



Comparison Between Ranibizumab Biosimilar, Innovator Ranibizumab and Bevacizumab in a Real-World Situation

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ABSTRACT

Introduction: To analyze the efficacy of biosimilar ranibizumab compared to innovator ranibizumab and bevacizumab.

Methods: We retrospectively analyzed consecutive patients treated with biosimilar ranibizumab for wet age-related macular degeneration (AMD) and macular edema (ME) (due to diabetes and vein occlusion) and compared them with ranibizumab- and bevacizumab-treated patients.

Results: Of 202 patients, 67 (33.2%) received biosimilar ranibizumab (BSR), 69 (34.2%) ranibizumab (RBZ) and 66 (32.7%) bevacizumab

(BEV). All patients received three consecutive injections followed by pro re nata dosing. The follow-up ranged from 3 to 24 months. The mean numbers of injections were 6.68 for RBZ, 6.4 for BEV and 4.7 for BSR. At 3 months, nAMD ($n = 115$, 56.9%) and ME ($n = 87$, 43.1%) groups showed significant improvement in vision and central foveal thickness (CFT) across all three agents. After ≥ 6 months, the effects were maintained in the AMD group but not in the ME group. Maximum effect was seen at 1 month. At no point in time was a significant difference noted among the three anti-vascular endothelial growth factor (anti-VEGF) agents. No major safety concerns were noted.

Conclusions: Biosimilar ranibizumab is comparable to innovator ranibizumab and bevacizumab in efficacy and safety.

Keywords: Anti VEGF; Biosimilar; Comparison with bevacizumab; DME; nAMD; Ranibizumab

The members of “The Sankara Nethralaya Vitreoretinal Study Group” are presented in the Acknowledgements section.

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Key Summary Points

In a developing country, the financial burden of continued anti-vascular endothelial growth factor (anti-VEGF) injections forces the patients to discontinue the treatment early. Introduction of the biosimilar of ranibizumab has led to a decrease in the cost of the injection thereby making it more sustainable

However, whether the efficacy of the biosimilar ranibizumab is comparable with that of the innovator ranibizumab or bevacizumab is not known

This study compared the efficacy of biosimilar ranibizumab with innovator ranibizumab and bevacizumab in a real-world situation. All three agents showed comparable efficacy across different indications such as diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD)

An equally effective biosimilar drug with much reduced cost makes the long-term treatment of DME and AMD cost-effective and sustainable. This will possibly reduce the non-compliance and give better results

INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) antibodies have become the mainstay of treatment for various vascular disorders including diabetic retinopathy, retinal vein occlusions (RVO), and wet age-related macular degeneration (AMD), among others [1]. India, with its growing diabetic population, has the largest number of patients requiring these injections [2]. However, treatment with multiple injections and multiple visits over very long time periods strains these needy patients financially.

Various ways are being explored to make the treatment more cost-effective and sustainable. Adopting more flexible dosing schedules to incentivize the treatment has been tried to reduce the drop-out rate. Introduction of Razumab (Intas Pharmaceuticals, Ltd., Ahmedabad, India), the biosimilar of ranibizumab, has reduced the cost of the injection thereby making it more feasible for a large section of the population to continue with long-term therapy.

Biosimilars are copies of the original molecule and are intended to have similar efficacy and mechanism of action. Razumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment with a molecular weight of 48 kDa. It is produced using an *E. coli* expression system in a nutrient medium with tetracycline. In India, the approximate cost of a vial of Razumab is 175 USD while for ranibizumab it is 322 USD. Bevacizumab is much cheaper since the cost is shared among many patients.

This biosimilar ranibizumab was approved by the Drug Controller General of India (DCGI) in 2015 after a phase 3 trial [3]. Pooled data from retrospective studies showed the safety and efficacy of Razumab for various indications including neovascular age-related macular degeneration (nAMD), RVO and diabetic macular edema (DME) [3–6]. However, comparative data with other anti-VEGF agents are lacking in the literature. We present our data comparing innovator ranibizumab, bevacizumab and biosimilar ranibizumab.

