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The efficacy of Intravitreal Brolucizumab versus Aflibercept in The Treatment of Diabetic Macular Edema

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ABSTRACT

Background: Diabetes patients frequently develop diabetic macular edema (DME), a microvascular complication that has become the leading cause of vision loss among the working adult population. In the diabetic retina, oxidative stress and chronic hyperglycemia lead to the upregulation of vascular endothelial growth factor (VEGF), which increases vascular permeability and breakdown of the inner blood-retinal barrier.

Objective: To compare the effect of intravitreal injection of brolucizumab and aflibercept (Eylea) in DME.

Patients and methods: The study was a randomized comparative prospective study that involved 62 eyes from 31 patients with DME who were randomly allocated into two groups using alternate assignment. Eyes in group I were treated with intravitreal injection of 2mg/0.05 mL aflibercept and eyes in group II were treated with intravitreal injection of 6mg/0.05 mL brolucizumab.

Results: Central macular thickness (CMT) was significantly lower at 3 months (277 ± 74.11 μm, 346.6±244.61 μm) and at 1 month (381.5±98.46 μm, 424.27±208.1 μm) compared to baseline (519.13±99.69 μm, 576.53±163.97 μm) in the aflibercept (Eylea) and brolucizumab groups, respectively ($P < 0.05$). It is worth noting that CMT decreased significantly more in the aflibercept group compared to the brolucizumab group. Vision was significantly lower after 3 months (0.13±0.11, 0.27±0.28) and at 1 months (0.36±0.12, 0.45±0.18) compared to before injection (0.55 ±0.06, 0.60±0.15) among aflibercept (eylea) and Brolucizumab groups respectively ($P<0.05$), it is worth to mentioned that, the vision was significantly more decreased after injection among aflibercept (eylea) group compared to Brolucizumab group. Although complications were observed, there was no statistically significant difference in their incidence between the aflibercept and brolucizumab groups ($P > 0.05$).

Conclusion: Both central macular thickness (CMT) and best-corrected visual acuity (BCVA) improved following treatment. However, brolucizumab has been associated with a higher risk of intraocular inflammation, retinal vasculitis, and retinal vascular occlusion. The relative efficacy of anti-VEGF agents appears to depend on baseline visual acuity, highlighting the importance of individualized treatment selection.

Keywords: Intravitreal Brolucizumab, Aflibercept, DME**,** VEGF.

INTRODUCTION

In the diabetic retina, oxidative stress and hyperglycemia cause an upregulation of VEGF, which breaks down the inner blood-retinal barrier and increases vascular permeability. DME is a common microvascular complication in patients with diabetes and has emerged as the primary cause of vision loss in the adult working population [(1)].

Increased permeability of the retinal blood vessels results in exudation and buildup of extracellular fluid in the retinal layers, which are characteristics of DME. VEGF contributes to the pathophysiology and development of macular edema by breaking down the blood–retinal barrier and increasing vascular permeability [(2)].

DME, a kind of diabetic retinopathy, is one of the leading causes of visual loss and is steadily increasing in prevalence globally (4.07% according to data as of March 2020) [(1)]. VEGF contributes to the formation of DME and is crucial in diabetic retinopathy. Anti-VEGF treatments have therefore demonstrated effectiveness in DME, and since their debut, the amount of visual loss associated with DME has declined [(3,4)]. A protein called VEGF raises vascular permeability and encourages angiogenesis. Vascular expansion and edema, which are common in vascular retinal illnesses such diabetic retinopathy and DME, are mostly caused by VEGF [(5,6)].

Neovascular age-related macular degeneration (nAMD)-related blindness has been decreased because of the therapeutic application of anti-VEGF [(7)]. Numerous trials have demonstrated the benefits of treating DME by inhibiting VEGF by intravitreal injection of anti-VEGF drugs [(8)]. DME can be managed using a variety of methods, including pars plana vitrectomy, subthreshold micropulse diode laser photocoagulation, intravitreal corticosteroids, and focal or grid laser photocoagulation. VEGF intravitreal injections, however, are now the gold standard treatment for DME globally [(9)].

