Newer Anti-VEGF "Brolucizumab" in NPDR with Persistent Diabetic Macular Edema (DME); a Real-life Experience

Abul Bayan Shamsudduha[1], Nazmun Nahar[2], Tariq Reza Ali[3], M A Bashar Sheikh[4], Shahinur Rahman[5]

Abstract

Purpose: *To evaluate safety and effectiveness of Brolucizumab for Persistent Diabetic Macular Edema (DME) patients.*

Design: *Retrospective study.*

Method: *To report the real-life Brolucizumab therapeutical outcomes with Non-Proliferative Diabetic Retinopathy (NPDR) with Diabetic macular edema (DME). Materials and Methods: A total of 20 eyes of 15 patients diagnosed with Non-Proliferative Diabetic Retinopathy (NPDR) with persistent DME were Retrospective evaluated over a 3-month follow up eyes received a 5-month loading phase scheme. Study duration was April 2022 to August 2023 at Lions Eye Institute and Hospital and Harun Eye Foundation Hospital, Dhaka.*

The main outcome measures were best-corrected visual acuity (BCVA) in the Snellen chart and central retinal thickness (CRT) change. In addition, patients were undergone supervision with fluid resolution in the retina specifically Intra-Retinal Fluid (IRF) and/or Sub-Retinal Fluid (SRF).

Result: *A significant improvement of BCVA was observed with 80% of study eyes and 20% of eyes were not significant. On the other hand, CRT was also within normal limit with 90% study eyes and 10% were not significant.*

Conclusion: *Brolucizumab is demonstrated to be a safe and efficient alternative in improving both the anatomical and functional parameters of eyes NPDR with Persistent DME in this small series of patients.*

Keywords: *Diabetic Macular Edema (DME); Anti-Vascular Endothelial Growth Factor(Anti-VEGF); Brolucizumab (VSIQQ); Central Retinal Thickness(CMT). Non-proliferative Diabetic Retinopathy (NPDR)*

Introduction

The prevalence of Persistent Diabetic Macular Edema (DME), a manifestation of diabetic retinopathy, is continuously rising worldwide (4.07% based on data up to March 2020) and has become one of the major causes of vision loss in the diabetic population[1, 2]. VEGF plays an essential role in diabetic retinopathy and is involved in the development of DME. As such, anti-VEGF therapies have shown efficacy in DME[3] and DME-related vision loss has decreased since their introduction. Anti-VEGF therapy is

1. Professor, Department of Vitreo-Retina, Lions Eye Institute & Hospital, Agargaon, Dhaka & Consultant, Harun Eye Foundation Hospital, Dhanmondi, Dhaka.
2. Professor, Department of Vitreo-Retina, Lions Eye Institute & Hospital, Agargaon, Dhaka
3. Associate Professor, Department of Vitreo-Retina, BSMMU, Dhaka. & Consultant, Harun Eye Foundation Hospital, Dhanmondi, Dhaka.
4. Professor & Consultant, Harun Eye Foundation Hospital, Dhanmondi, Dhaka & President Bangladesh Vitreo- Retina Society (BVRS)
5. Professor & Director General (DG), Lions Eye Institute & Hospital, Agargaon, Dhaka.

Address of Correspondence: Abul Bayan Shamsudduha, Professor, Department of Vitreo-Retina, Lions Eye Institute & Hospital, Agargaon, Dhaka & Consultant, Harun Eye Foundation Hospital, Dhanmondi, Dhaka. Email: abduha72@yahoo.com

now considered the standard of care, with additional laser photocoagulation and steroid injections as second-line options if required[4].

Despite the establishment of highly effective intra-vitreal anti-VEGF therapy as the standard of care for DME[5], a high treatment burden and thus an unmet need has still remained in this population. To achieve disease control in a real-world setting, many patients with DME receive more than seven injections in the first year of treatment. An average patient spends 2 h at an injection appointment plus 4 hours traveling to and from the appointment. With many relying on family and friends for transportation, this can place a considerable burden on the professional and private lives of both patients and their caregivers [6].