METHODS

This is a retrospective, single-center, observational, comparative case series conducted at a tertiary eye hospital in South India from January 2018 to December 2019. The study protocol was approved by the institutional review board and followed the tenets of the Declaration of Helsinki. A general written consent was obtained from the patients at the time of treatment, which included consent for the use of data for research purposes. The study included patients with nAMD and macular edema (ME) secondary to diabetic retinopathy (DR) or

RVO, treated with intravitreal injections of either ranibizumab biosimilar, ranibizumab or bevacizumab. The patients were free to choose any of the three agents. All patients received at least three consecutive injections followed by pro-re-nata dosing. The minimum follow-up in the study was 3 months. A period of 2–4 weeks from the scheduled visit was allowed.

Adult patients, treatment-naïve or previously treated with other anti VEGF/steroids/laser, were included in this study. Patients with insufficient follow-up, or who switched from one agent to the other during the course of the study, were excluded. Patients with a history of recent ocular surgery within the past 3 months or those who underwent surgery during the course of the study were excluded. Presence of media opacities, refractive error ± 6 D and active/past intraocular inflammation were criteria for exclusion. Patients with unstable systemic parameters, end-stage renal disease, cerebrovascular disease, autoimmune disorders, inflammatory bowel disease, hepatitis, and pregnant or lactating women were excluded. All injections were given at a standard dose of 0.05 ml with the same aseptic precaution protocol. The patients were seen the day following the injection and on the 4th day to detect any reaction. They were initially followed up monthly for the first 3 months and thereafter on PRN basis, at the advice of the treating physician.

At baseline, demographic data such as age, gender, study eye, comorbidities, previous treatment history, duration of disease and history of glaucoma were collected for each patient. Best-corrected visual acuity (BCVA) recorded with Snellen chart was converted to LogMAR for the purpose of statistical comparison. At each visit, the BCVA, intraocular pressure (IOP) with applanation tonometry, presence or absence of anterior chamber cells and flare were recorded. Dilated fundus examinations by indirect ophthalmoscopy and slit-lamp biomicroscopy with a 78-D lens were done. The central foveal thickness (CFT) was measured with the Cirrus spectral domain optical coherence tomography (SD-OCT) (Carl Zeiss Meditec, Dublin, CA).

The outcomes were measured in terms of change in BCVA, CFT and drug safety. A ≥ 1 line (Snellen chart) or ≥ 5 letters (LogMar chart) change in BCVA and $\geq 10\%$ change in the CFT from the previous visit were considered improvement or worsening. Drug safety was noted in terms of presence of anterior or posterior chamber reaction.

Statistical Analysis

Statistical analysis was performed with Statistical Package for Social Sciences version 20.0 software (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as mean and standard deviations and categorical variables as frequency and percentage (%). Normality of the quantitative variables was assessed by Kolmogorov-Smirnov and Shapiro-Wilk test. Parametric tests were used for normally distributed variables and non parametric tests were used for non-normally distributed variables. Baseline variables between different injection groups were compared by Kruskal-Wallis H test. In each injection group, to compare between baseline and 6 months, variable Wilcoxon signed-rank test was used. Mann-Whitney U test was used to compare among injections at every visit. A p value < 0.05 was considered significant.

RESULTS

A total of 1447 case records were searched and 202 patients were identified as eligible for the study, which included 69 patients in the ranibizumab (RBZ) (Lucentis, Novartis Ltd.) group, 66 in the bevacizumab (BEV) (Avastin, Roche) group and 67 in the biosimilar ranibizumab (BSR) (Razumab, Intas Pharmaceuticals, India) group. The cohort had patients with mean age of 62.33 ± 12.64 (range 26–88) years and a male preponderance ($n = 125$, 61.9%). Most were treatment naïve ($n = 181$, 89.6%). The patients were divided into two groups: active neovascular AMD ($n = 115$, 56.9%) and ME secondary to either DR or RVO ($n = 87$, 43.1%). Table 1 gives the demographic details. The mean duration of the macular pathology was 2.57 ± 2.99 (0.25–24) months. The follow-up ranged from 3

