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Original Article

Efficacy of Intravitreal Injection Brolucizumab in Naïve Centre Involved Diabetic Macular Edema

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ABSTRACT

Aims and Objectives: Study of efficacy of treatment with brolucizumab intravitreal injections in Naïve center involved DME in relation to -
1. Visual acuity (VA) outcome
2. Resolution of macular edema in respect to macular OCT thickness and fluid reduction in macula.
3. Average number of injections required up to desired effects.
(Naive DME is defined as having a thickened retina (≥350 μm) on optical coherence tomography (OCT) with persistent cystic changes (less than a 15% reduction in central retinal thickness)
Study center: Regional institute of ophthalmology (RIO), Gauhati Medical College, Guwahati
Study design: A Prospective, observational study with off-level use of Brolucizumab injection in naive Centre involved DME.
Study Population: Patients, who are coming to RIO, GMCH having naive Centre involved DME with central foveal thickness (CFT) ≥ 300 μm lasting 3 months or more
Study period: Jan 2022-Dec 2022 with interim analysis will be done after 3 months.
Sample size: Required no of eyes (20)
Materials And Methodology: 20 eyes of 20 patients with Diabetic Macular Edema were selected prospectively and recruited for intravitreal injection Brolucizumab at baseline and evaluated monthly till 3 months.The patients were given additional brolucizumab for macular edema when required on the basis of optical coherence tomography findings.Patients were evaluated for improvement in Visual acuity,Macular Thickness and complications.
Results: Visual Acuity of patients receiving intravitreal injection of Brolucizumab is increased by more than 4 lines and OCT thickness was maintained for more than 3 months in majority of the cases. At 6 months follow up,the mean visual acuity improved to 62.45(±20) letters and the central macular thickness decreased to 249(± 20)μm($p<0.00001$).Re injection was required after 3 months when macular edema recurrs.
Conclusions: Use of Intravitreal Brolucizumab in cases of Diabetic Macular Edema showed improvement in mean Visual Acuity,with low rates of adverse events in 3 months follow up period. The duration of effect following each intra vitreal injection of Brolucizumab was maintained for more than 3 months.

Keywords*: Diabetic Macular Edema, Brolucizumab, Visual Acuity, Optical Coherence Tomography, Central Macular Thickness.*

INTRODUCTION

Diabetic macular edema is one of the leading causes of visual impairment and blindness throughout the world [1].The management of DME has been revolutionized by the widespread adoption of Intravitreal injection of Anti-VEGF agents. [2] Introduction of Anti VEGF such as Bevacizumab ,Ranibizumab,Brolucizumab and Aflibercept has shifted the treatment paradigm. This Anti VEGF agent inhibits the effect of Vascular Endothelial growth factor,which is involved in the pathophysiology of macular edema and neovascularisation .Management of DIABETIC MACULAR EDEMA with Anti vascular endothelial growth factor (Anti-VEGF) therapy has become the current standard treatment procedure.[3,4]

Brolucizumab is an Intravitreal Anti VEGF agent to receive latest approval in 2019 and in India,the drug was recently launched in October 2020 as Pagenex by Novartis India Limited ,Mumbai.It is a Humanised single chain antibody fragment and weighs 26kDa.[5] It is smaller than other anti VEGF agents in size and has a high binding affinity.[6]Its lasts longer in the eye and thus permits less frequent dosing.[7] Studies have indicated that early ,intensive, and individualized treatment with Brolucizumab provides improved Visual acuity (VA) along with underlying disease modification in Diabetic Macular edema.[8]

Our study will prospectively assess the efficacy of intra vitreal injection Brolucizumab in Center involved naïve Diabetic Macular edema presenting with poor visual acuity in terms of visual acuity,Macular thickness and complications and with monthly follow up till 3 months on a series of patients attending Regional Institute of Ophthalmology (RIO),Gauhati Medical College and Hospital(GMCH),Guwahati,Assam.GMCH being a tertiary referral centre of North East India, this study will reflect a scenario of success rate in the region of North East India.Since not much study has been done in this area till now,so this study has been been carried out in our Institution.

MATERIALS AND METHODS

This is a hospital based prospective,observational study with off level use of Brolucizumab injection in Naïve centre involved Diabetic macular edema which was conducted in REGIONAL INSTITIUTE OF OPHTHALMOLOGY, GAUHATI MEDICAL COLLEGE AND HOSPITAL,during the period of January 2022 to December 2022.

