Clinical Ophthalmology Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Comparative Analysis of Intravitreal Dexamethasone Implant (Ozurdex) and Brolucizumab Injection in the Treatment of Diabetic Macular Edema with Hyperreflective Intraretinal Dots: A Retrospective Study

Somnath Chakraborty[1], Jay Umed Sheth[2]

[1]Department of Vitreoretinal Services, Retina Institute of Bengal, Siliguri, West Bengal, India; [2]Department of Vitreoretinal Services, Shantilal Shanghvi Eye Institute, Mumbai, Maharashtra, India

Correspondence: Somnath Chakraborty, Senior Consultant, Department of Vitreoretinal Services, Retina Institute of Bengal, Siliguri, West Bengal, India, Email somnathboom@gmail.com

Purpose: This retrospective study aimed to compare the efficacy and safety of intravitreal Dexamethasone Implant (DEX) and Brolucizumab Injection in treating Diabetic Macular Edema (DME) with Hyperreflective Intraretinal Dots (HRID).

Patients and Methods: A single-center retrospective study in India included 40 eyes (20 per group) with controlled diabetes and HRID on optical coherence tomography. Patients received either DEX or Brolucizumab, with outcomes assessed at various intervals up to 24 weeks. Primary measures included Best-Corrected Visual Acuity (BCVA), Central Macular Thickness (CMT), and safety parameters.

Results: Both treatment groups demonstrated comparable baseline characteristics. Both treatments significantly improved the BCVA at weeks 4, 12, and 24, with the DEX implant showing significantly better results at week 12 than brolucizumab (P=0.04). In treatment-naïve eyes, BCVA improvements were similar across all time points. In recalcitrant DME eyes, DEX showed significant BCVA improvements at all time points, while brolucizumab showed significant improvements only at weeks 4 (P=0.005) and 24 (P=0.04). The CMT also improved with both treatments, with DEX showing superior reduction at weeks 4 (P=0.003), 12 (P=0.003), and 24 (P=0.002) respectively. In treatment-naïve eyes, DEX showed consistently better CMT reductions. In refractory DME eyes, both treatments significantly reduced CMT, with DEX performing better at week 12 (P=0.042). DEX required fewer injections (DEX: 1.5±0.61; brolucizumab: 2.4±0.82; P=0.0002) and less supplementary laser treatment (DEX:8/20, 40% eyes; brolucizumab: 16/20, 80%; P=0.01) compared to brolucizumab. No adverse events were observed in either group.

Conclusion: The study suggests the potential superiority of intravitreal DEX implant over brolucizumab in managing DME with HRID. DEX exhibited sustained positive responses in BCVA and CMT, requiring fewer injections and supplementary interventions. Future research should explore extended follow-up durations, personalized treatment strategies, and refined biomarkers to optimize DME management.

Keywords: diabetic macular edema, dexamethasone implant, Ozurdex, brolucizumab, hyperreflective intraretinal dots

Introduction

Diabetic Macular Edema (DME) is a leading cause of vision impairment in individuals with diabetes mellitus (DM), posing a significant global health burden.[1,2] Its multifactorial pathogenesis, marked by vascular endothelial dysfunction and chronic inflammation, often leads to fluid accumulation within the macula, precipitating visual impairment if left unchecked.[2] While several treatment modalities have emerged over the years, managing recalcitrant cases, especially those characterized by hyper-reflective intraretinal dots (HRID), presents a clinical challenge.[3]

Received: 6 August 2024
Accepted: 30 September 2024
Published: 15 October 2024

As the prevalence of diabetes continues to escalate globally, the burden of DME is poised to rise, necessitating effective and tailored therapeutic approaches. In the past two decades, the management landscape for DME has witnessed remarkable advancements, particularly with the advent of intravitreal pharmacotherapy.[2,4] Among the diverse array of therapeutic options available, two primary classes of drugs have emerged as key players in the treatment of DME: anti-vascular endothelial growth factor (anti-VEGF) agents and steroids.[2,4] Anti-VEGF agents, including bevacizumab, ranibizumab, aflibercept, brolucizumab, and faricimab have gained prominence in the treatment of DME.[2,4–8] By directly inhibiting VEGF, these agents aim to curtail abnormal angiogenesis, reduce vascular leakage, and mitigate the pathological changes associated with macular edema.[1] Despite their success, challenges persist in the long-term management of DME with anti-VEGF therapies. The need for frequent intravitreal injections, potential tachyphylaxis, and the financial burden associated with sustained treatment raises questions about the feasibility and sustainability of these regimens.[2,4] Intravitreal injections of steroids, such as triamcinolone acetonide, or sustained-release implants like dexamethasone (DEX), target the inflammatory cascade involved in DME pathophysiology.[2,4,9,] By mitigating inflammation and stabilizing the blood-retinal barrier, steroids aim to reduce edema and preserve visual function.[9] While steroids present an alternative avenue for DME management, concerns about potential side effects, including elevated intraocular pressure and cataract formation, necessitate careful consideration.[9–13] The balance between therapeutic efficacy and safety becomes pivotal in the selection of steroid therapies.[4,12,14]

