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Research Article

EVALUATION OF VISUAL OUTCOME AND CLINICAL RESPONSE OF INTRAVITREAL ANTI VEGF AGENTS IN VARIOUS INDICATIONS

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ABSTRACT

Objectives: The aim of the study was to evaluate efficacy of ranibizumab and aflibercept in Choroidal neovascular membrane (CNVM) and chronic macular edema secondary to diabetes mellitus and retinal vein occlusion in the Central India population.

Methods: The present study was a prospective and observational study conducted among patients attending the outpatient department, and retina clinic were grouped as per various indications of anti-vascular endothelial growth factor (anti-VEGF) treatment. Patients were then followed up on day 7, 1-month interval during which visual acuity assessment, fundus examination, and optic coherence tomography was done to measure central retinal thickness which was compared with baseline data.

Results: Two different anti-VEGF agents were used among study participants. Out of 43 study participants, ranibizumab was given in 32 (74.4%) of which seven patients had age-related macular degeneration (ARMD), four had myopic CNVM, 14 had diabetic retinopathy (DR), and seven had macular edema – secondary to retinal vein occlusion. Aflibercept was given in 11 (25.6%) of the study participants, of which six had DR, four had CNVM-Myopia, and one patient had macular edema – secondary to retinal vein occlusion.

Conclusion: In our study, both anti-VEGF agents showed significant reduction in central macular thickness (CMT) after every injection. Our study suggests that Aflibercept is more effective in reducing CMT.

Keywords: VEGF, Aflibercept, Ranibizumab, Retina, CNVM, Visual outcomes.

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INTRODUCTION

Macula and fovea are the light sensitive area of retina responsible for central vision. Various retinal disorders such as age-related macular degeneration (ARMD), proliferative diabetic retinopathy (DR), and myopic choroidal neovascular membrane (CNVM), which are the leading cause of severe visual loss, damages the retina by inducing neovascularization. Under normal circumstances, vascular endothelial growth factor (VEGF) is required for normal vascular development, but sometimes due to various factors such as hypoxia, oxidative stress to retina and RPE, alteration in Bruch's membrane, accumulation of lipid metabolic byproducts, overexpression of VEGF and its receptor occurs resulting in neovascularization, increasing vascular permeability, and leakage causing retinal and macular edema [1]. To protect the retina and to reverse the progression of disease, downregulation of VEGF and its receptors is required. This is achieved by intravitreal injection of anti-vascular endothelial growth factor (Anti VEGF). Anti-VEGF are small RNA like molecules that binds exclusively and with high affinity to human VEGF and its receptors and inhibits its action [2]. Various clinical trials have been done to study the efficacy of intravitreal. Anti-VEGF in ARMD, CNVM, DR, and retinal vein occlusion, in which efficacy was assessed on the basis of mean increase in best corrected visual acuity (BCVA) from baseline and decrease in central retinal thickness compared to baseline [3]. In the present scenario, various studies have reported difference in efficacy of Anti VEGF agents. Here, we are conducting this study, to evaluate efficacy of ranibizumab and aflibercept in CNVM and chronic macular edema secondary to diabetes mellitus and retinal vein occlusion in Central India population.