Diabetic macular edema (DME) can be managed using a variety of treatment modalities, including pars plana vitrectomy, subthreshold micropulse diode laser photocoagulation, intravitreal corticosteroids, and focal or grid laser photocoagulation. However, intravitreal anti-VEGF injections are currently considered the gold standard for DME treatment worldwide [(9)].

Preclinical and clinical studies have shown the importance of VEGF as a major mediator in DME and proliferative diabetic retinopathy, and anti-VEGF medications are currently the first-line treatment for DME. In order to cure ocular illnesses, anti-VEGF drugs were created, and a comprehensive clinical study demonstrated their beneficial benefits on DME [(10)].

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The dangers associated with intravitreal injection are well-defined and include endophthalmitis and temporary intraocular pressure rise. Numerous studies have examined the safety and effectiveness of intravitreal anti-VEGF injection in addition to the hazards associated with the injection itself. Retinal detachment, cataracts, endophthalmitis, increased intraocular pressure, vitreous hemorrhage, uveitis and ocular inflammation, floaters, and retinal vascular alterations are among the numerous ocular side effects linked to the intravitreal injection of these drugs that have been documented. Long-term anti-VEGF medication has also raised concerns about the possibility of glaucomatous optic neuropathy [(11)].

This study aimed to compare the effect of intravitreal injection of brolucizumab and aflibercept (Eylea) in DME.

PATIENTS AND METHODS

This randomized, comparative, prospective study included 62 eyes from 31 patients with diabetic macular edema (DME) who attended the Ophthalmology Department at Menoufia University Hospitals. The included subjects were randomly allocated using alternate assignment into two groups: Group 1 consisted of 32 eyes treated with an intravitreal injection of 2 mg/0.05 mL aflibercept, and Group 2 consisted of 30 eyes treated with an intravitreal injection of 6 mg/0.05 mL brolucizumab.

All the eyes were followed up at one and three months after the injection. The outcomes of the study were visual acuity, central subfield thickness.

Inclusion criteria: Patients aged 18 years or older with type 1 or type 2 diabetes mellitus (T1DM or T2DM), on a stable antidiabetic regimen for at least three months, and with visual impairment due to diabetic macular edema (DME) involving the center of the macula, as assessed by best-corrected visual acuity (BCVA) using Snellen's chart at four meters, were included.

Exclusion criteria: Patients were excluded if they had any ocular diseases in the study eye at screening, including cataract, vitreous hemorrhage, retinal vascular occlusion, or retinal detachment; any active intraocular or periocular infection or inflammation; iris neovascularization associated with vitreomacular traction; idiopathic or autoimmune uveitis; amblyopia; or prior treatment with anti-VEGF agents.

All study participants underwent comprehensive assessments:

Full history taking with emphasis on age, history of chronic diseases or eye diseases, history of eye trauma or eye operations, history of drug intake. A detailed ocular examination was undertaken, with BCVA measured using Snellen's Chart and then translated to log MAR using (visual acuity conversion tables). Intraocular pressure was measured using a Goldmann applanation tonometer and a Slit lamp examination, as well as a dilated fundus examination with +90 and +78 diopter Volk lenses and indirect ophthalmoscopy. Fundus fluorescein angiography was performed utilizing the Topcon fundus camera **(Figure 1A).** Diabetic foveal thickness using spectral domain tomography cirrus 5000 (Cirrus 5000 HD-Optical coherence Tomography), **(Figure 1A).**