The HRID observed on optical coherence tomography (OCT) in DME reflects various pathological changes that occur within the retina.[3] The presence of these HRIDs within the retinal layers has been linked to increased disease severity and resistance to conventional treatments.[3] The exact nature of HRID can vary, and they may represent different components, including lipid-laden macrophages, fibrin deposits, exudation, or inflammatory cells, such as activated microglia or macrophages.[2,3] Dexamethasone, by virtue of its anti-inflammatory action, is postulated to quell the microglial activation and inflammatory cells associated with these dots.[2,3] Brolucizumab, a single-chain humanized antibody fragment, on the other hand, reduces vascular permeability in DME, therefore contributing to the mitigation of the vascular abnormalities underlying the formation of these dots.[5,6]

In this study, we will delve into our clinical experience with twenty eyes each treated with a DEX implant and brolucizumab, shedding light on the anatomical and functional outcomes observed in the context of HRID in treatment-naïve DME.

Materials and Methods

This was a retrospective study conducted at a single tertiary eye care center in India, from January 2023 to January 2024. The study was approved for conduct by the Institutional Review Board of the Retina Institute of Bengal in Siliguri, India, and was carried out in accordance with the tenets outlined in the Declaration of Helsinki. Written consent was obtained from all patients before intravitreal therapy and data collection.

Design

All patients aged ≥ 18 years with controlled diabetic status (glycated hemoglobin ≤ 8%), and the presence of center-involving treatment-naïve DME or previously treated center-involving recalcitrant DME with HRID were included in the study. Discrete and well-circumscribed intraretinal particles, ranging from 20 to 40 μm in diameter, were defined as HRID. These dots exhibited equal or higher reflectivity when compared to the retinal pigment epithelium (RPE) band on SD-OCT. A masked retina specialist (S.C.) manually counted the number of HRIDs on the SD-OCT. Any vitreoretinal pathology other than DR, severe media opacities that prevented the observation of the ocular fundus, and a history of any retinal surgery, systemic vasculitis, or uveitis were among the exclusion criteria.

The included patients were explained the choice of both brolucizumab and the DEX implant, and the final decision about the choice of therapy was based on the physician's discretion. All intravitreal injections were performed under strict aseptic conditions in the operating room. The patients were reviewed on days 1, 7, 30, 90, and 180 post-intravitreal therapy. At each visit, a detailed ocular evaluation was performed, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), anterior and posterior segment examination, and SD-OCT. The decision to re-treat the patient was made based on the pro re nata (PRN) rationale.

Outcome Measures

Changes in BCVA and central macular thickness (CMT) on days 30, 90, and 180 from baseline were the study's primary outcome measures. Additionally, the resolution of the subretinal fluid (SRF) and intraretinal fluid (IRF) was assessed. A detailed safety analysis was performed too.

Statistical Analysis

The statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean and mean ± Standard deviation (SD) for continuous variables. The Paired-*t* test was used to assess the changes in the BCVA, CMT, and IOP from the baseline. *P* values < 0.05 indicated statistical significance.

Results

Study Cohort

Twenty eyes each with DME having HRIDs were treated with brolucizumab and DEX implant. The mean age of the study participants in both groups was comparable (brolucizumab: 56.16 [± 6.14] years; DEX: 55.15 [± 5.83] years; *P*=0.61). In terms of gender distribution, both groups were nearly identical, with a majority of participants being males (brolucizumab- M: F = 14:6; DEX- M: F = 13:7). In both the groups, there were 11 eyes each which were previously treated and 9 eyes each that were treatment-naïve. The demographic characteristics of the study population are outlined in Table 1.

Best-Corrected Visual Acuity

At baseline, both the groups had comparable BCVA (*P*=0.9). Both arms demonstrated significant visual improvements at the end of weeks 4 (Brolucizumab: *P*<0.0001; DEX: *P*<0.0001), 12 (Brolucizumab: *P*=0.002; DEX: *P*<0.0001), and 24 (Brolucizumab: *P*=0.001; DEX: *P*<0.0001) respectively. The BCVA was significantly better in eyes that were treated with the DEX implant compared to those that were treated with brolucizumab at weeks 12 (*P*=0.04), but not at weeks 4 (*P*=0.83) and weeks 24 (*P*=0.13) respectively.

In treatment-naïve eyes, both the groups were comparable in terms of BCVA at baseline (*P*=0.6), and weeks 4 (*P*=0.26), 12 (*P*=0.13), and 24 (*P*=0.06) respectively. The BCVA improved significantly from the baseline in both arms at weeks 4, 12, and 24 respectively.

