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# Transitioning from Aflibercept to Biosimilar Ranibizumab in Diabetic Macular Edema (DME): (The TRANSFORM-DME Trial) a Multicenter Observational Study

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**Purpose:** To evaluate visual and anatomical outcomes following a switch from intravitreal Aflibercept (IVI AFL) (T1) to biosimilar Ranibizumab (B-RBZ) (T2) in patients with diabetic macular edema (DME).

**Methods:** This was a multicenter observational study, analysing medical records of consecutive, treatment-naïve centre-involving DME patients having a baseline visual acuity (VA) of ≥55 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. DME patients, having received monthly loading doses of IVI AFL(T1) and responsive to it, who subsequently shifted to B-RBZ(T2) motivated by financial constraints rather than a lack of efficacy to IVI AFL were identified.

**Results:** This study included 57 participants (mean age: 54.23 ± 6.91 years), with 80.7% male patients. VA improved during T1, from 61.4 ± 11.74 ETDRS letters at baseline to 72.7 ± 8.05 ETDRS letters (mean change: +11.2 letters, 95% CI: 9.1 to 13.4; $p < 0.001$). During T2, VA declined slightly over 12 months with a mean VA of 69.9 ± 3.78 ETDRS letters at the 12-month mark (+8.5 letters from baseline; $p < 0.001$). Mean central macular thickness (CMT) during T1 reduced from 411.9 ± 34.62 µm at baseline to 279.3 ± 9.96 µm (mean change: −132.6 µm, 95% CI: −142.2 to −122.9 µm; $p < 0.001$). CMT remained stable over the 12-month follow-up period, with minimal fluctuations. Subretinal fluid (SRF) and intra retinal fluid (IRF) were present in 84.2% and 91.2% of eyes, respectively, decreasing to 5.3% and 7.0% at the time of switch ($p < 0.001$). In T2 phase, 22.8% and 21.1% exhibited SRF and IRF, respectively, at the end of the study.

**Conclusion:** Transitioning to biosimilar Ranibizumab (Razumab) after initial treatment with aflibercept in patients with DME preserved visual and anatomical benefits over a 12-month period, with only minor variations in SRF and IRF. These results underscore the efficacy of biosimilar Ranibizumab as a cost-effective option for managing DME.

**Keywords:** diabetic macular edema, anti VEGF, aflibercept, biosimilar ranibizumab

## Introduction

The International Diabetes Federation reports that approximately 537 million adults were living with diabetes in 2021, a number expected to rise to 783 million by 2045.[1] The increasing incidence of diabetes contributes to the higher prevalence of diabetic retinopathy (DR) and in turn diabetic macular edema (DME). Both DR and DME, are direct consequences of chronic hyperglycaemia.[2] DME represents a significant complication of DR, which is the foremost cause of vision impairment among working-age adults.[2] The pathogenesis of DME is closely linked to vascular endothelial growth factor (VEGF), a protein that promotes angiogenesis and increases vascular permeability. The advent of anti-VEGF therapy has revolutionized the management of retinal vascular diseases like DME. These agents inhibit the action of VEGF, thereby stabilizing or improving vision in patients with retinal vascular conditions.[2,3] Clinical trials like

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the RISE and RIDE studies have confirmed the benefits of ranibizumab in DME.[4] Similarly, AFL has also shown significant visual improvements in DME.[5,6] Bevacizumab, although used off-label, is widely employed due to its low cost and has shown comparable efficacy.[6] The DRCR.net Protocol T study demonstrated that IVI AFL outperforms other anti-VEGF agents such as bevacizumab and ranibizumab (RBZ) in patient groups with vision poor baseline vision, leading to its preferential recommendation in treatment guidelines for DME.[7] 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.[8] Bevacizumab, though a much cheaper alternative, has been found to be associated with cluster endophthalmitis, as observed in India.[9]

This is where biosimilar anti-VEGF agents have emerged as a safer alternative. Biosimilars are nearly identical copies of an original biologic drug that has lost patent protection.[10] 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.[11] In India, a RBZ biosimilar (Razumab®; Intas Pharmaceuticals, Ahmedabad, India) was approved for intravitreal use by the Drug Controller General India (DCGI) in 2015.[11] It has shown good efficacy for most retinal disorders in limited studies; more than 100,000 injections have already been used in India alone.[11,12] Although there are reports of switching from AFL to RBZ in cases of DME that show less than appropriate response to aflibercept,[13] there are no documented instances of switching from aflibercept to the biosimilar ranibizumab, especially for economic reasons rather than due to recalcitrant DME.

