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Original Research Article

"Evaluation of Safety Intravitreal Anti VEGF Agents in a Tertiary Care Institute"

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Abstract

Introduction: A majority of recent researches suggesting that VEGF plays a significant role in initiation of neovascularization and has been introduced for treatment of vascular and exudative diseases of retina. There are certain adverse effects which were evident with the use of intravitreal injection of anti VEGF. Here we are conducting this study, to evaluate safety profile of Ranibizumab and Aflibercept in CNVM and chronic macular oedema secondary to Diabetes mellitus and retinal vein occlusion in central India population.

Method: Present study was a prospective and observational study conducted among patients attending the OPD, and retina clinic were 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 clinical examination was also done.

Results: In the present study, no sight threatening complications were seen with Ranibizumab. Most common side effect after first injection of Ranibizumab was conjunctival congestion 24 (72.73 %) followed by ocular pain 5 (15.15%) and subconjunctival hemorrhages 4 (12.12%). On comparing Mean interval between first and second injection of Ranibizumab and Aflibercept injections, it was observed that mean interval between two injections in Ranibizumab administered group was 8-10 weeks and in Aflibercept administered group was 16-18weeks.

Conclusion: In order to treat retinal disorders optimally, anti VEGF drugs must be injected repeatedly over months, requiring multiple clinical visits and high cost of treatment.

Keywords: VEGF, Aflibercept, Ranibizumab, Retina, CNVM, Side effects

Introduction

VEGF is a homo dimeric glycoprotein that is a heparin binding growth factor specific for vascular endothelial cells. VEGF and its receptors are primarily located in Retinal Pigment Epithelium (RPE), vascular endothelium and muller cells [1]. A majority of recent researches suggesting that VEGF plays a significant role in initiation of neovascularization and has been introduced for treatment of vascular and exudative diseases of retina, being licensed for ARMD, Diabetic retinopathy, Retinal vein occlusion and Myopic CNVM. Various types of Anti-VEGFs acting via different mechanisms are clinically available, some are FDA approved like Ranibizumab, Pegaptanib, Aflibercept while others like Bevacizumab is being used as OFF-label drug. Despite halting the disease and improving vision, repeated and long-term injections of Anti VEGF, may increase the chance of ocular and systemic adverse effect [2]. There are certain adverse effects which were evident with the use of intravitreal injection of anti VEGF like ocular inflammation, subconjunctival hemorrhage, increased intra ocular pressure, floaters, vitreous hemorrhage, retinal tears, retinal detachment and endophthalmitis and systemic adverse events include hypertension, myocardial infarction, stroke, arterio-thromboembolic events [3]. In the present scenario, various studies have reported difference in safety profile of these agents. Here we are conducting this study, to evaluate safety profile of Ranibizumab and Aflibercept in CNVM and chronic macular oedema secondary to Diabetes mellitus and retinal vein occlusion in central India population.

Material and Methods:

Present study was a prospective and observational study conducted among patients attending the OPD, and retina clinic were 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, any evidence of uveitis. Intra ocular (IOP) of all patients were recorded with the help of 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 with the on Cirrus HD OCT using 512x128 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 4.0mm from limbus in infero-temporal quadrant in phakic eye and 3.5 mm in pseudo phakic eye under topical anesthesia and topical antibiotic given for 1 week. Patients were followed up on next day to look for site discomfort, transient elevation of IOP, inflammation, redness, floaters or any ocular discomfort. Patients were then followed up on day 7, 1-month interval during which they were enquired about any adverse event. Comparison between those receiving intravitreal Ranibizumab and aflibercept was done.

Statistical Analysis:

Data was collected and entered simultaneously in statistical package for social sciences (SPSS) version 23 and coded appropriately. The data was analysed 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±SD (Min- Max) and results on categorical measurements are prepared in number (%). The statistical software SPSS version 20 (The Standard Protocol for Social Sciences) were used for analysis.. Significance was set at standard 0.05.

