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A Study on the Outcomes of Intravitreal Bevacizumab in the Treatment of Diabetic Macular Edema

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ABSTRACT

Background and Objectives: VEGFs play a key role in the pathogenesis of DME by promoting angiogenesis and break down of the blood-retinal barrier, causing interstitial edema. Currently, anti-VEGFs are considered to be the first line of treatment of DME. The current study was done to assess the 6 monthly outcomes in namely, the BCVA using Snellen's acuity test and CMT using OCT, in patients treated with at least a single dose of 1.25mg of intravitreal bevacizumab (Avastin), which is a fully humanised MAB active against VEGF.

Materials and methods: This is a prospective, non-randomised interventional study, done over a period of 18 months at a tertiary health care centre in Bangalore. A total of 50 patients (67 eyes) diagnosed with DME were enrolled in the study and underwent complete ocular examination including BCVA using Snellen's acuity testing, ophthalmoscopic examination and OCT. Patients were then treated with 1.25mg intravitreal bevacizumab (single or multiple doses) and followed up for 6 months at 2 monthly intervals. The main treatment outcome measures considered were CMT and BCVA and the same were recorded at each follow-up visit. Snellen's BCVA was converted to logMAR for analysis.

Results: The mean age was 55.62 ±13.88 years (range 27-78 years). Mean baseline logMAR BCVA was 0.79 and the final mean BCVA was 0.36, a difference that was statistically significant ($p<0.01$). Mean CMT by OCT at baseline was 412.5 ± 43.3µm which reduced to a mean of 258.8 ± 46.4µm at 6 months ($p<0.01$). Recurrence was noted in 24% (16/67 eyes) of patients, the mean time of recurrence being 19.3 weeks. 21 eyes needed a second injection while 3 eyes required a third injection. 2.9% of the eyes (2 patients) developed uveitis as a local complication but no systemic complications were noted during the course of the study.

Conclusion: Intravitreal bevacizumab has shown promising outcomes in the treatment of DME with significant improvement in BCVA and CMT in treated patients. Although the follow-up period in this study is short and the instance of recurrence is quite high, it still seems to be very effective in controlling DME in the short term.

Keywords: Diabetic macular edema (DME); Optical coherence tomography (OCT); best corrected visual acuity (BCVA); Vascular endothelial growth factor (VEGF); Avastin

I. INTRODUCTION

Diabetes mellitus is a chronic disease which has grown by leaps and bounds over the last decade, and India has also been impacted tremendously by it. Approximately 425 million people globally between the ages of 20 to 79 years are living with diabetes mellitus (DM) and it has been anticipated that by the year 2045, 629 million individuals in the same age group will suffer from the disease[1]. As the number of individuals living with diabetes surges, the number of diabetic patients living with its complications, including diabetic retinopathy (non-proliferative and proliferative diabetic retinopathy), and diabetic macular edema is also increasing. There has been an estimated increase of diabetic retinopathy and diabetic macular edema cases to 191.0 million and 56.3 million respectively[2]. Diabetic macular edema (DME) is the most common cause of visual loss in patients with diabetes mellitus. It primarily involves the central vision, and it can vary from mild blurring to total blindness, consequently concerning independence as well as quality of life[3]. Diabetic macular edema is exemplified by central accumulation of fluid surrounding the macula because of widespread capillary leakage as well as localized edema[4]. The Early Treatment Diabetic Retinopathy Study (ETDRS) describes Clinically Significant Macular Edema (CSME) as:

- Retinal thickening within 500 µm of the macular center.
- Exudates within 500 µm of the macula (central part) and if linked with retinal thickening, the thickening itself may be external to 500 µm.

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- Retinal thickening of disc area (1500 μm) or larger, any component of which is within one-disc diameter of the macular center[6].

