

Efficacy and Safety of an Indian Bevacizumab BIOSimilar (BEVATAS) for Retinal Vein Occlusion (BIOS-RVO Study)

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Purpose: To evaluate the efficacy and safety of Bevatas[®], an Indian bevacizumab biosimilar, in the management of both Central Retinal Vein Occlusion (CRVO) and Branch Retinal Vein Occlusion (BRVO) (BIOS-RVO).

Patients and Methods: The BIOS-RVO study was a retrospective interventional study conducted at a single tertiary eye care facility in India. 154 treatment-naïve eyes with RVO (CRVO: 62 eyes; BRVO: 92 eyes) received intravitreal bevacizumab biosimilar (IVBb) therapy. Data on best-corrected visual acuity (BCVA), central macular thickness (CMT), and intraocular pressure (IOP) were collected at baseline and at 3, 6, and 12 months post-therapy.

Results: The average age of participants was approximately 55.99 (+12.56) years, with a nearly equal gender distribution (M:F = 49.4:50.6). Age differences between BRVO and CRVO groups were not significant ($P=0.501$), but gender distribution varied significantly ($P=0.035$), with more males in the CRVO group. Significant improvements in BCVA were observed in both CRVO and BRVO groups at 3 months, 6 months, and 1 year compared to baseline ($P<0.001$). Both groups showed significant reductions in CMT throughout the follow-up period ($P<0.001$). The mean number of injections was higher in the CRVO group (5.27[±1.45]) compared to the BRVO group (4.27 [±1.28]) ($P<0.001$). Significant IOP increases were observed at 1 month ($P<0.001$) and 6 months ($P<0.001$) in both BRVO and CRVO groups, although not clinically significant. Safety analysis revealed no additional ocular or systemic adverse events during the study period.

Conclusion: The BIOS-RVO study demonstrates that Bevatas is an effective and safe treatment option for both CRVO and BRVO. These findings support the use of Bevatas as a cost-effective alternative to branded anti-VEGF agents, particularly in resource-limited settings.

Keywords: retinal vein occlusion, bevacizumab, biosimilar, Bevatas

Introduction

Retinal vein occlusion (RVO) is the second most prevalent retinal vascular disorder, following diabetic retinopathy, and it inevitably contributes to visual impairment.^{1,2} The estimated incidence of RVO in the population in general ranges from approximately 0.5% to 1.8%.^{1,2} Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are the two main types of RVO, each with its distinct clinical presentation and management challenges.³ Both conditions are associated with vision loss due to macular edema (ME), ischemia, and neovascularization.¹⁻³

Over the past few decades, the treatment landscape for RVO has evolved significantly, with anti-vascular endothelial growth factor (anti-VEGF) agents emerging as a cornerstone in the management of these conditions.^{4,5} VEGF plays a pivotal role in the pathogenesis of RVO by promoting vascular permeability, inflammation, and neovascularization.⁵ Anti-VEGF agents, such as bevacizumab, ranibizumab, and aflibercept, have demonstrated efficacy in improving visual acuity and reducing macular edema in patients with RVO, revolutionizing the treatment paradigm for these conditions.^{4,5} Despite the proven benefits of anti-VEGF therapy, the high cost of these agents poses a significant economic burden on

healthcare systems worldwide, particularly in low- and middle-income countries (LMICs). Biosimilars, which are biologic products that are highly similar to an approved reference product with no clinically meaningful differences in terms of safety, efficacy, and quality, offer a promising solution to this economic challenge.^{6–9} By providing a more affordable alternative to branded anti-VEGF agents, biosimilars have the potential to improve access to essential treatments for RVO and enhance health economics, especially in resource-limited settings.^{6–9} Few studies have also demonstrated these biosimilars to be comparable to the innovator molecules, both in terms of efficacy and safety.⁸

Biosimilars of bevacizumab have been developed as more affordable alternatives, maintaining similar quality, safety, and efficacy profiles.¹⁰ Bevatas[®], a biosimilar of bevacizumab developed by Intas Pharmaceuticals in India, is a cost-effective alternative to Avastin[®], a drug manufactured by Genentech and Roche, with a 4mL vial price of \$144, compared to the \$400 price of Avastin.¹⁰ Bevatas represents a promising option for RVO treatment, potentially expanding access to effective anti-VEGF therapy and improving health outcomes for patients worldwide.

