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Safety and Efficacy of Brolucizumab Injection among Patients with Diabetic Retinopathy & DME in a Tertiary Care Hospital– A Prospective Study

Dr. Ziaul Ahsan Mukta[1*], Dr. Dilara Khatun[1], Dr. Tasnim Khanom[2], Dr. H N Ashequr Rahman[3], Dr. Md. Harun Bin Yousuf[4], Dr. Mashrur Al Bashir[5], Dr. Al- Nawaz[4], Dr. Nabila Noor Dutee[4], Dr. Kamrun Nahar Siddique[6]

[1]Consultant, Department of Ophthalmology, Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh
[2]Associate Professor, Department of Ophthalmology, Dr. Sirajul Islam Medical College & Hospital Ltd, Dhaka, Bangladesh
[3]Medical Officer, Department of Vitreo-retina, Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh
[4]Medical Officer, Department of Ophthalmology, Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh
[5]Medical Officer, Department of Ophthalmology, National Institute of Ophthalmology & Hospital, Dhaka, Bangladesh
[6]Medical Officer, Department of Retina, Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh

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***Corresponding author:** Dr. Ziaul Ahsan Mukta
Consultant, Department of Ophthalmology, Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh

Abstract **Original Research Article**

***Introduction*:** Diabetic Retinopathy (DR) is the leading cause of vision loss in adults aged 20–74 years. From 1990–2010, DR ranked as the fifth most common cause of preventable blindness and fifth most common cause of moderate to severe visual impairment. Previous research has implicated vascular endothelial growth factor (VEGF) in the pathogenesis of diabetic retinopathy (DR). Antivascular endothelial growth factor (anti-VEGF) therapy has become the treatment of choice for retinal vascular disorders such as diabetic macular edema (DME). ***Aim of the Study*:** The aim of this study was to evaluate the safety and efficacy of brolucizumab injection in patients with diabetic retinopathy. ***Methods*:** This was a prospective observational study and was conducted in the Department of Ophthalmology of Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh during the period from February, 2022 to February, 2023. In our study we took 300 patients with diabetic retinopathy & DME. All of them were given 6mg IVI brolucizumab injection. ***Result*:** In our study we found majority (35%) of our patients were aged 55-64 years and most of our patients were male (60%).We found the mean age was 56.53± 9.74 years and mean blood glucose was 98.8 ± 1.4 mg/dL. All patients had Type 2 diabetes. We found 20% NPDR, 47.33% PDR & 32.67% DME patients. The mean eye vision of our patients was 66.02± 4.02 and the mean kept reducing significantly till 18th week. Before treatment the mean of OCT was 427.04 ± 18.07 and after treatment we found 413.21 ± 11.12, 384.03 ± 14.02 & 254.19 ± 9.02 at 6th, 12th & 18th week respectively. ***Conclusion*:** In our study, we found a few complications of brolucizumab like no improvement of vision, nephropathy, cardiovascular disease was present among our patients. Although there were more adverse effects of brolucizumab but in our study we only found mild uveitis. The administration of anti-VEGF medicines in PDR is an emerging field. Although PRP is considered the first line of treatment for PDR, anti-VEGF medicines are gradually finding their place in PDR management.

Keywords: Brolucizumab injection, PDR, DME, DM.

INTRODUCTION

Diabetic Retinopathy (DR) is the leading cause of vision loss in adults aged 20–74 years [1]. From 1990–2010, DR ranked as the fifth most common cause of preventable blindness and fifth most common cause of moderate to severe visual impairment [2]. In 2010, of an estimated 285 million people worldwide with diabetes, over one-third have signs of DR, and a third of these are afflicted with vision-threatening diabetic retinopathy (VTDR), defined as severe non-proliferative DR or proliferative DR (PDR) or the presence of diabetic macular edema (DME) [3]. With increasing prevalence of diabetes mellitus and increasing life span of persons with diabetes, diabetic retinopathy (DR) is set to be the leading global cause of vision loss in many countries [1]. Whereas proliferative diabetic retinopathy (PDR) is the most common vision-threatening lesion in type 1 diabetes, DME is more common in type 2 diabetes and is the leading cause of moderate vision loss in diabetic individuals, owing to the high prevalence of type 2 diabetes. Apart from the