In recalcitrant DME eyes, no significant difference in BCVA was seen between both the groups at baseline (*P*=0.54), and at weeks 4 (*P*=0.22), 12 (*P*=0.15), and 24 (*P*=0.81) respectively. For eyes treated with the DEX implant, a significant improvement in BCVA was noted at week 4 (*P*=0.003), which was maintained at weeks 12 (*P*=0.005), and 24 (*P*=0.003) respectively. In the recalcitrant DME eyes treated with the brolucizumab, however, although the BCVA improvement achieved statistical significance levels at weeks 4 (*P*=0.005) and 24 (*P*=0.04), the visual improvement was not significant at week 12 (*P*=0.09). The BCVA results for the study population are summarized in Tables 2–4.

Table 1 Demographic Characteristics of the Study Population

Characteristic	Brolucizumab Arm	DEX Arm	*P* value
Age (years)			
Mean (±SD)	56.16 (± 6.14)	55.15 (± 5.83)	0.612
Gender			
Male	14 (70%)	13 (65%)	0.8
Females	6 (30%)	7 (35%)	
Treatment Status			
Treatment-naïve DME	9 (45%)	9 (45%)	
Recalcitrant DME	11 (55%)	11 (55%)	

Abbreviations: SD, Standard deviation; DEX, Dexamethasone; DME, Diabetic Macular Edema.

Table 2 Changes in the Best-Corrected Visual Acuity (BCVA) in the Study Population Through 24 weeks

		Brolucizumab Arm BCVA (logMAR)	P value (Intra-group)	DEX Implant Arm BCVA (logMAR)	P value (Intra-group)	P value between the Groups
Baseline	Median (IQR)	0.8 (0.6–1)	NA	0.8 (0.6–1)	NA	0.899
4 weeks		0.5 (0.3–0.6)	<0.0001	0.3 (0.3–0.5)	<0.0001	0.83
12 weeks		0.6 (0.35–0.75)	0.002	0.5 (0.23–0.6)	<0.0001	0.038
24 weeks		0.3 (0.3–0.58)	0.001	0.3 (0.23–0.)	<0.0001	0.134

Abbreviations: BCVA, Best-corrected visual acuity; DEX, Dexamethasone; logMAR, Logarithm of the Minimum Angle of Resolution; IQR, Interquartile range.

Table 3 Changes in the Best-Corrected Visual Acuity (BCVA) in the Treatment-Naïve Diabetic Macular Edema Eyes Through 24 weeks

		Brolucizumab Arm BCVA (logMAR)	P value (Intra-group)	DEX Implant Arm BCVA (logMAR)	P value (Intra-group)	P value between the Groups
Baseline	Median (IQR)	0.8 (0.8–1)	NA	0.8 (0.7–1)	NA	0.6
4 weeks		0.5 (0.3–0.6)	0.007	0.3 (0.3–0.5)	0.007	0.263
12 weeks		0.6 (0.4–0.7)	0.011	0.5 (0.2–0.55)	0.011	0.125
24 weeks		0.3 (0.2–0.55)	0.011	0.3 (0.2–0.3)	0.007	0.061

Abbreviations: BCVA, Best-corrected visual acuity; DEX, Dexamethasone; logMAR, Logarithm of the Minimum Angle of Resolution; IQR, Interquartile range.

Table 4 Changes in the Best-Corrected Visual Acuity (BCVA) in the Recalcitrant Diabetic Macular Edema Eyes Through 24 weeks

		Brolucizumab Arm BCVA (logMAR)	P value (Intra-group)	DEX Implant Arm BCVA (logMAR)	P value (Intra-group)	P value between the Groups
Baseline	Median (IQR)	0.6 (0.6–0.8)	NA	0.8 (0.6–1)	NA	0.538
4 weeks		0.5 (0.3–0.6)	0.005	0.5 (0.3–0.5)	0.003	0.218
12 weeks		0.6 (0.3–0.8)	0.085	0.5 (0.3–0.6)	0.005	0.153
24 weeks		0.3 (0.3–0.6)	0.036	0.3 (0.3–0.5)	0.003	0.805

Abbreviations: BCVA, Best-corrected visual acuity; DEX, Dexamethasone; logMAR, Logarithm of the Minimum Angle of Resolution; IQR, Interquartile range.

Central Macular Thickness

At baseline, both the groups had comparable CMT (P=0.264). However, after the treatment, the CMT reduction was significantly better with the DEX implant compared to brolucizumab injections at weeks 4 (P=0.003), 12 (P=0.003), and 24 (P=0.002) respectively. Both the groups showed significant improvement in the CMT at weeks 4 (Brolucizumab: P<0.0001; DEX: P<0.0001), 12 (Brolucizumab: P=0.001; DEX: P<0.0001), and 24 (Brolucizumab: P<0.0001; DEX: P<0.0001) respectively, from the baseline.

