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Brolucizumab versus aflibercept for recalcitrant diabetic macular edema in Indian real-world scenario – The BRADIR study

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ABSTRACT

Purpose: To compare the safety and efficacy of aflibercept with brolucizumab for recalcitrant diabetic macular edema (DME).

Observations: At week 52, no significant visual improvement was noted in the eyes treated with either brolucizumab ($P = 0.527$) or aflibercept ($P = 0.393$). The CMT decreased significantly after brolucizumab therapy ($P = 0.012$), but not with aflibercept ($P = 0.284$) at 52 weeks. The proportion of patients with IRF and SRF reduced significantly in both arms. The mean number of brolucizumab injections was significantly lower (3.93[±1.28]) than aflibercept (4.75[±1.62]) ($P = 0.037$) over the 52 weeks. At 52 weeks, 76.67 % of eyes treated with brolucizumab attained full macular dryness (CMT<300 μm with absence of SRF and IRF) compared to 50 % of eyes treated with aflibercept ($P = 0.036$). Subconjunctival hemorrhage was the only adverse event observed in the study ($P = 0.701$); no other systemic or ocular adverse events, such as intraocular inflammation, were reported.

Conclusion and importance: The BRADIR study suggests that brolucizumab might have an edge over aflibercept in visual and anatomical outcomes that lasted 52 weeks with reduced injection frequency in case of recalcitrant DME.

1. Introduction

Diabetes mellitus (DM), a chronic metabolic condition, is afflicting populations worldwide at an unprecedented speed.[1] There were 463 million diabetics worldwide in 2019, with diabetic retinopathy (DR) affecting 30 % of them.[1,2] The prevalence of diabetes has rapidly increased in lower-middle-income countries (LMICs), and it is estimated that India's prevalence will surge from 9.6 % in 2021 to 10.8 % by 2045.[2] Microvascular complications, such as diabetic macular edema (DME), are common in patients with DM.[3] It is one of the primary factors contributing to vision impairment in the working-age population.[1,2]

Currently, anti-vascular endothelial growth factor (VEGF) medications are the first-line treatment for DME involving the center.[4] By re-establishing the blood-retina barrier's integrity, these agents reduce edema along with improving vision.[3] However, to maintain the visual and structural benefits, these anti-VEGF drugs must be given at regular intervals over time. This poses a substantial financial and logistical burden, not only on the patients but also on the healthcare system as a whole. This highlights the need for novel molecules and treatment regimens that can produce sustained effects with reduced injection frequency and increased patient adherence. Aflibercept (AFL; Eylea®, Regeneron, Tarrytown, NY), brolucizumab (BRZ; Beovu®, Novartis), and faricimab (Roche/Genentech, Basel, Switzerland) are among the longer-acting medications that have received approval from the US Food and Drug Administration (US-FDA) for the treatment of DME.[4,5] In the phase III clinical studies KITE and KESTREL, Brolucizumab 6 mg is compared to Aflibercept 2 mg for eyes with center-involving DME (ci-DME) over a period of 2 years.[6] The interim 52-week analysis demonstrated that brolucizumab was non-inferior to aflibercept therapy in terms of visual acuity improvement.[6] In addition, the eyes that were

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treated with brolucizumab exhibited superior anatomical outcomes with an encouraging benefit-risk ratio.[6]

While randomized controlled trials (RCTs) remain the gold standard for evaluating the efficacy and safety of medical interventions, real-world evidence is becoming increasingly important in complementing RCTs by providing valuable insights into treatment outcomes in more diverse patient populations and clinical settings.[7,8] Real-world evidence is especially useful in understanding the utility of medical interventions for patients with multiple comorbidities who may be excluded from RCTs due to strict exclusion criteria.[7,8] Furthermore, real-world evidence can also provide information on the long-term effectiveness and safety of treatments, which may not be captured in the relatively short follow-up periods of RCTs. With the increasing availability of electronic health records and other large databases, real-world evidence has become more accessible and feasible to collect and analyze.