The need for regular injections also puts pressure on healthcare services, with ophthalmology appointments accounting for 10% of all outpatient appointments across the National Health Service, largely driven by the need for medical retina consultations[7]. On top of this, patients may require extra healthcare visits for comorbidities, since patients with DME are also more likely to experience disease- and treatment-independent comorbidities than non-diabetic patients with DME and healthy controls, respectively, and visit healthcare facilities more often[8].

Brolucizumab is an intra-vitreal anti-VEGF drug indicated for use in adults for the treatment of DME, approved in Switzerland since 2 June 2022 for DME[9]. With a molecular weight of 26kDa, brolucizumab allows for higher molar dosing versus other anti-VEGF therapies, with a longer duration of action and improved tissue penetrability. Preclinical data and phase II/III trials support the use of a once every 12 weeks (q12w) brolucizumab maintenance regimen immediately after the loading phase, offering a reduction in injection number/treatment burden for patients with DME when compared with previous anti-VEGF options[10].

Study Design: Retrospective randomized selection without gender, age, race, year of diabetes of patients. Considered only patients who received previously almost 6-month other Anti-VEGFs and patients were well controlled their blood sugar level.

Methods

Participants: Randomized open mask in this retrospective observational study, 15 patients (20 eyes) NPDR with persistent DME showing visual impairment and/or persistence of macular edema on Optical Coherence Tomography (OCT) were enrolled and followed up for 3 months at both the eye.

Table 1. ***Demographic and clinical ophthalmic data of the patients enrolled in the study.***

Characteristic Age-Range (SD)		**Years 55 +-(5)**	**Resistance Years 55 +-(5)**
Gender	Male	10	12
	Female	5	8
No of Eyes			20
lens Status	Phakic	7	7
	Pseduphakic	13	13

*All patients were provided with an informed consent for participation in the study.

The inclusion criteria only NPDR with persistent DME more than 6 months also previously treated with other anti VEGF and visual impaired patients.

The ocular exclusion criteria considered were previous treatment with Brolucizumab; concomitant ocular pathologies, such as PDR with persistent diabetic retinopathy, retinal vascular occlusions, uveitis, vitreo-retinal interface pathologies; surgical or para-surgical procedures, such as laser photocoagulation and/or vitrectomy within the last 6 months in the study eye.

Table 2: ***Treatment of NPDR with persistent DME patients with Brolucizumab***

Patients' selection	Base line assessment	Treatment regimen	Monitoring
Consider. 1. Treatment NPDR with persistent DME patients. 2. Poor responder (Patients switching from other Anti-VEGF treatment due to heigh treatment demand and/ or insufficient response/Persistent IRF).	Pre-treatment assessment. 1. Standard assessment: Analysis (Bilateral IOP, VA, Slit lamp, Dilated fundus and OCT) 2. Optional assessment: FA and /Or Color fundus photography	Brolucizumab Loading dose. 1. Treatment NPDR with persistent DME: injection every 6 weeks for the first 5 dose. 2. Adapting the number of loading injection can be considered best on DA. Patients switching from other ANTI-VEGF therapy. 1. Expert Opinion is to not use loading injection in patients switching from other ANTI-VEGF therapy if not required by DA.	Visit following from the first Brolucizumab injection. At or prior to each intra-vitreal injection: Assess DA and exclude an IOI. 1. Perform an IOP, VA, Slit lamp, Dilated fundus and OCT examination. 2. Ask patients about subjective changes in their vision, including loss of vision, red eye, Photo phobia, and presence of floaters, consider discontinuation of treatment if visual and anatomical outcomes indicate no benefit from continued treatment.
Treat with Caution. 1. Bangladeshi patients 2. Patients with history of and/or treat with auto immune diseases including any form of Uveitis. 3. Patients with limited vigilance, inability to come for additional assessment or poor mental status or compliance		Maintaining treatment. Direct interval extension to every 12 weeks or adjustment to every 8 weeks if required by DA. Individualize injection interval best on DA and consider a treat and extend regimen. Do not give patients intra-vitreal injection less than 8 weeks apart.	

DA; Disease Activity

All participants underwent four examinations (baseline, 1, 2, and 3 months after treatment) that included: BCVA (Snellen chart) anterior segment slit lamp bio microscopy, binocular indirect ophthalmoscopy, and Optical Coherence Tomography (OCT).

