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ORIGINAL RESEARCH

Efficacy of an Indian Bevacizumab BIOSimilar (BEVATAS) for Type 1 and Aggressive Posterior Retinopathy of Prematurity (BIOS-ROP Study)

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Purpose: To evaluate the role of an Indian bevacizumab biosimilar (Bevatas®), for the management of type 1 retinopathy of prematurity (ROP) and aggressive posterior ROP (APROP) over 24-weeks.

Patients and Methods: A retrospective, single-center, interventional study of 144 eyes of type 1 (100 eyes) and APROP (44 eyes). All eyes received a single dose of 0.625mg Bevatas injection, and were advised additional laser therapy for suboptimal response.

Results: The study population had a mean gestational age of 28.94 (±2.32) weeks, an average birth weight of 1.2 (±0.34) kg, and modest male predominance (52.05%). Complete regression of ROP was seen in 65.97% of 144 eyes after 24 weeks of bevacizumab monotherapy, and in 97.22% of eyes (140 eyes) after adding laser photocoagulation. The remaining four eyes (all had APROP) developed Stage 4 ROP and needed vitreous surgery. After monotherapy with bevacizumab biosimilar, type 1 ROP eyes had significantly higher rate of complete ROP regression than APROP eyes (87% vs 18.18%; $P<0.00001$). All eyes with type 1 ROP, and 90.91% of eyes with APROP, regressed after receiving additional laser therapy. The study population experienced no ocular or systemic adverse effects.

Conclusion: The BIOS-ROP study demonstrates that intravitreal bevacizumab biosimilar monotherapy offers significant benefit for type 1 ROP, but not APROP. Low-cost biosimilars can help sustain healthcare systems in lower-middle income countries (LMICs) with escalating healthcare expenditures. They can also improve healthcare equity by making vision-saving therapies like bevacizumab more affordable and accessible.

Keywords: retinopathy of prematurity, laser photocoagulation, bevacizumab, biosimilar, bevatas

Introduction

Retinopathy of Prematurity (ROP) continues to be a significant clinical concern in neonatal medicine, affecting the visual development and quality of life of premature infants worldwide.[1,2] The pathophysiology of ROP is intricately linked to aberrant vascular development within the developing retina of premature infants.[1,2] Insufficient vascularization during the early stages is followed by uncontrolled neovascularization in the later phases, culminating in potentially sight-threatening complications such as retinal detachment and fibrovascular proliferation.[1,2]

As one of the leading causes of childhood blindness, ROP underscores the need for effective, accessible, and cost-efficient treatments. Traditionally, therapeutic interventions for ROP have relied upon ablative treatments like laser photocoagulation, which, while effective, can carry the risk of peripheral visual field loss and damage to the developing retina.[3] The advent of anti-vascular endothelial growth factor (anti-VEGF) agents has transformed the treatment landscape for ROP.[4] Bevacizumab, a humanized monoclonal antibody targeting VEGF, has gained substantial attention for its remarkable efficacy in treating various ocular neovascular diseases in adults.[5] More recently, its off-label use in ROP has demonstrated impressive results, leading to significant structural and functional improvements in the retinas of premature infants.[2] The BEAT-ROP study evaluated the role of bevacizumab for ROP eyes with zone 1 and zone 2 with plus disease

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and compared it to laser therapy.[2] The authors found that bevacizumab reduced retreatment need at 54 weeks post-conception age in infants with ROP compared to laser treatment (6% vs 22%; P=0.002).[2] Also, the treatment effect was significant in eyes with zone 1 disease compared to zone 2 (P=0.003).[2] The results of the RAINBOW trial suggest that the effectiveness of administering intravitreal ranibizumab at a dosage of 0.2 mg is similar to, and may even exceed, that of laser therapy in the management of type 1 ROP.[6] The FIREFLEYE trial found that intravitreal aflibercept did not meet the primary outcome criterion for noninferiority in infants who achieved treatment success at week 24, compared to laser photocoagulation.[7] The noninferiority of intravitreal aflibercept was not demonstrated due to a higher laser photocoagulation response rate than in the RAINBOW and BEAT-ROP trials, and a larger study population would have been needed to demonstrate noninferiority due to the smaller difference.[2,6,7]

