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ORIGINAL RESEARCH

Quantitative Assessment of En-face OCT-Derived Minimum Intensity Fluid Changes Following Ranibizumab Biosimilar Therapy in Macular Neovascularization Secondary to nAMD and PCV

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Purpose: This retrospective study aimed to evaluate the efficacy of a new regulatory approved ranibizumab biosimilar (RzB), Oceva® (Sun Pharmaceutical Industries Limited, Mumbai, India), in treating macular neovascularization secondary to neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV), using Minimum-Intensity based changes observed on en-face optical coherence tomography (OCT) (en-face MI OCT).

Patients and Methods: Thirty-six eyes with treatment-naïve MNV underwent three loading doses of RzB. Best-corrected visual acuity (BCVA) and the proportions of eyes with subretinal fluid (SRF), intraretinal fluid (IRF), and subretinal hyperreflective material (SHRM) were assessed. En-face MI OCT-based analysis was conducted to quantify changes in fluid area and perimeter.

Results: At 12 weeks, there was a statistically significant improvement in BCVA from 0.94 {≈20/174} (± 0.59) logMAR to 0.84 {≈20/138} (± 0.61) logMAR (P=0.04). En-face MI OCT revealed a significant reduction in the median area of fluid from 0.9 mm² (IQR 0.62–4.56) to 0.32 mm² (IQR 0.1–0.64) (P=0.007), and in the median perimeter of fluid from 10.95 mm (IQR 7.26–25.67) to 6.02 mm (IQR 1.76–7.93) (P=0.0005). The proportion of eyes with SRF, IRF, and SHRM decreased from baseline (83.33%, 66.67%, and 58.33% respectively) to 12 weeks (58.33% [P=0.015], 38.89% [P=0.013], and 13.89% [P<0.001]). No adverse events were reported.

Conclusion: Treatment with the novel RzB showed promising outcomes in improving visual parameters and reducing fluid accumulation in patients with MNV secondary to nAMD and PCV. Minimum Intensity-based analysis provided detailed insights into fluid dynamics, demonstrating its utility in evaluating treatment responses in MNV. This study contributes to the initial assessment of RzB in clinical practice, highlighting its potential efficacy in managing MNV.

Keywords: ranibizumab, biosimilars, optical coherence tomography, en-face imaging, minimum intensity

Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible visual loss in older adults globally.[1] With aging populations, the burden of AMD is increasing rapidly. Nearly 200 million people were affected in 2020, projected to reach 288 million by 2040.[1] Although neovascular (wet) AMD accounts for less than 10% of all AMD cases, it causes most vision-threatening disease and legal blindness.[1,2] In Asia, home to some of the fastest-aging populations, AMD is already a major cause of blindness, with rising cases driven by lifestyle changes and longer lifespans.[3] Among those with nAMD, the prevalence of polypoidal choroidal vasculopathy (PCV) ranges from 18% to 50%, varying by ethnicity and geography.[4,5] In Asian populations, PCV may comprise 23–64% of nAMD cases, particularly among anti-VEGF-resistant patients, while in non-Asian groups it ranges from 4–20%.[4,5] This growing burden of macular neovascularization (MNV) due to nAMD and PCV presents major public health and socioeconomic challenges, as central vision loss greatly affects quality of life and imposes high costs.

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Intravitreal inhibition of vascular endothelial growth factor (VEGF) is the standard treatment for MNV.[2,6] Ranibizumab (Lucentis®; Genentech, South San Francisco, CA/Roche, Basel, Switzerland) and similar biologics block VEGF-A, the key driver of pathologic MNV and vascular leakage.[2,6] These agents lead to rapid regression of abnormal vessels and resolution of intra- and subretinal fluid, improving retinal structure and vision.[2,6] Clinical trials have shown substantial visual gains and reduced disease activity with repeated anti-VEGF therapy.[2,6] However, many patients still have persistent or recurrent fluid, and disease progression may continue despite treatment.[7] The need for frequent injections, often monthly or in treat-and-extend regimens, also places a heavy burden on patients, caregivers, and healthcare systems.[8]

Optical coherence tomography (OCT) is indispensable for diagnosing and managing MNV.[2] Modern spectral-domain (SD) and swept-source (SS) OCT provide high-resolution, cross-sectional macular images that reveal fluid and tissue changes noninvasively.[1] In clinical practice, OCT is used at nearly every visit to assess disease activity and guide retreatment. Key OCT-derived biomarkers, particularly IRF, SRF, pigment epithelial detachments (PEDs), and subretinal hyperreflective material (SHRM), are closely tracked as indicators of exudation.[1,9] The presence and distribution of these fluid compartments carry prognostic significance: for example, intraretinal (cystoid) fluid predicts poorer outcomes than SRF, and persistent IRF is generally associated with worse vision.[1,2,9] By contrast, SRF is often better tolerated and may signal a milder disease course.[9,10] Extensive SHRM (representing fibrin, hemorrhage, fibrosis, or active neovascular tissue) is linked to worse baseline vision and limited visual gains if persistent.[1,9–12] OCT also enables measurement of central retinal thickness (CRT), widely used as a surrogate metric.[1] Overall, OCT allows sensitive detection of MNV activity and is central to individualized retreatment decisions.