OCT was performed using OCT setting an acquisition protocol that consisted of a Macula Analysis and a Radial Scan. In all patients, central retinal thickness (CRT) was recorded and assessed by measuring the distance between the vitreo-retinal surface and retinal pigment epithelium (RPE) at the foveal center.

The main outcome measures were BCVA and CRT change over a 3-month follow-up. In addition, patients were stratified on the basis of fluid accumulation site, whether intraretinal (IR), sub-retinal (SR), to separately assess the occurring BCVA change in each group.

Results

A total of 20 eyes of 15 patients, 10 males (67%) and 5 females (33%) affected by NPDR with Persistent DME, were retrospectively enrolled. The mean age was 55 years.

No significant differences were found between each group with regards to age and gender.

Table 3. ***Functional and morphological data of NPDR with persistent DME patients.***

	Time	BCVA	CRT
Resistance	0 MO	6/36	450
	1.5 MO	6/36	400
	3 MO	6/24	340
	4.5 MO	6/18	290
	6 MO	6/9	230

MO: Months; B: baseline; BCVA: best-corrected visual acuity; CRT: Central Retinal Thickness.

NPDR with Persistent DME a significant improvement of BCVA was observed regarding CRT, it did significantly change. A line graph comparing the outcome of BCVA, CRT and Fluid resolution. Loading doses of Brolucizumab injection was enough to achieve a significant reduction in the fluid accumulation and both anatomic and functional stabilization of the disease until the end of the follow-up.