The patients were selected from outdoor as well as indoor. Informed consent was obtained from each of the patients after explaining the purpose of the design.

A total of 20 eyes were included in the study group.All newly diagnosed cases of Diabetic Macular Edema after thorough clinical examination and relevant investigations were included in this study.

Study Population:

Patients, who are coming to RIO, GMCH having naive Centre involved DME with central foveal thickness (CFT) ≥ 300 µm lasting 3 months or more

Inclusion criteria:

1. Age 40 years and above
2. Patients with center involved DME

Exclusion criteria

1. Patients treated for RVO, RAO, AMD, mCNV and Glaucoma etc.
2. Treatment exposed with DME.
3. Uncontrolled Diabetics
4. Patients with geographic atrophy or fibrosis
5. Switchover patients to other anti-VEGF, if any
6. Patient with any history of allergy, asthma, heart disease etc

PRE INJECTION WORK UP

After the initial screening, cases of Retinal vein occlusion were evaluated with:

- Visual acuity assessment (With and without Pinhole) using ETDRS chart
- Detailed history was taken.
- Intraocular pressure measurement.
- Gonioscopy
- Fundus evaluation
- Spectral Domain Optical Coherence Tomography (OCT -FMT) for assessing:
    i. Central subfield thickness (CST)
    ii. Macular volume
    iii. Presence or absence of sub retinal fluid
    iv. Foveal contour
- Fundus Flourescein Angiography (FFA) wherever necessary.

Investigations included
i) Fasting Blood Sugar
ii)Post Prandial Blood Sugar
iii)Glycosylated Haemoglobin (HbA1C)
iv)Fasting lipid Profile
v)Serum Creatinine
vi)ECG
The nature of the study was explained to the patient and/or attendant for their co-operation and selective documentation.

A detailed proforma was made for all the patients meeting the aforementioned criteria.

Data were collected at the first visit after the DIABETIC MACULAR EDEMA onset and reviewed till all sequential follow ups.

PRE INJECTION MEDICATION
Topical Antibiotic (Moxifloxacin) was started one day prior to the procedure.

WORKUP FOR INJECTION

- After selection of patients ,they were taken up for Anti VEGF Injection
- DOSE: The intravitreal dose of Brolucizumab Was 6 mg (0.05mL of 120 mg/mL).
- After proper anti-septic dressing,topical anaesthesia(Lignocaine 4%) and 5% povidine iodine is instilled into the conjunctival sac and washed off.
- The Brolucizumab injection is given 3.5 mm and 4mm from limbus in pseudophakic and phakic eye respectively primarily in the Supero temporal region (other sites are also chosen depending upon the comfortability of the patient).
- Mild pressure is applied with tip of cotton bud during withdrawal of the injection to prevent regurgitation of the injected material and topical antibiotic and povidine iodine applied over the injected eye.
- This was followed by pad and bandaging were done kept overnight.

POST INJECTION MANANGEMENT

- Oral analgesic is prescribed as and when required.
- Dressing was done the next day with topical antibiotic and proper check up was done as per the protocol.
- Here,Slit Lamp Examination and Fundus Examination was done to rule out any untoward defect. IOP and visual acuity was also measured.
- Patients were instructed to use the same Topical Antibiotic which was started one day earlier was continued as 1 hourly on First day and 6 times/day for 2 weeks.
- Patients are advised to maintain ocular hygiene and to avoid contact with water in the eye where injection was given for 1 week.

POST INJECTION FOLLOW UP
Patients were followed up and evaluated monthly till the period of 3 months following Anti VEGF injection.

- At each visit Visual acuity assessment,Slit Lamp Examination,Intraocular pressure,Fundus evaluation and OCT-FMT were done and records were documented.
- In Optical Coherence Tomography (OCT -FMT) examination,Central subfield thickness (CST), Macular volume,Presence or absence of sub retinal fluid,Foveal contour was evaluated.

To measure the effectiveness of Brolucizumab age of the patient, initial best corrected visual acuity (BCVA) and the number of injections administered in the first 3 months were noted.

STATISTICAL ANALYSIS
The data were presented as the mean standard deviation (SD). Statistical differences between pre and post treatment clinical data were assessed using a paired t-test.A p-value of less than 0.05 was considered to be statistically significant.