In the treatment-naïve group, although the CMT was comparable between the groups at baseline (P=0.653), at all the subsequent visits, the CMT reduction was better with the DEX implant as compared to brolucizumab (weeks 4: P=0.034; week 12: P=0.046; week 24: P=0.008). In the DEX implant group, the CMT reduction was significant at all the visits (weeks 4: P<0.0001; week 12: P=0.0401; week 24: P<0.0001). However, for the treatment-naïve eyes receiving brolucizumab injection, the CMT reduction was significant at week 4 (P=0.015) and week 24 (P=0.006), but not at week 12 (P=0.065).

In the refractory DME eyes, both the arms showed significant reduction in the CMT from the baseline at all the visits (weeks 4: DEX- P<0.0001, brolucizumab- P<0.0001; week 12: DEX- P=0.005, brolucizumab- P=0.002; week 24: DEX- P<0.0001, brolucizumab- P<0.0001). On comparing both the groups, the CMT difference was not significant at baseline (P=0.252), and at weeks 4 (P=0.063) and 24 (P=0.065). However, the CMT reduction at week 12 was significantly better

with the DEX implant compared to brolucizumab (*P*=0.042). A summary of the CMT outcomes for the study population is provided in Tables 5–7.

Additional Treatment

The mean number of DEX implants was 1.5 (± 0.61), with eight eyes (40%) requiring a second dose and one eye (5%) requiring a third dose of the implant. In the brolucizumab arm, 12 eyes (60%) received three doses of the injection, while four eyes (20%) each received two doses and one dose respectively. The mean number of injections was found to be significantly lower with the DEX implant in comparison to brolucizumab amongst all the study eyes (*P*=0.0002), and also in treatment-naïve (*P*=0.002) and refractory DME (*P*=0.01) eyes. Supplementary focal laser was required significantly more in brolucizumab eyes (16/20; 80%) compared to DEX implant eyes (8/20; 40%; *P*=0.01).

Safety Analysis

There were no observed ocular or systemic adverse events in either group, including intraocular inflammation (IOI), increased IOP, or the development of cataracts.

Figures 1 and 2 are representative cases illustrating the OCT changes after intravitreal DEX implant and brolucizumab.

Table 5 Changes in the Central Macular Thickness (CMT) in the Study Population Through 24 weeks

		Brolucizumab Arm CMT (µm) (Mean ± SD)	*P* value (Intra-group)	DEX Implant Arm CMT (µm) (Mean ± SD)	P value (Intra-group)	P value between the Groups
Baseline	Median	485.6 ± 91.52	NA	457.7 ± 60.58	NA	0.264
4 weeks	(IQR)	337.55 ± 87.11	<0.0001	272 ± 20.92	<0.0001	0.003
12 weeks		408.80 ± 84.64	0.001	329.4 ± 75.72	<0.0001	0.003
24 weeks		331 ± 67.41	<0.0001	275.25 ± 28.64	<0.0001	0.002

Abbreviations: CMT, Central macular thickness; DEX, Dexamethasone; IQR, Interquartile range.

Table 6 Changes in the Central Macular Thickness (CMT) in the Treatment-Naïve Diabetic Macular Edema Eyes Through 24 weeks

		Brolucizumab Arm CMT (µm) (Mean ± SD)	*P* value (Intra-group)	DEX Implant Arm CMT (µm) (Mean ± SD)	P value (Intra-group)	P value between the Groups
Baseline	Median	494.44 ± 101.31	NA	475 ± 76.62	NA	0.653
4 weeks	(IQR)	344 ± 80.53	0.015	274.33 ± 27.11	<0.0001	0.034
12 weeks		408.66 ± 70.49	0.065	333.33 ± 76.74	0.001	0.046
24 weeks		328.11 ± 49.16	0.006	269.55 ± 23.58	<0.0001	0.008

Abbreviations: CMT, Central macular thickness; DEX, Dexamethasone; IQR, Interquartile range.

Table 7 Changes in the Central Macular Thickness (CMT) in the Recalcitrant Diabetic Macular Edema Eyes Through 24 weeks

		Brolucizumab Arm CMT (µm) (Mean ± SD)	*P* value (Intra-group)	DEX Implant Arm CMT (µm) (Mean ± SD)	P value (Intra-group)	P value between the Groups
Baseline	Median	478.36 ± 87.04	NA	443.54 ± 42.26	NA	0.252
4 weeks	(IQR)	332.27 ± 95.71	<0.0001	271.63 ± 15.5	<0.0001	0.063
12 weeks		408.9 ± 98.16	0.005	326.18 ± 78.46	0.002	0.042
24 weeks		333.36 ± 81.78	<0.0001	279.9 ± 32.57	<0.0001	0.065

Abbreviations: CMT, Central macular thickness; DEX, Dexamethasone; IQR, Interquartile range.