In recent years, "en face" OCT imaging, which produces frontal sections of retinal layers, has added a new dimension to retinal imaging.[13] En face modes (sometimes called C-scans) can isolate particular slabs of interest (for example, the sub-retinal pigment epithelium [RPE] or photoreceptor layers) and display pathology over a large area.[13] Within this framework, the technique of minimum-intensity projection (also called OCT-MI) has emerged as a quantitative tool.[14] In an OCT-MI image, the darkest (minimum reflectivity) pixel from each A-scan within a slab is plotted in en face format.[14] This highlights areas where tissue reflectivity is abnormally low. OCT-MI analysis has proven useful in other retinal conditions: for example, in hydroxychloroquine toxicity the minimum-intensity values in the outer nuclear layer become significantly elevated as photoreceptors degenerate.[14] Likewise, in geographic atrophy (GA) of AMD, increased MI at the lesion margins predicts sites of impending expansion, reflecting early photoreceptor and RPE disruption before it is visible en face.[15] These studies illustrate that OCT-MI can sensitively detect outer retinal disruption by quantifying subtle reflectivity changes. By analogy, it can be suggested that using MI en-face imaging, a method that highlights the darkest (least reflective) areas, could be a valuable but underused approach for measuring IRF and SRF in MNV. Since fluid appears as areas of low reflectivity (dark regions) on these scans, treating these fluid pockets as "dark lesions" could offer new, objective ways to quantify exudation in MNV.

Biosimilar anti-VEGF agents were introduced to improve affordability and access compared to originator biologics.[8,16,17] India approved the first ranibizumab biosimilar (RzB), Razumab® (Intas Pharmaceuticals, Ahmedabad, India), in 2015,[18,19] with several others following globally.[20–22] In India, biosimilars have seen rapid uptake: as evidenced by multiple surveys of retina specialists.[21,23,24] Oceva® (Sun Pharmaceutical Industries Limited, Mumbai, India) is a ranibizumab biosimilar approved in early 2023 (CDSCO clearance MF/BIO/23/000020, 24 March 2023).[25] While these agents promise to improve treatment affordability, real-world data on their anatomic and functional outcomes is still emerging. In particular, no study to date has used advanced OCT-based quantification to compare fluid dynamics under biosimilar therapy.

With rising biosimilar use and advances in retinal imaging, studies using OCT biomarkers to evaluate real-world efficacy are needed. This study addresses that gap by assessing the newer RzB, in treatment-naïve MNV, using en-face minimum intensity OCT to quantify fluid area and perimeter changes.

Materials and Methods

This was a retrospective, single-center study conducted at Shantilal Shanghvi Eye Institute in India, focusing on patients diagnosed with treatment-naïve MNV secondary to nAMD and PCV who received three monthly loading doses of the RzB, between September 2023 and December 2024. The study protocol was approved by Shantilal Shanghvi Foundation

Ethics Committee (SSF[SSEI]/LEC/2024/002) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was secured from all participants for both treatment and data publication.

Inclusion criteria comprised patients aged 50 years or older with active treatment-naïve MNV secondary to nAMD or PCV. We excluded eyes with MNV secondary to causes other than AMD and PCV (eg, myopia, inflammatory CNV), significant media opacities impeding reliable OCT imaging, concurrent diabetic retinopathy, advanced glaucoma, or history of intraocular surgery (other than uncomplicated cataract extraction) within the prior three months.

At baseline, each patient underwent a comprehensive assessment that included best-corrected visual acuity (BCVA) measured on a Snellen chart (converted to logMAR for analysis), intraocular pressure by Goldmann applanation tonometry, anterior segment examination with slit-lamp biomicroscopy, dilated fundus evaluation with 90D and 20D lenses, and SD-OCT (Cirrus HD-6000; Carl Zeiss Meditec, Dublin, CA, USA). Indocyanine green angiography (ICGA) was performed at baseline to differentiate between nAMD and PCV.