The introduction of biosimilars, biologic products that are highly similar to the reference innovator biologic (in this case, bevacizumab),[8–11] has the potential to revolutionize ROP management. Biosimilars offer a unique opportunity to expand access to cutting-edge therapies while potentially reducing the economic burden associated with treatment.[8–11] The advent of biosimilar versions of bevacizumab for ROP introduces new complexities and opportunities in the field, including regulatory considerations, real-world effectiveness, and ethical implications. Bevatas®, developed by Intas Pharmaceuticals in Ahmedabad, India, is a biosimilar version of bevacizumab that is currently marketed in India.[12] This biosimilar offers a more cost-effective alternative, with a price of $144 for a 4mL vial, in comparison to the innovator molecule Avastin®, which is manufactured by Genentech in South San Francisco, CA and Roche in Basel, Switzerland, and is priced at $400 for a 4mL vial.[12]

In an era where precision medicine and innovative therapeutics are transforming healthcare landscapes, the evaluation of bevacizumab biosimilars for ROP treatment is both timely and imperative. This research endeavors to contribute to the ongoing discourse surrounding the optimal management of ROP and offers insights that may influence clinical practice guidelines, healthcare policies, and the future of ROP care. Our primary aim is to assess the efficacy and safety of the bevacizumab biosimilar (Bevatas®) in the management of ROP (BIOS-ROP study). Through our article, we will explore of the potential of biosimilars, particularly Bevatas®, in revolutionizing ROP management by offering cost-effective alternatives. We will also discuss the regulatory and real-world effectiveness associated with the introduction of biosimilar versions of bevacizumab. Lastly, a timely and imperative evaluation of Bevatas® through the BIOS-ROP study will be provided, aiming to contribute valuable insights to clinical practice, healthcare policies, and the future of ROP care.

Materials and Methods

The BIOS-ROP study was a retrospective, single-center, interventional study conducted at a single tertiary eye care center in India. A medical chart analysis of a consecutive cohort of newborns diagnosed with type 1 ROP and APROP who received treatment with intravitreal bevacizumab biosimilar (IVBb) over the period from June 2021 to March 2023 was performed. The study was carried out in accordance with the tenets outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of the Retina Institute of Bengal in Siliguri, India. The parent or guardian of each child provided written informed consent for treatment and data collection.

Design

For the ROP screening, a comprehensive history and fundus examination with a binocular indirect ophthalmoscope and +20 D lens was performed. The International Classification of Retinopathy of Prematurity (ICROP) was used to grade ROP into stages and zones.[13] The examination of all eligible newborns was conducted by a senior Vitreoretinal surgeon (S.C.) who possesses 15 years of expertise. Type 1 ROP is characterized as: (1) any ROP with plus disease in zone I; (2) stage 3 ROP in zone I; and (3) stage 2 or 3 ROP with plus disease in zone II.[13] Infants with type 1 ROP received 0.625 mg of IVBb in the operation theatre under aseptic conditions. The newborns underwent periodic assessments, occurring on a weekly basis during the first month, every two weeks until the 12th week, and then every two to four weeks until the 24th week. Commencing four weeks subsequent to the initial administration of bevacizumab, the decision to pursue any further treatments, such as laser treatment, was left to the discretion of the attending physician. Specifically,

rescue treatment with laser photocoagulation was performed if there was any worsening of the ROP stage compared to the prior visit or if the ROP persisted 28 days after IVBb therapy.

Outcome Measures

The primary outcome of interest was the proportion of infants who did not exhibit any active ROP at the 24-week stage after starting the treatment. The secondary outcome measure assessed the percentage of infants necessitating further interventions, such as laser photocoagulation and/or surgery.

Statistical Analysis

The statistical analysis was performed out using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean and mean ± Standard deviation (SD) for continuous variables. Categorical variables were described using percentages, and paired categorical data were analysed using the Chi-square test. P values < 0.05 indicated statistical significance.