Table 1 Demographic details of the study population

	Type of injections		
	Ranibizumab (<i>n</i> = 69)	Bevacizumab (<i>n</i> = 66)	Biosimilar ranibizumab (<i>n</i> = 67)
Age (years)			
Mean	66.36 ± 9.53	62 ± 13.95	58.49 ± 13.026
Range	50–87	27–88	26–84
Sex <i>n</i> (%)			
Male	43 (62.3)	41 (62.1)	41(61.2)
Female	26 (37.7)	25 (37.9)	26 (38.8)
Eye <i>n</i> (%)			
Right eye	35 (50.7)	33 (50.0)	32 (47.8)
Left eye	34 (49.3)	33 (50.0)	35 (52.2)
Previous treatment <i>n</i> (%)			
Treatment naïve	62 (89.9)	57 (86.4)	62 (92.5)
Previous BEV	7 (10.1)	3 (4.5)	1 (1.5)
Previous RBZ	0	5 (7.7)	0
Previous IVTA	0	1 (1.5)	1 (1.5)
Previous laser	0	0	3 (4.5)
Comorbidities <i>n</i> (%)			
Nil	14 (25.5)	19 (34.5)	20 (29.9)
Hypertension	49 (71.0)	35 (53.0)	30 (44.7)
Diabetics	33 (47.8)	37 (56.1)	31 (46.3)
Ischemic heart disease	4 (5.8)	0	1 (1.5)
Diagnosis <i>n</i> (%)			
ME	29 (42.0)	31 (47.0)	27 (40.1)
nAMD	40 (58.0)	35 (53.0)	40 (59.7)
Follow-up duration (months)			
Mean ± SD	14.64 ± 12.46	11.03 ± 5.24	7.79 ± 5.40
Range	4–78	6–22	3–21

IVTA intravitreal triamcinolone acetonide, *ME* macular edema, *nAMD* neovascular age-related macular degeneration

to 24 months. There were five (7.2%) patients in the RBZ group, 7 (10.6%) in the BEV and 5 (6.7%) in the BSR group who received treatment in both eyes.

Visual Outcome

All three anti-VEGF agents showed statistically significant improvement in the BCVA in both groups at 3 months (Table 2). No significant

Table 2 Analysis of the change in visual acuity and change in the central foveal thickness within a short 3-month follow-up after treatment with anti-VEGF and comparison among the three agents, namely ranibizumab (RBZ), bevacizumab (BEV) and biosimilar ranibizumab (BSR)

nAMD short follow-up		RBZ (n = 40)	BEV (n = 35)	BSR (n = 40)	RBZ vs BEV p value	BEV vs BSR p value	RBZ vs BSR p value
BCVA							
Pre-treatment		0.59 ± 0.59	0.45 ± 0.23	0.77 ± 0.65	0.99	0.10	0.15
Post-treatment		0.42 ± 0.4	0.36 ± 0.26	0.51 ± 0.42	0.32	0.68	0.25
p value		0.007	0.007	0.004			
Change in BCVA (95% CI)		0.17 ± 0.37 (- 0.06 to 0.22)	0.09 ± 0.23 (- 0.01 to 0.35)	0.26 ± 0.48 (- 0.29 to 0.11)	0.99	0.60	0.62
CFT							
Pre-treatment		302.15 ± 203.84	302.15 ± 203.84	297.34 ± 154.88	0.74	0.36	0.17
Post-treatment		178.82 ± 98.55	212.68 ± 100	259.14 ± 240.22	0.01	0.96	0.10
p value		< 0.01	< 0.01	< 0.01			
Change in CFT (95% CI)		123.33 ± 209.91 (- 45.73 to 123.09)	84.65 ± 152.38 (- 46.06 to 97.32)	110.28 ± 148.19 (- 70.51 to 96.61)	0.34	0.52	0.57
Macular edema short follow-up							
		RBZ (n = 29)	BEV (n = 31)	BSR (n = 27)	RBZ vs BEV p value	BEV vs BSR p value	RBZ vs BSR p value
BCVA							
Pre-treatment		0.62 ± 0.41	0.54 ± 0.30	0.63 ± 0.33	0.64	0.32	0.75
Post-treatment		0.47 ± 0.30	0.37 ± 0.18	0.37 ± 0.29	0.17	0.72	0.21
p value		0.007	0.001	< 0.01			
Change in BCVA (95% CI)		0.15 ± 0.27 (- 0.13 to 0.11)	0.16 ± 0.22 (- 0.04 to 0.22)	0.25 ± 0.27 (- 0.24 to 0.04)	0.59	0.24	0.13
CFT							
Pre-treatment		628.89 ± 247.38	574.48 ± 211.29	587.44 ± 231.07	0.36	0.69	0.63
Post-treatment		441.82 ± 222.63	433.55 ± 177.33	305.74 ± 163.15	0.39	0.37	0.97

Table 2 continued

Macular edema short follow-up	RBZ (<i>n</i> = 29)	BEV (<i>n</i> = 31)	BSR (<i>n</i> = 27)	RBZ vs BEV <i>p</i> value	BEV vs BSR <i>p</i> value	RBZ vs BSR <i>p</i> value
<i>p</i> value	0.006	0.001	< 0.01			
Change in CFT (95% CI)	187.07 ± 321.86 (− 94.27 to 186.55)	140.93 ± 194.25 (0.75–280.78)	281.70 ± 314.71 (− 266.79 to 77.53)	0.99	0.07	0.16

Significant *p* values are in bold type

difference was noted among the three agents. A similar trend was noticed at 6 months (Table 3).