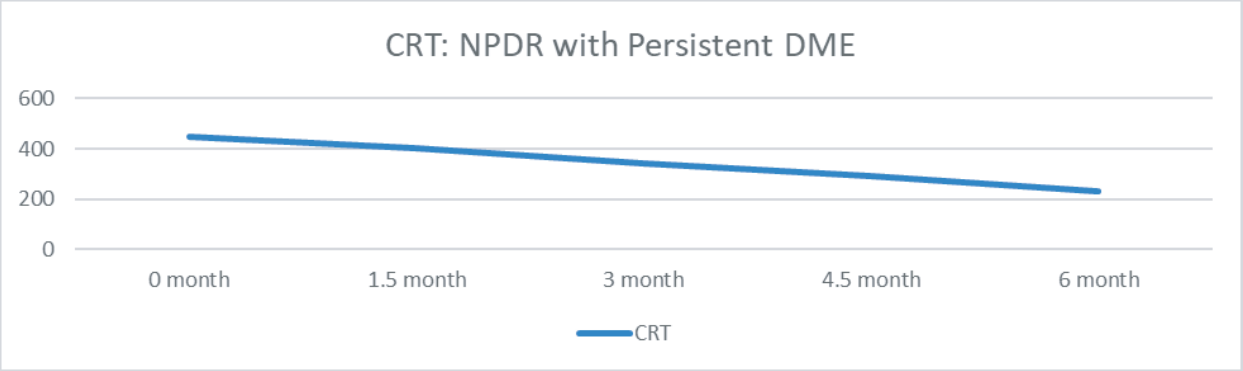

Figure 1: (A) CRT changes over time

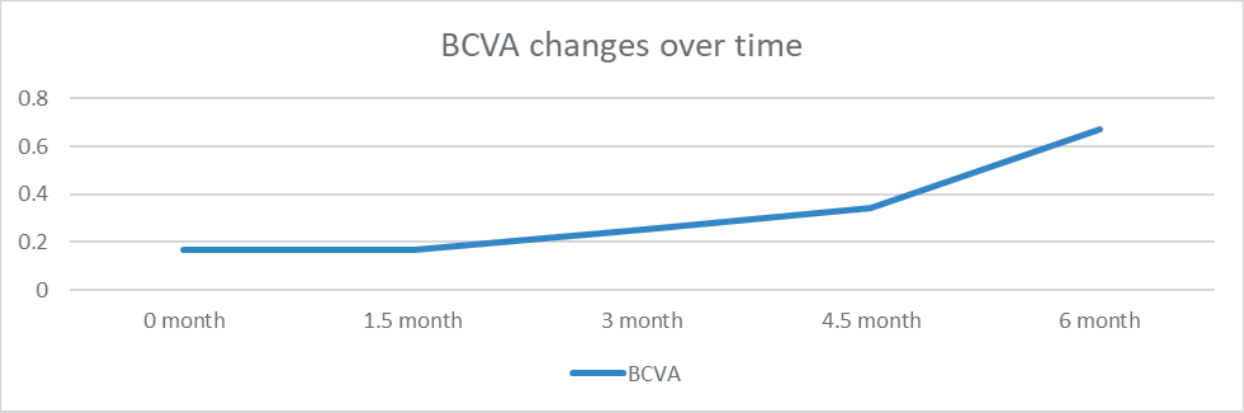

Figure 1: (B) BCVA changes over time

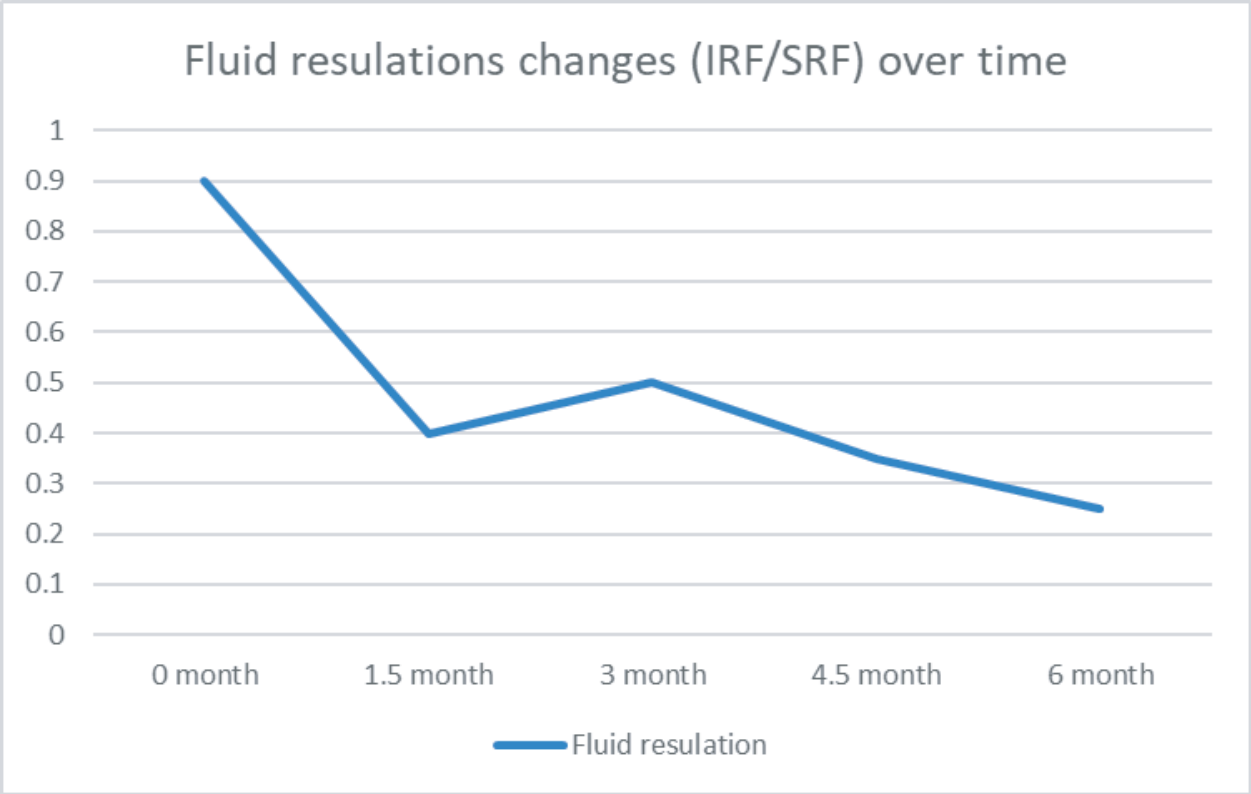