Results:

In present study, we observed that mean age of participants with Age Related Macular Degeneration was 57 ± 23 years, Myopic CNVM was 58 ± 10 years, Macular Oedema secondary to Diabetic Retinopathy was 57 ± 11 years and Macular Oedema Secondary to Retinal Vein Occlusion was 57 ± 09 years. Also, most of the patients of CNVM due to age related macular degeneration were males and myopic CNVM were more common among females. Intravitreal Ranibizumab was administered in 32 (74.4%) patients of which 7 patients had Age Related Macular Degeneration, 4 patients had myopic CNVM, 14 patients had Diabetic Retinopathy and 7 patients had Macular Oedema - Secondary to Retinal Vein Occlusion. Intravitreal Aflibercept was administered in 11 cases. In the present study, no sight threatening complications were seen with Ranibizumab. However, minor complications were there which were mostly present in initial 7 days which got relieved subsequently on symptomatic treatment. Most common side effect after first injection of Ranibizumab was conjunctival congestion 24 (72.73 %) followed by ocular pain 5 (15.15%) and subconjunctival hemorrhages 4 (12.12%). After second injection most common side effect was conjunctival congestion 22 (73.33%) followed by ocular pain and subconjunctival haemorrhage 4 (13.3%). In the study group, most common side effect after first injection of Aflibercept was congestion 7 (100%). After second injection congestion was most common side effect 5 (83.3%) followed by pain 1 (16.7%). On comparing Mean interval between first and second injection of Ranibizumab and Aflibercept injections, it was observed that mean interval between two injections in Ranibizumab administered group was 8-10 weeks and in Aflibercept administered group was 16-18weeks.

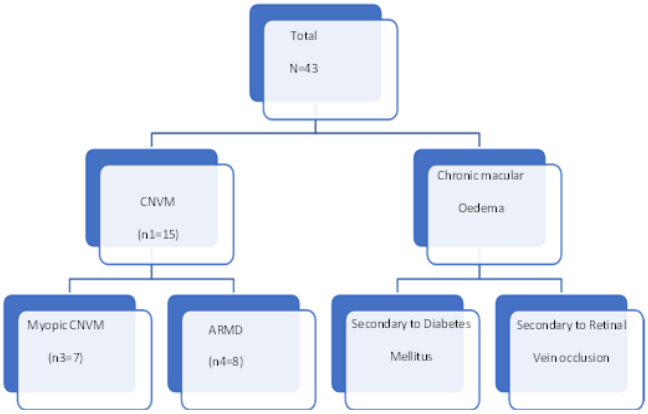

Table: 1 Type of injection used and indication for intravitreal Anti VEGF

Indication	Injection	
	Ranibizumab	Aflibercept
	Frequency (%)	Frequency (%)
CNVM- Age Related Macular Degeneration	7(21.9)	0(.)
CNVM- Myopic	4(12.5)	4(36.4)
Macular Oedema – Diabetic Retinopathy	14(43.8)	6(54.5)
Macular Oedema - Secondary to Retinal Vein Occlusion	7(21.9)	1(9.1)
Total	32 (74.4)	11 (25.6)