RESULTS
In this prospective clinical study of 20 eyes which were diagnosed with DIABETIC MACULAR EDEMA in our institute were treated with intravitreal injection Brolucizumab during January 2022 to December 2022.Results and data obtained from this study are as follows:

1.AGE
The mean age of DIABETIC MACULAR EDEMA.There were 12 cases of male and 8 cases of female.

Gender	No. of patients	Percentage
Male	12	60%

Female	8	40%

2.PREDISPOSING FACTORS

In our study ,we got.

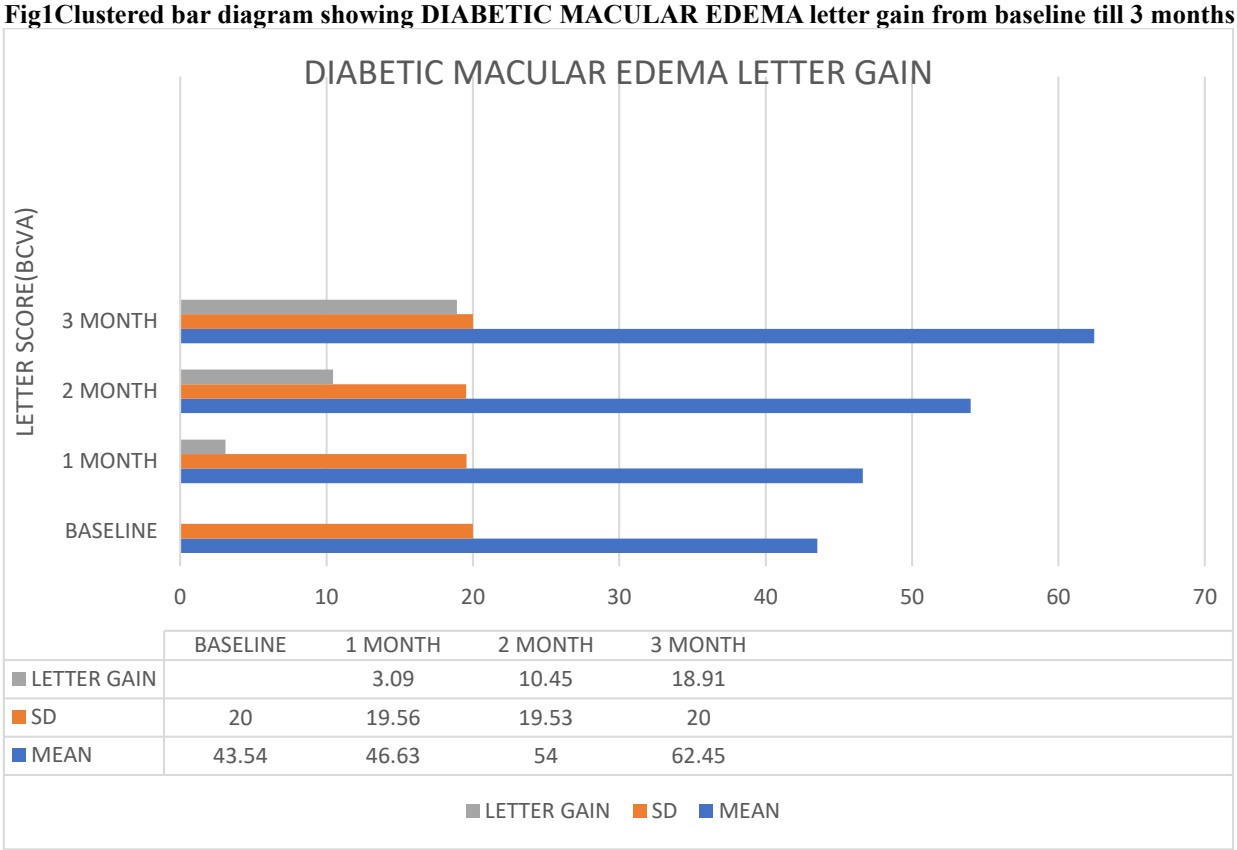
Predisposing factor	No. of Patients	Percentage(%)
Hypertension	11	55%
Diabetes Mellitus	20	100%
Hyperlipidemia	17	85%
Glaucoma	4	20%

3.VISUAL ACUITY OUTCOMES

In our study,it was observed that the mean (±SD)BCVA in DIABETIC MACULAR EDEMA was 43.54(±20) letters at baseline and was 62.45(±20) letters at 3 months after treatment with IVI Brolucizumab.From baseline,there was a significant improvement in BCVA by 18.91(±9) at 3 months.This was statistically significant($p<0.00001$).The maximum gain in BCVA was achieved during 3 month which was 18.91 letters.