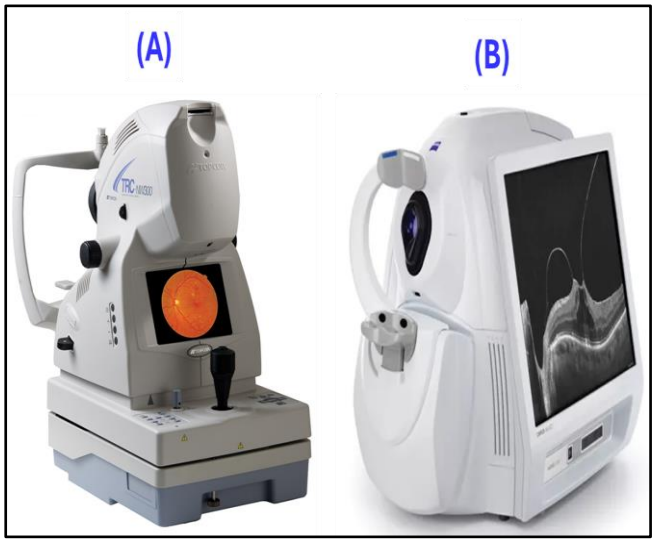

Figure (1): (a) Topcon fundus camera and (b) Cirrus 5000 HD-OCT.

Procedure for intravitreal injection

Both groups received injections of anti-VEGF drugs into their eyes, and the patients were monitored for one and three months following the treatment. Injections of 2 mg/0.05 mL aflibercept (Eylea; Regeneron Pharmaceuticals, NY, USA) and 6 mg/0.05 mL brolucizumab were administered to all eyes in both groups I and II, respectively. Prior to injection, 0.4% Benoxinate eye drops were used to produce topical anesthetics. The anti-VEGF medication was injected into the vitreous cavity following cleaning, draping, and appropriate topical anesthetic.

For intravitreal injection, a 27-gauge needle was utilized, positioned 4 mm from the limbus in phakic patients and 3.5 mm in pseudophakic patients. After the procedure, a visual assessment was conducted to make sure the intraocular pressure was not too high. Post-operative antibiotic eye drops, such as Tobramycin, were advised for three days.

Postoperatively

Three months following the injection, the patients were evaluated to determine their optimal BCVA. IOP, or intraocular pressure. The central macular thickness (CMT) was measured at one and three months using optical coherence tomography (OCT). Monthly loading injections should be administered to patients three times in a row. OCT (optional) should be collected at visits 1 and 3 to give early treatment response data, and visual acuity (VA) should be evaluated at each visit during the loading period. Eight weeks following the third loading dosage, the fourth dose is given (to determine the

duration of the next treatment interval, VA and OCT should be evaluated at visit 4 and at each consecutive visit). With active illness, the treatment interval is maintained after the fourth injection; with inactive disease, it is prolonged by two or four weeks. Based on certain criteria (loss of 5 ETDRS letters or more because of disease activity, IRF, new macular hemorrhage, and/or unstable SRF), the treatment interval can be shortened, maintained, or prolonged after the fifth injection.

Sample size estimation

Based on review of past literature conducted by **Brown *et al.*** [9] who found that KESTREL experienced 1.1% and 2.1% of ocular significant adverse events (brolucizumab 6 mg and aflibercept, respectively), while KITE experienced 2.2% and 1.7% of these events, respectively. A sample size of 32 (50 for each group) was determined using statistics and the Sample Size Pro software version 6. With a 95% confidence level, to satisfy the power of the study 80%.

***Ethical Consideration*:**

This study was ethically approved by Menoufia University's Faculty of Medicine (IRB approval id, 7/2023 OPHT-5). Written informed consent of all the participants' parents or guardians was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human subjects.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0. The Shapiro-Wilk test was used to confirm that the data had a normal distribution. While mean ± SD is used for quantitative data, standard deviation (standard deviation) and frequency are utilized for qualitative data. The X^2-test is used to compare qualitative category data. While comparing quantitative data that is consistently distributed (parametric) between two groups. Nonparametric data were compared using the Wilcoxon test. Statistical significance was defined as a two-tailed P value <0.05.

RESULTS

In the current study, 72 eyes from 36 patients with diabetic macular edema (DME) attended the Ophthalmology Clinics at Menoufia University Hospital**.** Ten eyes were excluded from the study (4 patients declined to give consent, and 6 did not meet the inclusion criteria). Out of the 62 eyes eligible for participation, 32 eyes in Group I were treated with an intravitreal injection of 2 mg/0.05 mL aflibercept, and 30 eyes in Group II received an intravitreal injection of 6 mg/0.05 mL brolucizumab.

