



Transitioning from Aflibercept to Biosimilar Ranibizumab in Neovascular AMD (The TRANSFORM Trial): A Multicenter Observational Study

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Purpose: This study investigates the efficacy of transitioning patients with neovascular age-related macular degeneration (nAMD) from aflibercept (T1) to biosimilar ranibizumab (T2), an approach not previously documented in literature.

Methods: In this multicenter observational study, patients over 50 years of age with nAMD were shifted from intravitreal aflibercept (IVI AFL) to biosimilar ranibizumab (B-RBZ) due to financial constraints. This study employed standardized ophthalmological methods to assess visual acuity (VA), central macular thickness (CMT), and subretinal and intraretinal fluid. Statistical analyses included paired *t*-tests, Wilcoxon signed-rank tests, and linear regression.

Results: A total of 29 eyes (12 males and 17 females) were analyzed. Mean age was 72.55 ± 6.43 years. VA improved significantly during T1, with a mean increase from 55.0 ± 10.2 to 70.0 ± 8.5 ETDRS letters at the switch time point ($p < 0.01$), then a slight decrease to 62.3 ± 8.9 at 12 months ($p < 0.05$) was noted during T2. The mean CMT decreased notably from 400 ± 50 to 290 ± 45 μm at the switch. The final CMT at 12 months after switching to B-RBZ was 280 ± 40 μm ($p < 0.01$). There was a significant decrease in the retinal and intra retinal fluid during T1, followed by a gradual increase during T2. A significant correlation ($p < 0.05$) was noted between the presence of intraretinal fluid and increased injection frequency of B-RBZ.

Conclusion: The switch from IVI AFL to IVI B-RBZ in patients with nAMD demonstrated efficacy in maintaining the VA and macular anatomy, with some challenges in fluid management.

Keywords: neovascular AMD, aflibercept, biosimilar ranibizumab, subretinal fluid, intraretinal fluid

Introduction

Age-related macular degeneration (AMD) is a leading cause of visual impairment and morbidity, especially among the elderly.¹ While dry AMD is more common and progresses slowly, neovascular AMD (nAMD) is more aggressive and can lead to rapid vision loss.¹

Globally, the aging population has seen an increase in the incidence of AMD, making it a major public health issue, and the number of people with AMD is projected to reach 288 million by 2040.²

The introduction of anti-VEGF (vascular endothelial growth factor) therapy has revolutionized the treatment of wet AMD.³ Anti-VEGF drugs, such as bevacizumab, ranibizumab, aflibercept, brolicizumab, and faricimab, inhibit the growth of abnormal blood vessels in the retina and reduce fluid leakage, which is the primary cause of vision loss in nAMD.⁴ These drugs not only halt disease progression in many patients but also improve visual acuity in a significant number of cases.⁴ However, despite the effectiveness of anti-VEGF therapy, the high cost of these biologic drugs is

a significant barrier that limits accessibility for many patients. Consequently, physicians tend to use cheaper bevacizumab in an off-label form.⁵ However, its use can also be associated with cluster endophthalmitis, as observed in India.⁶

This is where biosimilar anti-VEGF agents have emerged. Biosimilars are nearly identical copies of an original biological drug that has lost patent protection.⁷ They are developed to have the same safety, efficacy, and quality profile as their reference products but are typically available at a lower cost and can offer a 35–50% discount on the innovator molecule.⁷

In India, a ranibizumab biosimilar (Razumab[®]; Intas Pharmaceuticals, Ahmedabad, India) was approved for intravitreal use by the Drug Controller General India (DCGI) in 2015.⁸ It has shown good efficacy for most retinal disorders in limited studies; more than 100,000 injections have already been used in India alone.⁹

While there are reports on the shift from aflibercept to ranibizumab in nAMD non-responsive to aflibercept,^{1,3,4} there are no reports of switching to the biosimilar ranibizumab. The purpose of the current study was to analyze how eyes with nAMD respond to switching from aflibercept to the biosimilar ranibizumab.