The purpose of the current study was to analyze how eyes with DME respond to switching from IVI AFL to the biosimilar ranibizumab (B-RBZ) (Razumab), where switching has been done to reduce the cost of treatment.

## Methods

This multicenter, retrospective observational study was conducted across three hospital networks in eastern India. The study adhered to the tenets of the Declaration of Helsinki, Good Clinical Practice Guidelines, and International Council for Harmonization standards. The protocol was approved by the ethics committee of Disha Eye Hospitals, Kolkata, West Bengal, India (Reg. number ECR/846/Inst/WB/2016/RR-19: EC-2023-31), and informed consent was obtained from all participating patients who underwent intravitreal injections.

All patients were treated by fellowship-trained retina specialists. We reviewed electronic medical records of consecutive, treatment-naïve DME patients aged 18 years and older, with a baseline visual acuity (VA) of 55 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or better. Amongst these patients, those who received an initial phase (T1) of treatment with intravitreal aflibercept (AFL) 2.0 mg in 0.05 mL— three monthly loading doses administered between July 2020 and June 2021 were next demarcated. From this cohort, patients who migrated to B-RBZ were identified. Eligibility criteria required patients to have received at least three monthly loading doses of IVI AFL before transitioning to B-RBZ (T2). The switch was motivated exclusively by financial constraints rather than a lack of efficacy to IVI AFL. The transition to B-RBZ occurred after a treatment-free period of ≥8 weeks and ≤12 weeks following the last IVI AFL. Patients in this cohort were not considered refractory according to the DRCR.net definition of persistent/refractory DME.[7] Exclusion criteria included any previous ocular surgery within six months prior to baseline, prior laser photocoagulation, the presence of other retinal diseases, glaucoma, history of intravitreal steroids, vitreous haemorrhage or contraindications to anti-VEGF therapy.

During the second phase of treatment (T2), patients received intravitreal injections of biosimilar ranibizumab (Razumab) 0.5 mg in 0.05 mL, administered on a pro re nata (PRN) basis. Data from monthly evaluations were collected (conducted according to the hospital's PRN treatment protocol), including clinical assessments and spectral-domain optical coherence tomography (SD-OCT) examinations (Cirrus 5000, Carl Zeiss Meditec Inc., Dublin, CA). The decision to administer additional injections during T2 was based on clinical findings—such as central macular thickness (CMT) measurements and VA assessments—following standard retreatment criteria for DME.[7] Only patients with consistent evaluations for one year after the initiation of B-RBZ were included in the analysis. Data collected from medical records encompassed de-identified demographic information, baseline characteristics, treatment details, and outcomes. Key outcome measures were VA, measured in logMAR and converted to ETDRS letters, CMT, assessed using SD-OCT and presence of subretinal fluid (SRF) and intraretinal fluid (IRF). All data was documented at baseline, at the time of the

switch, and at 3, 6, and 12 months post-switch. Adverse events were identified from medical records during follow-up visits.

Data were stored in Microsoft Excel and analyzed using STATA 12.1 I/C (StataCorp, College Station, Texas, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. For normally distributed continuous variables, paired t-tests were used to assess the significance of differences; the Wilcoxon signed-rank test was employed for non-parametric data. Changes in VA and CMT from baseline to each follow-up visit were analysed accordingly. Categorical variables were compared using the chi-square test. The presence of SRF and IRF at different time points was analysed to determine significant changes from baseline. Mean changes, standard deviations, and 95% confidence intervals were calculated for VA and CMT. The proportions of patients with SRF and IRF at each time point were expressed as percentages, and trends over time were visualized through line graphs. A p-value of <0.05 was considered statistically significant.