In our study, age and sex were comparable between the studied patients (p>0.05), (not shown in table). In addition, baseline central macular thickness (CMT) did not show a statistically significant difference between the groups (P > 0.05) (Table 1).

However, CMT was significantly reduced at 3 months (277 ± 74.11 μm, 346.6 ± 244.61 μm) and at 1 months (381.5±98.46 μm, 424.27±208.1 μm) compared to baseline values (519.13±99.69 μm, 576.53±163.97 μm,) among aflibercept (eylea) and Brolucizumab groups respectively (P<0.05). Notably, the reduction in CMT was significantly greater in the aflibercept group compared to the brolucizumab group (Figure 2).

Table (1): A Comparison between CMT before injection after 1 and after 3 months of the studied groups.

Central macular thickness		**Aflibercept (Eylea) group (n=32)**	**Brolucizumab group (n=30)**	***P value***
Before injection	Mean ± SD	519.13 ± 99.69	576.53 ± 163.97	0.245
	Range	348 – 742	429 – 1078	
After 1 month of injection	Mean ± SD	381.5 ± 98.46	424.27 ± 208.1	0.466
	Range	228 – 584	228 - 1100	
After 3 months of injection	Mean ± SD	277 ± 74.11	346.6 ± 244.61	0.286
	Range	167 – 399	178 - 1194	
P value of paired test		P1=0.003*, P2=.001*, P3=.015*	P1=0.012*, P2=.001*, P3=.001*	

**Significant; P1: before injection Vs after 1-month; P2: before injection Vs after 3-months; P3: after 1-month Vs after 1-month*