Methods

This multicenter retrospective observational study was conducted in a group of eye hospitals in eastern India. The study adhered to the tenets of the Declaration of Helsinki, Good Clinical Practice Guidelines, and International Council for Harmonization. Our protocol was approved by the Institutional Review Board of the Disha Eye Hospital (Reg. number ECR/846/Inst/WB/2016/RR-19: EC-2023-30). Informed consent was obtained from all participating patients who underwent intravitreal injections. We collected data from our hospital network and the patients were treated by fellowship-trained retinal specialists.

Participants were included if they were ≥ 50 years of age, had a previously untreated subfoveal choroidal neovascularization (CNV) lesion secondary to nAMD in the study eye with evidence of activity documented on OCT by the presence of subretinal fluid or intraretinal fluid, leakage from CNV detected by fluorescein angiography (FA), and had a baseline visual acuity of 20/40 or worse. Indocyanine green angiography (ICGA) at baseline was performed if deemed necessary by the treating retinal specialist.

A review of medical records of consecutive nAMD patients with initial phase (T1) of treatment with intravitreal injection (IVI) aflibercept (AFL) 2.0 mg in 0.05 mL between July 2020 and June 2021: three loading doses at 1 month interval and the next two at a fixed interval of 8 weeks were identified. Due to a patient support program run by BAYER, India, wherein purchasing 2 aflibercept injections entitles patients in India to receive an additional 3 injections of aflibercept free of cost. Hence, the decision to have patients who had received 5 injections of aflibercept. Patients from this cohort who subsequently shifted to biosimilar ranibizumab (B-RBZ) (T2) (due to issues related to higher cost of aflibercept and not lack of efficacy) were identified. The patients in T2 were treated with intravitreal biosimilar ranibizumab 0.5mg in 0.05mL using a pro re nata (PRN) regimen. However, evaluation was monthly as per hospital protocol for PRN treatment, with clinical and SD OCT examination. Patients who had regular evaluations for a year from the initiation of B-BRZ were taken up for analysis. Repeat injections were advised at any point during the evaluation period if there was persistence or increase in subretinal or intraretinal fluid (SRF/IRF), the central macular thickness (CMT) was ≥ 300 μm , or there was an increase of ≥ 100 μm in CMT. At baseline, the diagnosis of nAMD was confirmed by fluorescein angiography (FA) spectral domain optical coherence tomography (SD-OCT) at the time of switching the presence of an active lesion on FA, fluid on SD-OCT, or hemorrhage under the fovea, noted in clinical records, was necessary for the eye to be included in the analysis. IVI with anti-VEGF (aflibercept/biosimilar ranibizumab) was performed in the operating room by fellowship-trained retinal surgeons. During treatment with IVI AFL, patients received injections, as mentioned above, and T2 patients received PRN B-RBZ when signs of active neovascularization were present. For the analysis, eyes with only type 1 and type 2 macular neovascularization (MNV) were considered. Patients with other vision-impairing diseases, such as glaucoma or cataract, history of retinal laser use within 6 months prior to the first injection, other coexisting retinal diseases, and vitreoretinal surgery were excluded from the study. The flowchart of the selection process is shown in [Figure 1](#).

The main outcome measure was the change in BCVA before and after switching. Noninferiority was investigated using the mean change and 95% confidence interval of the BCVA in the ETDRS. The noninferiority limit of five ETDRS letters was considered, as was used in the CATT study.¹⁰ Secondary outcome measures were changes in CMT at the switch from baseline and subsequently at further follow-up up to 12 months, obtained by SD-OCT (Cirrus, Carl Zeiss