Due to their rigorous methodology and delivery conditions, RCTs like KITE and KESTREL offer valuable evidence for ci-DME management[6]; nevertheless, the outcomes from these controlled scenarios are rarely duplicated in real-world settings. Furthermore, in a real-world context, the retinal physician is more likely to encounter a mix of treatment-naive and previously treated eyes with refractory DME. While the phase III DME trials only evaluated treatment-naive patients, there is no evidence comparing the brolucizumab and aflibercept molecules in recalcitrant eyes.[6] To address this knowledge gap, in this study, the authors compare and report the 52-week visual and anatomical outcomes of the two anti-VEGF agents for recalcitrant DME in a real-world setting. The study also examines the safety profiles of the two agents and provides valuable insights for clinicians in selecting the most appropriate treatment option for their patients with recalcitrant DME.

2. Materials and methods

2.1. Study design

The BRADIR study was a retrospective, single-center, medical chart review performed at a tertiary eye care institute in India. The study was approved by the Ethics Committee and adhered to the tenets of Declaration of Helsinki, Good Clinical Practice guidelines and International Council for Harmonization. Each participant signed a written informed consent form granting permission for treatment and collection of data.

2.2. Study population

All consecutive patients who presented to the Department of Vitreoretina of the Institute between February 2021 to October 2021 and were followed up for twelve months from the day of first injection, with Type 1 or Type 2 DM, an age of $\geq$18 years, a controlled diabetes status (HbA1C $\leq$ 8 mg/dl), and recalcitrant DME were eligible for inclusion in the study. Patients were excluded from the study if they had any vitreoretinal pathology other than DR, media opacities obscuring fundus evaluation, previous anti-VEGF injection (bevacizumab/ranibizumab) within 30 days of the presentation, prior history of laser photocoagulation (macular/panretinal), and a history of any retinal surgery, a systemic inflammatory disorder, or uveitis. a subpar reduction in CMT (less than 15 %) over the past six months after at least three anti-VEGF injections or the presence of IRF and or SRF.[9,10] Patients were treated by 10 fellowship-trained retina specialists.

2.3. Treatment

All eligible patients included in the study were given information on both treatment alternatives, namely aflibercept, and brolucizumab. After weighing the benefits and risks of each anti-VEGF medication, the patient made an informed decision and freely chose that particular molecule. The patient underwent intravitreal injection (IVI) of aflibercept (2 mg in 0.05 mL) or brolucizumab (6 mg in 0.05 mL) under strict aseptic conditions. Topical 0.5 % moxifloxacin eye drops were advised for one-week post-injection. Following the treatment, the patients were evaluated on days one and seven, and subsequently at four weekly intervals (±3 days). Any additional treatments were done "pro-re-nata (PRN)" basis based on fixed criteria: When an eye lost one Snellen line of vision, had persistent edema (CMT >300 μm), or experienced a CMT worsening or improvement of less than 15 %, it received an additional course of therapy. At every visit, the physician recorded specifics about any ocular or systemic side effects the patient had experienced. Additionally, the following evaluation was done at each visit: best corrected visual acuity (BCVA) on a Snellen chart, intraocular pressure (IOP) with Goldmann applanation tonometer (AT), anterior segment evaluation using a slit-lamp biomicroscope, fundus examination using the slit lamp biomicroscope (+90D lens) and indirect ophthalmoscopy (+20D lens), and spectral-domain optical coherence tomography (SD-OCT) was performed at all the visits. From the electronic medical database, the demographic, clinical, and imaging data from the baseline and weeks four, 12, 24, 36, and 52 were retrieved. We used Zeiss Cirrus 5000 (Carl Zeiss Meditec, Dublin, CA, USA) for acquiring the images. Macular Cube protocol was used which acquires 128 B-scans each composed of 512 A-scans. CMT was measured using built in software.

2.4. Outcome measures

The outcome measures were the visual and anatomical response of aflibercept and brolucizumab in terms of changes in BCVA, CMT, and proportion of eyes with intraretinal (IRF) and subretinal (SRF) respectively. Additionally, a detailed safety analysis was performed too. Two independent graders (D.C., S.M) performed all image analyses. Whenever there were differences, the graders re-evaluated the images and reached a mutually agreed-upon conclusion.