consequences on vision, the presence of DR and DME is a sign of other organ system issues associated with diabetes [4]. In many countries, DR is not only the most frequent cause of preventable blindness among individuals of working age (20– 65 years), but also a frequent cause of vision loss in elderly populations. In the U.S.A., an estimated 29 % of adults with diabetes have DR and 3 % have DME [5]. The prevalence rates are similar between those aged 40–64 years and those aged 65 years and older (28 % vs 30 % for DR and 4 % vs 5 % for vision-threatening DR). Outside of the U.S.A., similarly high rates have been reported in other Western countries as well as in developing countries [6-11]. In particular, Asia has emerged as the global epicenter of the diabetes epidemic and the proportion of individuals with DR will be on the rise with increasing numbers and lifespans of people with diabetes, especially in China and India [12]. Few population-based studies have reported the incidence and progression of DR or DME. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) in the U.S.A., the overall 10-year incidence of retinopathy was 74 %, and among those with retinopathy at baseline, 64 % developed more severe retinopathy and 17 % progressed to develop PDR [13]. About 20 % of type 1 diabetes and 14-25 % of type 2 diabetes developed DME over a 10-year follow-up period [14]. Data from the 25-year follow-up of the WESDR type 1 diabetes cohort show that virtually all patients (97 %) developed retinopathy over time, with a third to a half going on to develop vision-threatening disease (42 % developed PDR, 29 % developed DME and 17 % developed clinically significant DME [the more severe spectrum of DME]) [15, 16]. Epidemiological studies and clinical trials over the past 30 years have provided data on the prevalence, incidence and natural history of DR, and its associated risk factors. It is widely recognized that the risk of vision loss due to DR can be reduced by effective control of serum glucose and blood pressure, and by its early detection and timely treatment. There are now more studies focused on DME, which is currently amenable to new treatments such as anti-vascular endothelial growth factor (VEGF) agents [17]. The pro-angiogenic cytokine vascular endothelial growth factor (VEGF) is considered the primary factor involved in neovascularization in PDR.4 In the base of PDR pathophysiology stands angiogenesis [18]. VEGF activates two tyrosine kinase receptors, VEGFR-1 and VEGFR-2. These receptors regulate physiological and pathological angiogenesis. VEGFR-2 is expressed mostly on vascular endothelial cells.14 Activation of VEGFR-2 stimulates endothelial cell proliferation, migration, and survival, as well as angiogenesis and microvascular permeability as in PDR [19]. Previous research has implicated vascular endothelial growth factor (VEGF) in the pathogenesis of diabetic retinopathy (DR). Although many studies reviewed the use of anti-VEGF for diabetic macular oedema, little has been written about the use of anti-VEGF for proliferative diabetic retinopathy (PDR) [20]. Antivascular endothelial growth factor (anti-VEGF) therapy has become the treatment of choice for retinal vascular disorders such as diabetic macular edema (DME) [21, 22]. Pegaptanib sodium (Macugen®, Eyetech/OSI Pharmaceuticals, New York, NY, USA), ranibizumab (Lucentis®; Genentech, S. San Francisco, CA/Roche, Basel, Switzerland), aflibercept (Eylea®, Regeneron, Tarrytown, NY), and brolucizumab (Beovu®; Novartis, Basel, Switzerland) are four antivascular endothelial growth factor (antiVEGF) agents that the US Food and Drug Administration (FDA) has approved for intraocular usage [23-25]. Amongst them, brolucizumab is the latest to receive approval for neovascular age-related macular disorders (nAMD). In the case of DME, two phase 3 clinical studies, KESTREL and KITE, are underway to assess the role of brolucizumab, while its off-label usage in eyes with recalcitrant DME has already been described [26, 27]. In our study we aimed to evaluate the safety and efficacy of brolucizumab injection in PDR & DME patients of our institution.