Despite the increasing use of anti-VEGF agents in RVO management, there remains a need for comprehensive evaluation of biosimilars like Bevatas in this patient population. This study aims to evaluate the efficacy and safety of Bevatas in the management of both CRVO and BRVO (BIOS-RVO), providing valuable insights into its potential role in RVO treatment. The BIOS-RVO study is a continuum of the BIOS-ROP study, which evaluated Bevatas for the management of retinopathy of prematurity (ROP).¹⁰

Materials and Methods

The BIOS-RVO study is an interventional, retrospective study carried out at a single tertiary eye care facility in Eastern India (Siliguri, West Bengal). The study comprised consecutive patients with treatment-naïve RVO and ME who sought treatment at the Vitreoretinal services between June 2022 and August 2023. All eyes received treatment using intravitreal bevacizumab biosimilar (IVBb) therapy. The study was approved by the Institutional Review Board of the Retina Institute of Bengal in Siliguri, India, and was conducted in compliance with the tenets outlined in the Declaration of Helsinki. Patients gave written informed consent for both therapy and data collection.

Data were collected from electronic medical records, including demographic information, baseline characteristics, best corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure (IOP), and number of injections. Visual acuity was measured using the Snellen chart and converted to a logarithm of the minimum angle of resolution (logMAR) for analysis. Central macular thickness was assessed using optical coherence tomography (OCT) (Maestro2, Topcon Healthcare, New Jersey, USA), and intraocular pressure was measured using Goldmann applanation tonometry. These parameters were evaluated at baseline and 3, 6, and 12 months (± 2 weeks) following the initiation of IVBb therapy. Patients were administered IVBb in three monthly loading doses, followed by a pro-re-nata (PRN) regimen.

Outcome Measures

The primary outcome measure was the changes in the BCVA and the CMT at the end of 3, 6, and 12 months after starting the therapy. The secondary outcome measure included a safety analysis, including IOP changes, inflammation, retinal detachment (RD), vitreous hemorrhage (VH), subconjunctival hemorrhage (SCH), and so on. Furthermore, a comprehensive assessment of the number of injections was conducted as a secondary measure of the treatment.

Statistical Analysis

The Statistical analysis was performed by SPSS 23.0 version. Categorical variables were described by taking number and percentages. Normality of the continuous data was done using Shapiro Wilk test. Continuous variables were described as mean and variation of each observation from the mean value (Standard deviation) represented as mean \pm SD (analyzed using independent *t* test) if they followed normal distribution and were described as Median (IQR) if they followed non normal distribution (analyzed using Mann Whitney *U*-Test). Paired continuous data was analyzed using Paired *T* test (if following normal distribution) or Wilcoxon signed rank test (if following non normal distribution). Variables with a *P*-value of <0.05 were considered statistically significant.

Results

Study Cohort

The study included a total of 154 eyes of 154 patients diagnosed with RVO, with 92 eyes having BRVO and 62 eyes having CRVO. The average age of the participants was 55.99 years, with a standard deviation (SD) of 12.56. The gender distribution was almost equal, with 76 males (49.35%) and 78 females (50.65%). When comparing the two groups, the average age for BRVO patients was 55.46 (+1.52) years, and for CRVO patients, it was 56.92 (+14.2) years. The difference in age between the two groups was not statistically significant ($P=0.501$). However, there was a significant difference in gender distribution between the two groups, with a higher percentage of males in the CRVO group (59.7%) compared to the BRVO group (42.4%) ($P=0.035$). Table 1 provides the demographic details of the study population.