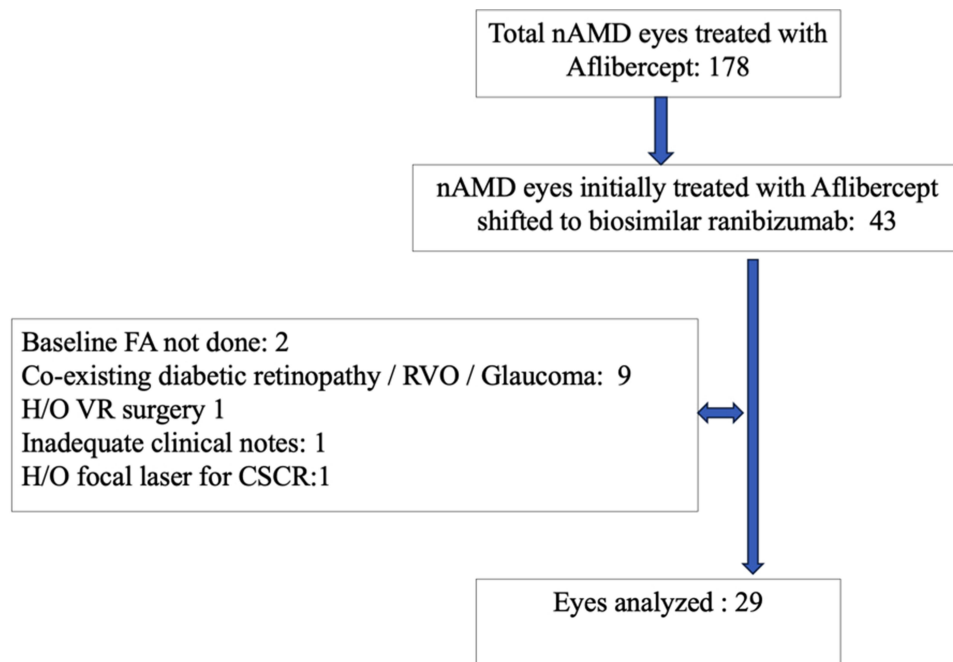


Figure 1 Flowchart of the selection process.

Meditec Inc., Dublin, CA). The presence or absence of sub-retinal fluid (SRF) and intraretinal fluid (IRF) CRT was noted, and a correlation between fluid status and the injection frequency of biosimilar ranibizumab was noted. During all follow-up periods, patients underwent a complete ophthalmic examination, including SD-OCT. FA and ICG were performed at baseline in all eyes, and thereafter as deemed necessary¹¹ by the treating physician, comprising fellowship trained retina surgeons. Adverse events were ascertained from records, as per the hospital protocol, to identify and inquire for any such events during follow-up through monthly patient questioning.

All data were stored in Microsoft Excel and analyzed using STATA 12.1 I/c (Stata Corp, Fort Worth, Texas, USA) normality of distribution was checked using the Shapiro–Wilk test, a paired *t*-test was used to test the significance of differences, and the Wilcoxon signed-rank test was used to compare continuous variables. Pearson’s correlation coefficient was used to explore the relationship between patient age and total number of injections, providing insights into treatment patterns among different age groups. For the comparison of categorical variables, we used the chi-squared test. Statistical significance was set at $p < 0.05$.

Results

Of the 178 eyes of 132 unique patients who received IVI AFL during the study period, for nAMD the inclusion criteria and were included in the analysis. Detailed demographic data are presented in [Table 1](#).

Table 1 Demography

Characteristics	
Number of patients	29
Age (years) Mean (\pm SD)	72.55 (6.43)
Males	12 (41.4%)
Females	17 (58.6%)
Total number of aflibercept in each eye	5
Mean number of biosimilar ranibizumab after switch injections Mean (\pm SD)	6.79 (1.11)

Visual Acuity (VA)