OBJECTIVE OF THE STUDY

The main objective of the study was to evaluate the safety and efficacy of brolucizumab injection in patients with diabetic retinopathy and DME.

METHODOLOGY & MATERIALS

This was a prospective observational study and was conducted in the Department of Ophthalmology of Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh during the period from February, 2022 to February, 2023.

In the present study we took 300 patients with diabetic retinopathy & DME and all of them were given 6 mg IVI brolucizumab injection.

These are the following criteria to be eligible for the enrollment as our study participants: a) Patients aged 35 years or more than 35 years; b) Patients with diagnosis of type 2 Diabetes Mellitus (DM) & Diabetic macular edema (DME) ; c) Patients with PDR diagnosis having no previous PRP treatment ; d) Patients with dimness of vision were included in the study And a) Patients with concomitant conditions or ocular disorders; b) Patients with any previous surgical complications; c) Patients taking treatment with intraocular corticosteroids; d) Patients with any history acute illness (e.g., renal or pancreatic diseases, ischemic heart disease etc.) were excluded from our study.

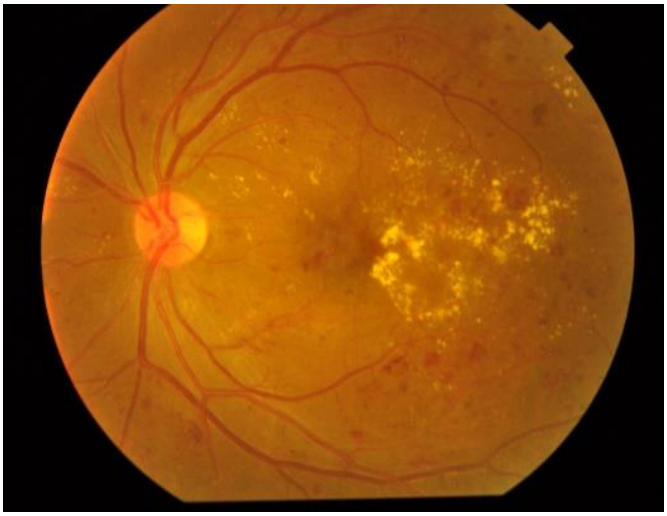

Figure 1: CFP view before treatment

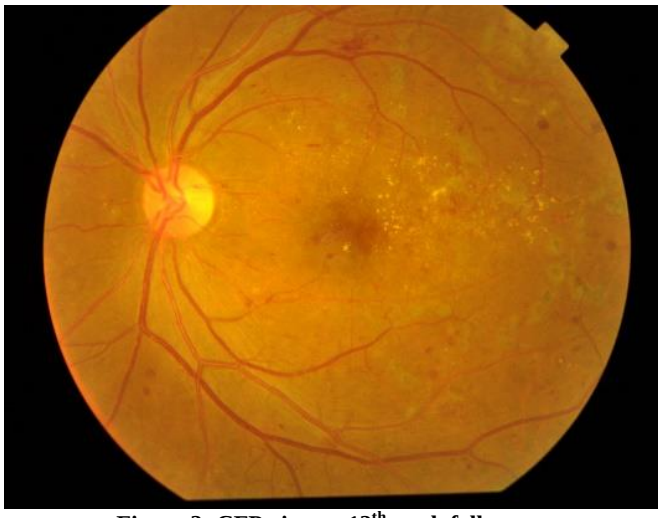

Figure 2: CFP view at 12th week follow up

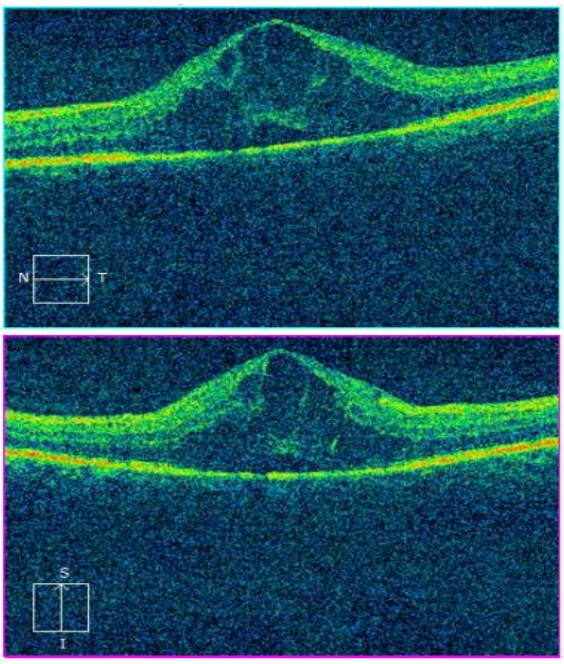

Figure 3: OCT view before treatment

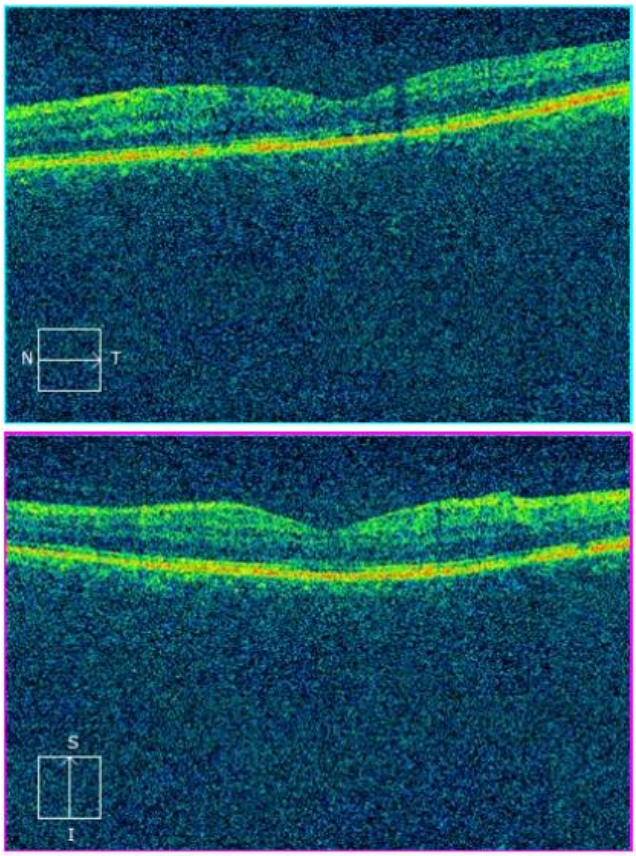

Figure 4: OCT view at 12th week follow up

Statistical Analysis

All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS 23 (Statistical Package for Social Sciences) for windows version 10. Probability value <0.05 was considered as level of significance. The study was approved by Ethical Review Committee of Bangladesh Eye Hospital & Institute Ltd, Dhaka, Bangladesh.