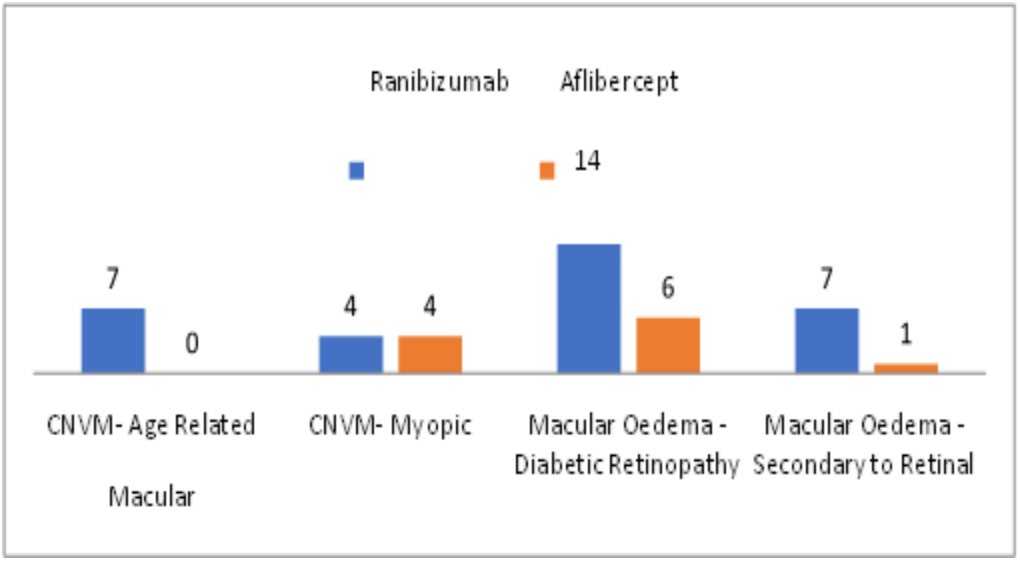

Figure 2: Type of injection used and indication for intravitrealAnti VEGF

Table 2: Side effects of Ranibizumab after first and second injection in the study group.

Side Effects		First Injection	Second injection
		No of cases(%)	No of cases(%)
SIGHT THREATNING	Retinal Detachment	0	0
	Vitreous Haemorrhage	0	0
	Endophthalmitis	0	0
NON-SIGHT THREATNING	Congestion	24(72.7)	22(73.3)
	Subconjunctival Haemorrhage	4(12.1)	4(13.3)
	Pain	5(15.2)	4(13.3)

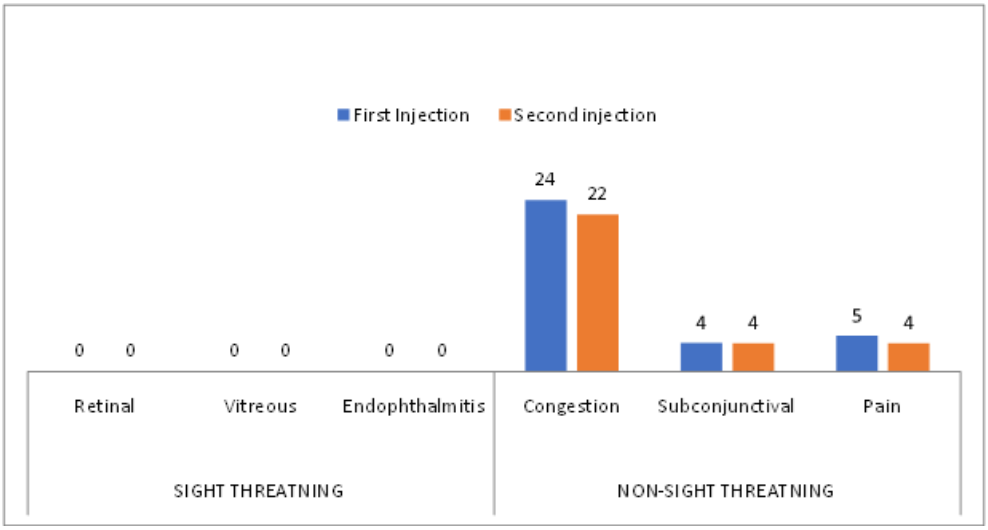

Figure 3: Side effects of Ranibizumab after first and second injection inthe study group.

Table 3: Side effects of Aflibercept after first and second injection

Side Effects		First Injection	Second injection
		No of cases (%)	No of cases (%)
SIGHT THREATNING	Retinal Detachment	0	0
	Vitreous Haemorrhage	0	0
	Endophthalmitis	0	0
NON-SIGHT THREATNING	Congestion	7(100)	5(83.3)
	Subconjunctival Haemorrhage	0	0
	Pain	0	1(16.7)