The baseline VA in the cohort followed a normal distribution (Shapiro–Wilk, $p = 0.167$). Mean VA (converted to ETDRS letters) improved from 55.0 ± 10.2 at baseline to 70.0 ± 8.5 at the switch, indicating a notable enhancement. This trend persisted across subsequent follow-ups, with mean VA scores remaining significantly better than baseline ($p < 0.05$, at each time point), as evidenced by the paired t -tests. VA at final follow-up of 12 months was 62.3 ± 8.9 ETDRS letters, an improvement of around 7.6 ETDRS letters in VA from baseline. Repeated-measures ANOVA further corroborated these findings, confirming the statistical significance of VA improvement over time ($F(5, 140) = 16.26$, $p < 0.0001$). Detailed VA changes are presented in [Table 2](#), and [Figure 2](#) shows the trend; the paired sample t -test resulted in a p -value of approximately 0.0015, indicating that the improvement in visual acuity (from baseline to the 12-month follow-up) was statistically significant. Linear regression analysis for VA showed a strong positive relationship between higher baseline visual acuity and higher visual acuity at the switch, and a positive correlation at the final follow-up. A two-sample t -test failed to show noninferiority of the visual status at the final follow-up compared to the switch; however, there was an improvement in mean visual acuity at the final follow-up compared to baseline.

Central Macular Thickness (CMT)

The baseline CMT did not follow a normal distribution (Shapiro–Wilk, $p = 0.011$). However, there was a significant reduction in the post-treatment switching. The mean CMT decreased from $400 \pm 50 \mu\text{m}$ at the baseline to $290 \pm 45 \mu\text{m}$ at the switch, reflecting a substantial reduction. This decrease was maintained for over 12 months, with a mean CMT of $280 \pm 40 \mu\text{m}$ at the final follow-up. The Wilcoxon signed-rank test validated the significance of these reductions at each follow-up compared to the baseline ($p < 0.005$). Repeated-measures ANOVA indicated a significant overall change in CMT across the study period ($F(5, 140) = 150.84$, $p < 0.0001$).

The consistently low p -values across all time points demonstrate that the changes in CMT were not due to random chance but were significantly altered from the baseline values.

Detailed values are presented in [Table 3](#) and the trend in [Figure 3](#)

Sub Retinal Fluid (SRF) and Intraretinal Fluid (IRF)

At baseline, the prevalence of SRF was 96.55%. A substantial decrease in the proportion of patients with SRF to 17.24% was observed at the time of switching to biosimilar ranibizumab. Subsequent follow-ups after switching to the biosimilar ranibizumab (T2) showed a gradual increase in the presence of SRF, reaching 44.83% at the 12-month mark, suggesting partial re-emergence of SRF over time.

Intraretinal fluid showed a similar pattern. Initially, 55.17% of patients exhibited IRF at baseline. This proportion significantly reduced from T1 to 6.90% at the time of switching, demonstrating an effective response to the initial treatment. The proportion of patients with IRF at T2 increased moderately but remained relatively stable from 3 months onwards, with 34.48% of patients showing IRF at the 12-month follow-up. Linear regression analysis revealed

Table 2 Visual Acuity at Different Time Points

Time Point	Median ETDRS Letters	IQR ETDRS Letters	Statistical Significance
Baseline	55	16.5	N/A
At Switch	61.5	15	$p < 0.05$
3 months after switch	61.5	15	$p < 0.05$
6 months after switch	61.5	6.5	$p < 0.05$
9 months after switch	61.5	6.5	$p < 0.05$
12 months after switch	61.5	6.5	$p < 0.05$