RESULT

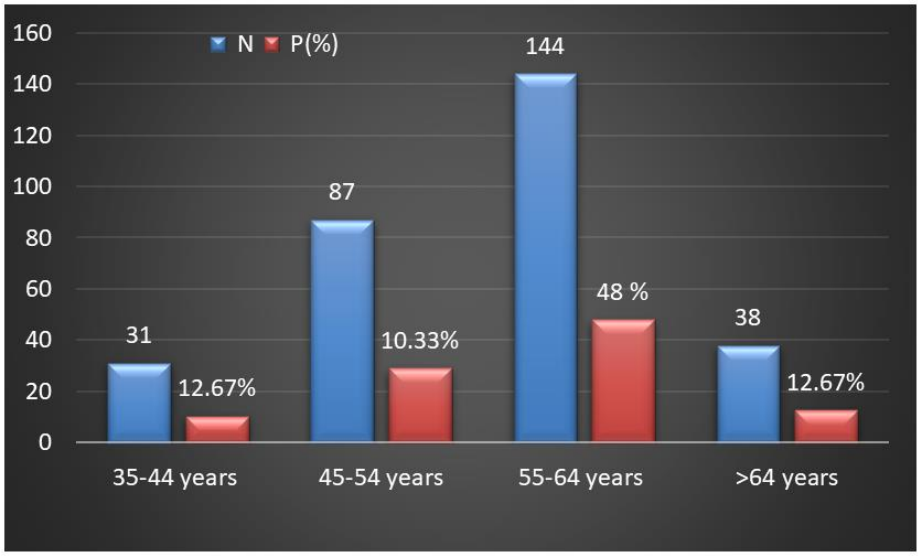

Figure 5: Age distribution of our study patients

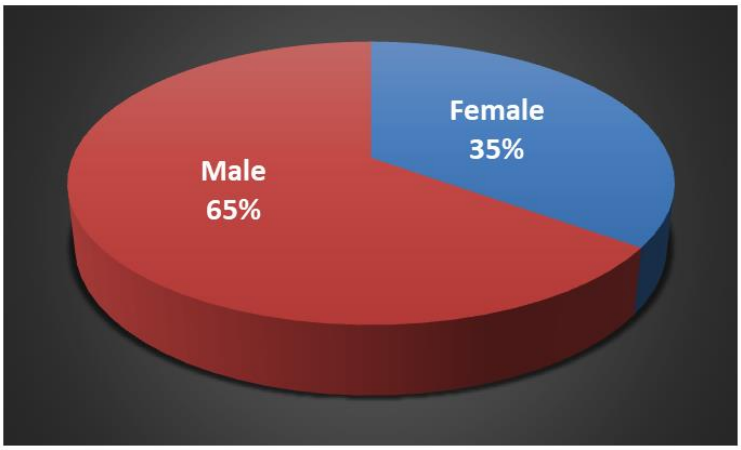

Figure 6: Gender distribution of study participants

Table 1: Baseline characteristics of our study respondents

Baseline characteristics	N	P(%)	P-value
Age (Years)			
Mean±SD	56.53± 9.74		0.000
BMI (kg/m^2)	38.48± 14.89		0.351
Mean blood glucose (mg/dL)	98.8 ± 1.4		0.021
Co-morbidities			
HTN	171	57%	
Hypotension	43	14.33%	
Hyperglycemia	37	12.33%	
Hypoglycemia	23	7.67%	
Hyperthyroidism	19	6.33%	
Hypothyroidism	7	2.33%	

Table 2: Distribution of our study participants based on fundus examination

General Fundus	Total		One eye		Both eyes	
	N	P(%)	N	P(%)	N	P(%)
NPDR	60	20%	45	75%	15	25%
PDR	142	47.33%	42	29.58%	100	70.4%
DME	98	32.67%	60	61.22%	38	38.78%

Table 3: Distribution of our study subjects based on OCT & Eye vision

Variables	Eye Vision	OCT(µm)	P-value
Before treatment	66.02± 4.02	427.04 ± 18.07	0.412
After treatment			
At 6th week	52.14± 9.02	413.21 ± 11.12	0.041
At 12th week	39.21 ± 10.12	384.03 ± 14.02	0.012
At 18th week	18.07 ± 6.18	254.19 ± 9.02	0.001

Table 4: Complications & Adverse effects of brolucizumab injection among diabetic retinopathy patients

Complications & Adverse effects	N	P(%)
Complications		
No improvement of vision	20	6.67%
Nephropathy	11	3.67%
Peripheral neuropathy	9	3%
Cardiovascular disease	12	4%
No Complications	248	82.67%
Adverse effects		
Mild Uveitis	43	14.33%
No adverse effects	257	85.67%

In figure 5 we distributed our participants based on their age. Majority (48%) of our patients were aged 55-64 years, followed by 29% & 12.67% were aged 45-54 & above 64 years old respectively.