In Wisconsin epidemiologic study of Diabetic retinopathy, the frequency of macular oedema was 20% and 24.5% in type I and type II diabetes mellitus respectively[7]. DME can arise at any diabetic retinopathy stage and change the macular structure impacting its function significantly[8]. The key facilitators in the pathogenesis of DME are vascular endothelial growth factors (VEGF). VEGF encourage angiogenesis and trigger the collapse of blood-retina barrier (BRB) by breaking the tight junctions between retinal endothelial cells. The breakdown leads to accumulation of plasma proteins like albumin that build up oncotic pressure in the neural interstitium, causing interstitial oedema and consequently, macular oedema. Recent scientific data has found high levels of VEGF in ocular fluids of patients suffering from proliferative diabetic retinopathy (PDR)[9,10,11]. These studies also uncovered that the growth of new vasculature from the retina or optic nerve was believed to be occurring because of VEGF release into the vitreous cavity as a reaction to ischemia. Additionally, injection of VEGF into normal primate eyes stimulates the same pathological processes observed in diabetic retinopathy, involving microaneurysm formation and enhanced vascular permeability[12,13].

DME is detected using a condensing lens of 90D or 78D with the help of a slit lamp biomicroscopy that uncovers the existence and whereabouts of macular thickening, exudates, as well as cystoid changes. Optical Coherence Tomography (OCT) helps in the confirmation of diagnosis by offering retinal sectional images and hence facilitates in assessment of structural modifications in the macula. This is helpful in evaluating pre as well as post treatment macular architecture and follows up macular alterations over a long period.

For nearly three decades now, laser photocoagulation has been the backbone of management for DME patients; however, this has a restricted role in enhancing vision because of edema[14]. The latest introduction of anti-VEGF therapy has been presenting encouraging reversal of the damaged vision[15]. Presently, the first line management of DME is anti-VEGFs which include Bevacicumab, Aflibercept or Ranibizumab. Nevertheless, anti-VEGFs have a brief half-life, also macular swelling is expected to occur again, and hence multiple injections have to be provided[16].

Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a complete full- length humanized monoclonal antibody which gets attached to all the VEGF subtypes and is used effectively in tumour therapy as a systemic drug. Recent research publications have established the utility of intravitreal injection of Bevacizumab in decreasing macular edema occurring because of central retinal vein occlusion (CRVO), vascular permeability as well as fibrovascular proliferation in retinal neovascularization as a consequence to PDR and choroidal neovascularization consequent to age-related macular degeneration (AMD)[17]. A handful of studies have assessed the outcomes of intravitreal

Bevacizumab in instances of diabetic macular oedema, but majority of them are from the Western countries. In pan-America research by Arevalo et al., the authors discovered that primary intravitreal Bevacizumab appear to deliver stability or improvement in visual acuity, optical coherence tomography, as well as fluorescein angiography in DME cases at follow-up of 6 months. Nevertheless, such studies are few in number and there is an obvious shortage of relevant research studies in the Indian population. Hence, it was decided to evaluate the outcomes of intravitreal Bevacizumab in the management of diabetic macular oedema, in a tertiary care teaching hospital in India. This study will help add important evidence related to this novel therapy, which can help Indian ophthalmologists in managing DME cases in a better way.

OBJECTIVES:

• To assess changes in BCVA in patients treated with intravitreal Bevacizumab

• To assess the changes in central retinal thickness (macular) in patients using SD-OCT (Spectral Domain-Optical Coherence Tomography).

II. METHODOLOGY

The present study was a prospective, non-randomized, interventional study conducted in a tertiary care hospital in India for a period of 18 months (1.5 years). A sample size of 50 was calculated after considering the prevalence of DME to be 7% as quotes in studies conducted previously. After obtaining clearance from the institutional ethics committee, 50 patients who presented to the Department of Ophthalmology who were clinically diabetic and diagnosed with DME and satisfied the following inclusion and exclusion criteria, were

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enrolled in the study after obtaining written and informed consent.

Inclusion criteria:

- Patients willing to give informed consent.
- Patients with DME treated with at least one intravitreal injection of 1.25mg bevacizumab
- Clear ocular media

Exclusion criteria:

- Patients not willing to give informed consent.
- Patients (eyes) with DME previously treated with laser photocoagulation or intravitreal triamcinolone acetate,
- Macular ischemia
- Presence of an epiretinal membrane or vitreomacular traction syndrome.
- Patients with a history of uncontrolled hypertension or recent thromboembolic event

Participant's demographic details, relevant history and duration of symptoms were recorded as per the pre-structured proforma. Patients were counselled about the disease and process of the study. A complete ocular examination was performed including baseline BCVA (using Snellen's chart), slit lamp biomicroscopy and fundoscopic examination. Baseline OCT parameters were assessed prior to the intervention (intravitreal Bevacizumab). The retinal thickness of the central 1mm retina was obtained using the macular thickness map. Patients were then subjected to the said intervention (intravitreal Bevacizumab), in single or multiple sittings.

