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

Dhanashree Ratra (✉ ghanashreeratra@gmail.com)

Sankara Nethralaya <https://orcid.org/0000-0001-5687-6384>

Krishnakanta Roy

Sankara Nethralaya

Sneha Giridhar

Sankara Nethralaya

Sushant Madaan

Sankara Nethralaya

Research Article

Keywords: Biosimilar, ranibizumab, anti VEGF, comparison with bevacizumab, nAMD, DME

Posted Date: May 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-462708/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Ophthalmology and Therapy on November 5th, 2021. See the published version at <https://doi.org/10.1007/s40123-021-00416-4>.

Abstract

Purpose

To analyze the efficacy of biosimilar ranibizumab as 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) and compared them with ranibizumab and bevacizumab treated patients.

Results

Out of 202 patients, 67 (33.2%) received biosimilar ranibizumab (BSR), 69 (34.2%) ranibizumab (RBZ) and 66 (32.7%) bevacizumab (BEV). All patients received 3 consecutive injections followed by pro re nata dosing. The follow up ranged from 3 -24 months. The mean number of injections were 6.68 RBZ, 6.4 BEV and 4.7 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 3 agents. After ≥ 6 months, the effects were maintained in AMD group but not in ME group. Maximum effect was seen at 1 month. At no point of time, significant difference was noted among the 3 anti VEGF agents. No major safety concerns were noted.

Conclusions

Biosimilar ranibizumab is comparable to innovator ranibizumab and bevacizumab in efficacy and safety. It can be added to the list of available anti VEGF agents for the treatment of vascular disorders.

Introduction

Anti-vascular endothelial growth factor (VEGF) antibodies have become the main stay of treatment for various vascular disorders including diabetic retinopathy, vascular occlusions (RVO), and wet age related macular degeneration (nAMD), among others. India, with her growing diabetic population is leading with the largest number of patients requiring these injections [1]. However, the multiple injections, with multiple visits, over a very long period puts a strain on the pockets of these needy patients. Bevacizumab, despite being an off label drug is more prevalent because it is cheaper and more affordable.

Various ways are being explored to make the treatment more cost effective and sustainable. Adopting more flexible dosing schedules to incentivizing the treatment have 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 likely more feasible by a large section of the population to continue with long term therapy.

This biosimilar ranibizumab was approved by the Drug Controller General of India (DCGI) in 2015 after a phase 3 trial [2]. Pooled data from retrospective studies showed the safety and efficacy of Razumab in various indications including nAMD, RVO and diabetic macular edema (DME) [2-5]. However, there has not been any comparative study with other anti VEGF agents. We present our data of comparison between ranibizumab, bevacizumab and biosimilar ranibizumab.

Materials And Methods

This is a retrospective, single centre, 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 purpose. 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. All patients received at least 3 consecutive injections followed by pro re nata dosing. A minimum follow up of 3 months was included for the study.

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 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 of ± 6 D, 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 same aseptic precautions 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 like 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. A dilated fundus examination 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 as 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 injections groups were compared by Kruskal-Wallis H test. In each injection group to compare between baseline and 6th month variable Wilcoxon Signed Ranks test was used. Mann Whitney U test was used to compare among injections at every visit. A p value less than 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 who received ranibizumab (RBZ) (Lucentis, Novartis Ltd), 66 patients who received bevacizumab (BEV) (Avastin, Roche) and 67 patients who were treated with biosimilar ranibizumab (BSR) (Razumab, Intas Pharmaceuticals, India). The cohort had patients with mean age of 62.33 ± 12.64 (range 26-88) years and a male preponderance (n=125, 61.9%). Majority of them were treatment naïve (n=181, 89.6%). The patients were divided into 2 groups; those with active neovascular AMD (n=115, 56.9%) and those with ME secondary to either DR or RVO (n= 87, 43.1%). Table 1 gives the demographic details. The mean duration of the macular pathology either CNV or ME was 2.57 ± 2.99 (0.25- 24) months. The follow up ranged from 3 to 24 months. Some patients who did not come for the 3rd month visit but came 2 – 4 weeks later were included in the study. There were 5 (7.2%) patients in RBZ group, 7 (10.6%) in BEV and 5 (6.7%) in BSR group who received treatment in both eyes.