METHODS

Present study was a prospective and observational study conducted among patients attending the outpatient department, and retina clinic was grouped as per various indications of anti-VEGF treatment. relevant history regarding diminution of vision, characteristics of DOV, duration, metamorphopsia, central or paracentral scotoma, and the duration and progression of these symptoms were taken. A thorough examination comprised of-distant visual acuity- unaided, aided and with pin hole, was measured by Snellen's chart and then converted into LogMAR. and near vision was recorded. Anterior segment examination was done under high magnification of slit lamp to rule out any pathology of conjunctiva, sclera, cornea, iris, anterior chamber, pupil, and any evidence of uveitis. Intraocular of all patients were recorded with the help of an applanation tonometer. Posterior segment examination was done under mydriasis by direct and indirect ophthalmoscope and +90 D slit lamp biomicroscopy. Optic coherence tomography (OCT) was done to determine central macular thickness (CMT) with the on Cirrus HD OCT using 512×128 macular cube acquisition protocol. After explaining seriousness of disease, nature of treatment, the potential risks, benefits, adverse effects, alternative treatment options, and possible treatment outcomes Ranibizumab 0.5 mg/Aflibercept 2 mg was given intravitreally at 4.0 mm from limbus in inferotemporal quadrant in phakic eye and 3.5 mm in pseudophakic eye under topical anesthesia and topical antibiotic given for 1 week. Comparison between those receiving intravitreal ranibizumab and aflibercept was done. Patients were followed up on next day for visual acuity assessment and fundus examination. Patients were then followed up on day 7, 1-month interval during which visual acuity assessment, fundus examination, and OCT were done to measure central retinal thickness which was compared with baseline data. Clinical efficacy was evaluated in the form of visual outcome and anatomical efficacy in terms of decrease in CMT on OCT. Comparison between those receiving intravitreal ranibizumab and aflibercept was done.

Table 1: Comparison of mean improvement in visual acuity (functional improvement) in logMar units after first and second injection of ranibizumab

Visual Acuity	First injection		p-value	Second injection		p-value
	Baseline	After 1 month		Baseline	After 1 month	
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age-related macular degeneration	0.97 (0.5)	0.85 (0.6)	0.084	1.1 (0.5)	0.95 (0.5)	0.007
Myopic	1.15 (0.6)	1.05 (0.7)	0.391	1.15 (0.6)	1.1 (0.6)	0.391
Diabetic retinopathy	1.03 (0.4)	0.98 (0.4)	0.030	1.03 (0.4)	0.98 (0.4)	0.030
Secondary to retinal vein occlusion	1.21 (0.5)	1.1 (0.5)	0.122	1.36 (0.4)	1.21 (0.5)	0.121

Table 2: Comparison in mean improvement in visual acuity according to EDTRS scores after first and second injection of ranibizumab

Indication	ETDRS score difference (first injection)		ETDRS difference (second injection)	
	Mean	SD	Mean	SD
CNVM-Age-related macular degeneration	6.43	7.48	7.14	4.88
CNVM-Myopic	5.00	10.00	2.50	5.00
Macular edema – diabetic retinopathy	3.21	5.75	2.50	3.80
Macular edema – secondary to retinal vein occlusion	5.00	7.64	5.00	7.64

SD: Standard deviation

Table 3: Functional and anatomical outcome of intravitreal ranibizumab in cases of macular edema secondary to central retinal vein occlusion with reference to onset to CRVO

Duration (Months)	cases	Visual acuity			Central macular thickness			
		Baseline	After 1 month	p-value	Baseline	After 1 month		p-value
		Mean	Mean		Mean	Mean	Mean difference	
<3	2	1.00	0.83	0.031	360	310	50	0.000
3–6	5	1.03	0.99	0.52	364	313	51	0.000
>6	1	1.17	1.17		384	365	19	

Table 4: Comparison of mean improvement in visual acuity (functional improvement) in logMar units after first and second injection of aflibercept

Visual acuity	First injection		p-value	Second injection		p-value
	Baseline	After 1 month		Baseline	After 1 month	
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Myopic	1.04 (9)	0.82 (19)	0.037	1.04 (9)	0.87 (14)	0.006
ME diabetic retinopathy	0.91 (36)	0.82 (33)	0.082	1.02 (37)	0.95 (39)	0.190

SD: Standard deviation

Table 5: Comparison in mean improvement in visual acuity according to EDTRS scores after first and second injection of aflibercept

Aflibercept	ETDRS difference (first injection)		ETDRS difference (second injection)	
	Mean	SD	Mean	SD
CNVM- Myopic	8.75	8.54	8.75	2.50
Macular edema-diabetic retinopathy	4.17	4.92	7.50	4.18

SD: Standard deviation

Statistical analysis

Data were collected and entered simultaneously in Statistical Package for the Social Sciences (SPSS) version 23 and coded appropriately. The data were analyzed keeping in view the aims and objectives of the study. Descriptive and inferential statistical analyses were carried out in the present study. Results on continuous measurements are present on Mean±Standard deviation (Min-Max) and results on categorical measurements are prepared in number (%). The statistical software SPSS version 20 was used for analysis. Significance was set at standard 0.05.