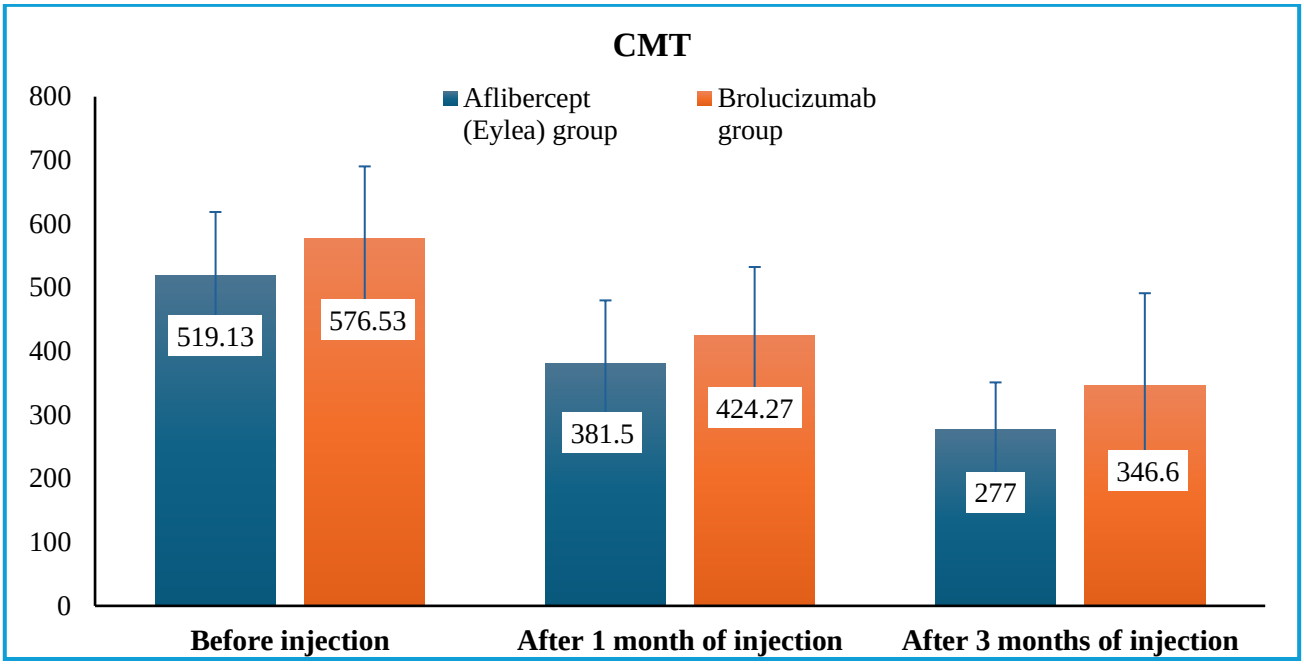

Figure (2): Distribution of CMT before injection compared to after 1 and 3 months of the studied groups.

In the same trend Vision was CMT did not significant differences among aflibercept (eylea) and Brolucizumab groups under study (p>0.05), **(Table 2).** However, it was significantly lower after 3 months (0.13±0.11, 0.27±0.28) followed 1 months (0.36±0.12, 0.45±0.18) compared to before injection (0.55 ±0.06, 0.60±0.15) among aflibercept (eylea) and Brolucizumab groups respectively (P<0.05), it is worth to mentioned that, the vision was significantly more decreased after injection among aflibercept (eylea) group compared to Brolucizumab group **(Figure 3).**

Table (2): Comparison between vision before injection, after 1 month and after 3 months of the studied groups.

Vision		**Aflibercept (Eylea) group (n=32)**	**Brolucizumab group (n=30)**	***P value***
Before injection	Mean ± SD	0.55 ± 0.06	0.60 ± 0.15	0.192
	Range	0.48 - 0.6	0.48 - 1	
After 1 month of injection	Mean ± SD	0.36 ± 0.12	0.45 ± 0.18	0.125
	Range	0.1 - 0.6	0.3 - 1	
After 3 months of injection	Mean ± SD	0.13 ± 0.11	0.27 ± 0.28	0.056
	Range	0 - 0.3	0 - 1.08	
P value of paired test		P1=0.034*, P2=.002*, P3=.043*	P1=0.037*, P2=.001*, P3=.019*	

**Significant; P1: before injection Vs after 1-month; P2: before injection Vs after 3-months; P3: after 1-month Vs after 1-month.*