Visual outcome

All the 3 anti VEGF agents showed statistically significant improvement in the BCVA in both the groups in the short follow up upto 3 months. Table 2 gives the details about the pre and post-treatment mean BCVA at 3 months. In nAMD, the change in BCVA (in logMAR) was 0.17 ± 0.37 , 0.09 ± 0.23 , 0.26 ± 0.48 in the RBZ, BEV and BSR groups respectively. However the change in BCVA was not significantly different across the 3 anti VEGF agents. Similarly, the change in BCVA was 0.15 ± 0.27 , 0.16 ± 0.22 , 0.25 ± 0.27 in RBZ, BEV and BSR groups in the short follow up of ME which was not significant across the 3 agents. A similar trend was noticed with longer duration of follow up. Although both RBZ and BSR showed significant visual improvement 6 months after treatment in the nAMD group, when compared among the 3 anti VEGF agents, this change was not significant (0.21 ± 0.39 , 0.04 ± 0.26 , 0.26 ± 0.58 , p values 0.08,

0.18, 0.98). The long term follow up of ME revealed 0.12 ± 0.4 , 0.09 ± 0.32 , 0.62 ± 0.37 logMAR change in the BCVA which was not significant across the agents indicating similar efficacy. (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 respectively showed improvement of ≥ 1 line in visual acuity after 1 month. This percentage reduced to 12.5, 5.7, 4 % by the end of 6 months. (Table 4) Majority of patients showed stable vision. But at 6 months, a small percentage of patients viz. 8.3, 9.4, 4 % showed worsening by ≥ 1 line. At no point of time, any significant difference was noted between the 3 agents, except at month 5, when the difference between RBZ and BEV was significant ($p = 0.03$). 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, finishing with slightly higher vision at 6 months from baseline. RBZ showed slightly lesser improvement, but the baseline BCVA was also worse than the other 2 groups. However, these differences were not significant between the agents. Similar trend is observed in the nAMD group where BSR group showed poorer baseline BCVA with lesser visual gain at 6 months. But these differences were not statistically significant.

Central foveal thickness-

In the nAMD group, the central foveal thickness consistently showed significant reduction in all the groups lasting upto 6 months. (Tables 2,3) However, this reduction was not significantly different between the 3 anti VEGF agents indicating non-inferiority of one over the other. In the ME group, there was significant reduction of macular thickness at 3 months in all groups (187.07 ± 321.86 , 140.93 ± 194.25 , 281.70 ± 314.71 , $p = 0.006$, 0.001 , <0.01 in RBZ, BEV, BSR groups). But at 6 months, only the reduction in the RBZ group was statistically significant (226.00 ± 326.25 , $p=0.002$). The BEV and BSR groups showed reduction in CFT which did not reach statistical significance (223.97 ± 306.84 , $p= 0.09$ and 105.64 ± 264.14 , $p= 0.19$ respectively). Comparison of the 3 agents did not reveal any significant differences either at 3 or 6 months. This was suggestive of comparable efficacy of all the 3 agents in reducing retinal thickness.

Month-wise analysis of the CFT showed a good reduction at the end of 1st month with 75.4, 63.6 and 62.7% patients showing $\geq 10\%$ reduction in RBZ, BEV, BSR groups respectively. (Table 5) However, by 6 months this percentage was reduced to 39.5, 34 and 24% in the 3 groups. Moreover, nearly 20.9, 13.2, 28% patients in the RBZ, BEV and BSR groups showed increase in the macular thickness at 6 months. The ME subgroup revealed a lot of fluctuation in the CFT resulting in a saw tooth pattern on the graphical representation (Figure 1) but the nAMD patients showed maximum reduction just after 1 injection which was then maintained through 6 months. All the 3 agents showed similar pattern 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 mm of Hg in RBZ, BEV and BSR groups respectively. No significant changes were seen in the IOP at any point of time. The mean number of

injections received during the study period were 6.68 in RBZ, 6.4 in BEV and 4.7 in BSR group. The mean follow up in each group was 12.78 ± 6.11 , 11.03 ± 5.24 and 7.79 ± 5.40 months in RBZ, BEV and BSR respectively.

During the study period, there were no incidences of any local or systemic adverse drug reactions. None of the injections showed any inflammatory reactions. There were no occurrences of endophthalmitis.

Discussion

A biosimilar is essentially a copy of the original molecule and is supposed to have the same therapeutic effect. But the manufacturing process of a biosimilar differs which might cause a change in efficacy or safety. 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 with the other 2 agents. No major adverse events were noted with any of the 3 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.² The subgroup analysis of patients with nAMD (n= 103) and RVO (n= 160) showed that it was effective ranibizumab in treating various indications for anti VEGF treatment [3,4]. Another retrospective, multi-centre 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. Based on the evidence from the early studies, it was approved by the Drug Controller General of India in 2015. But no comparative studies between the biosimilar and innovator ranibizumab or bevacizumab have been reported so far.