After preparing the eye using 5% povidone-iodine, an eyelid speculum was used to stabilize the eyelids. A 1.25 mg (0.05ml) injection of bevacizumab was performed 3.5-4 mm posterior to the limbus, through the inferotemporal pars plana using a 30-gauge needle under topical anesthesia.

Patients were followed up for a period of 6 months at regular two-month intervals (2nd, 4th and 6th month).

At each follow up visit, BCVA (using Snellen's acuity chart), Fundoscopy and macular OCT parameters were assessed. Patients received repeat injections when there was a recurrence of DME or when there was no significant initial improvement in CMT (<100μm) from the baseline on follow up. Recurrence was defined as a decrease of BCVA (decrease in Snellen's acuity by one or more lines) or increase in CMT or both, after partial or complete resolution in previous follow-up visits.

The Snellen's BCVAs of patients were converted to logMAR scale (logarithm of minimum angle of resolution) for analysis. The main outcome measures considered were BCVA and CMT. All data was analysed using descriptive statistics, namely mean, standard deviation and percentage, wherever applicable. Repeated measures analysis of variance (ANOVA) was used to compare mean values to analyse mean retinal thickness and logMAR visual acuity statistically. A P value of<0.05 was considered to be statistically significant.

III. RESULTS

A total of 50 patients were enrolled. The mean age was noted to be 55.62 + 13.88 years (range: 27-78 years). Number of males in study was 26 (52%). 17 of the cases (34%) had both eyes affected. Majority of enrolled cases were between 51-60 years' age group (n=16, 32%). 9 patients each were between 61-70 years and 71-80 years. A total of 67 eyes were analysed for the study. 17 patients had both eyes affected, while 33 patients had only one eye affected. 33 of the eyes affected in study were affected by severe NPDR. 31 eyes had PDR while 3 cases had moderate NPDR. The mean logMAR was found to significantly decrease over the follow-up period (p<0.05).

The mean values are represented below in table 5.2 and figure 5.5.

Table 5.2: Mean logMAR at various time-points of follow-up

Time of assessment	Mean logMAR	P value
Baseline	0.79 ± 0.19	**<0.01***
2 months	0.53 ± 0.19	
4 months	0.42 ± 0.17	
6 months	0.36 ± 0.16	

P<0.05 considered significant by repeated-measures ANOVA test.