2.5. Statistical analysis

The Statistical analysis was performed by SPSS 23.0 version. For statistical analysis, Snellen BCVA measurements were converted to logMAR BCVA. Categorical variables were described by taking percentages (analyzed using the Chi-Square test). Continuous variables were described as mean and variation of each observation from the mean value (Standard deviation) represented as mean ± SD (analyzed using independent *t*-test) if they followed a normal distribution and were described as Median (IQR) if they followed a non-normal distribution (analyzed using Mann Whitney *U* Test). Continuous Paired data were analyzed using Wilcoxon Signed Rank Test (For non-normal distribution). Paired categorical data were analyzed using the McNemar test. Variables with a P value < 0.05 were considered statistically significant.

3. Results

3.1. Study cohort

Fifty-eight eyes of 58 patients with recalcitrant DME were included in the study. Thirty of these eyes were treated with IVI brolucizumab, while the remaining 28 were treated with IVI aflibercept. Both groups were comparable in terms of age (brolucizumab: 64.7 [±8.86] years; aflibercept: 66 [±9.45] years; $P = 0.59$) and gender distribution ($P = 0.18$). The mean number of injections before switching was likewise comparable between the two groups (brolucizumab: 7.63 [±0.89]; aflibercept: 7.54 [±1.04]; $P = 0.35$). The details of the previous anti-VEGF therapy regimen was not known in a majority of the patients, since most of them were referred cases. Table 1 provides the demographic and baseline information about the study participants.

Table 1
Demographic characteristics of the study population.

Baseline Data			Brolucizumab (N = 30)	Aflibercept (N = 28)	P value
Age (years)		Mean ± SD	64.7 ± 8.86	66 ± 9.45	0.592
Gender	Males	Number	24 (80)	18 (64.3)	0.181
	Females	(Percentage)	6 (20)	10 (35.7)	
Number of Injections		Mean ± SD	3.93 ± 1.28	4.75 ± 1.62	**0.037**

Abbreviations: SD, Standard deviation.

3.2. Best-corrected visual acuity

There was no significant difference between the two groups in the BCVA at baseline ($P = 0.236$) or any of the subsequent visits up to week 52 ($P = 0.247$). In the aflibercept arm, the median BCVA improved until week 24 (P = 0.078), after which it returned to its baseline levels at 36 weeks (P = 0.474), and dropped further at 52 weeks (P = 0.527). However, none of these BCVA changes in the aflibercept arm were statistically significant. At the same time, for eyes that received brolucizumab injections, the BCVA improved significantly at week 24 ($P = 0.006$), but the significance level was not maintained at week 52 ($P = 0.393$). The BCVA results for the study eyes are outlined in Table 2 and Fig. 1.

3.3. Central macular thickness

Both groups were comparable in the CMT at baseline ($P = 0.441$) and all subsequent visits ($P = 0.276$). In the aflibercept group, the CMT decreased significantly at weeks 4 ($P = 0.003$) and 12 ($P = 0.013$); however, in subsequent visits, even though the CMT decreased, the significance level was not maintained. In contrast, the CMT improved at all visits from baseline in the brolucizumab arm, which was significant at all visits except week 24 (52-week: $P = 0.012$). Table 3 provides the CMT findings from the study population and Fig. 2 provides the box plot illustrating the CMTchanges.

3.4. Subretinal and intraretinal fluid

The proportion of patients with IRF and SRF were comparable between groups at baseline and all subsequent visits up to 52 weeks (IRF-Baseline: $P = 0.464$; 52-week: $P = 0.113$; SRF- Baseline: $P = 0.905$; 52-week: $P = 0.453$). After receiving brolucizumab therapy, the percentage of patients with IRF and SRF significantly decreased at 12 (IRF: $P < 0.001$; SRF: $P < 0.001$), 24 (IRF: $P < 0.001$; SRF: $P = 0.002$), and 52 (IRF: $P < 0.001$; SRF: $P = 0.001$) weeks. Similarly, the IRF and SRF reduction was significant even after aflibercept therapy at all visits, except for the SRF reduction at week 24 ($P = 0.092$). Tables 4 and 5 demonstrate the changes in the IRF and SRF status of the study eyes throughout the course of 52 weeks.