RESULTS

In the present study, intravitreal ranibizumab was administered in 32 (74.4%) patients of which seven patients had ARMD, four patients had myopic CNVM, 14 patients had DR, and seven patients had macular edema – secondary to retinal vein occlusion. Intravitreal aflibercept was administered in 11 cases. Two different anti-VEGF agents were used among study participants. Out of 43 study participants, ranibizumab was given in 32 (74.4%) of which seven patients had ARMD, four had myopic CNVM, 14 had DR, and seven had macular edema – secondary to retinal vein occlusion. Aflibercept was given in 11 (25.6%) of the study participants, of which six had DR, four had CNVM-Myopia, and one patient had macular edema – secondary to retinal vein occlusion.

Ranibizumab group

In our study, functional outcome was measured in the form of improvement in visual acuity. Snellen acuities were converted to logarithm of minimum angle of resolution (logMAR) to facilitate

Table 6: Comparison of mean of central macular thickness (anatomical improvement) in different study groups after first and second injection of Aflibercept

Visual acuity	First injection			p-value	Second injection			p-value
	Baseline	After 1 month	Absolute value		Baseline	After 1 month	Absolute value	
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Myopic	399.5 (86.5)	308.5 (81.9)	91	0.00	394.8 (85.4)	306.5 (78.7)	88.3	0.00
ME diabetic retinopat hy	409.7 (124.1)	311.3 (100.3)	98.4	0.00	371.3 (41.2)	301 (34.6)	70.3	0.03

SD: Standard deviation

statistical analysis. The paired student t-test was used to compare the mean visual acuity before and after injection. Above table shows the comparison of mean of logMAR before and after first and second injection of ranibizumab. It was found that in all four groups, there was decrease in mean value of BCVA from baseline to after 1 month of ranibizumab injection. However, functional improvement in the form of improvement in visual acuity was significantly seen in patients with ARMD and DR. Mean increase in visual acuity after first injection of ranibizumab was 6.43 l in ARMD group, 5 l in myopic CNVM, 3.2 l in DR, 5 l in macular edema secondary to vein occlusion. Similarly, after the second injection, there was an improvement of 7.14 l in ARMD group, 2.50 l in myopic CNVM, 2.5 l in DR, 5 l in macular edema secondary to vein occlusion. In the present study, no statistically significant improvement in mean LogMAR was observed when intravitreal ranibizumab was administered within 3 months or after 3 months of onset of Central Retinal Vein Occlusion (CRVO). However, reduction in CMT was found to be statistically significant in patients who received intravitreal injection within 6 months of onset of CRVO.

Aflibercept group

In cases where, afliberecpt was given statistical significant difference in mean values of Visual acuity was seen in patients myopic CNVM after every injection, while no significant difference was seen in other groups. As a number of cases of ARMD and macular edema secondary to vein occlusion were very less, we have not included it for statistical analysis. According to ETDRS scores, mean increase in visual acuity after first injection of ranibizumab was 8.75 l in myopic CNVM, 4.17 l in DR, 5 l in macular edema secondary to vein occlusion. Similarly, after second injection there was an improvement of 8.75 l in myopic CNVM, 7.5 l in DR. Significant decrease in CMT was seen in all patients of myopic CNVM (91μm) and DR (98.4μm) after 1 month of first injection. CMT decreased by 88.3 in myopic CNVM, 70.3 in DR after second injection. As a number of cases of ARMD and macular edema secondary to vein occlusion were very less, we have not included it for statistical analysis.