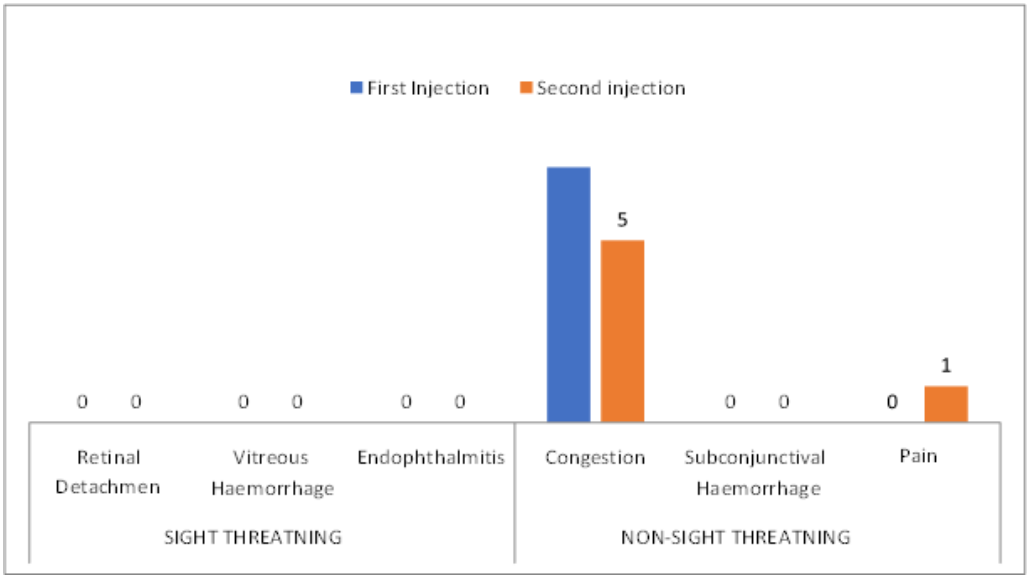

Figure 5: Side effects of Aflibercept after first and second injection.

Table 6: Mean interval in months between Anti VEGF injections

	Injection				t Value	P Value
	Ranibizumab		Aflibercept			
	Mean	Standard Deviation	Mean	Standard Deviation		
Interval between Injection	2.48	1.01	4.00	.63	4.60	**0.00**

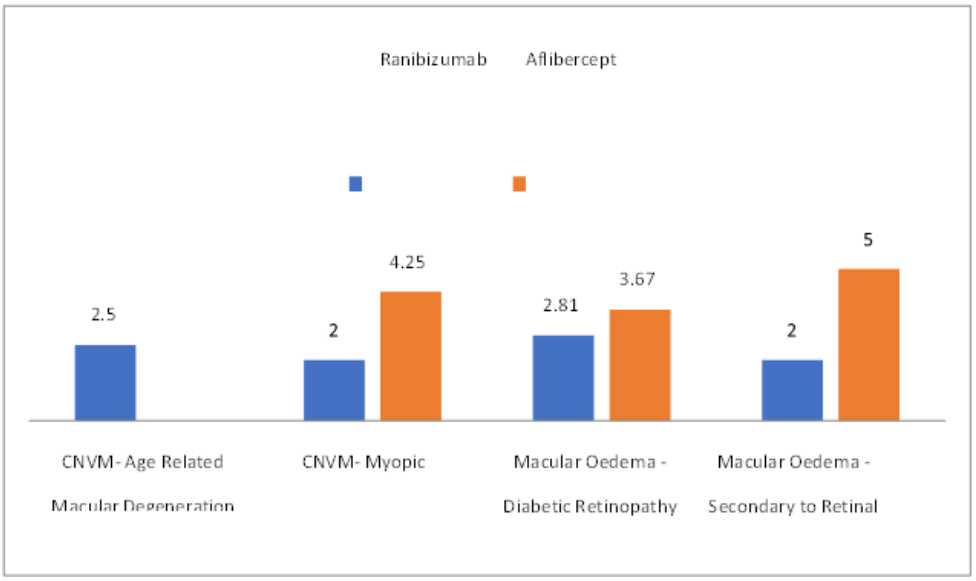

Figure 6: Comparison of Mean interval between first and secondinjection of Ranibizumab and Aflibercept among different diagnosis

Discussion:

In present study, 43 cases were included which fulfilled the inclusion criteria. Out of these 43 cases, 7 were myopic CNVM and 8 were ARMD. There were 28 cases of chronic macular oedema out of them 20 were secondary to diabetes mellitus and 8 were secondary to retinal vein occlusion. Two different anti VEGF agents were used among study participants. Out of 43 study participants, Ranibizumab was given in 32 (74.4%) of which 7 patients had ARMD, 4had myopic CNVM, 14 had Diabetic Retinopathy and 7 had Macular Oedema - Secondary to Retinal Vein Occlusion. Aflibercept was given in 11 (25.6%) of the study participants, of which 6 had Diabetic Retinopathy, 4 had CNVM-Myopia and 1 patient had Macular Oedema - Secondary to Retinal Vein Occlusion.

In the present study, no sight threatening and systemic complications were observed. With Ranibizumab injections, only non-sight threatening side effects were seen. Congestion (73%) and sub conjunctival haemorrhage (6.2%) was most commonly observed after second injection and pain (15%) was most common after first injection. According to ***Chakraborty et al*** [4] adverse events (AEs) were noted with 21.03% of injections, although 97.12% of them were non-serious. Most common side effect reported was subconjunctival haemorrhage (8.2%), transient blurring of vision (6.5%) and mild ocular pain (5.27%). **Marina study (2006)** [5] reported that most common side effects after Ranibizumab injection were sub-conjunctival haemorrhage (8%) and raised IOP (6%). **Harbor study (2013)** [6] also reported that conjunctival haemorrhage and pain were the most common side effects and enopthalmitis was seen in < 1% of the study subjects. On administration of intravitreal Aflibercept no sight threatening and systemic side effects were observed. Non-sight threatening side effects, conjunctival congestion was most common after both injections. Ocular pain was only seen in 1 patient after second injection. 4 patient had no side effect after first injection and 5 patients had no side effect after second injection. In ***View study*** [7], most frequent ocular adverse events after Aflibercept was conjunctival haemorrhage, eye pain, retinal haemorrhage, and reduced visual acuity. The most frequent serious non-ocular adverse events were myocardial infarction and atrial fibrillation noted in <1% of patients for the overall study population. According to ***Pielen et al*** [5], most common ocular adverse events reported were conjunctival haemorrhage, raised intra ocular pressure, reduced visual acuity and pain.

In present study it was found that mean duration between two injections was more/longer for Aflibercept (4 months) as compared to 2.48 months in cases of Ranibizumab. ***Salles et al*** [8] in their study reported that mean treatment interval was significantly longer in the Aflibercept(10 weeks) group compared with the Ranibizumab group (6 weeks). These findings are in accordance with ours. According to ***Rasmusen et al*** [9]**,**the interval between the first injection and the first follow-up was 102 days and 114 days ($p < 0.0001$), respectively, for the Ranibizumab and Aflibercept cohorts. ***Reiech et al*** [10] in their study reported that mean treatment interval was significantly longer in the Afliberceptgroup compared with the Ranibizumab group (8 weeks)

Conclusions:

In order to treat retinal disorders optimally, anti VEGF drugs must be injected repeatedly over months, requiring multiple clinical visits and high cost of treatment. Therefore, it is necessary to understand the nature, magnitude and burden of side effects which patient experience, which could reveal opportunities to change practice patterns to optimize patients experiences and outcomes. No sight threatening or systemic side effects were observed in our study. Both Anti VEGF agents were generally well-tolerated and the safety risks appear to be reasonably small relative to the benefits of therapy. Also, Interval between two injections required was also longer for Aflibercept as compared to Ranibizumab.

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Conflicts of interest: No potential conflict of interest relevant to this article was reported

Limitations and scope:

Major limitation of the present study are its small sample size due to COVID 19 pandemic and the duration of study was small. Also, patient was given choice regarding selection of anti VEGF agent with majority of patients selecting intravitreal Ranibizumab because of the cost effectiveness resulting in less number of cases in Aflibercept group. Studies with large sample size and long duration should be carried out, to see the long-term safety of intravitreal injections of Anti VEGF.

Ethical approval: Approved from the institutional ethical committee, GMC Bhopal, M.P.

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