Analysis of monthly change in the BCVA revealed that 31.9%, 27.3% and 40.3% patients in the RBZ, BEV and BSR group showed improvement of ≥ 1 line after 1 month. At 6 months, this percentage reduced to 12.5%, 5.7% and 4% (Table 4). At 6 months, 8.3%, 9.4% and 4% showed worsening by ≥ 1 line. Except at month 5 (RBZ vs BEV $p = 0.03$), no significant difference was noted among the three agents. The number of patients available for follow-up at each month varied. The details are given in Table 4.

Figure 1 shows the graphical representation of the change in the BCVA every month. In the ME group, BEV and BSR almost follow the same curve. RBZ showed less improvement, but the baseline BCVA was also worse than in the other two groups. A similar trend is observed in the nAMD group where the BSR group showed poorer baseline BCVA with less visual gain at 6 months.

Central Foveal Thickness

In the nAMD group, the central foveal thickness reduced in all the groups lasting up to 6 months (Tables 2 and 3). In the ME group, there was significant reduction of macular thickness at 3 months in all groups, but at 6 months, only the reduction in the RBZ group was statistically significant (226.00 ± 326.25 , $p = 0.002$). Comparison of the three agents did not reveal any significant differences at either 3 or 6 months.

Month-wise analysis of the CFT showed reduction at the end of the 1st month with 75.4%, 63.6% and 62.7% patients showing $\geq 10\%$ reduction in RBZ, BEV, BSR groups, respectively (Table 5). By 6 months, this percentage was reduced to 39.5%, 34% and 24%, respectively; 20.9%, 13.2% and 28% patients in the RBZ, BEV and BSR groups showed increase in macular thickness. The ME subgroup revealed many fluctuations in the CFT resulting in a saw-tooth pattern on the graphical representation (Fig. 1), but the nAMD patients showed maximum reduction after just one injection, which was then maintained through

Table 3 Analysis of the change in visual acuity and change in the central foveal thickness with a long follow-up of ≥ 6 months after treatment with anti-VEGF and comparison among the three agents, namely ranibizumab (RBZ), bevacizumab (BEV) and biosimilar ranibizumab (BSR)

nAMD long follow-up	RBZ (n = 37)	BEV (n = 35)	BSR (n = 26)	RBZ vs BEV p value	BEV vs BSR p value	RBZ vs BSR p value
BCVA						
Pre-treatment	0.60 ± 0.60	0.45 ± 0.23	0.86 ± 0.73	0.94	0.09	0.12
Post-treatment	0.39 ± 0.35	0.41 ± 0.25	0.60 ± .60	0.32	0.40	0.14
p value	0.001	0.20	0.02			
Change in BCVA (95% CI)	0.21 ± 0.39 (0.01–0.32)	0.04 ± 0.26 (– 0.02 to 0.46)	0.26 ± 0.58 (– 0.21 to 0.31)	0.08	0.18	0.98
CFT						
Pre-treatment	310.59 ± 207.62	297.34 ± 154.88	380.27 ± 285.30	0.93	0.51	0.38
Post-treatment	174.51 ± 81.44	220.34 ± 98.02	268. ± 320.41	0.02	0.86	0.15
p value	< 0.01	0.002	0.003			
Change in CFT (95% CI)	136.08 ± 174.59 (– 19.97 to 138.13)	77 ± 161.74 (– 136.92 to 66.38)	112.27 ± 218.34 (– 79.27 to 126.89)	0.07	0.46	0.55
Macular edema long follow-up						
BCVA						
Pre-treatment	0.68 ± 0.46	0.54 ± 0.3	0.51 ± 0.32	0.37	0.66	0.29
Post-treatment	0.57 ± 0.38	0.45 ± 0.35	0.45 ± 0.43	0.16	0.72	0.21
p value	0.12	0.07	0.07			
Change in BCVA (95% CI)	0.12 ± 0.4 (– 0.16 to 0.22)	0.09 ± 0.32 (– 0.75 to 0.24)	0.62 ± 0.37 (0.29–0.76)	0.73	0.87	0.64
CFT						
Pre	647.81 ± 265.48	574.48 ± 211.28	535.00 ± 213.65	0.32	0.74	0.28
Post	421.81 ± 238.79	377.29 ± 199.99	429.35 ± 229.95	0.58	0.46	0.89
p value	0.002	0.09	0.19			