## Results

The study included 57 participants aged between 40 and 68 years, with a mean age of 54.23 ± 6.91 years, indicating a moderately diverse age group. The age distribution was such that half of the participants were 53 years or younger. The cohort was predominantly male, comprising 46 males (80.7%) and 11 females (19.3%). The Shapiro–Wilk test for normality yielded a p-value of 0.131 for the age distribution, suggesting that it did not significantly deviate from a normal distribution.

Visual acuity: At baseline, the mean visual VA was 61.4 ± 11.74 ETDRS letters. In T1 following treatment with IVI AFL, VA improved significantly to 72.7 ± 8.05 letters, reflecting a mean change of +11.2 letters (95% confidence interval (CI): 9.1 to 13.4; $p < 0.001$). In T2 phase of treatment with IVI B-RBZ, a slight decline in VA was observed. At 3 months post-switch, the mean VA was 70.3 ± 3.35 letters (95% CI: 69.1 to 71.5), decreasing slightly to 69.7 ± 3.13 letters at 6 months (95% CI: 68.5 to 71.0). By 9 and 12 months post-switch, the mean VA had stabilized at 69.9 ± 3.78 letters (Figure 1) with the 12-month VA showing a 95% CI of 68.3 to 70.8. Overall, the mean change in VA from baseline to 12 months post-switch was +8.5 letters ($p < 0.001$). Notably, the difference in VA between the time of switch and the 12-month follow-up was −3.1 letters, which met the criteria for non-inferiority, with a 95% CI ranging from −4.50 to −1.69 letters.