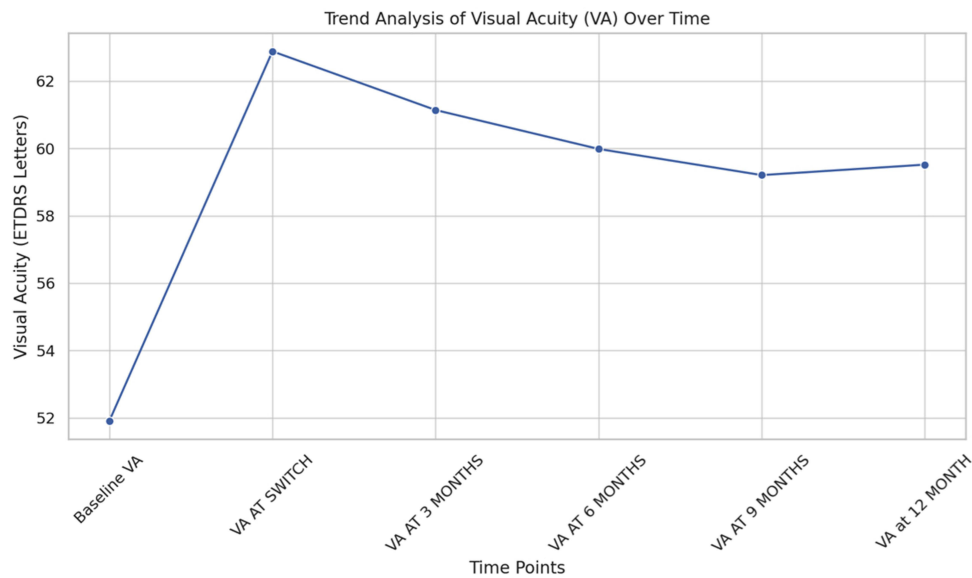


Figure 2 Trend analysis of visual acuity over time.

a significant correlation between the presence of IRF at 12 months and the number of biosimilar ranibizumab injections required. A strong positive correlation (correlation coefficient, 0.921; $p < 0.001$) was noted, indicating that patients with persistent IRF were more likely to require an increased number of injections. This relationship was less pronounced but still notable for SRF (correlation coefficient, 0.495; $p = 0.006$). The detailed values are presented in [Table 4](#), and the trends in the proportions are shown in [Figure 4](#).

Correlation Analysis Between Patient Age and Number of Injections

A strong positive correlation (coefficient: 0.9199) was found between patient age and the total number of injections, indicating that older patients tended to receive more injections. This significant correlation (p -value: $1.74e-12$) suggests age as a potential factor in treatment frequency.

Discussion

This study aimed to evaluate the efficacy of a treatment regimen involving switching from intravitreal aflibercept to biosimilar ranibizumab, and to understand the various factors influencing patient outcomes. The key parameters assessed were VA, CMT, subretinal fluid, and intraretinal fluid. In addition, we investigated the relationship between patient age and number of injections administered.

Table 3 Central Macular Thickness (CMT) at Different Time Points

Time Point	Median CMT	IQR CMT	Statistical Significance
Baseline	393	35	N/A
At Switch	290	10	$p < 0.05$
3 months after switch	290	22	$p < 0.05$
6 months after switch	296	12	$p < 0.05$
9 months after switch	299	18	$p < 0.05$
12 months after switch	299	20	$p < 0.05$