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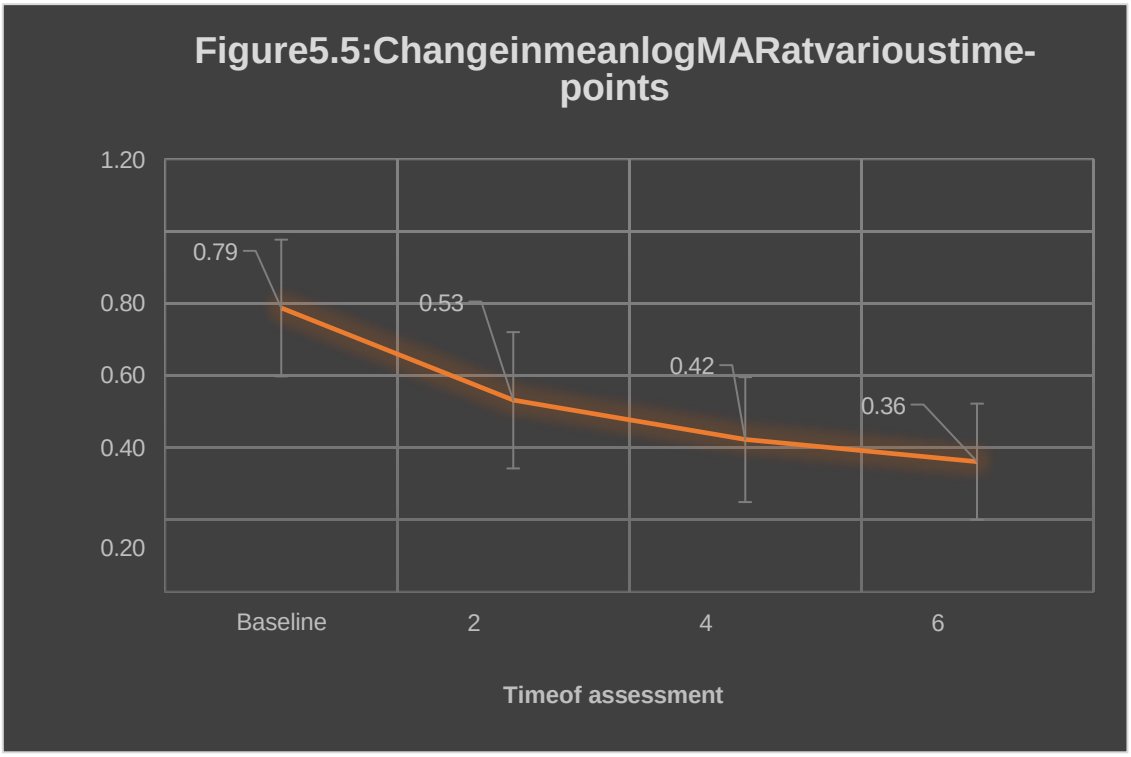
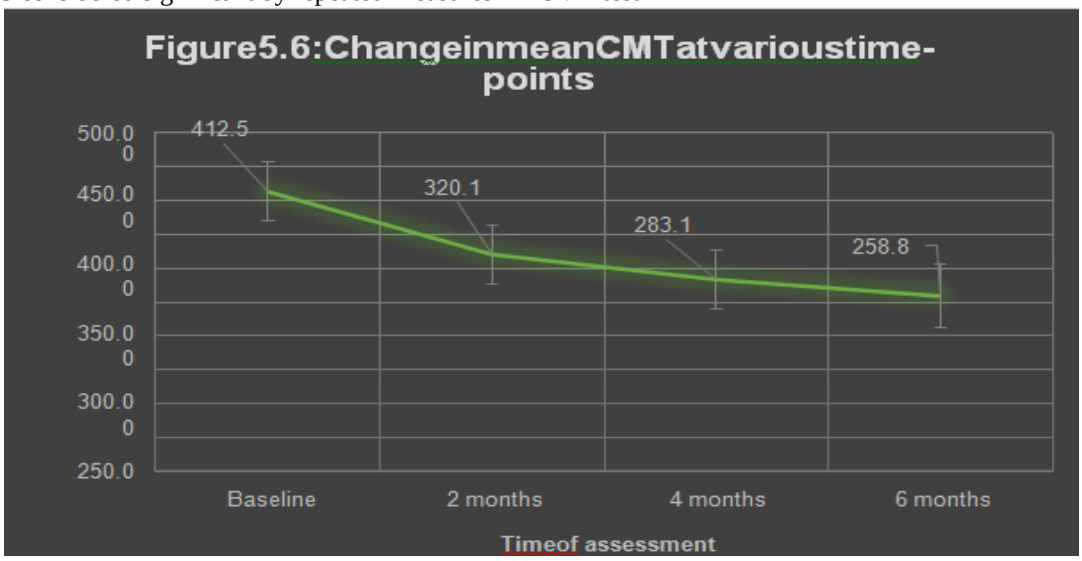


The mean CMT was found to significantly decrease over the follow-up period ($p<0.05$).
The mean values are represented below in table 5.3 and figure 5.6.

Table 5.3: Mean CMT at various time-points of follow-up		
Time of assessment	Mean CMT (µm)	P value
Baseline	412.57 ± 43.31	**<0.01***
2 months	320.1 ± 43.42	
4 months	283.19 ± 43.41	
6 months	258.85 ± 46.47	