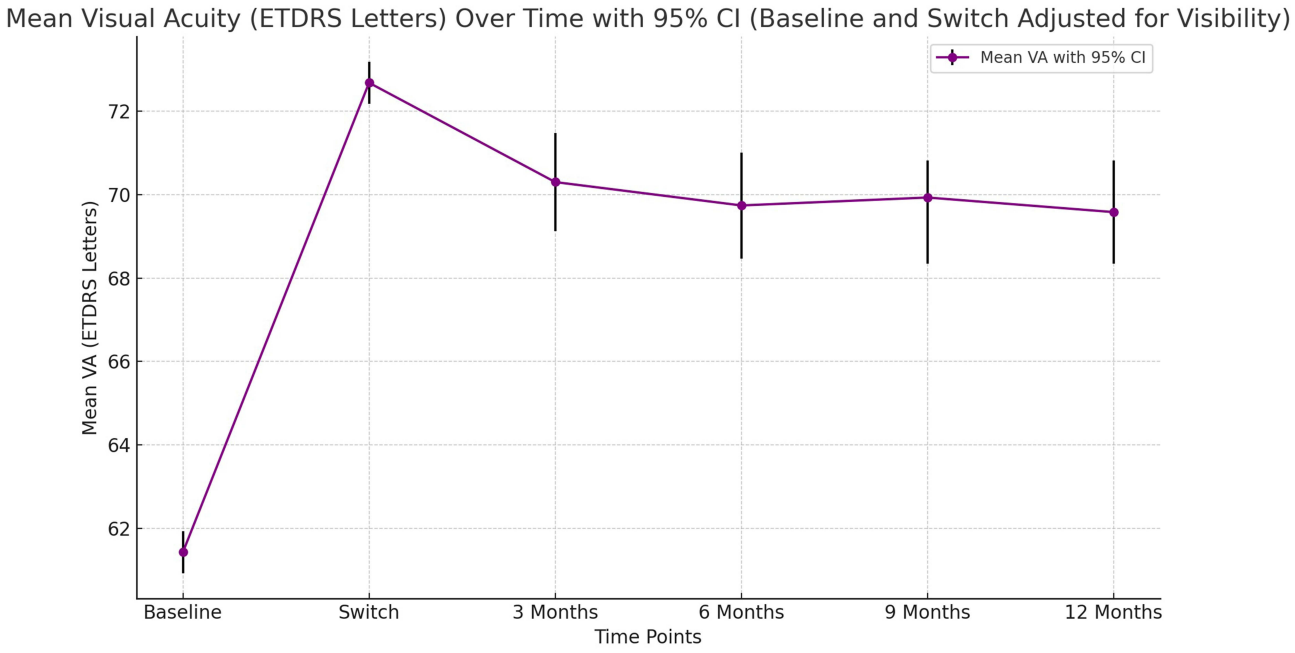


**Figure 1** Trend analysis of visual acuity over time.

Central macular thickness: At baseline, the mean CMT was 411.9 ± 34.62 µm. This value decreased significantly during T1 to 279.3 ± 9.96 µm, reflecting a mean change of −132.6 µm (95% CI: −142.2 to −122.9 µm; $p < 0.001$). Post-switch, in T2 the CMT measurements exhibited minor variations over time. At 3 months after the switch, the mean CMT was 289.9 ± 5.81 µm (95% CI: 288.3 to 291.4 µm). This increased slightly to 296.1 ± 6.60 µm at 6 months post-switch (95% CI: 294.4 to 297.9 µm). By 12 months after the switch, the mean CMT had stabilized at 294.8 ± 5.20 µm (95% CI: 293.3 to 296.4 µm) (Figure 2). These changes in CMT in T2 were minimal and remained within the predefined non-inferiority margin of 25 µm.

Subretinal fluid: SRF was present in 48 eyes (84.2%) at baseline, while 9 eyes (15.8%) were free from SRF. By the time of the switch to B-RBZ, there was a statistically significant reduction in the presence of SRF, with 54 eyes (94.7%) being SRF-free and only 3 eyes (5.3%) exhibiting residual SRF ($p < 0.001$; 95% CI: 87.5% to 99.3%). Following the switch, SRF recurrence was monitored at 3, 6, and 12 months. At three months post-switch, 50 eyes (87.7%) remained SRF-free, while 7 eyes (12.3%) showed SRF; this change was not statistically significant compared to the time of the switch ($p = 0.12$). At six months post-switch, the number of SRF-free eyes decreased slightly to 47 (82.5%), with SRF present in 10 eyes (17.5%); this change also did not reach statistical significance ($p = 0.07$). By twelve months post-switch, 44 eyes (77.2%) were SRF-free, whereas 13 eyes (22.8%) exhibited SRF (Figure 3). The increase in SRF presence at 12 months compared to the time of the switch was statistically significant ($p = 0.03$). However, despite the observed increase, the proportion of eyes with SRF at 12 months remained significantly lower than at baseline ($p < 0.05$).

Intraretinal fluid: At baseline, intraretinal fluid (IRF) was present in 52 eyes (91.2%), with only 5 eyes (8.8%) being IRF-free. Following three loading doses of IVI AFL (T1), there was a significant reduction in IRF presence, with 53 eyes (93.0%) being IRF-free and 4 eyes (7.0%) showing persistent IRF ($p < 0.001$; 95% CI: 86.4% to 98.2%). Following the switch, in T2 IRF status was assessed at 3, 6, and 12 months. At three months post-switch, 50 eyes (87.7%) remained IRF-free, while 7 eyes (12.3%) exhibited IRF; this change was not statistically significant compared to the time of the switch ($p = 0.12$). At six months post-switch, 48 eyes (84.2%) had no IRF, and 9 eyes (15.8%) showed IRF ($p = 0.08$). By twelve months post-switch, 45 eyes (78.9%) were IRF-free, whereas 12 eyes (21.1%) had IRF (Figure 4). The increase in