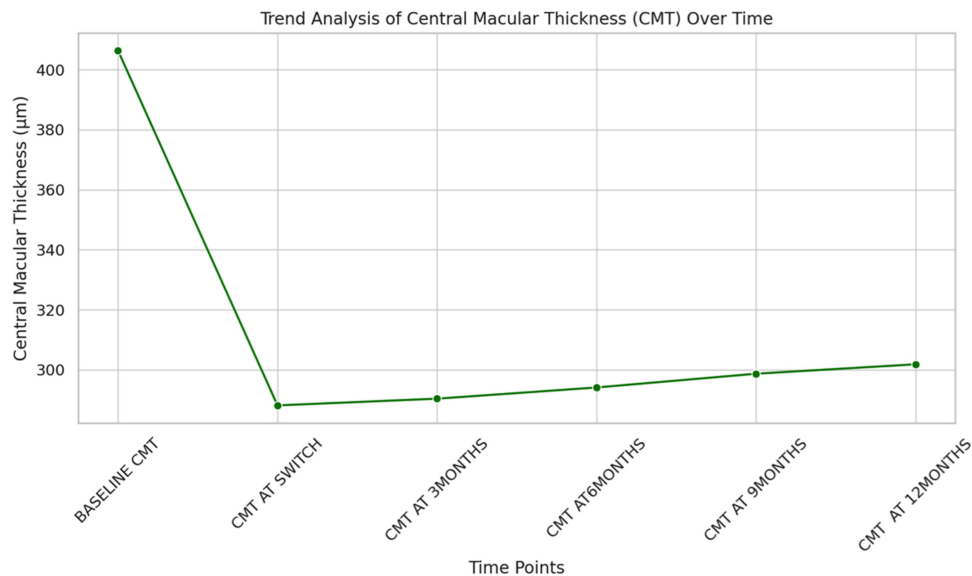


Figure 3 Trend analysis of central macular thickness.

Significant improvements in VA were observed at switch and subsequent follow-ups (up to 12 months) compared to baseline. Visual acuity improved to 70 ETDRS letters after five IVI AFL in the T1 phase, indicating the effectiveness of aflibercept in initially providing a robust improvement in vision. Subsequently, with the change to B-RBZ at T2, the improvement persisted with respect to the baseline vision (at 63 ETDRS letters) but was inferior to the VA at switch. While studies reporting a switch from aflibercept to biosimilar ranibizumab have not been reported in the literature, there are reports of nAMD eyes shifting from aflibercept to innovator ranibizumab or bevacizumab.^{12,13} In a study by Salabati et al, nAMD eyes that were stable or improved on aflibercept but switched to ranibizumab worsened.¹²

However, patients with nAMD who have shown a suboptimal response to aflibercept may benefit from switching to ranibizumab, as noted by Gale et al.¹⁴

We noted a significant reduction in CMT during the study period. The Wilcoxon signed-rank test showed a consistent decrease in thickness across the time points. These changes suggest a sustained response to both T1 and T2 treatment regimens, with CMT showing favorable trends post-switch to B-RBZ. Salabati et al noted that in eyes that had to be shifted to ranibizumab from aflibercept due to inflammation following aflibercept treatment, the mean CMT increased.¹² Marquis et al reported that eyes with nAMD refractory to aflibercept benefited from switching to ranibizumab, and CMT decreased following the switch.¹⁵ The context of switching can have an important bearing on anatomical status. In their retrospective study on shifting anti-VEGF, it was noted that switching therapy for medical reasons may have a more beneficial effect on visual acuity than when switching is performed strictly for economic reasons.¹⁶ The current analysis differs from the above studies in that the shift was from aflibercept to biosimilar ranibizumab instead of the innovator molecule.

Table 4 Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) at Different Time Points

Time Point	SRF Count	SRF Proportion	IRF Count	IRF Proportion	SRF Statistical Significance	IRF Statistical Significance
Baseline	28	0.965517	16	0.551724	N/A	N/A
At switch	5	0.172414	2	0.068966	$p < 0.05$	$p < 0.05$
At 3 months	7	0.241379	7	0.241379	$p < 0.05$	$p < 0.05$
At 9 months	10	0.344828	10	0.344828	$p < 0.05$	$p = 0.113$
At 12 months	13	0.448276	10	0.344828	$P < 0.05$	$p = 0.113$



Figure 4 Subretinal and intraretinal fluid over time.