Results

Study Cohort

One-hundred and forty-four eyes of 73 infants received IVBb treatment. The mean gestational age was 28.94 (±2.32) weeks, and the average birth weight was 1.2 (±0.34) kg. The gender distribution exhibited a modest male preponderance, with males comprising 52.05% and females comprising 47.95% of the study population.

Based on the ROP classification, an equal number of cohort eyes were diagnosed with Aggressive posterior retinopathy of prematurity (APROP) and Zone 2 Stage 3+ (44 eyes; 30.56%), respectively. This was followed by Zone 2 Stage 2+ (30 eyes; 20.83%), Zone 1 Stage 3+ (14 eyes; 9.72%), and Zone 1 Stage 2+ (12 eyes; 8.33%). All APROP were present in Zone 1. The baseline characteristics of the study population are elaborated in Table 1.

Treatment Outcomes

Monotherapy with the bevacizumab biosimilar resulted in complete regression of ROP in nearly two-thirds of the 144 study eyes (95 eyes; 65.97%) by 24 weeks after starting the treatment (intravitreal bevacizumab). A additional laser photocoagulation procedure was necessary for the remaining 49 eyes. Forty-five of these 49 eyes showed total ROP regression at 24-weeks. The four remaining eyes exhibited progression to the Stage 4 ROP and subsequently underwent

Table 1 Demographic Characteristics of the Study Population

Characteristic	Number of Infants (Total 73) / Number of Eyes (Total 144)
Gestational Age (weeks)	
Mean (±SD)	28.94 (±2.32)
Birth weight (Kg)	
Mean (±SD)	1.2 (±0.34)
Gender	
Males	38 (52.05%)
Females	35 (47.95%)
ROP Zone 1	
Stage 2+	12 (8.33%)
Stage 3+	14 (9.72%)
ROP Zone 2	
Stage 2+	30 (20.83%)
Stage 3+	44 (30.56%)
APROP	
Zone 1	44 (30.56%)

Abbreviations: SD, Standard deviation; ROP, Retinopathy of prematurity.

Table 2 Treatment Outcomes of the Study Population

	Laser Therapy	Regressed ROP with Bevacizumab Biosimilar Monotherapy	Regressed ROP After Laser Photocoagulation	Total ROP Regression	Complications
Total Study Eyes (144)	49 (34.03%)	95 (65.97%)	45 (31.25%)	140 (97.22%)	4 eyes progressed to Stage 4 ROP; Underwent Surgery
ROP Zone 1 Stage 2+ (12 eyes)	2 (16.67%)	10 (83.33%)	2 (16.67%)	12 (100%)	Nil
ROP Zone 1 Stage 3+ (14 eyes)	0 (0%)	14 (100%)	0 (0%)	14 (100%)	Nil
ROP Zone 2 Stage 2+ (30 eyes)	2 (6.67%)	28 (93.33%)	2 (6.67%)	30 (100%)	Nil
ROP Zone 2 Stage 3+ (44 eyes)	9 (20.45%)	35 (79.55%)	9 (20.45%)	44 (100%)	Nil
Combined Non-APROS eyes (100)	13 (13%)	87 (87%)	13 (13%)	100 (100%)	Nil
APROP (44 eyes)	36 (81.81%)	8 (18.18%)	32 (72.73%)	40 (90.91%)	4 eyes progressed to Stage 4 ROP; Underwent Surgery

Abbreviations: ROP, Retinopathy of prematurity; APROP, Aggressive-posterior retinopathy of prematurity.

vitreous surgery. All of these four eyes had APROP at baseline. Overall, complete ROP regression was achieved in 97.22% of the study eyes by week 24. Each eye received a single dosage of bevacizumab biosimilar, followed by immediate initiation of laser therapy if ROP did not show signs of regression.