As far as the efficacy is concerned, this study did not find 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 [6]. It was noted that, as many as 6 head to head trials in nAMD and 5 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 [6].

In the current study, for all 3 agents the baseline BCVA dictated the final visual improvement. Poor baseline BCVA showed lesser 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) [7,8]. Comparatively, patients with better vision between 20/32- 20/40 gained only about 7.5 - 8.3 letters. It is logical that patients with poor vision harbour more severe disease which might show better response with more prolonged monthly treatment similar to protocol T study. However, the results might somewhat differ with a PRN dosing regimen. Moreover, 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 with all the groups maintaining BCVA gain and reduction in retinal thickness even at 6 months unlike in the ME group. This highlights the treatment problems in real world where patients are mostly treated on PRN basis unlike the fixed monthly dosing regimen in clinical trials. The sustainability of treatment and the compliance depends a lot on the cost of the treatment. In a developing country such as India, the sheer burden of continued anti VEGF treatment over an indefinitely long period, invariably results in under dosing. And as a result suboptimal visual outcomes are common. According to a 2017 analysis of prescription data for a cohort of Australian patients with nAMD, only about 40% of those who started anti-VEGF therapy were still receiving the index treatment one year later [9]. 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 % [10].

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, 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 [11]. Similarly another study by Weiss et al also demonstrated higher rates of non-adherence to treatment in DME (46%) than AMD (22%) with significant correlation to poorer visual outcomes in DME [12]. The main reason postulated for this non-compliance in DME patients was the presence of several other co-morbidities which may take precedence over the ocular treatment. Multiple hospitalizations also lead to a break in the ocular treatment. In developing nations, due to poor universal healthcare, low per capita income and out of pocket expenditure for the patients, this loss to follow up rate is higher. Apart from the low socioeconomic conditions, low education level, lack of awareness about treatment and poor doctor-patient communication are other important factors affecting the compliance [10-12]. 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 more common due to its lower cost. However, aliquoting of the drug poses a big problem. It needs to be done under 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 aliquoting, storing and using the bevacizumab injection [13]. The problems with aliquoting can be overcome with the use of 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. The authenticity of the vial can be checked by using a unique alphanumeric code, the Kezzler code, on the vial.

Unlike a generic drug, the biosimilar manufacturing process does not have a fixed chemical formula [14]. 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. Table 6 lists the key differences between a biosimilar and a generic drug. The 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, pharmacodynamics- pharmacokinetic and clinical studies to assess safety, efficacy and immunogenicity [15]. Strict pharmacovigilance, post marketing studies, reporting of adverse events and a risk management plan is 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. The retrospective nature of the study makes the evidence biased and less reliable. The treatment regimen followed was not uniform. There were a lot of dropouts and the number of eyes at long term follow up suffered on this account. We included both treatment naïve and previously treated patients which might affect the final outcome. But the majority of patients (86.4 - 92.5% among all the groups) were treatment naïve. We feel that the small percentage of treated patients will not have affected the results significantly. The study therefore gives us an idea about the comparative efficacy of the 3 agents in a real world scenario.

Conclusions

The biosimilar ranibizumab gives comparable results to innovator ranibizumab and bevacizumab without any major adverse profile. It overcomes the problems of high cost thereby making it more feasible by a large section of the population to continue with long term therapy. The single use vial of the biosimilar ranibizumab prevents the problems associated with fractionation or aliquoting of drug. Thus it can serve as a cost effective treatment option which can be preferable to both clinicians as well as the patients.

Declarations

Funding – None.

Conflicts of interest/Competing interests – None of the authors have any conflicts of interests.

Ethics approval - This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Medical Research Foundation, Sankara Nethralaya.

Consent to participate – Written informed consent was given by all the participants.

Consent for publication – Consent for publication of data was given by all the participants.

Availability of data and material – Most of the data is given in the manuscript. Data is freely available for perusal on request.

Code Availability – Not applicable

Authors' contributions – All authors made substantial contributions to the conception, design of the study and analysis, and interpretation of data.

DR, KR, SG, SM- Contributed significantly to the conception, design, analysis, interpretation of the data and review of the draft. They also collected the data, coded it, analyzed and interpreted it.

The Sankara Nethralaya Vitreoretinal Study Group- contributed to the interpretation of the data, writing of the draft and critically reviewing it.