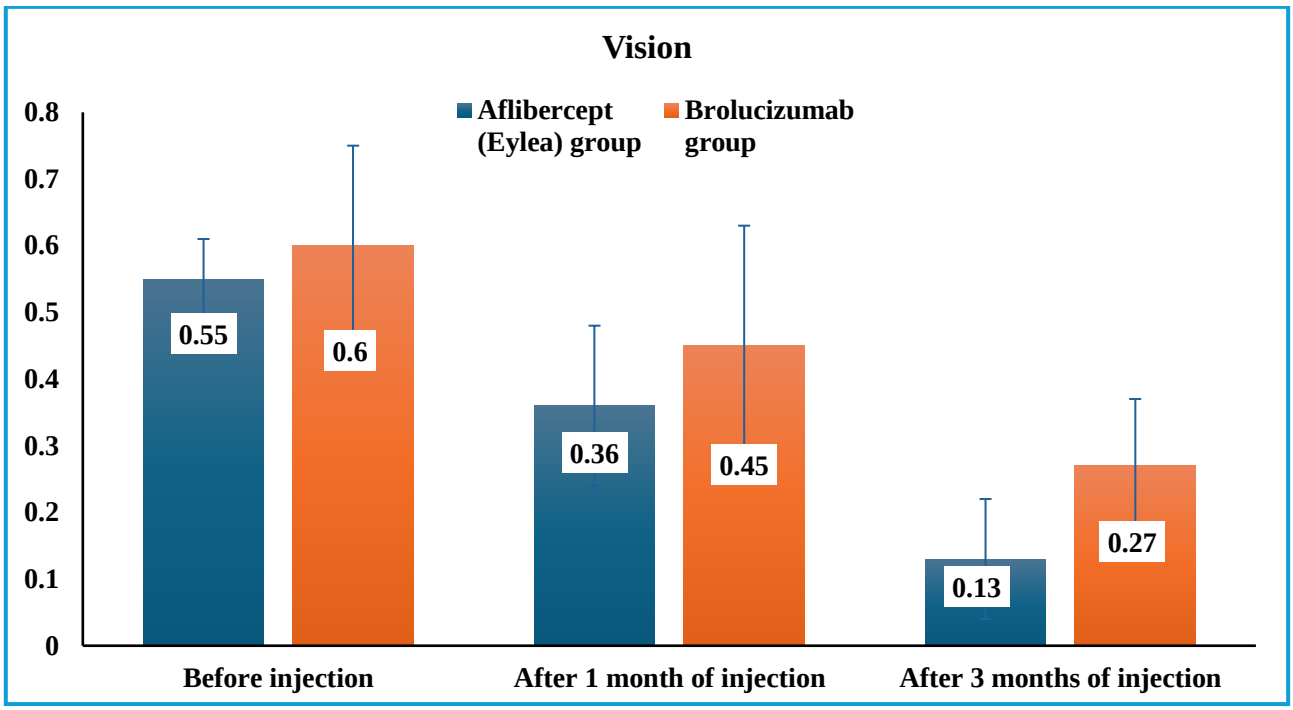

Figure (3): Distribution of CMT before injection compared to after 1 and 3 months of the studied groups.

Additionally, blurred vision after injection, and discomfort at the injection site were the most common complications among aflibercept (eylea) group by 37.5% and 31.25% patients, followed by Eye redness found in 25% of patients. While, Eye redness was the most common complication among Brolucizumab group by 33.33% patients, followed by Discomfort at the injection site, Blurred vision after injection, and Intraocular inflammation were found in 26.67% for each. Although, the presence of complications did not show a statically significant difference among aflibercept and Brolucizumab groups (p>0.05), **(Table 3).**

Table (3): Complications presence among the studied groups.

Complications	Aflibercept (Eylea) Group (n=32)	Brolucizumab group (n=30)	*P value*
Discomfort at the injection site	10 (31.25%)	8 (26.67%)	0.779
Eye redness	8 (25%)	10 (33.33%)	0.609
Blurred vision after injection	12 (37.5%)	8 (26.67%)	0.519
Intraocular inflammation	6 (18.75%)	8 (26.67%)	0.354
Endophthalmitis	0 (0%)	0 (0%)	---
Cataract formation	4 (12.5%)	2 (6.67%)	1.00
Elevated intraocular pressure	2 (6.25%)	0 (0%)	1.00

DISCUSSION

DME is a common microvascular complication in patients with diabetes and has emerged as the primary cause of vision loss in the adult working population. VEGF contributes to the formation of DME and is crucial in diabetic retinopathy.

In the diabetic retina, oxidative stress and chronic hyperglycemia cause an upregulation of VEGF, which breaks down the inner blood-retinal barrier and increases vascular permeability [(1)]. Anti-VEGF treatments have therefore demonstrated effectiveness in DME, and since their debut, the amount of visual loss associated with DME has declined [(3,4)]. Anti-VEGF usage in clinical practice has significantly decreased the incidence of blindness linked to AMI [(7)]. Thus, the current study was held to assess the difference between intravitreal injection of Brolucizumab and Aflibercept in management of DME.

In this case series, intravitreal brolucizumab and aflibercept injections for the treatment of DME patients were compared in a short-term real-life setting. We found that the visual and anatomical outcomes improved, but there was no significant difference between the two groups in terms of functional outcome or CMT changes. Following a 3-month customized "treat and extent" regimen of aflibercept and brolucizumab, the cohort demonstrated an improvement in mean best-corrected visual acuity (BCVA) to 0.13±0.11 and 0.27±0.28logMAR and a reduction in the mean CFT to 277±74.11 and 346.6±244.61μm respectively. These findings imply that there was no statistically significant difference between the two groups in terms of visual improvement, although a reduction in CFT was observed in both. This study

concluded that both agents significantly improved the visual result and CFT in individuals with DME. The treatment protocol consisted of one loading dosage, followed by a customized treat and extended regimen. Participants in this research had CFT≥325 μm and BCVA ≤20/40. A longer follow-up is necessary to evaluate and guarantee the long-term safety of both, even if no negative ocular effects were recorded throughout the follow-up period.