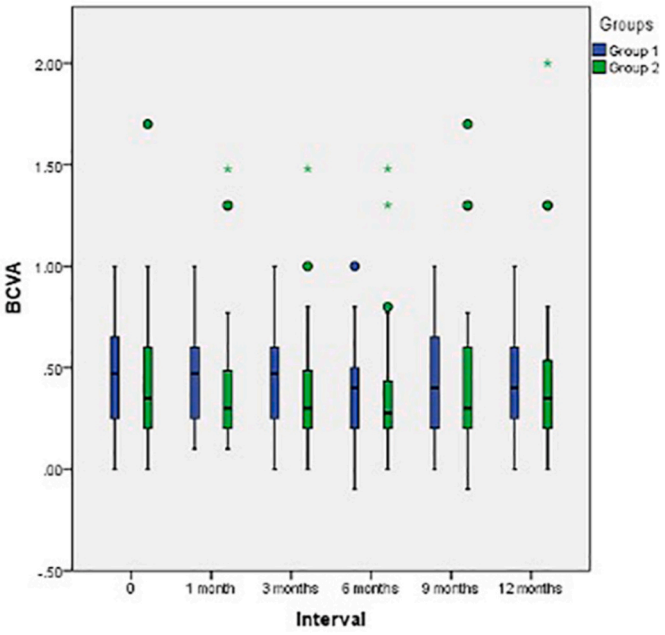

Fig. 1. Box plot illustrating the best-corrected visual acuity (BCVA) changes in both the groups (Group 1: Brolucizumab; Group 2: Aflibercept) through week 52.

3.5. Macular morphology

When compared, at 52 weeks, 76.67 % of eyes treated with brolucizumab achieved complete macular dryness (CMT≤300 μm with absence of SRF and IRF), in contrast to only 50 % of eyes treated with aflibercept ($P = 0.036$).

3.6. Number of injections

The mean number of brolucizumab injections administered during the study was significantly lower than the number of aflibercept injections (Brolucizumab: 3.93 [±1.28]; Aflibercept: 4.75 [±1.62]; $P = 0.037$). Figs. 3 and 4 show two examples of cases of recalcitrant DME being treated with brolucizumab and aflibercept, respectively.

3.7. Safety analysis

Subconjunctival hemorrhage was encountered in 3 eyes (10 %) treated with brolucizumab and 4 eyes (14.3 %) treated with aflibercept respectively ($P = 0.7$). No additional ocular or systemic adverse events, including intraocular inflammation (IOI), were observed in both study groups during 52 weeks.

Table 2
Best-corrected visual acuity changes in both the groups through 52 weeks.

BCVA		Brolucizumab (N = 30)	P value Intragroup compared with baseline	Aflibercept (N = 28)	P value Intragroup compared with baseline	P value between 2 groups
Baseline	Median	0.47 (0.25–0.65)	NA	0.3 (0.2–0.6)	NA	0.236
4 weeks	(IQR)	0.47 (0.24–0.6)	0.265	0.27 (0.2–0.5)	0.795	0.183
12 weeks		0.47 (0.25–0.6)	0.1	0.27 (0.2–0.477)	0.132	0.25
24 weeks		0.4 (0.2–0.525)	**0.006**	0.275 (0.2–0.417)	0.078	0.288
36 weeks		0.4 (0.2–0.65)	0.221	0.3 (0.2–0.6)	0.474	0.429
52 weeks		0.4 (0.25–0.61)	0.393	0.35 (0.2–0.502)	0.527	0.247

Abbreviations: BCVA, Best-corrected visual acuity; IQR, Interquartile range.

Table 3
Central macular thickness (CMT) changes in both the groups through 52 weeks.