In this study, 45.54 % patients gained >/=15 letters of BCVA and 54.54 % patients were having <15 letters of BCVA by 3 months.

Fig1Clustered bar diagram showing DIABETIC MACULAR EDEMA letter gain from baseline till 3 months



	BASELINE	1 MONTH	2 MONTH	3 MONTH
LETTER GAIN		3.09	10.45	18.91
SD	20	19.56	19.53	20
MEAN	43.54	46.63	54	62.45

Table 1 :BCVA letter score till 3 months after IVI

4.CHANGE IN CENTRAL FOVEAL THICKNESS(CFT)

Central Foveal thickness was assessed in all OCT images and it was defined as centre point thickness.

There was a significant decrease in CFT after the first IVI of Brolucizumab at 1 month in our studies and the decrease in thickness was maintained throughout the study.The difference at 1 month was statistically significant,as were differences at all subsequent graded assessments($p=0.00024$ at each time point). The mean (SD) central foveal thickness decreased from 546.09(±198.48) µm at baseline to 249(± 20) µm at 3 months.There was a significant reduction in CFT of 297.09 µm at 3 months.

OCT CFT (IN MICRON)

	BASELINE	1 MONTH	2 MONTH	3 MONTH
MEAN	546.09	296	283	249
SD	198.48	70.43	57.58	20
Decrease in CFT	0	-250.091	-263.091	-297.09

TABLE 2 : Decrease in CFT with IVI Brolucizumab in DIABETIC MACULAR EDEMA till 3 months

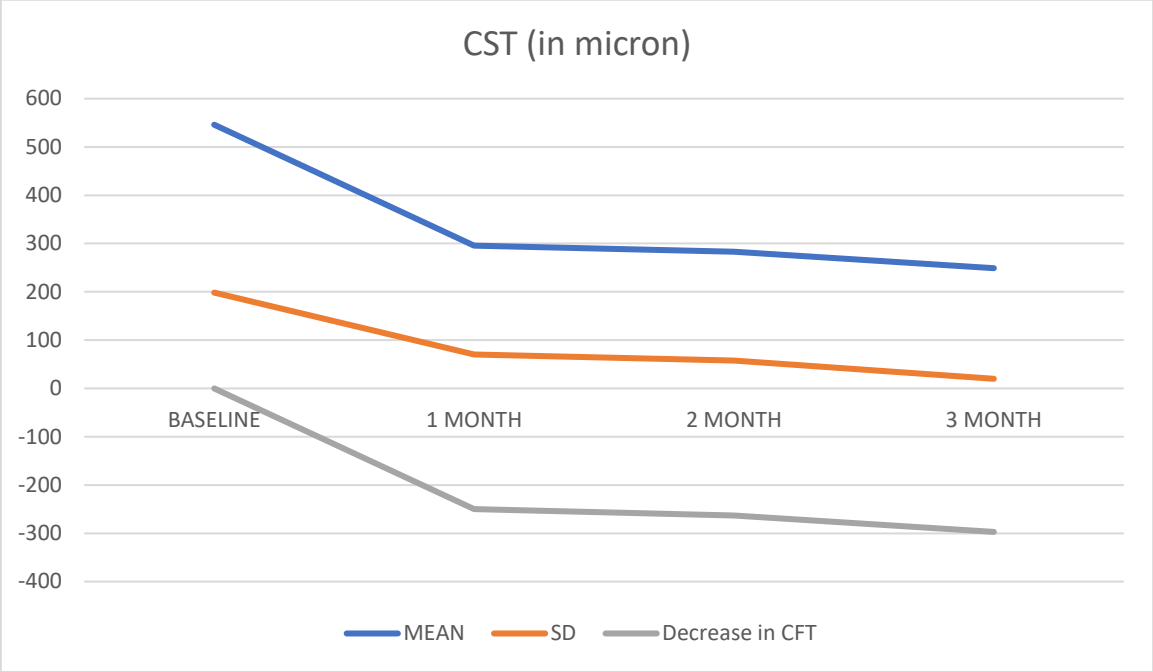


Figure 2: Line diagram showing decrease in CFT after IVI Brolucizumab at 3 months.