DISCUSSION

RanibizumabThe mean LogMAR among study participants with ARMD at baseline and after first injection was 0.97±0.50 and 0.85±0.55, respectively, with mean increase in visual acuity of 6.43 l. Similarly, after second injection, there was a decrease in mean LogMAR visual acuity from 1.15±0.6 to 0.95±0.52 with an improvement of 7.14 l. The observed difference was found to be statistically significant. Chin-Yee et al. [4], found a mean improvement in visual acuity of 5.4 l for wet ARMD following PRN (as needed) regimen of anti-VEGF, and about 10 l improvement following treat and extend regimen, with an average of 5.6 and eight injections over 12 months, respectively.

In patients with myopic CNVM, it was observed that at administration of first injection of ranibizumab, mean LogMAR visual acuity was 1.15±0.59 which decreases to 1.05±0.65with mean improvement of 5.00 l. After administration of second injection, mean LogMAR visual acuity was 1.15±0.59. Which decreases to 1.10±0.61. Ellabban *et al.* (3) in their study reported that mean visual acuity before treatment was 0.49 ± 0.37, after the loading phase, it was 0.23±0.28 and reduced to 0.24±0.31 at final examination.

Recent studies indicate that the prevalence of DR is proportionally rising, with the prevalence overall perhaps reaching 35% for any DR, 7% for proliferative DR, and roughly 7% for diabetic macular edema (DME). It was found that at administration of first injection of ranibizumab in patients of macular edema secondary to DR, mean LogMAR visual acuity was 1.03±0.4 which decreases to 0.98±0.44 with a mean improvement of 3.21 l which was statistically significant. According to James *et al.* [5], mean baseline BCVA was 0.47±0.30, which improved to 0.38±0.3 at 3 months and stabilized at 0.35±0.27 at 1 year and 0.34±0.26 at 2 years of follow-up [45].

In our study, it was found that at administration of first injection of ranibizumab among participants of macular edema – secondary to retinal vein occlusion, mean LogMAR was 1.21±0.46 which reduced to 1.10±0.49 with mean improvement of 5.00 l after first injection. LogMAR further reduced to 1.21±0.50 after second injection. According to Tunji *et al.* [6], the mean BCVA improved for all eyes from 1.67±0.91 at baseline to 1.21±1.01, 1.41±1.09, 1.44±1.17, and 1.50±1.27 at 1 month, 3 months, 6 months, and 1 year, respectively. Patients who had at least three injections were significantly more likely to have better visual outcomes than those who had <3 injections. Our study showed improvement with ranibizumab.

This increase in visual acuity was statistically significant in ARMD and DR. However, myopic CNVM and macular edema secondary to vein occlusion failed to show statistically significant improvement in visual acuity. This can be attributed to less number of subjects in these subgroups.

Mean CMT among study participants with ARMD was 359±43.6 at baseline and reduced to 295±41.4 μm, that is, reduction of 63.4 μm after first injection of ranibizumab. After 1 month of second injection mean CMT reduced by 68.8μm from baseline 383±28.7 which was found to be statistically significant. Out of seven patients, three patients showed improvement with Ranibizumab. Lalwani *et al.* [7], in their study (PrONTO) also found a significant reduction in CMT in patient with ARMD after ranibizumab injection with baseline CMT of 300 μm which reduced to 212 μm.

Mean CMT among study participants with myopic CNVM was 357±41.9 at baseline and reduced by 66 m (1291±37.5) after one first injection. After 1 month of second injection mean CMT reduced from 351±30.3 to 285±31.1, that is, reduction of 67.4 m. Ellabban et al. [3] in their study reported that mean CMT before treatment was395.9±143.9, after the loading phase of ranibizumab, it was 245.7±72.1 and reduced to 240.8±71.7 [42]. Highest Mean CMT among participants of macular edema secondary to DR was 371±48.5 at baseline and reduced to 294±39 after first injection. After 1 month of second injection, mean CMT was reduced by 72.9 m. Massin et al. [8] in their study reported that CMT decreased from 300 to 194 after ranibizumab at end of 12 month, after 3 monthly injections.