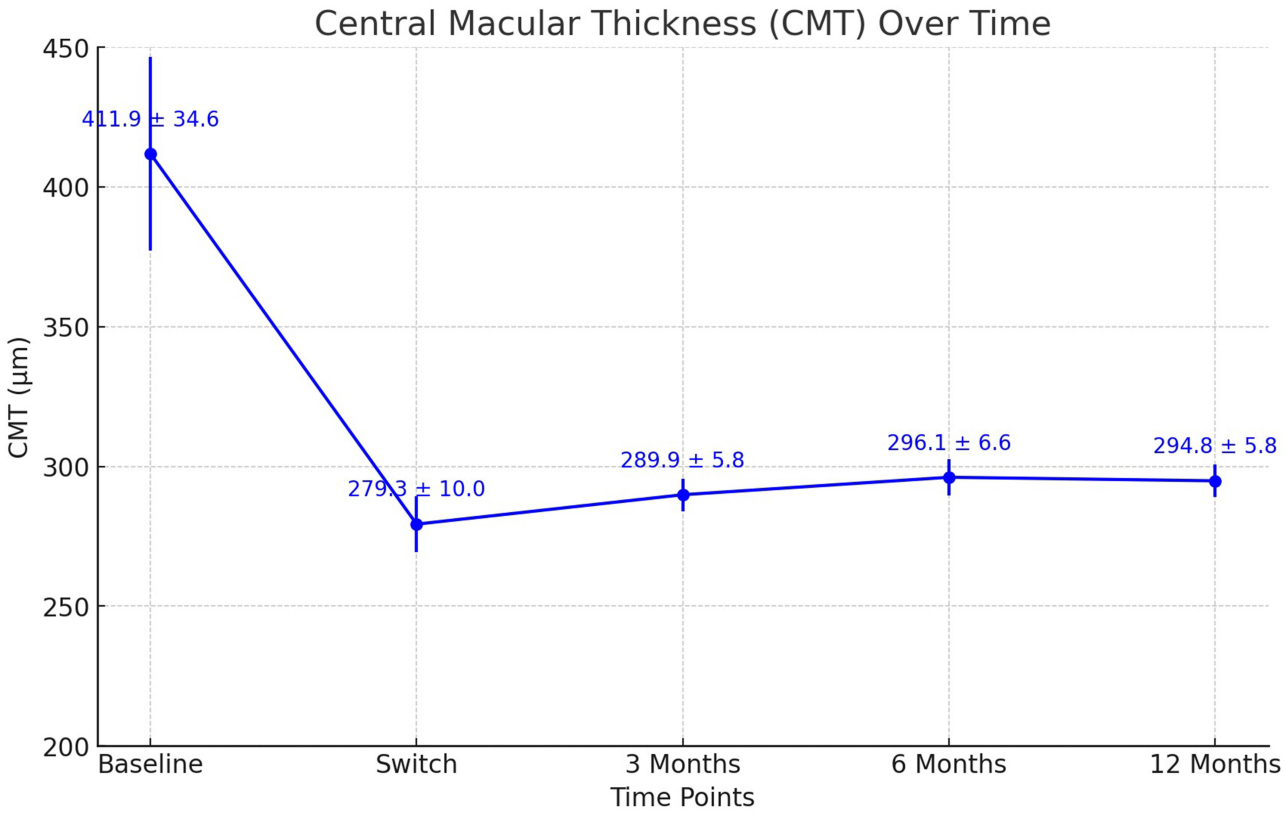


**Figure 2** Trend analysis of central macular thickness.

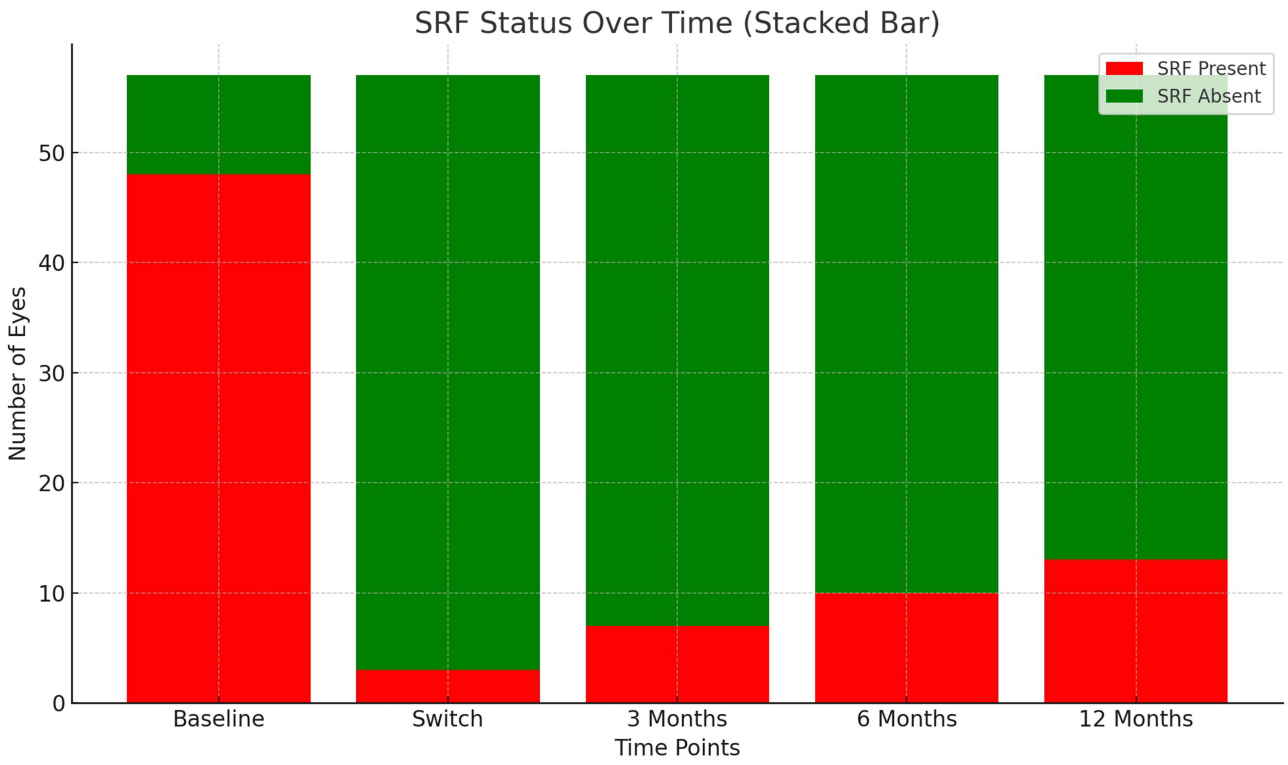


**Figure 3** Trend of Subretinal fluid over time.

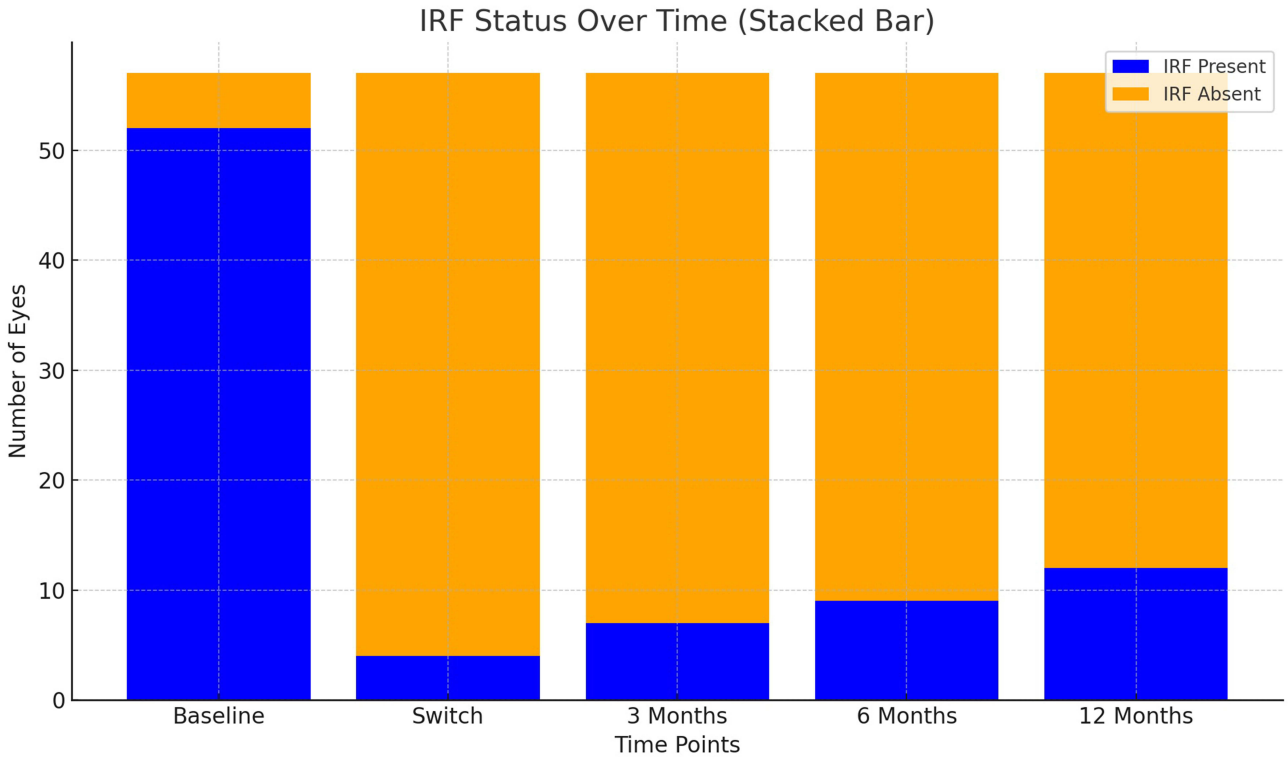


**Figure 4** Trend of Intraretinal fluid over time.

IRF presence at 12 months compared to the time of the switch was statistically significant ($p = 0.04$). However, despite this increase, the proportion of eyes with IRF at 12 months remained significantly lower than at baseline ($p < 0.001$). No serious systemic or ocular adverse events were noted in both T1 and T2 phase of the study.

## Discussion

Our study provides valuable insights into the outcomes of switching from aflibercept to biosimilar ranibizumab (Razumab) in patients with DME. The decision to switch was primarily driven by economic constraints rather than inadequate response to AFL, distinguishing this study from others, where, non-response to treatment is the usual catalyst for changing therapies. Despite the switch, patients maintained stable visual and anatomical outcomes, demonstrating the non-inferiority of B-RBZ (Razumab) compared to AFL. In our study, the mean visual acuity (VA) improved significantly during the initial IVI AFL treatment (T1), increasing from 61.4 ETDRS letters at baseline to 72.7 letters at the time of the switch. After transitioning to B-RBZ (T2), VA remained stable over the 12-month follow-up, with a slight reduction to 69.9 letters at 12 months. Importantly, the difference in VA between the time of the switch and 12 months post-switch met the criteria for non-inferiority.