Table 3 continued

Macular edema long follow-up	RBZ (<i>n</i> = 27)	BEV (<i>n</i> = 31)	BSR (<i>n</i> = 14)	RBZ vs BEV <i>p</i> value	BEV vs BSR <i>p</i> value	RBZ vs BSR <i>p</i> value
Change in CFT (95% CI)	226.00 ± 326.25 (− 165.32 to 169.38)	223.97 ± 306.84 (− 298.94 to 62.28)	105.64 ± 264.14 (− 70.73 to 311.45)	0.98	0.25	0.23

Significant *p* values are in bold type

6 months. All three agents showed similar patterns, and the differences among the agents were not statistically significant at any month (Table 5).

The baseline mean IOP was 14.41 ± 4 , 14.05 ± 2.63 and 14.3 ± 2.23 mmHg in RBZ, BEV and BSR groups, respectively. No significant changes were seen in the IOP at any time point. The mean numbers of injections received during the study period were 6.68 in the RBZ, 6.4 in the BEV and 4.7 in the BSR group. The mean follow-up in each group was 12.78 ± 6.11 , 11.03 ± 5.24 and 7.79 ± 5.40 months, respectively. During the study period, no complications related to injections were noted.

DISCUSSION

A biosimilar is essentially a copy of the original molecule and is supposed to have the same therapeutic effect. However, the manufacturing process of a biosimilar differs which might cause a change in efficacy or safety [7]. This comparative, retrospective study did not find ranibizumab biosimilar to be noninferior to the original ranibizumab or the off-label bevacizumab. It showed a similar efficacy with no statistically significant difference compared with the other two agents during the study period. No major adverse events were noted with any of the three agents.

In a retrospective pooled data analysis of 561 patients, the biosimilar ranibizumab (Razumab) was shown to maintain the initial improvement in BCVA and CFT through 12 weeks [3]. The subgroup analysis of patients with nAMD (*n* = 103) and RVO (*n* = 160) showed that it was effective in treating various indications for anti-VEGF treatment [3, 4]. Another retrospective multi-center study of 341 patients including nAMD, RVO, diabetic ME and myopic choroidal neovascularization showed significant improvements through all time points till the final follow-up at 48 weeks [6]. Based on the evidence from the early studies, it was approved by the Drug Controller General of India in 2015 [3, 4]. Recently, Sharma et al. [8] published comparative data between biosimilar and

Table 4 Change in the visual acuity every month from baseline till the last visit

	RBZ (<i>n</i> = 69) (%)	BEV (<i>n</i> = 66) (%)	BSR (<i>n</i> = 67) (%)	RBZ vs BEV <i>p</i> value	BEV vs BSR <i>p</i> value	RBZ vs BSR <i>p</i> value
Month 1						
Increased	22 (31.9)	18 (27.3)	27 (40.3)	0.68	0.36	0.60
Stable	42 (60.9)	44 (66.7)	32(47.8)			
Decreased	5 (7.2)	4 (6.1)	8 (11.9)			
<i>n</i>	69	66	67			
Month 2						
Increased	7 (10.1)	8 (12.1)	7 (10.4)	0.58	0.45	0.82
Stable	57 (82.6)	49 (74.2)	56 (83.60)			
Decreased	5 (7.2)	9 (13.6)	4 (6.0)			
<i>n</i>	69	66	67			
Month 3						
Increased	8 (13.6%)	7 (10.9)	11 (18.6)	0.90	0.15	0.16
Stable	46 (78.0)	54 (84.4)	47 (79.7)			
Decreased	5 (8.5)	3 (4.7)	1 (1.7)			
<i>n</i>	59	64	59			
Month 4						
Increased	6 (12.2)	2 (3.6)	4 (13.8)	0.67	0.44	0.77
Stable	37 (75.5)	49 (89.1)	22(75.9)			
Decreased	6 (12.2)	4 (7.3)	3 (10.3)			
<i>n</i>	49	55	29			
Month 5						
Increased	8 (18.6)	4 (8.5)	3 (16.7)	0.03	0.18	0.63
Stable	35 (81.4)	40 (85.1)	15 (83.3)			
Decreased	0	3 (6.4)	0			
<i>n</i>	43	47	18			
Month 6						
Increased	6 (12.5)	3 (5.7)	1 (4.0)	0.34	0.65	0.64
Stable	38 (79.2)	45 (84.9)	23 (92.0)			
Decreased	4 (8.3)	5 (9.4)	1 (4.0)			
<i>n</i>	48	53	25			
Last visit						