Mean CMT among the participants of macular edema secondary to vein occlusion at baseline was 369±53.1 μm and reduced to 290±47.7 μm after 1 month of first injection. After second injection, mean CMT was 282±40.4 reduced from baseline 356±54.9. Gündoğdu *et al.* [9] in their study reported that CMT decreased from 383.5±37.2 μm to 337.7±39.4 μm at the 1st month visit after intravitreal ranibizumab injection.

In our study, on comparing the functional and anatomical outcome of intravitreal ranibizumab in cases of macular edema secondary to CRVO with reference to onset of CRVO, there was a decrease in mean LogMAR visual acuity but was not statistically significant. However, reduction in CMT was found to be statistically significant in patients who received intravitreal injection within 6 months of onset of CRVO. However, DeCroos *et al.* [10] in their study observe that intravitreal ranibizumab improves foveal thickness in eyes with CRVO, but this does not always correlate with visual recovery. No difference in efficacy was observed when used for early (<90 days) versus late treatment (>90 days). This can be attributed to the pathomechanism of the development of macular edema secondary to CRVO and DME because we have seen statistically significant improvement in both visual acuity and CMT in cases of DME after intravitreal injection of Ranibizumab.

Aflibercept

In patients with myopic CNVM, it was observed that at administration of first injection of aflibercept, mean visual acuity was 1.04±0.09 which decreases to 0.82±0.19 with mean improvement of 8.75 l. The observed difference between baseline and final visual acuity after every injection was found to be statistically significant. Aflibercept was administered to six patients with DR, with mean LogMAR visual acuity of 0.91±0.36 which reduces to 0.82±0.33 after first injection with a mean improvement of 4.17 l. Rodríguez *et al.* [11] in their study (AQUILA) reported that mean best-corrected visual acuity improved from baseline to +8.1 ±17.7 in treatment-naïve (baseline: 54.5±19.4) and +4.6 ±15.4 l previously treated (baseline: 52.9±18.6). Shimizu *et al.* [12] in their study reported that the BCVAs were significantly better at 1 and 6 months after the IVA.

In patients of myopic CNVM mean CMT decreased by 91 μm, reduced from 399.5 to 308.5 and after second injection mean CMT reduced from 371±41.2 to 301±34.6. Mean CMT among study participants with DR at baseline was 409 which reduced to 311±100. 3 after 1 month of first injection. Similarly, after second injection, mean CMT reduced from 351±30.3 to 285±31.1. Statistically significant decrease in mean CMT was seen in all patients of myopic CNVM and DR after every injection of Aflibercept. As a number of cases of ARMD and macular edema secondary to vein occlusion were very less, we have not included it for statistical analysis.

Our findings suggest that aflibercept is more effective in reducing CMT in DR as compared to ranibizumab. Similar results were reported by Shimizu *et al.* [12], mean CMT was significantly reduced at 1, 3, and 6 months after both IVR and the IVA treatment although IVA was more effective. As a number of cases of ARMD and macular edema secondary to vein occlusion were very less, we have not included it for statistical analysis.

CONCLUSION

In present study, it was observed that there was decrease in mean LogMAR visual acuity showing improvement in visual acuity in different study subgroups. This increase in visual acuity was statistically significant in ARMD and DR. However, other groups failed to show statistically significant improvement in visual acuity. This can be attributed to less number of subjects in these subgroups. However, more studies with an increased number of cases and other biomarkers for non-resolving macular thickness should be considered to exactly ascertain the association between these. In our study, both anti-VEGF agents showed significant reduction in CMT after every injection. Our study suggests that aflibercept is more effective in reducing CMT.

Limitations and scope

Major limitation of the present study is its small sample size due to COVID-19 pandemic and the duration of study was small. Furthermore, patient was given choice regarding selection of anti-VEGF agent with the majority of patients selecting intravitreal ranibizumab because of the cost resulting in less number of cases in aflibercept group.

ETHICAL APPROVAL

Approved.

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CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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