CMT		Brolucizumab (N = 30)	P value Intragroup compared with baseline	Aflibercept (N = 28)	P value Intragroup compared with baseline	P value between 2 groups
Baseline	Median (IQR)	295.5 (243–367.5)	NA	323.5 (232.25–392.25)	NA	0.441
4 weeks		235.5 (217.25–265.25)	**<0.001**	251 (206.75–344.25)	**0.003**	0.375
12 weeks		231 (221–282.75)	**0.019**	236 (206.75–355.25)	**0.013**	0.828
24 weeks		249.5 (219–369.5)	0.133	243.5 (209–368.75)	0.083	0.919
36 weeks		236 (218–287.25)	**0.029**	283.5 (197.5–364.5)	0.151	0.35
52 weeks		243 (210.5–292.5)	**0.012**	246 (221.5–338.25)	0.284	0.276

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

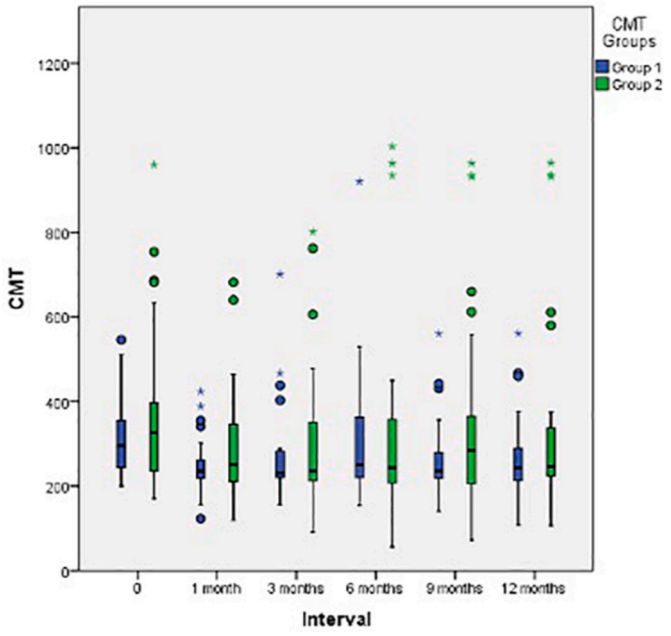

Fig. 2. Box plot illustrating the central macular thickness (CMT) changes in both the groups (Group 1: Brolucizumab; Group 2: Aflibercept) through week 52.

4. Discussion

In this first study comparing the efficacy and safety of aflibercept and brolucizumab for recalcitrant DME, the authors observed a superior anatomical response along with significantly fewer injections in the brolucizumab arm at 52 weeks. At the same time, visual improvement was comparable in both arms, with significant gains reported only with brolucizumab at 24 weeks. Additionally, both molecules had a favorable safety profile, with SCH being the only adverse event reported, and no IOI incidents occurring.

Visual impairment in DME is brought on by swelling or thickening of the foveal retinal tissue.[1,3] The management of DME has evolved significantly over the years, with modalities such as intravitreal anti-VEGF injections and corticosteroid implants proving to be more effective than the traditional gold standard of the grid and focal laser photocoagulation.[11–13] These newer treatments have been shown to be more effective in improving visual acuity and reducing macular thickness, leading to better outcomes for patients with DME.[11–13] Aflibercept and brolucizumab are among the more recent anti-VEGF molecules that have demonstrated excellent efficacy and reduced the overall therapeutic burden as a result of their extended half-life and durability.[6] Phase III KITE and KESTREL studies comparing brolucizumab to aflibercept for treating DME demonstrated that brolucizumab was non-inferior to aflibercept at the primary endpoint in the intermediate 52-week analysis.[6] It was shown that brolucizumab led to significant improvements in both vision and retinal morphology.[6] In the current study, patients treated with brolucizumab experienced improvements in their vision that lasted up to 52 weeks. However, in the aflibercept group, despite improvements in VA up to 24 weeks, the final VA at 52 weeks was lower than the baseline. This indicates that the benefits of brolucizumab may be more sustained over time compared to aflibercept. Additionally, brolucizumab was found to be generally well-tolerated with a low incidence of serious adverse events in this study. The most common adverse events reported were typical for intravitreal injections, such as sub-conjunctival hemorrhage.[14]