Table 4 continued

	RBZ (<i>n</i> = 69) (%)	BEV (<i>n</i> = 66) (%)	BSR (<i>n</i> = 67) (%)	RBZ vs BEV <i>p</i> value	BEV vs BSR <i>p</i> value	RBZ vs BSR <i>p</i> value
Increased	8 (14.8)	6 (13.3)	2 (3.9)	0.92	0.70	0.79
Stable	32 (59.3)	26 (57.8)	44 (86.3)			
Decreased	14 (25.9)	13 (28.9)	5 (9.8)			
<i>n</i>	54	45	51			

innovator ranibizumab in nAMD. They found no difference between the two at 8 weeks and 24 weeks.

Concerning efficacy, this study did not find a significant difference between bevacizumab versus innovator or biosimilar ranibizumab. In a meta-analysis collating results from 19 randomized clinical trials, involving 7459 patients, intravitreal bevacizumab was seen to be as effective as ranibizumab across all indications [9]. It was noted that as many as six head-to-head trials in nAMD and five trials in DME have suggested no difference in the efficacy of both these agents. The variations in the visual acuity outcomes were in fact related to the dosing regimen and the disease entity being treated [9].

In the current study, for all three agents the baseline BCVA dictated the final visual improvement. Poor baseline BCVA showed less visual gain at the end of 6 months. This is in contrast to the results of the DRCR.net protocol T study wherein patients with poorer vision (20/50–20/320) had superior outcomes with better improvement at 1 year (18.9, 14.2, 11.8 letters with aflibercept, ranibizumab and bevacizumab) [10, 11]. Comparatively, patients with better vision between 20/32 and 20/40 gained only about 7.5–8.3 letters. It is logical that patients with poor vision harbor more severe disease, which might show better response with more prolonged monthly treatment similar to the protocol T study. The results might somewhat differ with a PRN dosing regimen. The possibility of long-standing edema causing irreversible structural changes in the ellipsoid zone limiting the capacity for visual

improvement cannot be ruled out especially in eyes with baseline poor vision.

The long-term outcomes were better in the nAMD group than in the ME group with maintained benefits. This highlights the treatment problems in the real world where patients are mostly treated on a PRN basis unlike the fixed monthly dosing regimen in clinical trials. The sustainability of treatment and compliance greatly depends on the cost of the treatment. In a developing country such as India, under-dosing leading to suboptimal visual outcomes is common. According to a 2017 analysis of a cohort of Australian patients with nAMD, only 40% were still receiving the index treatment 1 year later [12]. In a study from India, the rate of loss to follow-up was reported to be as high as 51.5% and the most common reasons were non-affordability in 41.4% followed by non-improvement in vision in 28.4% [13].

When compared across the disease conditions, the non-compliance was seen to be higher in DME than in AMD. In a study from Germany by Ehlken et al. [14], the rate of non-compliance with treatment was highest in DME (44%) followed by AMD (32%) and BRVO (25%) with associated higher risk of vision loss in DME. Similarly, another study by Weiss et al. [15] also demonstrated higher rates of non-adherence to treatment in DME (46%) than in AMD (22%), with significant correlation to poorer visual outcomes in DME. The main reason postulated for this non-compliance in DME patients was the presence of several other comorbidities, which may have taken precedence over the ocular treatment. Multiple hospitalizations also lead to breaks in ocular