Best-Corrected Visual Acuity Outcomes

At baseline, the median LogMAR BCVA was comparable between the BRVO and CRVO groups, with values of 0.6 $\{\approx 20/80\}$ (IQR 0.48–0.78) and 0.6 $\{\approx 20/80\}$ (IQR 0.3–1), respectively ($P=0.89$). Significant improvements in BCVA were observed in both groups at 3 months, 6 months, and 1 year compared to baseline. For BRVO patients, the median BCVA improved from 0.6 LogMAR $\{\approx 20/80\}$ at baseline to 0.3 LogMAR $\{\approx 20/40\}$ at 3 months ($P<0.001$) and improved further to 0.2 LogMAR $\{\approx 20/30\}$ up to 1 year ($P<0.001$). Similarly, CRVO patients showed improvement from a baseline median BCVA of 0.6 $\{\approx 20/80\}$ to 0.39 $\{\approx 20/50\}$ at 3 months ($P=0.006$), 0.3 $\{\approx 20/40\}$ at 6 months ($P<0.001$), and 0.3 $\{\approx 20/40\}$ at 1 year ($P<0.001$). There were no statistically significant differences in BCVA outcomes between the BRVO and CRVO groups at any time point. Table 2 provides the BCVA changes in the study population.

Central Macular Thickness Outcomes

At baseline, the mean CMT was higher in the CRVO group ($622.85 \pm 112.33 \mu\text{m}$) compared to the BRVO group ($518.16 \pm 73.65 \mu\text{m}$) ($P<0.001$). Throughout the follow-up period, both BRVO and CRVO groups showed significant reductions in CMT ($P<0.001$), with mean CMT values decreasing to $273.74 \pm 13.84 \mu\text{m}$ for BRVO and $278.53 \pm 37.87 \mu\text{m}$ for CRVO at 1 year. At 1 year, the difference between the groups was not significant ($P=0.269$). Table 3 provides the CMT changes in the study population.

Table 1 Demographic Characteristics of the Study Population

Variables			BRVO (N=92)	CRVO (N=62)	RVO (N=154)	P value
Age		Mean \pm SD	55.46 \pm 11.52	56.92 \pm 14.2	55.99 \pm 12.56	0.501
Gender	Males	Number (Percentage)	39 (42.4)	37 (59.7)	77 (49.4)	0.035
	Females		53 (57.6)	25 (40.3)	79 (50.6)	

Abbreviations: SD, Standard deviation; BRVO, Branch retinal vein occlusion; CRVO, Central retinal vein occlusion; RVO, Retinal vein occlusion.

Table 2 Best-Corrected Visual Acuity (BCVA) Changes in Both the Groups Through 12 Months

LogMAR BCVA	BRVO (N=92)		CRVO (N=62)		P value Between the Groups
	Median (IQR)	P value with Baseline	Median (IQR)	P value with Baseline	
Baseline	0.6 (0.48–0.78)	NA	0.6 (0.3–1)	NA	0.888
3 months	0.3 (0.2–0.49)	<0.001	0.39 (0.2–0.78)	0.006	0.007
6 months	0.3 (0.2–0.49)	<0.001	0.3 (0.2–0.6)	<0.001	0.057
1 year	0.2 (0.05–0.3)	<0.001	0.3 (0.2–0.525)	<0.001	0.01

Abbreviations: IQR, Interquartile range; BRVO, Branch retinal vein occlusion; CRVO, Central retinal vein occlusion.

Table 3 Central Macular Thickness (CMT) Changes in Both the Groups Through 12 Months

CMT	BRVO (N=92)		CRVO (N=62)		P value Between the Groups
	Mean ± SD	P value with Baseline	Mean ± SD	P value with Baseline	
Baseline	518.16 ± 73.65	NA	622.85 ± 112.33	NA	<0.001
3 months	294.07 ± 26.87	<0.001	308.19 ± 54.29	<0.001	0.034
6 months	304.35 ± 60.92	<0.001	327.84 ± 85.82	<0.001	0.065
1 year	273.74 ± 13.84	<0.001	278.53 ± 37.87	<0.001	0.269

Abbreviations: CMT, Central macular thickness; BRVO, Branch retinal vein occlusion; CRVO, Central retinal vein occlusion; SD, Standard deviation.