Some patients with DME show persistent fluid despite intensive anti-VEGF treatment. In the case of these patients, switching anti-VEGF medications or starting intravitreal corticosteroid treatment is strongly recommended.[15–17] It has been shown that intravitreal steroids are beneficial for recalcitrant DME; nevertheless, their use is associated with side effects including the development of cataracts and elevated IOP.[16,17] Meanwhile, refractory DME has been demonstrated to benefit greatly from switching to longer-acting anti-VEGF medications such as aflibercept, brolucizumab, or faricimab.[4,5,15] Thus, anti-VEGF

Table 4
Changes in the proportion of patients with subretinal fluid in the study eyes through 52 weeks.

SRF		Brolucizumab (N = 30)	P value Intragroup compared with baseline	Aflibercept (N = 28)	P value Intragroup compared with baseline	P value between 2 groups
Baseline	Number (Percentage)	21 (70)	NA	20 (71.4)	NA	0.905
12 weeks		6 (20)	**<0.001**	10 (35.7)	**0.006**	0.181
36 weeks		9 (30)	**0.002**	13 (46.4)	0.092	0.198
52 weeks		7 (23.3)	**0.001**	9 (32.1)	**0.001**	0.453

Abbreviations: SRF, Subretinal fluid.

Table 5
Changes in the proportion of patients with intraretinal in the study eyes through 52 weeks.

IRF		Brolucizumab (N = 30)	P value Intragroup compared with baseline	Aflibercept (N = 28)	P value Intragroup compared with baseline	P value between 2 groups
Baseline	Number	27 (90)	NA	23 (82.1)	NA	0.464
12 weeks	(Percentage)	6 (20)	**<0.001**	8 (28.6)	**<0.001**	0.446
36 weeks		8 (26.7)	**<0.001**	11 (39.3)	**<0.001**	0.306
52 weeks		7 (23.3)	**<0.001**	12 (42.9)	**0.001**	0.113

Abbreviations: IRF, Intraretinal fluid.

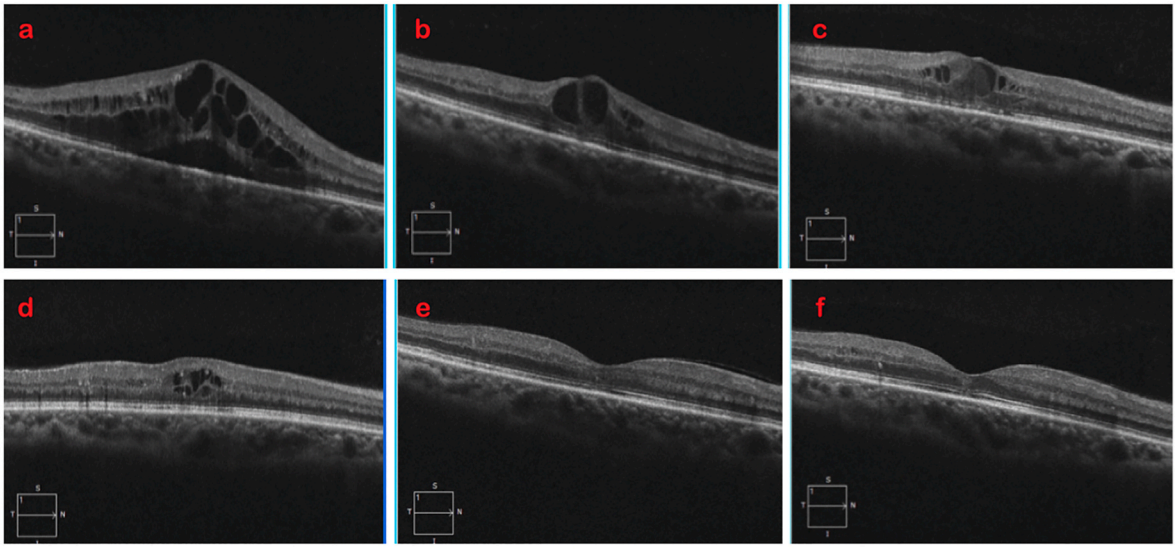

Fig. 3. Representative case of recalcitrant diabetic macular edema (DME) demonstrating improvement on the spectral-domain optical coherence tomography (SD-OCT) (a-at baseline, b 1months, c 3 months, d- 6 months, e−9 months, f-12 months) after intravitreal brolucizumab, which were given at baseline, 3 months 6 months and 9 months. The patients had previously received 6 ranibizumab injections over 9 months.