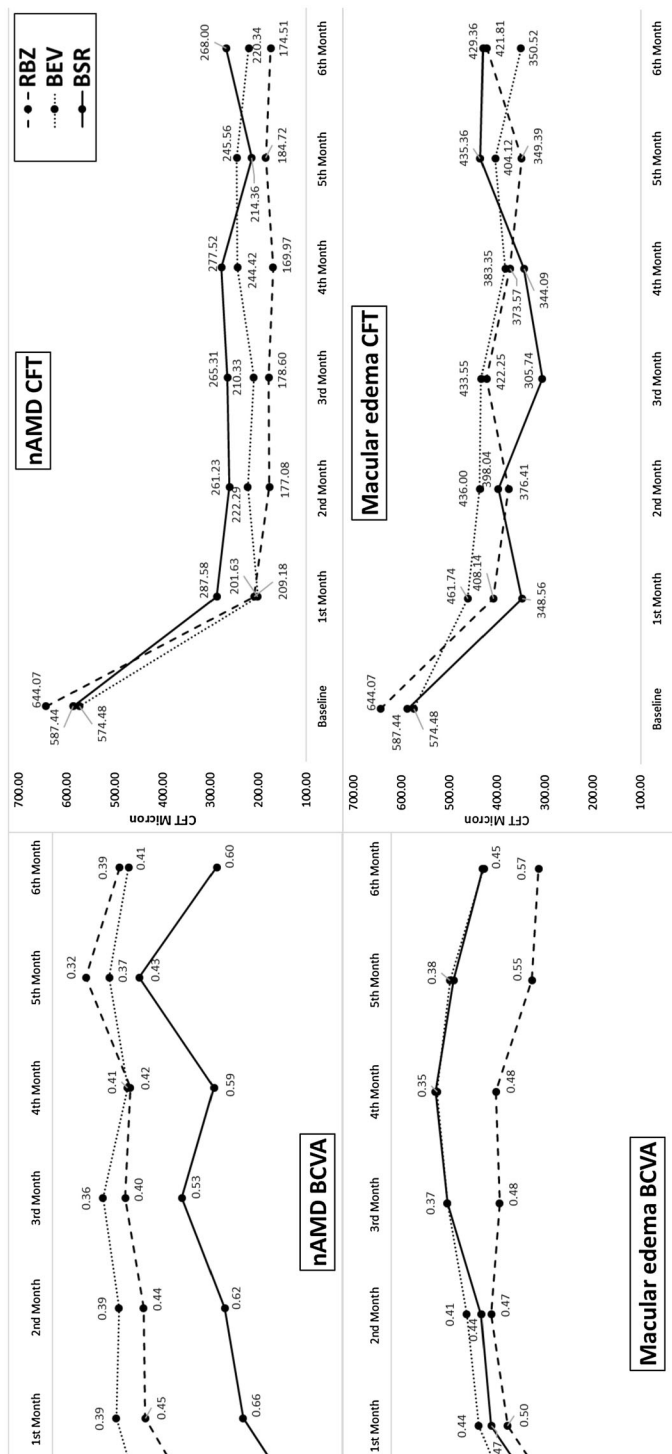


Fig. 1 Change in visual acuity (BCVA) and central foveal thickness (CFT) at each monthly visit in the nAMD and macular edema groups for biosimilar ranibizumab (BSR), ranibizumab (RBZ) and bevacizumab (BEV)

Table 5 Change in the central foveal thickness every month from baseline till the last visit

	RBZ (<i>n</i> = 69) (%)	BEV (<i>n</i> = 66) (%)	BSR (<i>n</i> = 67) (%)	RBZ vs BEV <i>p</i> value	BEV vs BSR <i>p</i> value	RBZ vs BSR <i>p</i> value
Month 1						
Decreased	52(75.4)	42 (63.6)	42 (62.7)	0.18	0.77	0.12
Stable	10(14.5)	17 (25.8)	15 (22.4)			
Increased	7 (10.1)	7 (10.6)	10(14.9)			
<i>n</i>	69	66	67			
Month 2						
Decreased	29 (42.0)	23 (34.8)	21(31.3)	0.29	0.80	0.18
Stable	26 (37.7)	25 (37.9)	28(41.8)			
Increased	14 (20.3)	18 (27.3)	18(26.9)			
<i>n</i>	69	66	67			
Month 3						
Decreased	18 (30.5)	21 (32.8)	24 (40.7)	0.92	0.36	0.31
Stable	26 (44.1)	26 (40.6)	22 (37.3)			
Increased	15 (25.4)	17 (26.6)	13 (22)			
<i>n</i>	59	64	59			
Month 4						
Decreased	15 (31.9)	15 (27.3)	8 (27.6)	0.90	0.92	0.85
Stable	17 (36.2)	26 (47.3)	14 (48.3)			
Increased	15 (31.9)	14 (25.5)	7 (24.1)			
<i>n</i>	47	55	29			
Month 5						
Decreased	10 (27.8)	13 (27.7)	6 (33.3)	0.75	0.63	0.81
Stable	18 (50.0)	26 (55.3)	6 (33.3)			
Increased	8 (22.2)	8 (17.0)	6 (33.3)			
<i>n</i>	36	47	18			
Month 6						
Decreased	17 (39.5)	18 (34.0)	6 (24.0)	0.98	0.15	0.22
Stable	17 (39.5)	28 (52.8)	12 (48.0)			
Increased	9 (20.9)	7 (13.2)	7 (28.0)			
<i>n</i>	43	53	25			
Last visit						