Number of Injections

The mean number of injections administered during the study period was significantly higher in the CRVO group (5.27 ± 1.45) compared to the BRVO group (4.27 ± 1.28) ($P < 0.001$). Within the CRVO group, 14 eyes were given only three loading doses, in contrast to 1, 11, 31, and 5 eyes that received 4, 5, 6, and 8 injections respectively. Similarly, in the BRVO group, 44 eyes required just three loading doses, while 1, 25, and 22 eyes required 4, 5, and 6 injections, respectively.

Safety Analysis

Baseline IOP was similar between the BRVO (16.14 ± 3.83 mmHg) and CRVO (16.42 ± 3.77 mmHg) groups ($P = 0.657$). While fluctuations in IOP were observed over the follow-up period, there were no clinically significant changes from baseline in either group. However, statistically significant increases in IOP were noted at various time points, particularly at 1 month ($P < 0.001$) and 6 months ($P < 0.001$) in both the BRVO and CRVO groups. Table 4 provides the IOP changes for the study population. No ocular or systemic adverse events were noted during the study period.

Discussion

The present study, BIOS-RVO, investigated the efficacy and safety of the Indian bevacizumab biosimilar, Beventas, in treating RVO, encompassing both BRVO and CRVO. The results demonstrated significant improvements in visual acuity and reductions in CMT in both BRVO and CRVO groups over a 12-month period. Interestingly, while the CRVO group necessitated a higher frequency of injections, both groups presented analogous safety profiles devoid of any notable ocular or systemic adverse events.

Table 4 Intraocular Pressure (IOP) Changes in Both the Groups Through 12 Months

IOP	BRVO (N=92)		CRVO (N=62)		P value Between the Groups
	Mean ± SD	P value with Baseline	Mean ± SD	P value with Baseline	
Baseline	16.14 ± 3.83	NA	16.42 ± 3.77	NA	0.657
1 Month	16.89 ± 3.86	0.014	18.05 ± 4.39	<0.001	0.095
3 months	17.24 ± 4.53	0.001	17.89 ± 4.45	<0.001	0.381
6 months	17.05 ± 4.64	0.012	18.98 ± 6.5	<0.001	0.046
1 year	16.01 ± 3.83	0.642	16.94 ± 3.69	0.081	0.136

Abbreviations: IOP, Intraocular pressure; BRVO, Branch retinal vein occlusion; CRVO, Central retinal vein occlusion; SD, Standard deviation.

Anti-VEGF agents have revolutionized the treatment landscape for RVO by targeting the underlying pathophysiology involving VEGF.^{4,5} VEGF plays a pivotal role in promoting vascular permeability, inflammation, and neovascularization, leading to macular edema, ischemia, and vision loss in RVO patients.^{4,5} By inhibiting VEGF activity, anti-VEGF agents like bevacizumab, ranibizumab, and aflibercept have demonstrated significant efficacy in improving visual outcomes and reducing macular edema in RVO patients.^{4,5}