When analyzing SRF and IRF, chi-squared tests were used to assess changes from baseline through each subsequent time point. The results indicated a significant decrease in both the SRF and IRF at the switch time point. However, a gradual increase in the prevalence of these fluids was noted in the months following the shift to the biosimilar ranibizumab; however, the final level of fluid was less than the baseline parameters. Previous studies have compared the effects of aflibercept and ranibizumab on subretinal fluid (SRF) and intraretinal fluid (IRF) resolution in patients with neovascular age-related macular degeneration (nAMD).^{16,17} A study specifically aimed to compare the effects of three initial doses of aflibercept and ranibizumab on serous pigment epithelial detachment (PED), SRF, and IRF in treatment-naïve nAMD patients. The results indicated that both drugs had similar effects on the regression of PED, SRF, and IRF during the initial loading phase, leading to the conclusion that both drugs had similar effects on these parameters in the macula of treatment-naïve patients with nAMD. However, the context of this study differed slightly. Initially, T1 patients received three monthly loading doses of IVI AFL, followed by two additional doses at interval of 8 weeks. During the T2 phase, IVI B-RBZ was injected following a PRN regimen. Interpreting changes in central macular thickness (CMT) and fluid levels (both subretinal fluid, SRF and intraretinal fluid – IRF) after switching from intravitreal aflibercept to biosimilar ranibizumab requires careful consideration of the clinical context and pharmacodynamics of these treatments. The observed trends, particularly the worsening of CMT and fluid levels after 6 months, could potentially be related to several factors.

First, according to ALTAIR study findings,¹⁸ aflibercept has been shown to have a lasting effect for up to 16 weeks in some patients. The initial reduction in the CMT and fluid levels can be attributed to the residual effect of aflibercept. After the switch, as the effect of aflibercept waned, the biosimilar ranibizumab may not have been as effective in maintaining reduced levels of CMT and fluid, leading to the observed worsening. Second, individual patient responses to the treatment varied significantly. Some patients may have responded better to aflibercept and less to the biosimilar ranibizumab, contributing to the observed trend. Third, the natural course of the underlying disease can influence these findings. Differentiating between the natural progression of the disease and the effects of a switch in treatment is important. Fourth, the observed trends may have been influenced by statistical variability and the sample size of the study. A more in-depth analysis, possibly including a control group that continued aflibercept treatment, could provide more definitive insights. This interpretation should be contextualized within a broader clinical picture, in conjunction with other relevant clinical data.

Our understanding of the role of fluids in nAMD is still evolving, and, in some instances, the observations reported in the scientific literature are conflicting and confusing. However, in a meta-analysis by Kodjikian et al,¹⁹ the presence of IRF, whether at baseline or recurring, was predictive of poor prognosis and increased injection frequency.

In the present study, during T1, ie treatment phase with aflibercept, the number of injections received by all eyes was five, post-switch to B-RBZ, the mean number of injections was 6.79 ± 1.11 . This number was similar to what was observed by Bro et al (6.8–7.6) when they analyzed shifting from aflibercept to bevacizumab.¹⁶ Randazzo et al noted a mean of eyes had received a mean of 4.45 (± 2.55) over 6 months after intravitreal injections of bevacizumab after a switch from aflibercept.¹³ Extrapolating this to a 12-month period, the number of injections is similar to our study.

In the current study, a significant correlation was observed between the presence of IRF at 12 months and the number of required biosimilar ranibizumab injections. A strong positive correlation (correlation coefficient: 0.921; $p < 0.001$) indicated that patients with persistent IRF were more likely to require an increased number of injections. This relationship was less pronounced but still notable for SRF (correlation coefficient, 0.495; $p = 0.006$).

Correlation Between Age and Number of Injections

A strong positive correlation (coefficient: 0.9199) was found between patient age and the total number of injections, indicating that older patients tended to receive more injections. This significant correlation (p value: $1.74\text{e-}12$) suggests that age is a potential factor affecting treatment frequency.

In contrast to our findings, other studies have suggested that there is no correlation between age and number of injections.^{20,21}

Further research may be necessary to conclusively determine whether and how age directly affects the number of anti-VEGF injections required to treat AMD.