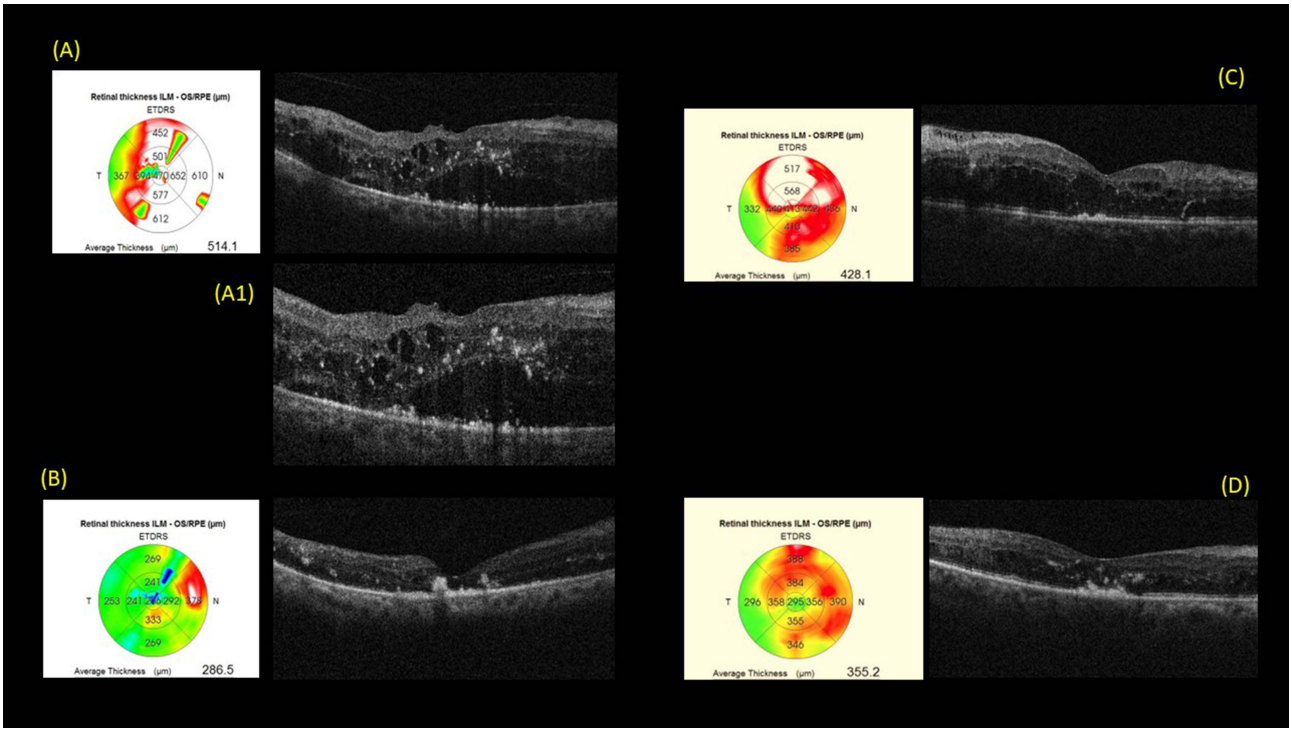

Figure 1 Spectral domain optical coherence tomography of the left eye of a patient with Diabetic macular edema (DME) showing presence of intraretinal cystoid changes, subretinal fluid, and presence of hyperreflective intraretinal dots at baseline (**A**). A magnified view to highlight the hyper-reflective foci (A1). One month after intravitreal brolucizumab therapy, there was significant reduction in the quantum of DME (**B**). However there was a recurrence noted at week 12 (**C**) for which second dose of brolucizumab was given. At 24 weeks, there was persistent DME (**D**) for which further injections were advised.