In figure 6 we showed gender distribution of study subjects. Majority of our patients were male (65%) compared to female (35%).

In table 1 we summarized the baseline characteristics of our patients. We found the mean age was 56.53± 9.74 years and mean blood glucose was 98.8 ± 1.4 mg/dL. All our patients (100%) had Type 2 diabetes. Majority (57%) of our patients had HTN & 12.33% had hyperglycemia.

In table 2 we distributed our patients based on general fundus. We found 75% & 25% NPDR patients with one eye & both eyes respectively. There were 29.58% & 70.4% patients of PDR with one eye & both eyes respectively. We found DME in 32.67% patients.

In table 3 we summarized the mean of OCT & eye vision of our study participants. The mean eye vision of our patients was 66.02± 4.02 and the mean reduced significantly till 18th week. Before treatment the mean OCT was 427.04 ± 18.07 and after treatment we found 413.21 ± 11.12, 384.03 ± 14.02 & 254.19 ± 9.02 at 6th, 12th & 18th week respectively.

In table 4 we distributed our patients based on their complications & adverse effects. Majority (82.67%) of our patients had no complications and there was no improvement of vision in 6.67%, followed by 4% had cardiovascular disease. We found no adverse effects in majority (85.67%) patients and mild uveitis was found 14.33% in our study.

DISCUSSION

DME patients with PDR frequently have DME. Although PRP can minimize the risk of severe visual loss in patients with high-risk PDR [28, 29]. There is a chance that macular oedema will worsen. A phase 3, randomized, multicenter clinical trial enrolling 345 eyes with a visual acuity of 20/320 or greater, DME receiving focal/grid laser, and diabetic retinopathy receiving PRP was done by the Diabetic Retinopathy Clinical Network. Subjects were assigned to one of three groups: sham treatment, 0.5 mg ranibizumab at baseline and 4 weeks, or 4 mg triamcinolone at baseline and sham treatment at 4 weeks. Ranibizumab improved mean changes (SD) in visual acuity letter score from baseline significantly. One eye developed endophthalmitis after receiving ranibizumab [30-32]. 64 PRP alone was compared by Filho *et al.,* and Cho *et al.,* compared PRP alone with PRP and ranibizumab or bevacizumab, independently, for cases with high-threat PDR. In these studies, the spare use of ranibizumab/ bevacizumab defended against the macular lump observed in eyes treated with PRP alone [33, 34].

Jorge *et al.,* reported on 15 eyes with persistent, active PDR in which one injection of bevacizumab was administered [34]. Fluorescein leakage improved after the 12-week follow-up, with no notable adverse effects [34]. At all-time intervals (1, 6, and 12 weeks), BCVA improved significantly from baseline, from 20/160 at baseline to about 20/125 at 12 weeks. These investigations demonstrate that IVB reduces leakage from diabetic neovascular lesions in patients with persistent, active PDR [34]. A few case series have documented a therapy combination of anti-VEGF and conventional treatment for PDR (PRP) [35-37]. Filho *et al.,* 88 conducted a prospective trial comparing PRP alone to PRP with ranibizumab in patients with high-risk PDR [33]. The first group received two sessions of PRP, while the second received intravitreal ranibizumab at the end of the first laser session. When compared to PRP, intravitreal ranibizumab following PRP resulted in a greater reduction in total area (mm2) of fluorescein leakage at week 48 [33]. Tonello *et al.,* found no significant improvement in BCVA in a similar research, however the total area of actively leaking NVs was considerably reduced in the PRP plus IVB group compared to the PRP group at weeks 4, 9, and 16 [36].