5.FREQUENCY OF DOSING

In 16 out of 20 cases,the effect of intravitreal injection Brolucizumab was maintained throughout 3 months.2 out of 20 cases required additional dose of intravitreal injection Brolucizumab at 2nd month of follow up and 2 cases required additional dose of intravitreal Brolucizumab at 3rd month.

COMPLICATIONS

During our checkup following injection,we found that cases out of 4 cases of 20 DIABETIC MACULAR EDEMA had Sub conjunctival haemorrhage,which resolved completely within 2 weeks of post injection.8 cases of DIABETIC MACULAR EDEMA had mild to moderate eye pain,some of which required oral analgesics and was controlled with 1 or 2 tablets. 2 of DIABETIC MACULAR EDEMA patients had developed rise in intraocular pressure following injection which is controlled with short course of anti-glaucoma medications. 1 case of DIABETIC MACULAR EDEMA also showed mild anterior chamber reaction following Anti VEGF injection which resolved with short course of Topical Steroids.No other patients developed any other ocular side effect.

Among Systemic complications we found that 1 out of 20 patients had developed transient rise in Blood pressure.All of them were managed with anti-hypertensive drugs.No other systemic side effects were evident.

COMPLICATIONS	NO. OF PATIENTS	PERCENTAGE (%)
Sub Conjunctival haemorrhage	4	20
Ocular Pain	8	40
Increase IOP	2	10
Anterior Chamber Reaction	1	5
Raised Blood Pressure	1	5

DISCUSSION

DIABETIC MACULAR EDEMA is one of the important sight threatening cause in Modern era.Taking this into consideration,we did this study where a detailed analysis of functional and anatomical outcomes in patients with Naïve centre involved Diabetic Macular Edema with Intravitreal anti-VEGF injection Brolucizumab who demonstrated poor visual acuity at presentation were done.

Other Studies showed that blocking VEGF with intravitreal Brolucizumab has a rapid and beneficial effect on visual function.This effect is due to the reduction in vascular leakage and preventing development of any neovascularisation that is mediated by VEGF.

CHANGE OF VISUAL ACUITY IN DIABETIC MACULAR EDEMA WITH IVI BROLUCIZUMAB

In our study,it was observed that the mean (±SD)BCVA in DIABETIC MACULAR EDEMA was 43.54(±20) letters at baseline and was 62.45(±20) letters at 3 months after treatment with IVI Brolucizumab.From baseline,there was a significant improvement in BCVA by 18.91(±9) at 3 months.This was statistically significant($p<0.00001$).The maximum gain in BCVA was achieved during 3 month which was 18.91 letters.

Therefore,the effect of IVI Brolucizumab in DIABETIC MACULAR EDEMA on visual acuity in ETDRS chart is comparable to most other studies.

LETTER GAIN IN DIABETIC MACULAR EDEMA WITH IVI BROLUCIZUMAB

In this study, 45.54 % patients gained >/=15 letters of BCVA and 54.54 % patients were having <15 letters of BCVA by 3 months.

Brolucizumab in Diabetic Macular Edema is comparable to most other studies.

CHANGE IN OCT IN DIABETIC MACULAR EDEMA AFTER IVI BROLUCIZUMAB

There was a significant decrease in CFT after the first IVI of Brolucizumab at 1 month in our studies and the decrease in thickness was maintained throughout the study.The difference at 1 month was statistically significant,as were differences at all subsequent graded assessments($p=0.00024$ at each time point). The mean (SD) central foveal thickness decreased from 546.09(±198.48) µm at baseline to 249(± 20) µm at 3 months.There was a significant reduction in CFT of 297.09 µm at 3 months.

Thus the change of OCT in DIABETIC MACULAR EDEMA following IVI Brolucizumab in our study was comparable to other studies.

CONCLUSION

From our present study we can conclude that intravitreal injection of Brolucizumab is found to be excellently efficacious and safe.Best visual acuity outcomes are achieved by treating immediately upon diagnosis of naïve centre involved Diabetic Macular edema.Intravitreal Brolucizumab injection appears to result in significant improvement in BCVA and reduction in macular edema as early as 1 month after 1st injection. The duration of effect following each intra vitreal injection of Brolucizumab was maintained for more than 3 months in majority of cases.Individualised injections of Brolucizumab showed promising short term results.Further studies are needed to prove the long term effect of Brolucizumab on patients with Diabetic Macular Edema.

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Conflicts of Interest: There are no conflicts of Interest.

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