All eligible eyes received three consecutive monthly intravitreal RzB, (0.5 mg/0.05 mL per dose) as loading therapy. Intravitreal injections were performed under aseptic conditions in a dedicated procedure room. Participants returned for follow-up one week after the first injection, with subsequent visits scheduled at 30, 60, and 90 days post-injection. Any emergent symptoms prompted additional, unscheduled assessments as needed.

SD-OCT volume scans (49 B-scans over a 20°×20° area) were acquired at baseline and all subsequent visits. En-face minimum-intensity projections were generated automatically by the Cirrus HD-6000 OCT system's built-in software from each 20°×20° macular cube scan. As described by Allahdina et al[14] and Stetson et al,[15] the device's proprietary algorithm examines every A-scan in a predefined retinal slab, locates the voxel of minimum reflectivity, and assembles those values into a two-dimensional en-face minimum-intensity map. These MI projections were exported directly from the OCT system and used for analysis. All imaging assessments were performed by a single masked grader (J.S.) with over 10 years of experience in retinal imaging to ensure consistency.

The primary outcomes included changes in BCVA and quantitative alterations in fluid area and perimeter on en-face MI OCT from baseline to week 12. Secondary outcomes encompassed the proportion of eyes exhibiting SRF, IRF, and SHRM at each time point, as well as the incidence of any ocular or systemic adverse events during the study period.

Statistical Analysis

Data analysis was conducted using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), as appropriate. Categorical variables were presented as frequencies and percentages. Paired changes in BCVA, fluid area, and perimeter from baseline to 12 weeks were assessed with the Wilcoxon signed-rank test. Changes in the proportion of eyes with SRF, IRF, and SHRM were evaluated with McNemar's test. A P-value <0.05 was considered statistically significant.

Results

Thirty-six eyes from 36 treatment-naïve patients completed the three-injection loading phase with the RzB and were included in the analysis. Of these, 20 eyes had nAMD and 16 eyes had PCV. The mean age of the cohort was 71.33 years (SD ± 9.48), with a slight female predominance (male: female ratio 16: 20).

Best-Corrected Visual Acuity Outcomes

At baseline, the mean BCVA was 0.94 ± 0.59 logMAR (≈20/174). Following three monthly loading doses of RzB, there was a statistically significant improvement in BCVA at 12 weeks, with mean logMAR improving to 0.84 ± 0.61 (≈20/138; P=0.04; Table 1). By week 12, 91.7% of eyes (33/36) showed visual improvement, 8.3% (3/36) maintained baseline acuity, and no eyes experienced any vision loss.

Quantitative En-Face OCT-MI Fluid Metrics

The median fluid area, as measured on en-face OCT-MI, decreased significantly from 0.9 mm² (IQR 0.62–4.56) at baseline to 0.32 mm² (IQR 0.1–0.64) at 3 months (P=0.007). Similarly, the median fluid perimeter was reduced from 10.95 mm (IQR 7.26–25.67) at baseline to 6.02 mm (IQR 1.76–7.93) at 3 months (P=0.0005; Table 1).

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Table 1 Changes in the Best-Corrected Visual Acuity (BCVA) and Minimum Intensity-Based Fluid Metrics on En-Face Optical Coherence Tomography (OCT) (En-Face OCT-MI) in the Study Cohort

	Baseline	3 Months	*P*-value
LogMAR BCVA	0.94 ± 0.59 {≈20/174}	0.84 ± 0.61 {≈20/138}	0.04*
Median Fluid Area (En-face OCT-MI) (mm^2)	0.9 (IQR 0.62–4.56)	0.32 (IQR 0.1–0.64)	0.007*
Median Fluid Perimeter (En-face OCT-MI) (mm)	10.95 (IQR 7.26–25.67)	6.02 (IQR 1.76–7.93)	0.0005*

Note: *Statistically significant.
Abbreviations: BCVA, Best-corrected visual acuity; OCT, Optical coherence tomography; MI, Minimum-intensity.

Table 2 Proportion of Eyes with Resolution of Fluid and Subretinal Hyperreflective Material (SHRM)

	Proportion of Eyes at Baseline	Proportion of Eyes at 3 Months	*P*-value
IRF	66.67%	38.89%	0.013*
SRF	83.33%	58.33%	0.015*
SHRM	58.33%	13.89%	<0.001*

Note: *Statistically significant.
Abbreviations: IRF, Intraretinal fluid; SRF, Subretinal fluid; SHRM, Subretinal hyperreflective material.

Resolution of Fluid and Subretinal Hyperreflective Material

The proportion of eyes with IRF decreased from 66.67% (24/36) at baseline to 38.89% (14/36) at 3 months, representing a 41.7% reduction (P=0.013). SRF was present in 83.33% (30/36) of eyes at baseline and declined to 58.33% (21/36) at 3 months, corresponding to a 30.0% reduction (P=0.015). Notably, the proportion of eyes with SHRM showed a marked reduction, from 58.33% (21/36) at baseline to 13.89% (5/36) at 3 months, reflecting a 76.2% decrease (P<0.001) (Table 2).