Figure 1: (C) Fluid resolution (IRF/SRF) over time

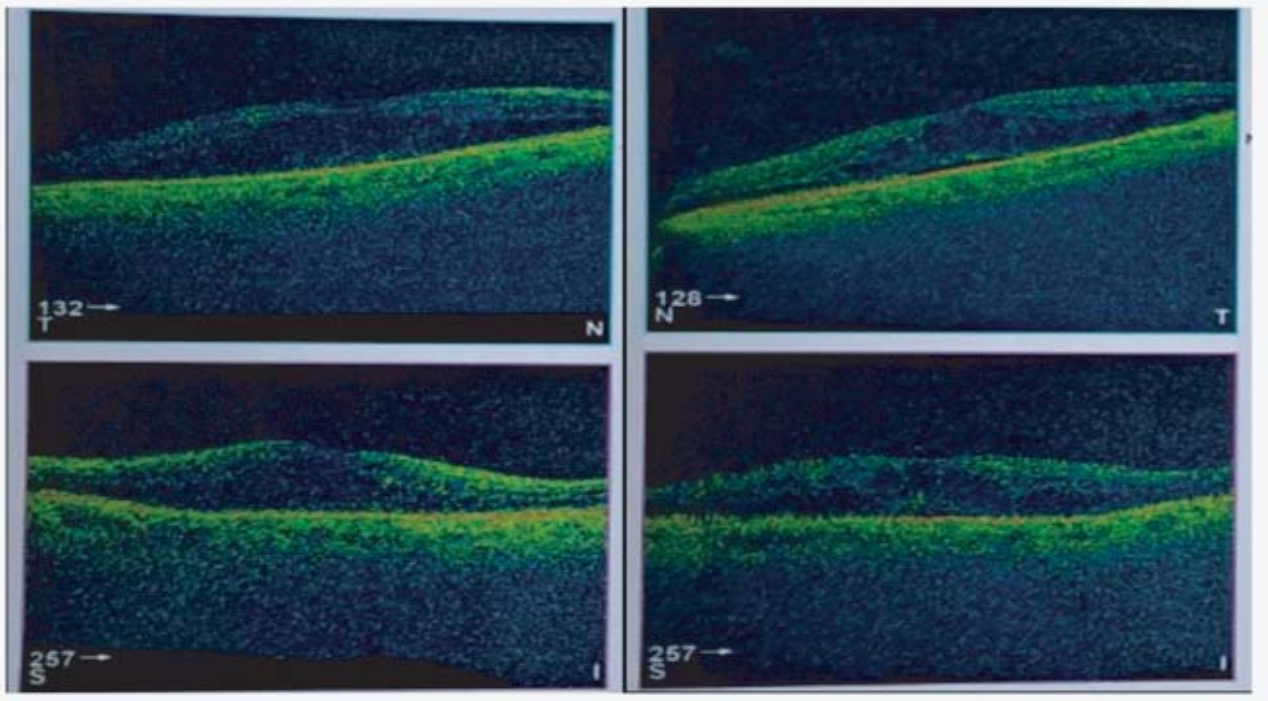

Figure 2. (A) Baseline OCT scan OCT of a NPDR with persistent DME patient displaying diffuse intra-retinal edema.