Our results align with other studies comparing the efficacy of biosimilars to innovator biologics. Mellen et al reported no significant change in VA after switching from aflibercept to the innovator ranibizumab in DME patients.[14] This implies RBZ may able to maintain vision after initial treatment with IVI AFL in DME. Further, a multicenter study by our group compared innovator and biosimilar RBZ in DME and found comparable VA improvements in both groups.[15] Considering the above and other available literature, a switch from IVI AFL to RBZ or B-RBZ in DME should be able to maintain vision. B-RBZ could additionally be a cost-saving option for the long-term management of DME. The DRCR.net Protocol T study demonstrated that IVI AFL might be the preferred initial treatment for patients with DME who present with poorer baseline vision (worse than 20/50), as it showed greater VA improvement compared to RBZ and bevacizumab during the first year of treatment. However, for patients with better baseline VA, all three agents performed similarly over two years.[7] Our study suggests that while IVI AFL may offer superior initial benefits for patients with lower baseline VA, switching to a biosimilar for maintenance can yield satisfactory functional outcomes while addressing economic considerations.

We observed a significant reduction in CMT after initial IVI AFL (T1), decreasing from 411.9 µm at baseline to 279.3 µm at the time of the switch. Post-switch, (in T2) CMT remained stable over the 12-month follow-up, with minimal fluctuations and within the predefined non-inferiority margin. This indicates that biosimilar ranibizumab is effective in maintaining anatomical improvements achieved with aflibercept. These results align with findings from the DRCR.net Protocol T study, which showed that AFL was superior in reducing CMT during the first year, particularly in patients with worse baseline vision.[7] However, over time, the study noted that the differences diminished, and the efficacy of aflibercept, ranibizumab, and bevacizumab became comparable. Our study supports the notion that while IVI AFL may be beneficial for rapid initial anatomical improvements, B-RBZ (Razumab) may be effective for maintaining these outcomes at a lower cost. Mellen et al also reported stable CMT after switching from aflibercept to innovator ranibizumab, with no significant deterioration in anatomical outcomes.[14] Additionally, our group noted comparable anatomical outcomes between innovator and biosimilar ranibizumab in DME management, reinforcing the role of biosimilars in maintaining stable anatomical outcomes over time.[15] The RETAIN study, which evaluated a treat-and-extend regimen with ranibizumab, reported sustained improvements in both visual and anatomical outcomes over 24 months.[16] It also underscored the importance of individualized treatment regimens in maintaining long-term anatomical stability in DME patients.