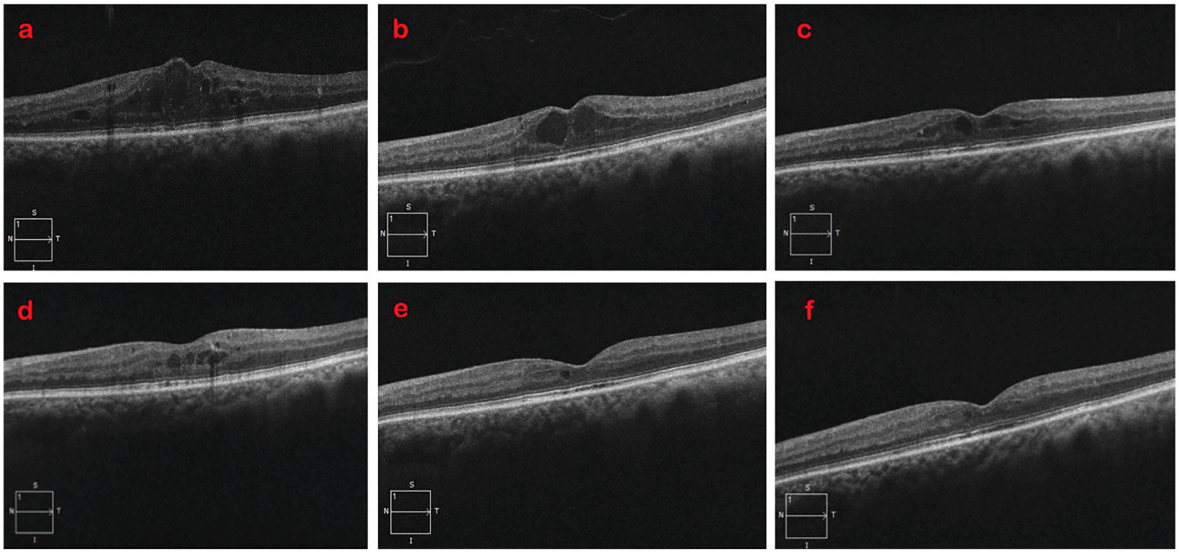

Fig. 4. Representative case of recalcitrant diabetic macular edema (DME) having undergone 5 ranibizumab injections over 7 months, demonstrating improvement on the spectral-domain optical coherence tomography (SD-OCT) after aflibercept therapy over 52 weeks. (a-at baseline, b-1months, c- 3 months, d- 6 months, e−9 months, f- 12 months). Patient received aflibercept injections at baseline, 4 and 8 weeks and 12 weekly thereafter.

medications are difficult to replace as first-line therapy for the management of DME, whether in treatment-naive or recalcitrant cases, because of the side effects associated with corticosteroids. In the present study, the eyes in both arms had received an average of more than seven injections prior to the switch. Upon switching, the macular thickness decreased in both arms over the course of the study. However, in the

aflibercept group, this improvement was significant only up to week 12, whereas the significance level was maintained through week 52 with the brolucizumab molecule. Based on fluid compartment stratification, 23.3 % of the eyes each had residual SRF and IRF 52 weeks after the brolucizumab injection. In contrast, after aflibercept therapy, residual SRF and IRF were detected in 32.1 % and 42.9 % of the eyes, respectively. Furthermore, brolucizumab was found to have a lower injection frequency compared to aflibercept, with patients receiving brolucizumab requiring fewer injections over the course of the study. This may lead to improved patient compliance and overall treatment satisfaction. Further research is needed to determine its place in the current treatment landscape and optimize dosing and administration.