Bevacizumab, originally conceived as a full-length humanized monoclonal antibody targeting VEGF-A for cancer therapeutics, has traversed therapeutic boundaries to find its niche in ophthalmology.¹¹ Its off-label utilization in ophthalmological conditions, especially RVO, stems from its undeniable cost-effectiveness juxtaposed against its counterparts, ranibizumab and aflibercept.¹¹ The MARVEL study compared bevacizumab and ranibizumab for macular edema secondary to BRVO.¹² The outcomes at the 6-month mark displayed comparable visual outcomes, albeit not achieving non-inferiority due to inherent variability.¹² Notwithstanding this caveat, both treatment arms sustained visual acuity above the clinically significant threshold of 20/40, coupled with a notably low incidence of adverse events.¹² In the SCORE2 trial, bevacizumab demonstrated non-inferiority to aflibercept in macular edema secondary to retinal vein occlusion.¹³ Both drugs yielded significant visual improvements, with similar adverse event rates.¹³ In the real-world, few studies have been performed to compare the different anti-VEGF agents. Rajagopal et al found that there was no significant difference in central foveal thickness (CFT) or VA at 6 months (0.33 logMAR gain for bevacizumab vs 0.34 for ranibizumab, $P=0.38$) in the CRAVE study.¹⁴ Similarly, another study comparing PRN aflibercept with bevacizumab in BRVO-related ME found no statistically significant differences in VA and CFT at the 1-year mark.¹⁵ Thus, current research suggests no substantial differences in the efficacy and safety outcomes among anti-VEGF agents for RVOs. The findings of the BIOS-RVO study are consistent with previous literature on the efficacy of bevacizumab in RVO treatment. Significant improvements in VA and reductions in CMT were observed in both the CRVO and BRVO groups, aligning with the results of previous clinical trials and real-world studies. The safety profile of Bevas was also favorable, with no clinically significant changes in intraocular pressure and no ocular or systemic adverse events noted during the study period. These findings further support the use of bevacizumab biosimilars as cost-effective alternatives to branded anti-VEGF agents in the management of RVO.

The safety analysis conducted as part of the BIOS-RVO study demonstrated that Bevas was well-tolerated, with no ocular or systemic adverse events reported during the study period. While fluctuations in IOP were observed, these changes were not clinically significant and did not necessitate intervention. It is noteworthy to mention that a recent study evaluating the safety profile of intravitreal bevacizumab (Avastin) as an off-label pharmacotherapeutic agent for various ocular conditions found that bevacizumab is a safe and economical pharmacotherapeutic agent that can be administered for a variety of ocular disorders.¹¹ The study conducted on 3806 injections of 1761 patients at a tertiary eye care center in India reported no systemic adverse events and a low incidence of ocular side effects, further reinforcing the safety profile of bevacizumab, including its biosimilars like Bevas.¹¹

In addition, the efficacy of Bevas has been demonstrated in the management of ROP in the BIOS-ROP study.¹⁰ The study found that intravitreal bevacizumab biosimilar monotherapy offers significant benefits for type 1 ROP.¹⁰ The study population experienced no ocular or systemic adverse effects, highlighting the safety and efficacy of Bevas in treating ROP.¹⁰ This study serves as a continuum where we evaluate Bevas for RVO (BIOS-RVO), further strengthening the evidence base for the use of Bevas across different ophthalmic conditions.

The high cost of branded anti-VEGF agents poses a significant economic burden on healthcare systems, particularly in LMICs.⁷ Bevas, a cost-effective biosimilar of bevacizumab, offers a promising solution to this economic challenge.¹⁰ With a 4mL vial price of \$144 compared to the \$400 price of Avastin, Bevas offers a more affordable alternative and helps improve access to essential treatments for RVO and enhance health economics. The cost-effectiveness of biosimilars can alleviate the financial burden on healthcare systems, enabling more patients to receive timely and effective treatment for RVO. Additionally, biosimilars like Bevas maintain similar quality, safety, and efficacy profiles to branded biologic agents, ensuring that patients receive high-quality care at a lower cost. These advantages highlight the potential of biosimilars to address unmet medical needs and improve health outcomes for RVO patients, especially in resource-limited settings.

To maximize the benefits of biosimilars in RVO management, several health policy changes can be proposed. Firstly, healthcare systems should prioritize the inclusion of biosimilars in treatment guidelines and formularies to promote their widespread adoption. This can be achieved through collaborations between healthcare providers, policymakers, and pharmaceutical companies to raise awareness about the safety and efficacy of biosimilars and streamline their integration into clinical practice. Secondly, regulatory agencies should implement policies to expedite the approval process for biosimilars and ensure rigorous monitoring of their quality, safety, and efficacy. This can facilitate timely access to affordable treatments for RVO patients while maintaining high standards of healthcare delivery. Lastly, healthcare reimbursement policies should be revised to incentivize the use of biosimilars and encourage cost-saving measures in RVO management. By implementing these health policy changes, healthcare systems can optimize the use of biosimilars and improve access to high-quality care for RVO patients worldwide.