Cho *et al.,* investigated the value of IVB prior to PRP as an adjuvant treatment. IVB was injected 1 week before PRP in his trial of 41 eyes from high-risk PDR patients. BCVA did not alter in the PRP 'Plus' group, while it was much worse in the PRP group after 3 months. When CME was present, there was no significant change in BCVA in either group. Hence, intravitreal anti-VEGF treatment before and after PRP has a significant effect in the treatment of high-risk PDR [34].

The widespread use of intravitreal anti-VEGF medication has revolutionized DME care. Newer compounds with longer half-lives and endurance, such as aflibercept and brolucizumab, have the potential to reduce total therapy burden [38]. Based on the favorable results of phase 3 trials testing IVI brolucizumab in the treatment of nAMD, prospective phase 3 studies (KITE and KESTREL) are being done to evaluate its function in the management of DME [38, 39]. In the interim results of the KITE and KESTREL investigations, which were published at the end of 2020, brolucizumab was shown to be noninferior to aflibercept in terms of mean change in visual acuity at one year [38]. In eyes with intractable DME, Chakraborty *et al.,* achieved remarkable structural and visual improvement with brolucizumab [38].

Studies have demonstrated that the relationship between molecule size and microvascular permeability is inverse [40]. Because of this, the brolucizumab

molecule, which has the smallest molecular weight of any anti-VEGF medication (brolucizumab (26 kDa) compared to bevacizumab (149 kDa), ranibizumab (48 kDa), and aflibercept (110 kDa), can readily enter the systemic circulation and have a contralateral effect. Moreover, altered inner blood-retinal barrier and increased vascular permeability are linked to diabetic retinopathy [41]. The systemic absorption of intravitreally delivered drugs may be influenced by these dysfunctional retinal vascular alterations. To the best of our knowledge, there have been no published reports of intravitreal brolucizumab harming PDR patients. Based on these promising results, our patient was prescribed IVI brolucizumab. In our study we found the mean OCT of our patients significantly reduced to 413.21 ± 11.12, 384.03 ± 14.02 & 254.19 ± 9.02 at 6^{th}, 12^{th} & 18^{th} week respectively [Table 3]. In our study majority (82.67%) of our patients had no complications and there was no improvement of vision in 6.67% patients, followed by 4% had cardiovascular disease. We found no adverse effects in majority (85.67%) patients and mild uveitis was found 14.33% in our study [Table 4]. Prominently, the use of anti-VEGF drugs for PDR is still considered off-label. There are currently no big, well-coordinated randomized trials in this domain that provide high-level data. Nonetheless, the information presented above can be used to justify treating PDR in specific reasons to enhance patient outcomes on a case-by-case basis when the practitioner is aware of the potential detrimental effects.

Limitations of the Study

Our study was a single centre study. In this study we found a few complications & only one adverse effect of brolucizumab injection among diabetic retinopathy patients within our short study period. There are more adverse effects like TRD, FAZ enlargement, rise in IOP, macular hole & endophthalmitis needs to be evaluated. After evaluating once those patients we did not follow-up them for a long term and have not known other possible interference that may happen in the long term with these patients.

Conclusion and Recommendations

In our study, we found a few complications of brolucizumab like no improvement of vision, nephropathy, cardiovascular disease was present among our patients. Although there were more adverse effects of brolucizumab but in our study we only found mild uveitis in our study. The administration of anti-VEGF medicines in PDR is an emerging field. Although PRP is considered the first line of treatment for PDR, anti-VEGF medicines are gradually finding their place in PDR management. This is especially true when performing PRP is difficult (as in vitreous hemorrhage and thick cataract) or when PRP has failed to prevent PDR progression. The downsides of anti-VEGF drugs are their short-term impact with time-dependent reperfusion of aberrant arteries, TRD via fibrous contraction, and the uncommon risk of endophthalmitis.

Therefore, further study with randomized controlled trials including larger sample size needs to be done to identify more adverse effects of brolucizumab injection among patients with DME & PDR.

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