups during 12 months of follow-up