Despite the promising results, our study has several limitations. First, the retrospective design of the study is a significant limitation. Retrospective studies inherently carry risks of selection bias and confounding variables, which can influence the results. Specifically, the data were collected from existing records without randomization, which may introduce biases related to patient selection and variations in treatment protocols. These biases could affect the generalizability of the findings to broader populations and may impact the observed efficacy and safety outcomes of Bevas. Secondly, there was variability in the timing of follow-up visits. Although the study aimed to assess outcomes at 3 months, 6 months, and 12 months, real-world factors resulted in some patients being evaluated outside of these exact time points. This variability in follow-up intervals may have introduced heterogeneity into the analysis and influenced the interpretation of treatment effects. Thirdly, the study was conducted at a single tertiary eye care facility in India, which may restrict the applicability of the results to other settings. We recognize that patient populations, healthcare systems, and treatment practices vary significantly across different regions and countries. For example, socioeconomic factors, healthcare accessibility, and treatment affordability can influence patient outcomes. Additionally, treatment protocols may differ due to variations in healthcare provider expertise, resource availability, and local clinical guidelines. Therefore, our findings may not fully generalize to institutions with different patient demographics or healthcare structures. Fourthly, the follow-up period was limited to 12 months. While the study provides valuable short-term data on the efficacy and safety of Bevas in the management of retinal vein occlusion (RVO), the long-term outcomes remain unknown. Longer-term studies are essential to fully assess the durability of the treatment effect and potential long-term safety concerns. Future research should explore the efficacy of Bevas beyond 12 months, as longer follow-up periods are crucial for understanding sustained treatment benefits, recurrence rates, and any delayed adverse effects. Finally, the absence of a control group receiving a different treatment or placebo is a major limitation. This restricts our ability to directly compare the efficacy of Bevas with other therapeutic options in the management of RVO. Without a control group, it is challenging to determine whether the observed outcomes are specific to Bevas or could be achieved with other agents. Future research should consider randomized controlled trials (RCTs) comparing Bevas to alternative treatments or a placebo, which would provide stronger evidence for its relative efficacy and safety. Additionally, a larger multicenter trial would help validate these findings in a broader and more diverse patient population.

Despite these limitations, the BIOS-RVO study has several strengths. Firstly, it provides real-world evidence of the efficacy and safety of Bevas, a biosimilar of bevacizumab, in the management of both CRVO and BRVO. Second, the study has a relatively large cohort of patients undergoing comprehensive evaluation. Lastly, the study evaluated clinically relevant outcomes, including BCVA, macular thickness, and IOP, providing comprehensive insights into the treatment effects of Bevas in RVO patients.

Conclusion

In conclusion, the BIOS-RVO study demonstrates the efficacy and safety of Bevas, an Indian bevacizumab biosimilar, in the management of both CRVO and BRVO. During the study period, both the BRVO and CRVO groups demonstrated significant visual acuity gains and CMT reduction. While the CRVO group required a greater frequency of injections, both groups exhibited similar safety profiles without significant ocular or systemic adverse events. With a 4mL vial price of \$144 compared to the \$400 price of Avastin, Bevas presents a more affordable alternative and potentially enhances health economics by improving access to essential treatments for RVO, especially in low- and middle-income countries. However, a detailed cost-effectiveness analysis is beyond the scope of this manuscript. We recommend that future studies

incorporate such evaluations to fully assess the economic benefits of Bevas. Additionally, by improving access to essential treatments for RVO and enhancing health economics, biosimilars like Bevas have the potential to transform the treatment landscape for RVO patients worldwide. Further research and health policy changes are needed to maximize the benefits of biosimilars in RVO management and ensure equitable access to high-quality care for all patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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