On subgroup analysis based on the ROP classification, bevacizumab biosimilar monotherapy achieved excellent ROP regression for eyes with Zone 1 (Stage 2+: 83.33%; Stage 3+: 100%) and Zone 2 (Stage 2+: 93.33%; Stage 3+: 79.55%) disease. When these non-APROP (type 1 ROP) eyes (a total of 100 eyes) were combined, the ROP regression rate was 87% (87/100 eyes) with the monotherapy, improving to 100% with additional laser therapy in the remaining 13 eyes. Nevertheless, the rate of ROP regression was much lower at 18.18% (8/44 eyes) in eyes with APROP that had only been treated with the biosimilar drug. The proportion of eyes attaining complete ROP regression after monotherapy with bevacizumab biosimilar was significantly greater in type 1 ROP eyes than in APROP eyes ($P<0.00001$).

Out of the remaining 36 APROP eyes with residual ROP, additional laser therapy was performed, resulting in the regression of ROP in 32 eyes. The rest of the four eyes had surgical intervention for Stage 4 ROP as previously mentioned. Complete ROP regression with the IVBb ± laser was achieved in 97.22% (140/144 eyes) of the study eyes. This regression was achieved in all type 1 ROP eyes (Zone 1 Stage 2+, Zone 1 Stage 3+, Zone 2 Stage 2+, Zone 2 Stage 3+) and in 90.91% of APROP eyes. No ocular or systemic adverse events were noted among the study population. The treatment outcomes are elaborated in Table 2.

Discussion

In the BIOS-ROP study, the researchers sought to assess the role of the bevacizumab biosimilar, Bevatas®, for the management of ROP. Our findings revealed an acceptable ROP regression rate of 65.97% in all of the study eyes, which increased to 87% if we only take into account the type 1 ROP eyes. However, the regression rate with the monotherapy was only 18.18% in eyes having APROP, which improved to 90.91% when an additional laser therapy was given. The intravitreal therapy raised no ocular or systemic safety concerns.

The management of ROP remains a complex and evolving challenge in neonatal medicine, demanding innovative approaches to optimize visual outcomes in preterm infants. Anti-VEGF therapy and laser photocoagulation are two primary treatment modalities for managing ROP. While both approaches have their merits, anti-VEGF therapy offers several advantages over laser photocoagulation in specific situations and patient populations.[14] Laser photocoagulation destroys peripheral retinal tissue to prevent ROP progression, potentially leading to permanent vision loss.[15] Anti-VEGF therapy, on the other hand, targets the underlying vascular abnormality without the need for extensive peripheral retinal ablation, reducing the risk of peripheral vision impairment.[14] Anti-VEGF treatment may also cause fewer structural alterations to the retina, potentially preserving a more natural retinal architecture.[2,14,15] Laser photocoagulation can induce myopia in infants, while anti-VEGF therapy has been linked to a lower risk of myopia development.[16] This

advantage is especially important for the long-term visual health of children. Laser photocoagulation can cause peripheral retinal scars, increasing the risk of retinal detachment.[17] Anti-VEGF therapy's more targeted approach minimizes this risk, especially in significant peripheral avascular areas. Some studies suggest that anti-VEGF therapy may result in better visual outcomes in certain cases, particularly in less aggressive forms of ROP.[4,14] Improved retinal vascularization and reduced neovascularization can lead to better long-term visual acuity.[14] Anti-VEGF therapy has also been found to be particularly effective in managing ROP in Zone I, which is closer to the center of the retina and associated with higher risk.[14] Laser photocoagulation in Zone I can be technically challenging and carry a higher risk of complications.[14,18] Finally, anti-VEGF therapy may lead to shorter hospital stays, as the procedure itself is less time-consuming compared to laser photocoagulation.[19] This can reduce healthcare costs and the overall burden on both the infant and their family. When comparing anti-VEGF therapies to laser treatment, a meta-analysis indicated that anti-VEGF drugs were equally effective and safer for treating type-1 ROP and APROP, although APROP demonstrating greater myopia progression.[20]