Brolucizumab is a single-chain humanized antibody fragment with a relatively low molecular weight of 26 kDa compared to other anti-VEGF compounds such as bevacizumab (149 kDa), ranibizumab (48 kDa), and aflibercept (110 kDa).[18] Brolucizumab's molecular weight is 4 times lower than aflibercept and 1.8 times lower than ranibizumab, allowing for a far greater molar dose to be administered (12-fold vs. 22-fold) than with the former two drugs, respectively.[18–20] Additionally, when brolucizumab binds to VEGF-A, the ratio is 2:1; nevertheless, even when the ratio is reduced to 1:1 over a period of time, it continues to completely block VEGF-A.[18–20] This makes brolucizumab a highly potent anti-VEGF therapy with the potential to reduce the number of injections needed to maintain efficacy in treating DME. Our findings validate these molecular characteristics by exhibiting improved visual and structural outcomes with fewer doses of brolucizumab than aflibercept. Thus, brolucizumab therapy decreases the burden of treatment on patients and healthcare systems while maintaining favorable outcomes.

Addressing the safety profile, the possibility of IOI is a concern with anti-VEGF agents, particularly brolucizumab. IOI was 4 % for brolucizumab and 1 % for aflibercept in the HAWK and HARRIER studies.[19] Brolucizumab 6 mg both had a 3.7 % and 1.7 % IOI rate in the KESTREL and the KITE studies respectively, while aflibercept had a 0.5 % and 1.7 % IOI rate respectively.[6] In our real-world investigation, however, we found that neither group experienced any IOI occurrences throughout the course of the entire 52-week period. Additional ocular or systemic adverse effects too were not reported in our study. In summary, our study conducted on brolucizumab for the treatment of DME shows promising results, but the limitations of the smaller sample size and shorter follow-up period need to be acknowledged. Longer-term safety data is necessary to fully assess the risk of adverse events associated with the drug. Nonetheless, the study adds to the growing body of evidence supporting the safety of brolucizumab as a treatment option for patients with DME.

Our study is limited by its retrospective design, lack of randomization potentially leading to selection bias, small sample size, lack of sample size calculation, and the use of the PRN regimen without an initial loading dose. The study aimed to improve the accessibility of treatment for individuals from lower-middle-income countries (LMICs), and the selection of the PRN regimen was a step toward achieving this goal. Therefore, the PRN regimen was considered a suitable option for the study participants due to its cost-effectiveness and flexibility, which aimed to improve their access to effective treatment and address the challenges they faced.

5. Conclusion

In summary, the BRADIR study has found that brolucizumab is an effective treatment option for recalcitrant DME, resulting in both visual and anatomical improvement lasting up to 52 weeks. Conversely, aflibercept did not exhibit significant improvement in macular thickness or visual acuity at the final visit. Moreover, brolucizumab also has a favorable safety profile and requires fewer injections than aflibercept for the treatment of recalcitrant DME. This finding may be particularly important for patients with limited financial resources or those who rely on government-funded healthcare systems. To summarize, findings from the BRADIR study indicates brolucizumab as a promising therapeutic alternative for recalcitrant cases of DME. It demonstrates a slight advantage over aflibercept in both visual and anatomical outcomes, sustained for 52 weeks, with a reduced injection frequency.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

CRediT authorship contribution statement

Debdulal Chakraborty: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ashish Sharma:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis. **Soumen Mondal:** Methodology, Data curation. **Jay Sheth:** Writing – review & editing, Writing – original draft, Validation. **Tushar Kanti Sinha:** Validation, Supervision. **Subhendu Boral:** Validation, Data curation. **Angshuman Mukherjee:** Investigation, Data curation. **Ranabir Bhattacharya:** Formal analysis, Data curation. **Ritobroto Maitra:** Formal analysis, Data curation.

Declaration of competing interest

AS has been a consultant for Novartis, Allergan, Bayer and Intas.

Other authors (DC, JS, SM, SB, AM, TKS, RB, RM) report there are no competing interests to declare.

Acknowledgments

Dr Debasish Bhattacharya, Chairman Disha Eye Hospitals, Kolkata, India.

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