Comparing intravitreal brolucizumab and aflibercept in the treatment-naive central involvement DME, **Elhamaky** [(12)] found no significant difference between the two groups in terms of decreased CFT and improved vision.

Another research by **Brown *et al.*** [(9)] showed that there was no significant difference in the improvement of vision between the two groups based on 52-week findings from two phase III pivotal trials of brolucizumab for DME. They also showed that the subjects had CFT≥335μm.

Furthermore, there was no discernible difference between the two groups in terms of the improvement of vision and the decrease in CFT, according to **Dugel *et al.*** [(9)] risk of inflammation, retinal vasculitis, and retinal occlusion-related events with brolucizumab. Additionally, **Valentim *et al.*** [(13)] showed that intravitreal aflibercept for DME significantly improves visual acuity and morphological outcomes when administered intravitreally (IVI) at a dose of aflibercept every eight weeks. They also showed that the BCVA of the included participants was ≤20/40.

Additionally, in a single eye with DME, **Chakraborty and Sheth** [(14)] observed a positive bilateral functional and morphological response to intravitreal brolucizumab injection. Most likely, the systemic influence was the source of this. **Brown *et al.*** [(9)] conducted two phase III pivotal trials of brolucizumab for DME, and their 52-week results showed a significant difference between the two groups in terms of CFT reduction and retinal fluid resolution. Additionally, the safety profile of the drug was acceptable and comparable to that of aflibercept in DME patients. Proved that brolucizumab 6 mg produced non-inferior vision gain in one year. It was administered in five loading doses every six weeks, followed by twelve-week dosing, with the option to reduce to every eight weeks if active DME was present during follow-up visits. It also revealed that all participants had BCVA ≤20/32 and that there were no safety issues with brolucizumab over aflibercept. Brolucizumab 6 mg caused 1.1%–2.2% of intraocular inflammation, whereas aflibercept caused 1.7%–2.1%.

Furthermore, **Dugel *et al.*** [(2)] showed that brolucizumab was associated with intraocular inflammation and retinal vasculitis, as well as an increased risk of inflammation, retinal vasculitis, and events related to retinal occlusion. Its immunogenicity may be attributed to type III, type IV, or mixed immune responses, along with the development of anti-drug antibodies, making it a complex issue to manage. Brolucizumab was linked to a 4.4% incidence of intraocular inflammation, compared to 1% with aflibercept. Additionally, **Valentim *et al.*** [(13)] demonstrated that intravitreal aflibercept for DME significantly improves visual acuity and morphological outcomes when an intraviral injection of aflibercept every eight weeks is used to treat the condition. This regimen consists of five doses every four weeks, followed by a fixed dose every eight weeks.

LIMITATIONS

There were many limitations of our study including a single center of our study which involved small sample size of patients, thus a multiple center study in different countries included large sample size of patients are needed to asses' possibility of use of both brolucizumab and aflibercept in the treatment of DME.

CONCLUSIONS

This study highlights the effectiveness of both brolucizumab and aflibercept in the treatment of DME, demonstrating improvements in visual acuity and reductions in macular edema. The findings confirm that that intravitreal anti-VEGF therapy is beneficial for managing DME, significantly CMT, and enhancing best corrected visual acuity. However, brolucizumab has been associated with a risk of intraocular inflammation, retinal vasculitis, and retinal occlusion-related events. The relative effects of anti-VEGF varied on baseline visual acuity. When the first visual acuity loss was minor, there were no discernible variations. Aflibercept was more successful in improving eyesight in those with poor initial visual acuity.

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