The choice of anti-VEGF medication for the treatment of ROP depends on several factors, including the specific characteristics of the ROP, economic considerations, and the preferences of the treating physician. Bevacizumab was one of the first anti-VEGF agents to be used for ROP and has been widely studied.[2] It is generally more cost-effective than the other anti-VEGF drugs, which can be an important consideration, especially in resource-constrained settings.[5] Ranibizumab is another anti-VEGF medication that has been investigated for ROP treatment. It is similar to bevacizumab but has a shorter half-life, potentially reducing the risk of systemic exposure.[6] The RAINBOW study conducted a comprehensive study on the efficacy and safety of ranibizumab in treating retinopathy of prematurity.[6] The results of this study provided strong evidence for the approval and endorsement of ranibizumab as the only anti-VEGF agent approved for the pharmacological treatment for ROP.[6] However, the continued widespread use of bevacizumab in an off-label capacity highlights the need for further research and guidelines to ensure optimal management of ROP. At the same time, a network meta-analysis was conducted to assess the retreatment rates of anti-VEGF drugs and laser therapy, revealing that ranibizumab exhibited a greater incidence of reactivation rates in comparison to laser therapy.[21] In the FIREFLEYE study, the primary endpoint of the proportion of newborns attaining treatment success at week 24 did not satisfy the criteria for noninferiority when intravitreal aflibercept was compared with laser photocoagulation.[7] Conclusions addressing the relative efficacy of intravitreal aflibercept and laser photocoagulation in this cohort were inconclusive, leading the authors to state that more research is needed.[7] Thus, when choosing an anti-VEGF agent, factors such as the stage and location of the disease, the gestational age of the infant, the presence of any systemic comorbidities, and health economics can all influence the decision. ROP guidelines and recommendations are constantly evolving due to new research and clinical best practices. Continuous learning and adaptation are essential for providing optimal care for premature infants at risk of developing ROP. Retinal specialists must possess a deep understanding of the retina's anatomical and physiological aspects, as well as various treatment options, to effectively diagnose and manage the condition, minimizing the risk of vision loss or other complications.

In a meta-analysis, the single treatment success rate of all three anti-VEGF agents was compared for type 1 ROP.[21] Bevacizumab has the best projected success rate for single-treatment outcomes (89.3%), followed by Aflibercept (80.7%), and Ranibizumab (74.0%), according to the study.[21] These results indicate that bevacizumab may be considered as the first-line treatment for type 1 ROP due to its higher success rate.[21] However, it is important to note that these success rates may vary in actual clinical practice. Additionally, individual patient characteristics and disease severity should also be taken into consideration when choosing the most appropriate treatment option. Certainly, in our data analysis, the success rate of the single-treatment with bevacizumab biosimilar monotherapy was 65.97%, and it surged to 87% when only particular cases of type 1 ROP were evaluated. The observed outcome closely mirrored the 89% success rate reported in a meta-analysis research with bevacizumab.[21] APROP is a severe, rapidly progressive form of ROP characterized by widespread retinal ischemia and diffuse vascular abnormalities, which may not be effectively addressed by anti-VEGF therapy alone.[2] Given the challenges posed by APROP, a comprehensive and multidisciplinary approach to its management is often necessary. This may involve the use of anti-VEGF therapy as a temporary measure to stabilize the condition, followed by laser photocoagulation or other treatments to address the underlying vascular abnormalities and ischemia. The findings of our study provide robust evidence for this premise, since the ROP regression rate of APROP eyes (all Zone 1) increased exponentially from 18.18% with bevacizumab treatment to 90.91% after laser

therapy. This highlights the necessity of a sequential treatment approach for APROP with anti-VEGF and laser, underscoring the need for a multidisciplinary approach to treating APROP, as it allows for a more comprehensive and effective treatment strategy.

Systemic safety remains a major concern with anti-VEGF therapy in infants.[4,22] The potential systemic developmental side effects of intraocular anti-VEGF medicines may affect treatment choices. Due to its shorter half-life, ranibizumab may have less adverse effects, which could compensate for the higher retreatment rate seen in eyes treated with ranibizumab.[21] However, the influence of intravitreal anti-VEGFs on developmental impact is debatable The amount of developmental delay that 5-year-olds who received either laser treatment or bevacizumab treatment experienced was not significantly different in a retrospective study.[23] Additional research is required to do a comparative analysis of the long-term developmental consequences associated with various anti-VEGF therapies for ROP.