Acknowledgements:

The Sankara Nethralaya Vitreoretinal (SNVR) Study group comprises of Drs Pramod Bhende, Muna Bhende, Girish Rao, Parveen Sen, Rajiv Raman, Vikas Khetan, Chetan Rao, Pradeep S, Vinata Muralidharan, Suganeswari G, Kumar Saurabh, Debmalya Das, Suchetana Mukherjee, Aditya Verma, Rajesh P S, Jaya Prakash V, Eesh Nigam, Charanya C, Sruthi S, Maitreyi Chowdhury, Kalpita Das,.

Significance: In a developing country, the financial burden of continued 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. Moreover, the efficacy of the biosimilar ranibizumab is comparable with that of the innovator ranibizumab or bevacizumab.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. Available at: <https://www.diabetesatlas.org>
2. Sharma S, RE-ENACT Study Investigators Group, Khan MA, Chaturvedi A. (2018) Real-life clinical effectiveness of Razumab (world's first biosimilar ranibizumab) in wet age-related macular degeneration, diabetic macular edema, and retinal vein occlusion: a retrospective pooled analysis. *Int J Ophthalmol Eye Res.* 6(4):377–83.
3. Sharma S, Khan MA, Chaturvedi A; RE-ENACT Study Investigators Group.(2018) Real Life Clinical Effectiveness of Razumab® (World's First Biosimilar Ranibizumab) in Wet Age-Related Macular Degeneration: A Subgroup Analysis of Pooled Retrospective RE-ENACT Study. *Int J Ophthalmol Eye* 6(2):368–373.
4. Sharma S, Khan MA, Chaturvedi A; RE-ENACT Study Investigators Group. (2019) Real-Life Clinical Effectiveness of Razumab® (the World's First Biosimilar of Ranibizumab) in Retinal Vein Occlusion: A Subgroup Analysis of the Pooled Retrospective RE-ENACT Study. *Ophthalmologica.* 241(1):24-31. doi: 10.1159/000488602. Epub 2018 Jun 26.
5. Sharma S, RE-ENACT 2 Study Investigators Group, Khan MA, Chaturvedi A .(2019) A Multicenter, Retrospective Study (RE-ENACT 2) on the use of Razumab™ (World's First Biosimilar Ranibizumab) in NAMD, DME, RVO and Myopic CNV. *J Clin Exp Ophthalmol* 10: 826-832.

6. Pham B, Thomas SM, Lillie E, Lee T, Hamid J, Richter T, et al. (2019) Anti-vascular endothelial growth factor treatment for retinal conditions: a systematic review and meta-analysis. *BMJ Open*. May 28;9(5):e022031. doi: 10.1136/bmjopen-2018-022031.
7. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. (2015) Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 372:1193–1203.
8. Cai S, Bressler NM. (2017) Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T. *Curr Opin Ophthalmol* 28:636–643.
9. Skelly A, Carius HJ, Bezlyak V, Chen FK. (2017) Dispensing patterns of ranibizumab and aflibercept for the treatment of neovascular age-related macular degeneration: a retrospective cohort study in Australia. *Adv Ther*. 34(12):2585-600.
10. Kelkar A, Webers C, Shetty R, Kelkar J, Labhsetwar N, Pandit A, et al. (2020) Factors affecting compliance to intravitreal anti-vascular endothelial growth factor therapy in Indian patients with retinal vein occlusion, age-related macular degeneration, and diabetic macular edema. *Indian J Ophthalmol*. 68:2143-2147.
11. Ehlken C, Helms M, Böhringer D, Agostini HT, Stahl A. (2017) Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. *Clin Ophthalmol*. 12:13-20.
12. Weiss M, Sim DA, Herold T, Schumann RG, Liegl R, Kern C, et al. (2018) Compliance and adherence of patients with diabetic macular edema to intravitreal anti-vascular endothelial growth factor therapy in daily practice. *Retina* 38(12):2293-2300
13. https://vrsi.in/wp-content/uploads/2018/02/Avastin_Guidlines_Book.pdf . Accessed on 1/9/2020.
14. Sharma A, Reddy P, Kupperman BD, Bandello F, Lowenstein A.(2018) Biosimilars in ophthalmology: “Is there a big change on the horizon? *Clinical Ophthalmology* 12: 2137–2143.
15. Sharma A, Kumar N, Kupperman BD, Bandello F, Lowenstein A. (2020) Understanding biosimilars and its regulatory aspects across the globe: an ophthalmology perspective. *Br J Ophthalmol* 104:2-7.