In our study, a high percentage of eyes exhibited SRF (84.2%) and IRF (91.2%) at baseline. Following initial treatment with IVI AFL (T1), there was a significant reduction in the presence of SRF and IRF. In T2 phase of treatment, after switching to B-RBZ, SRF and IRF levels remained relatively stable, with minimal recurrences. At 12 months post-switch, SRF was present in 22.8% of eyes, and IRF in 21.1%, both significantly lower than baseline levels. These outcomes are consistent with the DRCR.net Protocol T analysis, which found that anti-VEGF therapies effectively reduce SRF and IRF, correlating with improved best-corrected visual acuity (BCVA).[7] The study also highlighted the importance of controlling both types of retinal fluid in DME management.[7] Other studies have also demonstrated that anti-VEGF treatment effectively reduces IRF and SRF, resulting in improved central retinal thickness (CRT) and VA.[17] Their findings support our results,

indicating that B-RBZ can effectively control retinal fluid, maintaining both visual and anatomical stability in DME patients. Comparing AFL with some of the newer anti VEGF agents such as brolucizumab, it was noted in the KINGFISHER study that visual improvement between these agents was similar.[18] The comparative efficacy of aflibercept to newer anti-VEGF agents, more so with its proven safety, can be an important option in initiating treatment for DME.

It is noteworthy that the durability of a single IVI AFL injection has been reported to be roughly double that of RBZ.[19] This suggests that the VEGF suppressive effect after switching to B-RBZ may not be as sustained as with AFL. The eyes in our study received B-RBZ injections, >8 - <12 weeks of the last aflibercept injection. Hence, persistent or synergistic effect of aflibercept may not have contributed to the reduction of DME in our study in T2 phase. In the T1 phase, the patients received monthly injections of aflibercept, but in the T2 phase retreatment was on a pro re nata (PRN) regimen. While a monthly or treat and extend regimen would be the ideal scenario, in real-world resource constrained circumstances PRN treatment with strict follow-up is still an option as done in our study. PRN regimen is still commonly used in India for DME[20] and may have influenced the outcomes.

No serious systemic adverse events were noted during either the initial aflibercept treatment or subsequent biosimilar ranibizumab therapy. While we did not observe any significant adverse events in our study, the small sample size and retrospective nature make it difficult to draw definitive conclusions regarding safety. However, previous publications from our group have reported on the safety of B-RBZ (Razumab) in a large real-world series, supporting its favourable safety profile.[21] 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.[22] This study provides insights into the potential of biosimilar anti-VEGF like Razumab to make treatment more accessible and affordable, especially in cases of reduced funds or insurance restrictions.

Despite the valuable insights gained, several limitations must be acknowledged. The retrospective design carries inherent biases, such as selection and recall bias, potentially affecting the uniformity of follow-up intervals and treatment protocols. The limited sample size and follow-up period of 12 months restrict the generalizability of the findings. The absence of a randomized control group continuing aflibercept or innovator ranibizumab is a limitation. Furthermore, the study was not powered for safety analysis, and reliance on medical records may have led to underreporting of adverse events, particularly mild ones. Patient adherence to follow-up visits and treatment regimens posed challenges, especially since economic burden was a primary reason for switching therapies. Variability in follow-up intervals and potential undertreatment due to financial constraints may have influenced the outcomes. Finally, the study focused exclusively on patients with DME, limiting its applicability to other retinal conditions. Despite these limitations, this study represents the first real-world data on the efficacy of biosimilar ranibizumab (Razumab) following a switch from IVI AFL in Indian patients with DME.

## Conclusion

In conclusion, switching from aflibercept to biosimilar ranibizumab (Razumab) in patients with DME due to economic constraints did not compromise visual or anatomical outcomes over a 12-month period. Biosimilar ranibizumab (Razumab) proved to be non-inferior to aflibercept, offering a cost-effective option for long-term management of DME. These findings suggest that biosimilar ranibizumab is a viable alternative in settings where cost is a significant consideration. Larger, prospective studies with longer follow-up periods are warranted to further validate these results and explore the benefits of biosimilar ranibizumab in broader patient populations.

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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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