Shor et al noted a dose–response relationship between anti-VEGF injections and VA outcome only in patients with low baseline VA.²² Individual patient characteristics might need to be taken into account to customize treatment regimens and improve visual outcomes. Our findings highlight the complexity of nAMD treatment and the multifaceted nature of the response indicators. While improvements in VA and reductions in CMT were observed even after switching to the biosimilar ranibizumab, fluid status (especially IRF) emerged as a significant factor in determining the intensity of ongoing treatment. This underscores the need for a personalized approach for managing nAMD, in which fluid status, alongside VA and CMT, plays a crucial role in guiding treatment decisions.

We noted that five eyes were poor responders with persistence of SRF or IRF at all visits post-switch (SRF was present in all five IRF in two). These eyes were offered a switch to other anti-VEGF agents; however, they did not agree because of insurance issues. However, the VA at the final follow-up in these poor responders was not significantly different from that in the rest of the cohort (58 letters against a mean of 59 letters). Ashraf et al noted that aflibercept had a better fluid resolution than ranibizumab in eyes with nAMD.²³ We noted that after five injections of aflibercept, both the SRF and IRF were significantly reduced. Subsequently, after switching to the biosimilar ranibizumab, both SRF and IRF increased over time.

Since the durability of a single aflibercept injection has been noted to be roughly double that of ranibizumab,²³ the VEGF suppressive status after switching to the biosimilar ranibizumab may not be as adequate as that with aflibercept. The impact of the significant carry-over effects of aflibercept may be confounded by the direct treatment effects of the biosimilar, ranibizumab. However, the continuing nature of the disease process may negate any advantages beyond the initial few weeks post-switch.

The PRN regimen is still commonly used in India²⁴ and in phase T2, this was the regimen that was used. The CATT 5 years report notes that there were no obvious differences in visual acuity outcomes at 5 years between patients who were treated monthly for 2 years versus those treated with PRN for 2 years.²⁵ Hence, it can be interpolated that the difference with a fixed or T&E may not be very significant. However, our study lacked a control group; therefore, it is not possible to comment on how natural progression may have affected the outcomes.

No serious systemic adverse events were noted during the initial phase of aflibercept treatment or subsequent treatment with the biosimilar ranibizumab. While we also did not observe any serious events during either the T1 or T2 phase of the study, it should be mentioned that it is difficult to make any definite assumptions on adverse events due to the very small number of patients involved. However, our group has published the safety of biosimilar ranibizumab (Razumab[®]) in a large real-world series.²⁶

The major limitations of the present study are its retrospective design, limited sample size, relatively brief follow-up, lack of a control group, and the use of the PRN regimen. The study was not powered for safety analysis. Furthermore,

because the study was based on medical chart analysis, there is a risk of adverse events, particularly mild, that are underreported. While a retrospective study has limitations, real-world studies allow the inclusion of eyes with a wider range of CNV, which would be excluded from clinical trials. Despite these limitations, the results reported here represent the first real-world data regarding the efficacy of the biosimilar ranibizumab following a switch from aflibercept in Indian eyes with nAMD.

With increasing life expectancy and rising incidences of lifestyle diseases such as diabetes and hypertension, the number of patients requiring anti-VEGF therapy is projected to grow.²⁷ This study provides insights into the potential of biosimilar anti-VEGF to make treatment more accessible and affordable, especially in cases of reduced funds or insurance restrictions.

Conclusion

In summary, age-related macular degeneration is a significant cause of visual morbidity, especially in the aging population. The advent of anti-VEGF therapy has been a game-changer in the management of this condition, particularly wet AMD. However, the high costs of these drugs remain a challenge. Biosimilar anti-VEGF agents offer a promising solution to this problem, potentially making effective AMD treatment accessible to more patients and easing the financial burden on the health-care system. Therefore, they have the potential to play a crucial role in the future landscape of AMD treatment. Given that this study is a retrospective real-world analysis, it has inherent limitations. Therefore, a prospective randomized trial could provide more comprehensive information.

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Consent to Participate

The authors confirm that all research participants provided informed consent for involvement in this study.

Disclosure

The authors report no conflicts of interest in this work.

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