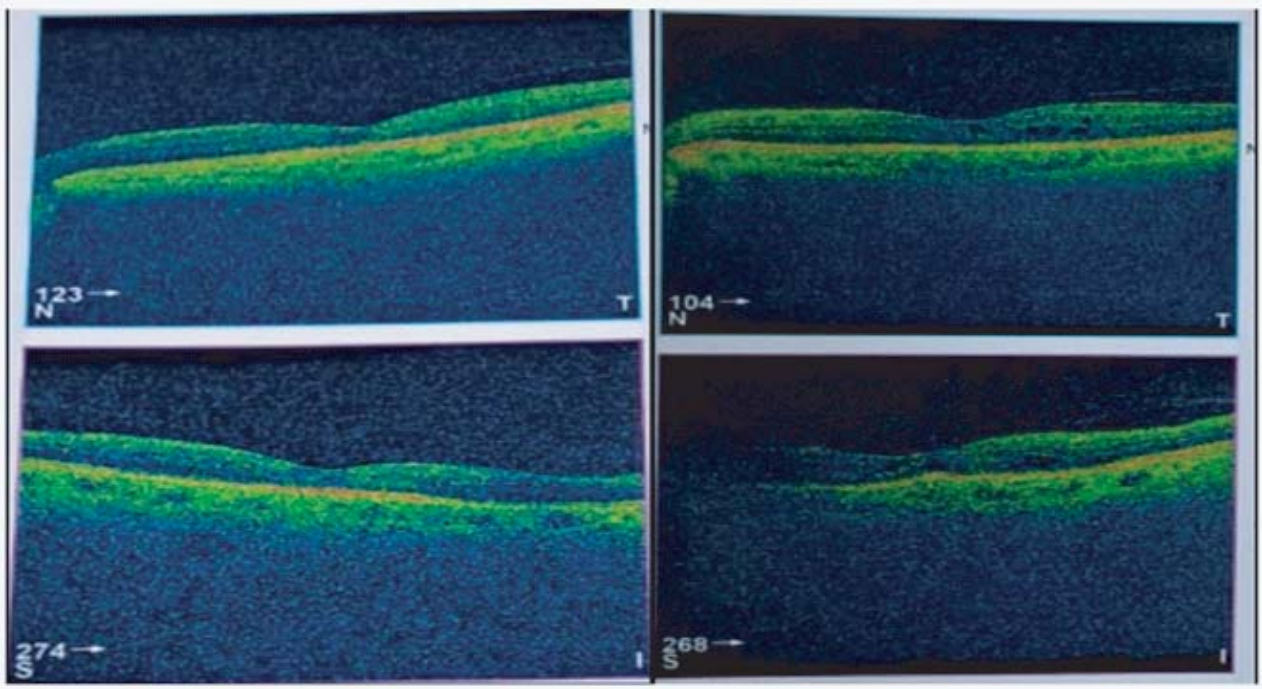

Figure 2. (B) A 5-month OCT scan displaying sub-retinal hyper reflective material and no residual edema of a NPDR with persistent DME patient.

Discussion

The treatment of NPDR with persistent DME has always been challenging throughout the years, aiming at identifying the most efficient treatment alternative to either improve or maintain BCVA over time. The relatively recent introduction of a novel anti-VEGF agent, Brolucizumab, was indeed proven to be a valid therapeutic option[11].

This study assessed and compared the early anatomical and functional changes of recurrent patients with persistent DME treated with a 6-week interval loading phase of Brolucizumab + ProReNata regimen of therapy.

The treatment was shown to be effective, demonstrating a significant recovery of retinal morphology and function. Indeed, BCVA and CRT significantly improved, and fluid accumulated at all levels (IR, SR) was significantly reduced at the end of the follow-up. It is important to note that persistent DME patients constantly showed a better improvement[12].

Multiple analyses have identified the presence of IRF and or SRF to be an important biomarker for disease activity and long-term outcomes in exudative retinal diseases, including DME. Specifically, persistence of IRF and or SRF has been associated with worse BCVA gains in subjects with DME[13].

Consistent with the 1 year and 4 months findings, the 16-week results demonstrated long-term efficacy and durability of brolucizumab in improving visual and anatomical outcomes in patients of NPDR persistent DME.

Limitation: Financial conditions of patients, distance from hospital, educational status, poor awareness, small sample size and short duration of follow up etc.

Recommendations: Brolucizumab may be alternative to steroid in recurrent NPDR with persistent DME considering side effects of steroid therapy.

Conclusion: In conclusion, the drug demonstrated to be effective in improving both the anatomical and functional parameters and shown to be successful at obtaining a dry (Fluid resolution) macula. Moreover, its efficiency also demonstrated in terms of the number of injections

needed to achieve such optimal outcomes compared to previous anti-VEGF agents. This agent is effective in treating NPDR with persistent DME patients, allowing significant improvement in fluid resolutions, BCVA and CRT. Also, these agents have well tolerated for recurrent NPDR with DME.

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