The use of anti-VEGF biosimilars as a more economic option compared to the innovator molecule is a topic that has garnered attention in the healthcare industry. Biosimilars are biological products that are highly similar to approved innovator biologics but typically come at a lower cost. The key factors for considering the bevacizumab biosimilar in our study included: 1) Cost-saving of up to a third with the biosimilar Bevatas®, in comparison to the innovator molecule Avastin®; 2) The lower cost of biosimilar bevacizumab can increase accessibility to this essential medication for a broader patient population; 3) Lower-cost biosimilars can contribute to the sustainability of healthcare systems, particularly in lower-middle income countries (LMICs) facing rising healthcare costs; 4) Cost-effective biosimilars can enhance healthcare equity by ensuring that vision-saving treatments like bevacizumab are accessible to a broader population, reducing disparities in care. However, it is important to note that while biosimilars offer cost savings and are designed to be highly similar to the reference product, they may not be identical. Therefore, healthcare providers and patients should work together to make informed treatment decisions based on individual clinical scenario. The efficacy of the biosimilar bevacizumab in the present study in achieving complete ROP regression for type 1 ROP (87%) is comparable to that seen with the innovator bevacizumab (89%) in previously published meta-analyses.[21] This suggests that the biosimilar bevacizumab can be a viable and cost-effective alternative for the treatment of type 1 ROP. However, further studies and long-term follow-up are required to assess the safety and efficacy of biosimilars in different clinical settings. Nonetheless, with careful consideration of individual patient needs and in collaboration with healthcare providers, biosimilars can provide a more affordable option without compromising treatment outcomes.

The retrospective design and brief follow-up limit the study. Also, only one dose of the biosimilar drug was given, and infants with inadequate responses received additional laser therapy. Due to a lack of pharmacovigilance studies on the biosimilar drug in infants, this safety measure was taken. Moreover, we did not perform serum VEGF assay to evaluate the safety aspect of the biosimilar agent. This exclusion might have impacted our assessment of the overall safety profile of the biosimilar drug. Further prospective studies with larger follow-up and more comprehensive evaluation, including fundus photographs and serum assays, is warranted to better understand the benefits and potential risks of this drug in this population.

Conclusion

To conclude, the BIOS-ROP study shows that the bevacizumab biosimilar, Bevatas®, causes complete ROP regression in almost two-third of the eyes at 24-weeks post-therapy. On stratification, the regression rate with the monotherapy was excellent for type 1 ROP eyes (87%), while for the APROP eyes, an additional laser treatment was required in 81.81% of the eyes. These findings highlight the potential of the bevacizumab biosimilar as a promising treatment option for ROP, particularly for type 1 ROP eyes. However, it is important to note that additional laser treatment was needed for a substantial number of APROP eyes, indicating that further research is needed to optimize the treatment approach for this particular subgroup of patients. The study's quantitative findings also shed light on the challenges associated with treating APROP eyes. Monotherapy with the biosimilar resulted in an 18.18% regression rate, emphasizing the need for a comprehensive approach. Importantly, the addition of laser therapy led to a substantial improvement, with a regression rate soaring to 90.91%. This quantitative insight emphasizes the significance of a sequential treatment strategy for APROP, showcasing the study's contribution to refining the management of this severe form of ROP. Additionally, long-term follow-up is necessary to assess the durability of the treatment response and potential late-onset complications. Also, the economic considerations

surrounding the use of bevacizumab biosimilars are of paramount importance. The BIOS-ROP study emphasizes the cost-saving potential of Bevatas® by offering a more affordable alternative, potentially increasing accessibility to essential medication for a broader patient population. The cost-effectiveness of biosimilars, especially in resource-constrained settings, can contribute to healthcare sustainability and equity by reducing disparities in care. Lastly, the BIOS-ROP study adds quantitative insights into the efficacy of the bevacizumab biosimilar, shedding light on its potential as a cost-effective and viable treatment option for ROP, particularly in type 1 ROP eyes. Our results contribute quantitatively to the ongoing discourse surrounding ROP management, offering valuable data for clinicians, policymakers, and researchers striving to optimize care for premature infants at risk of ROP.

Disclosure

The authors report no conflicts of interest in this work.

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