Tables

Table 1: Demographic details of the study population

		Type of Injections		
		Ranibizumab (N= 69)	Bevacizumab (N= 66)	Biosimilar ranibizumab (N= 67)
Age (years)	Mean	66.36 ± 9.53	62 ± 13.95	58.49 ± 13.026
	Range	50 - 87	27 - 88	26 - 84
Sex N (%)	Male	43 (62.3)	41 (62.1)	41(61.2)
	Female	26 (37.7)	25 (37.9)	26 (38.8)
Eye N (%)	Right Eye	35 (50.7)	33 (50.0)	32 (47.8)
	Left Eye	34 (49.3)	33 (50.0)	35 (52.2)
Previous Treatment N (%)	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 N (%)	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 N (%)	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 AMD

Table 2: Analysis of the change in visual acuity and change in the central foveal thickness within a short follow up of 3 months 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 = 39)	BEV (n = 35)	BSR (n = 35)	RBZ VS BEV P value (95% CI)	BEV VS BSR P value (95% CI)	RBZ VS BSR P value (95% CI)
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	0.17 ± 0.37	0.09 ± 0.23	0.26 ± 0.48	0.99	0.60	0.62
					(-0.06 -0.22)	(-0.01 -0.35)	(-0.29 -0.11)
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	123.33 ± 209.91	84.65 ± 152.38	110.28 ± 148.19	0.34	0.52	0.57
					(-45.73 -123.09)	(-46.06 - 97.32)	(-70.51- 96.61)
Macular Edema short follow up		RBZ (n = 28)	BEV (n = 31)	BSR (n = 27)	RBZ VS BEV P value (95% CI)	BEV VS BSR P value (95% CI)	RBZ VS BSR P value (95% CI)
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	0.15 ± 0.27	0.16 ± 0.22	0.25 ± 0.27	0.59	0.24	0.13
					(-0.13 - 0.11)	(-0.04 - 0.22)	(-0.24 - 0.04)
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
	P - value	0.006	0.001	<0.01			

Change In CFT	187.07 ± 321.86	140.93 ± 194.25	281.70 ± 314.71	0.99	0.07	0.16
				(-94.27 - 186.55)	(0.75 - 280.78)	(-266.79 - 77.53)

Table 3: Analysis of the change in visual acuity and change in the central foveal thickness with a long follow up of 6 months or more 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 (95% CI)	BEV VS BSR P value (95% CI)	RBZ VS BSR P value (95% CI)
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	0.21 ± 0.39	0.04 ± 0.26	0.26 ± 0.58	0.08 (0.01-0.32)	0.18 (-0.02 - 0.46)	0.98 (-0.21 - 0.31)
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	136.08 ± 174.59	77 ± 161.74	112.27 ± 218.34	0.07 (-19.97-138.13)	0.46 (-136.92 - 66.38)	0.55 (-79.27 - 126.89)
Macular Edema Long Follow Up		RBZ (n = 27)	BEV (n = 31)	BSR (n = 14)	RBZ VS BEV P value (95% CI)	BEV VS BSR P value (95% CI)	RBZ VS BSR P value (95% CI)
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	0.12 ± 0.4	0.09 ± 0.32	0.62 ± 0.37	0.73 (-0.16 - 0.22)	0.87 (-0.75 - 0.24)	0.64 (0.29 - 0.76)
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			
Change In CFT	226.00 ± 326.25	223.97 ± 306.84	105.64 ± 264.14	0.98	0.25	0.23
				(-165.32 - 169.38)	(-298.94 - 62.28)	(-70.73 - 311.45)

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

		RBZ (n = 69) (%)	BEV (n = 66) (%)	BSR (n = 67) (%)	RBZ VS BEV	BEV VS BSR	RBZ VS BSR
					P value	P value	P 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)			
	N	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)			
	N	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)			
	N	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)			
	N	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			
	N	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)			
	N	48	53	25			
Last visit	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)			

N	54	45	51
---	----	----	----

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

		RBZ (n = 69)(%)	BEV (n = 66)(%)	BSR (n = 67)(%)	RBZ VS BEV P value	BEV VS BSR P value	RBZ VS BSR P 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)			
	N	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)			
	N	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)			
	N	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)			
	N	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)			
	N	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)			
	N	43	53	25			
Last visit	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)			

N

52

44

20

Table 6: Differences between generic drugs and biosimilar agents

	Generics	Biosimilars
Product Characteristics	Small molecules Very stable No device	Large complex molecules For stability require special handling Device is often the key differentiator
Production	By chemical synthesis	Produced in living organisms Highly sensitive to manufacturing changes Comparatively high cost
Development	Very limited clinical trials (enough to demonstrate chemical similarity and purity)	Significant R&D needed Pharmacokinetics, pharmacodynamics studies and clinical trials required
Regulation	Abbreviated registration procedures	Defined regulatory pathway

Figures

Figure 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).