P<0.05 considered significant by repeated-measures ANOVA test



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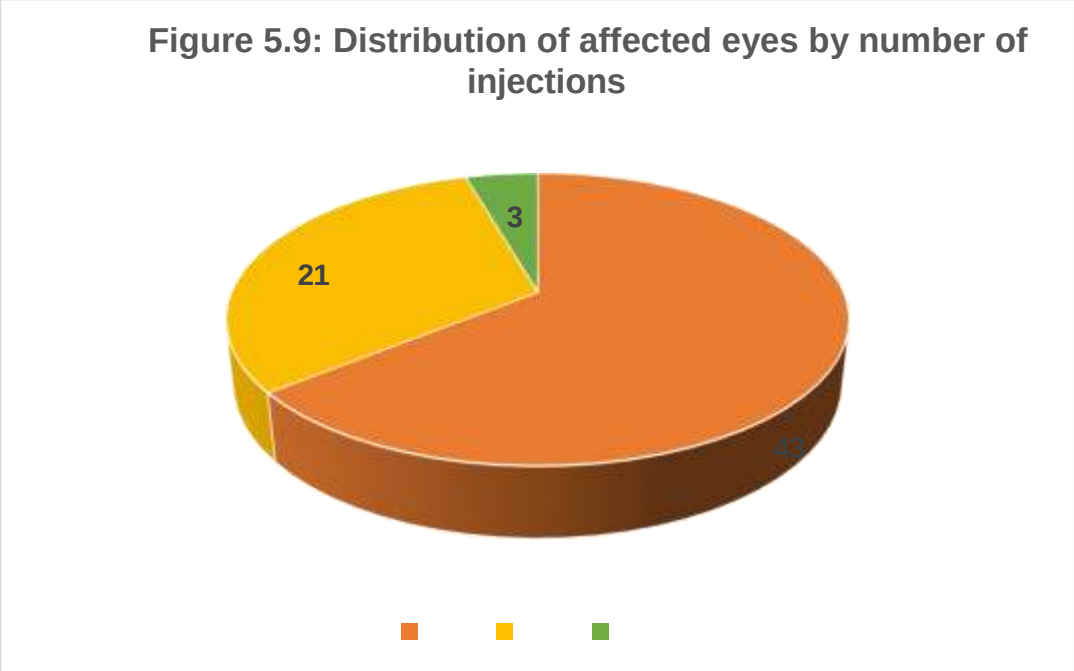
On assessing the BCVA status of the assessed eyes by Snellen's chart at 6 months' follow-up, it was noted that majority (58.21%) had more than 2 lines improvement. Overall, 91.05% eyes evaluated from the study had at least 1-line improvement. (Table 5.4).

Table 5.4: Final BCVA status at 6-months' follow-up by Snellen's Chartassessment

BCVA Status	Number of eyes assessed
No improvement	5 (7.46%)
1 line improvement	9 (13.43%)
2 lines improvement	13 (19.4%)
>2 lines improvement	39 (58.21%)
Decrease in visual acuity	1 (1.49%)

16 of the 67 eyes (24%) evaluated for study suffered from recurrence and the mean time of recurrence was 19.37 weeks. Recurrence was defined as a decrease in BCVA or increase in CMT or both.

43 of the 67 eyes evaluated were administered one injection, 21 eyes were administered two injections and 3 eyes received three injections. (Figure 5.9)



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Overall, 3 eyes i.e., 2.9% (2 patients) were affected by an adverse effect of the drug. Both these patients suffered from uveitis of which one patient had preexisting uveitis which got aggravated. There were no systemic side effects that were noted.

IV. DISCUSSION

On evaluating the demographic and patient details, mean age was noted to be 55.62 ±13.88 years (range: 27-78 years). Number of males in study was 26 (52%). 17 of the cases (34%) had both eyes affected. In other similar studies, identical findings were noted. Almost all the other studies had a mean patient age >50 years. In addition, almost all similar studies had male preponderance, as noted in our study.

33 of the eyes (49.25%) affected in study were affected by severe NPDR. 31 eyes (46.26%) had PDR while 3 cases (4.47%) had moderate NPDR. In the study by Vyas et al., majority of patients were in severe NPDR group (76.92%) followed by moderate proliferative diabetic retinopathy (PDR) group (15.38%) and early PDR (7.69%).[20] According to the study by Mahat et al., majority of the eyes were affected by moderate NPDR (44.8%), followed by 32.2% with severe NPDR (32.2%), while 18.3% had PDR.[22]

The mean logMAR was evaluated at 2 months, 4 months and 6 months from baseline, and it was noted that there was a significant reduction the mean logMAR at every follow-up compared to previous follow-up ($p<0.05$). The reduction in logMAR was statistically significant at last follow-up in almost all similar studies. This indicates that our findings are in agreement with those of other similar studies, which show that bevacizumab helps in significant improvement in the visual acuity of patients diagnosed with DME.The BCVA analysis was also done with the help of the Snellen chart, and the evaluated findings noted in a study. On assessing the BCVA status of the assessed eyes by Snellen's chart at 6 months' follow-up, it was noted that majority (58.21%) had more than 2 lines improvement. Overall, 91.05% eyes evaluated from the study had at least 1-lineimprovement. Similar findings were noted in the other studies by Khan et al., Vyas et al. and Fong et al.[18,20,21]