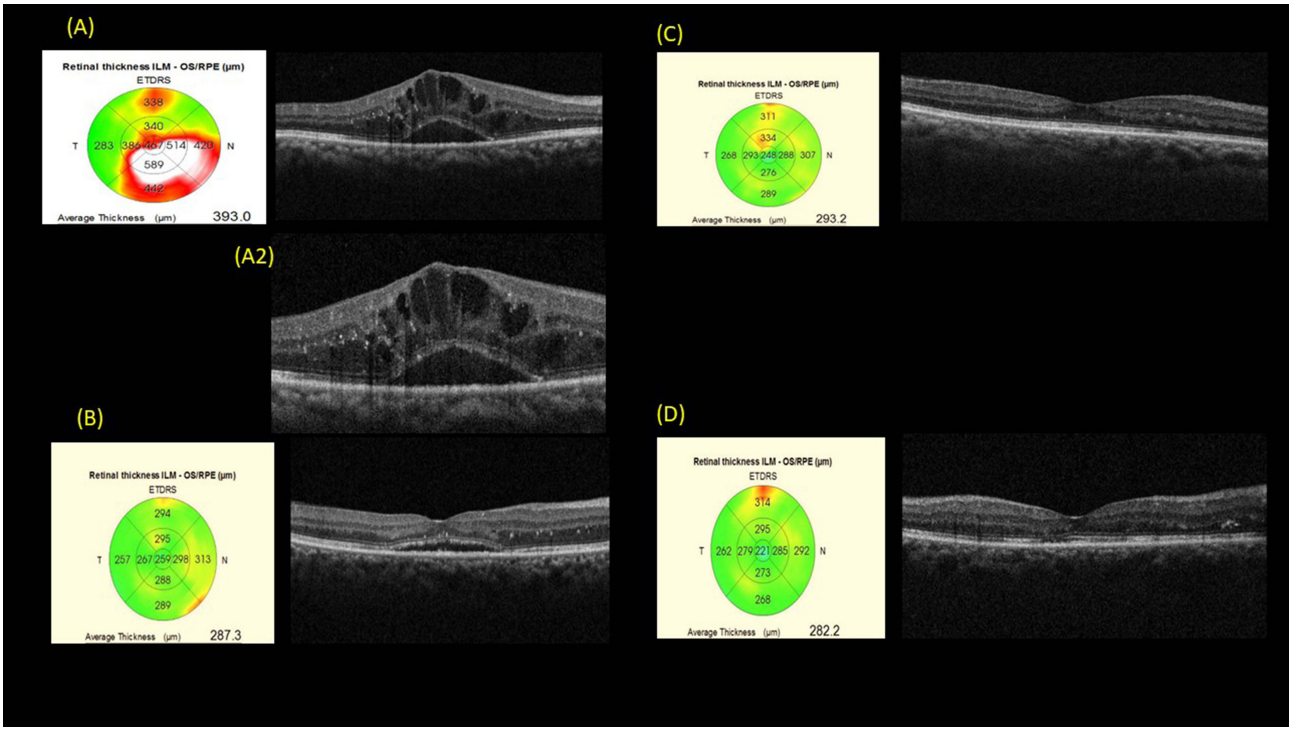

Figure 2 Spectral domain optical coherence tomography of the right eye of a patient with Diabetic macular edema (DME) with presence of hyperreflective intraretinal dots (**A**). A magnified view to highlight the hyper-reflective foci (A2). After a single dose of intravitreal dexamethasone implant, there was a significant reduction in Edema at 4 weeks (**B**), which resolved completely at 12 weeks (**C**), and was maintained upto week 24 (**D**).

Discussion

DME is a complex and multifaceted condition, and its management continues to evolve with the advent of novel therapeutic agents. This retrospective study aimed to compare the efficacy and safety of intravitreal DEX implant and brolucizumab injection in the treatment of DME with HRID. Our investigation contributes to the growing body of knowledge surrounding the optimal management of DME, especially in cases characterized by HRID, and sheds light on the potential advantages of steroids over anti-VEGF agents.

DME results from a cascade of events triggered by chronic hyperglycemia, leading to vascular endothelial dysfunction and subsequent breakdown of the blood-retinal barrier.[1] The presence of HRIDs on OCT has been associated with increased disease severity and resistance to conventional treatments.[3] The majority of these studies have pathological changes within the retina, may include lipid-laden macrophages, fibrin deposits, exudation, or inflammatory cells such as activated microglia or macrophages.[3] Understanding the nature of HRID is crucial for tailoring effective therapeutic interventions.

The findings of our study reveal distinct anatomical and functional outcomes in eyes treated with DEX implants compared to those receiving brolucizumab. The baseline characteristics of the study population were well-matched, emphasizing the reliability of the comparative analysis. One of the key parameters evaluated was the visual outcomes. Both treatment groups showed comparable BCVA at baseline, reflecting a similar level of visual impairment. However, compared to the brolucizumab arm, the visual acuity improvement with the DEX implant was significantly better amongst all the study eyes and the recalcitrant DME at weeks 12, indicating a sustained positive response lasting upto three months. This disparity in visual outcomes aligns with the known anti-inflammatory properties of steroids. Dexamethasone, by mitigating inflammation and stabilizing the blood-retinal barrier, may have a more pronounced impact on the microglial activation and inflammatory cells associated with HRID.[9,] This aligns with existing literature suggesting that the anti-inflammatory effects of steroids contribute to improved visual acuity in DME. Several additional studies have conducted comparisons between the DEX implant and anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) for the treatment of DME with HRID.[7,8,12–17] The majority of these studies have shown that the DEX implant exhibits a similar level of superiority to the current study.[3,12,13] The lack of previous studies comparing brolucizumab with the DEX implant highlights the novelty and importance of this current study. Demonstrating a similar superior efficacy of steroids opens up possibilities for alternative treatment options for patients with DME and HRID. Further research and clinical trials are needed to confirm these findings and explore the long-term effects and safety profiles of these treatments.