Table 5 continued

	RBZ (<i>n</i> = 69) (%)	BEV (<i>n</i> = 66) (%)	BSR (<i>n</i> = 67) (%)	RBZ vs BEV <i>p</i> value	BEV vs BSR <i>p</i> value	RBZ vs BSR <i>p</i> value
Decreased	19 (36.5)	16 (36.4)	6 (30.0)	0.98	0.54	0.56
Stable	16 (30.8)	13 (29.5)	6 (30.0)			
Increased	17 (32.7)	15 (34.1)	8 (40.0)			
<i>n</i>	52	44	20			

treatment. In developing nations, due to poor universal healthcare, low per capita income and out-of-pocket expenditures for the patients, this loss to follow-up rate is high. Apart from the low socioeconomic conditions, low education level, lack of awareness about treatment and poor doctor-patient communication are other important factors affecting compliance [13–15]. The reduced treatment cost of a biosimilar compared to the innovator molecule might result in higher compliance by making the treatment affordable.

Safety of the anti-VEGF is another important aspect. Bevacizumab, despite being an off-label treatment, is used more often because of its lower cost. However, alliquoting of the drug is challenging. It needs to be done with complete aseptic precautions by the compounding pharmacies. Even so, the risk of contamination and infection cannot be completely ruled out. In the absence of compounding pharmacies, the risk is higher. The Vitreoretinal Society of India has prepared detailed guidelines for alliquoting, storing and using bevacizumab injections [16]. The problems with alliquoting can be overcome by using single-dose vials such as the innovator or biosimilar ranibizumab. In the past, a few spurts of cluster endophthalmitis have been found to be due to the use of spurious bevacizumab [17]. The authenticity of the vial can be checked by using a unique alphanumeric code, the Kezzler code, on the vial.

Unlike a for generic drug, the biosimilar manufacturing process does not have a fixed chemical formula [18]. It involves production of the biosimilar molecule from living cells under controlled conditions. Even slight variations in

these conditions might lead to changes in the safety and efficacy of the biosimilar. Biosimilars undergo strict regulatory processes before they are approved for use. They are required to undergo analytical studies to establish similarity with the innovator molecule, animal studies, pharmacodynamic-pharmacokinetic analyses and clinical studies to assess safety, efficacy and immunogenicity [7]. Strict pharmacovigilance, post-marketing studies, reporting of adverse events and a risk management plan are mandatory for the final marketing approval for a biosimilar. These standardized, robust regulatory processes ensure the safety and quality of a biosimilar.

This study has several limitations. Its retrospective nature study makes the evidence biased and less reliable. The treatment regimen followed was not uniform. There were many dropouts, and the number of eyes at long-term follow-up suffered because of this. The baseline visual acuity differed in the groups. We included both treatment naïve and previously treated patients, which might have affected the final outcome. However, the majority of patients (86.4–92.5% among all the groups) were treatment naïve. We believe that the small percentage of treated patients did not affect the results significantly. The study therefore gives us an idea about the comparative efficacy of the three agents in a real-world scenario.

CONCLUSIONS

The biosimilar ranibizumab was seen to give comparable results to innovator ranibizumab and bevacizumab without any major adverse

profile. An ongoing large, multicenter, randomized, prospective trial of head-to-head comparison of the biosimilar ranibizumab with innovator ranibizumab will likely throw more light on the comparative efficacy and safety of the biosimilar.

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Data Availability. Most of the data are given in the manuscript. Data are freely available for perusal on request.

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