In the present study, after intravitreal bevacizumab treatment, the mean CMT was found to significantlydecrease over the follow-up period ($p<0.05$). The mean CMT at baseline in our study was 412.57 ± 43.31µm, which decreased to 258.85 ± 46.47µm at 6-monthfollow-up. This corroborates well with findings in other similar studies. The mean CMT thickness in the study by Kanji et al. decreased from 426.97 ± 148.358 µm to280.98 ± 95.89 µm at 30 weeks.[22] In another study by Vyas et al., mean CMT was 449.03±177.92 µm at baseline and it decreased significantly to 326.51± 175.06 µm ($p<0.001$) at 6 months.[20] In another study by Mahat et al., mean baseline CMT± SD in µm was 436.24 ± 142.2 measured by OCT, which decreased to307.1 ±105.49 at 18 weeks of assessment.[23] In the study by Mirshahi et al., in the DME group, the mean thickness decreased from 420.4 ± 47.3 µm at baseline to 316.7 ± 50.6 µm ($P<0.001$) one month after the last intravitreal injection.[24,25] The study by Joyce et al. also found that the mean CMT decreased from 512.99 µm at baseline to 322.80 µm at 12 months' follow-up.[19]

Recurrence in our study was defined as a decrease of BCVA (decrease in Snellen's acuity by one or more lines) or increase in CMT or both, after partial or complete resolution in previous follow-up visits.16 of the 67 eyes (24%) evaluated for study suffered from recurrence and the mean time of recurrence was 19.37 weeks. Most of the studies have not evaluated this parameter, and hence this is one of the strengths of our study. However, there is not much clarity in literature as to how to manage these recurrences. One of the studies by Vyas et al. mentions that recurrences were retreated at the discretion of the treating physician. Further injections were given in cases of recurrent subretinal or intraretinal fluid shown by OCT and visual deterioration. Although the authors could not establish the optimal administration time or the dosage from the study, they could estimate that visual acuity increases with decreased macular edema at 6 weeks post injection withblunted effect at 8-12 weeks post injection requiring another injection. In our study, 21 eyes were administered two injections and 3 eyes received three injections, depending on the recurrences and the response evaluated. On evaluating the adverse event pattern in study, 3 eyes i.e., 2.9% (2 patients) were affected by an adverse effect of the drug. Both these patients suffered from uveitis of which one patient had preexisting uveitis which got aggravated. There were no systemic side effects that were noted.

The study had various novelty factors and strengths, but there were a few limitations as well. The sample size was limited and the study was conducted at one study center. In addition, this was a single arm study and no comparison was done with other anti-VEGF therapy or other treatment modalities. Future studies can validate the study findings in an Indian setting with a bigger sample size and with a comparative study design which can help in validating our study findings.

V. CONCLUSION:

The current study was done to assess the treatment outcomes at 6 months, in patients with DME who had received at least a single injection (1.25mg) of IVB.

In the study, the mean logMAR BCVA improved from 0.79 at baseline to 0.36 at 6 months while the mean CMT improved from 412µm at baseline to 258 µm at 6 months. Both these parameters (BCVA and CMT) showed significant improvement in treated eyes. Although there.was a progressive decrease in CMT in patients during the course of the study, a more significant reduction was noted only at 2 months following treatment with a tapering of decrement on subsequent follow ups.

16 out of the 67 treated eyes (24%) showed recurrence of DME and the mean onset of recurrence was noted to be around 19 weeks. This suggests a waning in the effectiveness of IVB at around 4 months after treatment and the subsequent need for reinjections. However, majority of the patients did show stability or improvement in the BCVA even at the end of 6 months. 2.9% of treated eyes suffered from uveitis which resolved with treatment, no systemic side effects were noted.

Hence, this study suggests that anti-VEGF therapy, namely IVB, is indeed effective in the treatment of DME thus justifying its usage in current practice as the first line of treatment in the management of DME.

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