The CMT is a crucial parameter in assessing macular edema severity. The DEX implant group demonstrated significantly lower CMT levels at all the follow-up visits compared to the brolucizumab group. The greater reduction in CMT observed in the DEX implant group supports the idea that steroids may have a more profound impact on the underlying inflammatory processes driving DME. Steroids, by suppressing inflammation, potentially address multiple components contributing to HRID formation, including fibrin deposits and inflammatory cell infiltration.[10]

The study also explored the treatment frequency and additional interventions required during the 24-week duration. The DEX implant group required significantly fewer injections compared to the brolucizumab group in all study eyes, and also amongst the treatment-naïve and recalcitrant DME eyes. Only 9 out of 20 eyes (45%) in the DEX group needed a repeat implant, highlighting the sustained therapeutic effect of the steroid. In contrast, the brolucizumab group received an average of 2.4 injections per eye, indicating the need for more frequent administration. The reduced injection frequency with DEX implant aligns with concerns related to the sustainability and financial burden associated with frequent anti-VEGF injections. This difference in the number of injections has implications for patient compliance, convenience, and healthcare resource utilization. Moreover, in the brolucizumab group, 80% of eyes required supplementary focal laser photocoagulation, which was significantly more compared to the DEX implant group. This additional intervention suggests that despite the anti-VEGF action of brolucizumab, the inflammatory component contributing to HRID may not be adequately addressed.

Although identification of HRID is easy, differentiating it from hard exudates can be challenging in the case of DME. HRIDs can be differentiated from hard exudates by the absence of back shadowing.[15] Unlike hard exudates, which have

the ability to absorb light and obstruct tissue signals below, HRIDs do not exhibit this characteristic.[16] Also, in contrast to hard exudates, which are primarily found near the outer plexiform layer on OCT, HRDs are dispersed across the retinal layers.[15] Furthermore, it should be noted that HRIDs may be observed in diabetic individuals who do not exhibit evident signs of retinopathy.[16] This suggests that the blood-retinal barrier remains intact, effectively preventing the intra-retinal migration of RPE cells.[16,17] Therefore, the most probable rationale for HRDs is to reflect the appearance of stimulated microglia and other inflammatory cells.[16,17] Hence, the most plausible explanation for the occurrence of HRIDs is their derivation from activated microglia.[16,17] This suggests that targeting inflammation may be crucial in managing DME, particularly in cases with the presence of HRID.[15–17] Intravitreal steroids, as demonstrated in the study, exhibit a more robust impact in reducing inflammation, leading to superior anatomical and visual outcomes when compared to anti-VEGF treatments.

The safety profile of both treatments was favorable, with no observed ocular or systemic adverse events. This includes the absence of intraocular inflammation (IOI), increased IOP, or the development of cataracts. The lack of adverse events underscores the safety of both treatment modalities in the context of our study population. Nonetheless, a larger-scale, long-term prospective study is warranted to comprehensively evaluate the safety profiles and compare them with existing literature.

The limited sample size of 20 eyes per treatment group in our study poses a limitation, affecting the generalizability and statistical power of the findings. Additionally, being a retrospective study, inherent biases, and confounding variables might influence the outcomes. The 24-week follow-up period, while sufficient for observing certain outcomes, may not capture the long-term safety and efficacy of these interventions. Longer follow-up periods are essential to assess sustained treatment effects and potential late-onset adverse events. The study's exclusion criteria, including pre-existing retinal pathologies, may limit the representation of the broader population of DME patients. Furthermore, the relatively homogenous patient population might not reflect the diversity seen in real-world clinical settings. Also, the decision-making process for selecting either brolucizumab or the dexamethasone implant was based on the physician's discretion. This introduces a potential bias that could impact the comparability of the two groups. Finally, conducting the study in a single tertiary eye care center in India might limit the extrapolation of findings to other geographic regions or healthcare settings with different patient demographics and disease characteristics.

Future studies should incorporate extended follow-up durations to assess the long-term safety and durability of treatment effects. This is particularly relevant given the chronic nature of DME and the potential for late-onset adverse events. Also, conducting prospective, randomized trials with larger sample sizes and standardized treatment protocols would strengthen the evidence base. Randomized allocation would mitigate selection bias, providing more robust comparisons between dexamethasone implant and brolucizumab. Stratifying analyses based on diabetic retinopathy severity and other relevant patient characteristics can enhance our understanding of treatment responses and safety profiles in specific subgroups. We also recommend further exploring HRID as a biomarker for treatment response and disease progression which could aid in tailoring personalized treatment strategies. Correlating HRID characteristics with clinical outcomes may guide individualized therapeutic approaches.

Conclusion

In conclusion, our comparative analysis of intravitreal DEX implant and brolucizumab in the treatment of DME with HRID suggests a potential superiority of the steroid approach. The dexamethasone implant demonstrated better visual and anatomical outcomes, requiring fewer injections and showing a more rapid and sustained effect on the macular thickness. These findings align with the existing literature on the role of steroids and anti-VEGF agents in managing DME, emphasizing the need for a balanced consideration of therapeutic efficacy and safety. Future directions should focus on refining biomarkers, exploring combination therapies, leveraging advanced imaging techniques, and explore individualized treatment strategies to further optimize DME management strategies.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gupta N, Mansoor S, Sharma A, et al. Diabetic retinopathy and VEGF. *Open Ophthalmol J*. 2013;7:4–10. doi:10.2174/1874364101307010004
2. Bandello F, Battaglia Parodi M, Lanzetta P, et al. Diabetic macular edema. *Dev Ophthalmol*. 2017;58:102–138.
3. Huang H, Jansonius NM, Chen H, Los LI. Hyperreflective dots on OCT as a predictor of treatment outcome in diabetic macular edema: a systematic review. *Ophthalmol Retina*. 2022;6(9):814–827. doi:10.1016/j.oret.2022.03.020
4. Chauhan MZ, Rather PA, Samarah SM, Elhusseiny AM, Sallam AB. Current and novel therapeutic approaches for treatment of diabetic macular edema. *Cells*. 2022;11(12):1950. doi:10.3390/cells11121950
5. Chakraborty S, Sheth JU. Contralateral effect following intravitreal brolucizumab injection in diabetic macular edema. *Case Rep Ophthalmol Med*. 2022;2022:3755249. doi:10.1155/2022/3755249
6. Chakraborty D, Sheth JU, Boral S, Sinha TK. Off-label intravitreal brolucizumab for recalcitrant diabetic macular edema: a real-world case series. *Am J Ophthalmol Case Rep*. 2021;24:101197. doi:10.1016/j.ajoc.2021.101197
7. McCloskey CF, Mongan AM, Chetty S, McAteer DMJ, Quinn SM. Aflibercept in diabetic macular oedema previously refractory to standard intravitreal therapy: an Irish retrospective study. *Ophthalmol Ther*. 2018;7(1):173–183. doi:10.1007/s40123-018-0123-0
8. Laiginhas R, Silva MI, Rosas V, et al. Aflibercept in diabetic macular edema refractory to previous bevacizumab: outcomes and predictors of success. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(1):83–89. doi:10.1007/s00417-017-3836-1
9. Fraser-Bell S, Kang HK, Mitchell P, Arnold JJ, Tainton J, Simonyi S. Dexamethasone intravitreal implant in treatment-naïve diabetic macular oedema: findings from the prospective, multicentre, AUSSIEDEX study. *Br J Ophthalmol*. 2023;107(1):72–78. doi:10.1136/bjophthalmol-2021-319070
10. Sharma A, Sheth J, Madhusudan RJ, Sundaramoorthy SK. Effect of intravitreal dexamethasone implant on the contralateral eye: a case report. *Retin Cases Brief Rep*. 2013;7(3):217–219. doi:10.1097/ICB.0b013e31828993a1
11. Sharma A, Sheth J. Intravitreal dexamethasone implant for macular edema following uncomplicated phacoemulsification. *Eur J Ophthalmol*. 2015;25(3):e5. doi:10.5301/ejo.5000559
12. He Y, Ren XJ, Hu BJ, Lam WC, Li XR. A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema. *BMC Ophthalmol*. 2018;18(1):121. doi:10.1186/s12886-018-0779-1
13. Rübsam A, Wernecke L, Rau S, et al. Behavior of SD-OCT detectable hyperreflective foci in diabetic macular edema patients after therapy with anti-VEGF agents and dexamethasone implants. *J Diabetes Res*. 2021;2021:8820216. doi:10.1155/2021/8820216
14. Vujosevic S, Toma C, Villani E, et al. Diabetic macular edema with neuroretinal detachment: OCT and OCT-angiography biomarkers of treatment response to anti-VEGF and steroids. *Acta Diabetol*. 2020;57:287–296. doi:10.1007/s00592-019-01424-4
15. Ceravolo I, Oliverio GW, Alibrandi A, et al. The application of structural retinal biomarkers to evaluate the effect of intravitreal ranibizumab and dexamethasone intravitreal implant on treatment of diabetic macular edema. *Diagnostics*. 2020;10(6):413. doi:10.3390/diagnostics10060413
16. Vujosevic S, Bini S, Midena G, Berton M, Pilotto E, Midena E. Hyperreflective intraretinal spots in diabetics without and with nonproliferative diabetic retinopathy: an in vivo study using spectral domain OCT. *J Diabetes Res*. 2013;2013:491835. doi:10.1155/2013/491835
17. Vujosevic S, Simó R. Local and systemic inflammatory biomarkers of diabetic retinopathy: an integrative approach. *Invest Ophthalmol Vis Sci*. 2017;58(6):BIO68–BIO75. doi:10.1167/iovs.17-21769