Safety Analysis

No ocular or systemic adverse events were observed during the follow-up period. All injections were well tolerated, and no patient required discontinuation of therapy.

Figures 1 and 2 illustrates representative cases from the study population.

Discussion

In this study, three monthly injections of the RzB, produced significant visual improvement and markedly reduced the fluid in patients with MNV due to nAMD and PCV. These results parallel prior reports that ranibizumab biosimilars achieve visual and anatomical outcomes comparable to innovator ranibizumab.[18,26] Our findings therefore confirm that the novel biosimilar is effective in improving vision and resolving exudation in nAMD/PCV over the loading phase.

A primary novelty of our work is the application of en-face OCT-MI to objectively map and quantify exudative fluid in nAMD and PCV. Unlike conventional B-scan OCT, which provides qualitative cross-sectional views of fluid, en-face MI imaging collapses each A-scan to its lowest-intensity value, highlighting hyporeflective spaces across the macula.[13] In practice, fluid appears as black regions on the MI en-face map,[27] whereas normal retina (with higher minimum intensity) appears gray or white. In fact, Nicholson et al described how, in active exudation, "the en-face image generated has black regions corresponding to fluid".[27] By isolating these dark areas, our analysis could compute the total fluid area and perimeter, capturing both the size and complexity of fluid pockets across the macula.

En-face OCT-MI has been used previously in other retinal diseases to detect subtle outer retinal changes.[14,15] For example, OCT-MI analysis provides a quantitative measure of photoreceptor/outer nuclear layer integrity and was shown to detect early hydroxychloroquine toxicity with high sensitivity.[14] Similarly, increased MI at GA margins has been linked to lesion growth.[15] Our study is among the first to leverage MI en-face imaging specifically for exudative changes.

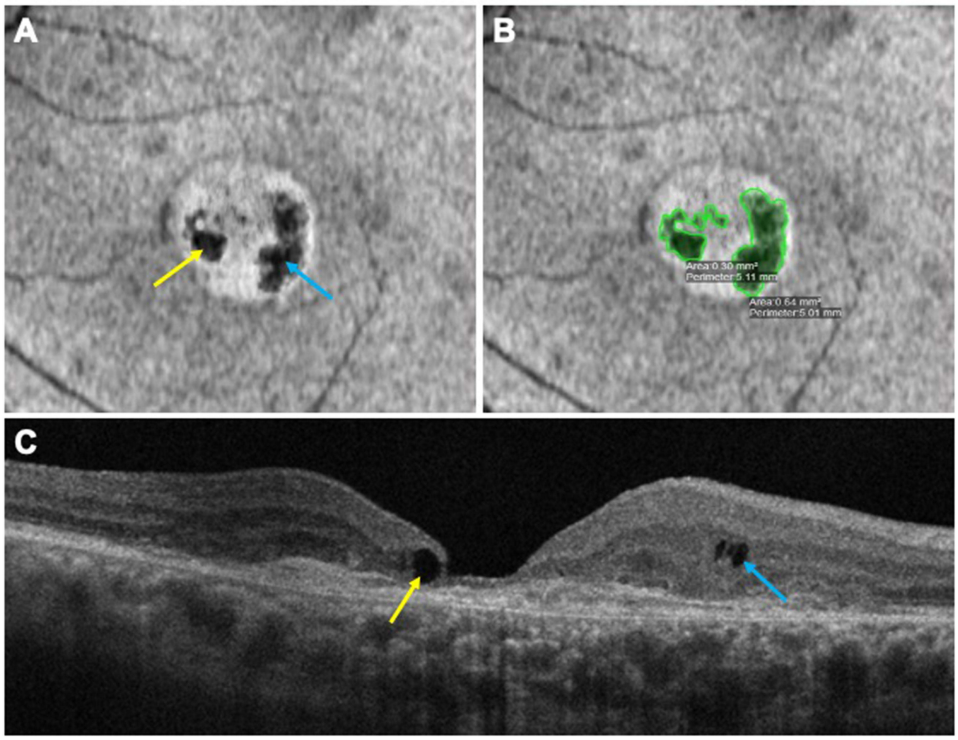

Figure 1 Minimum-intensity en-face optical coherence tomography (en-face OCT-MI) of a patient (**A**) demonstrates two distinct hyporeflective areas corresponding to the loci of intraretinal fluid (IRF). The measurements of fluid area and perimeter are shown in (**B**) on en-face OCT-MI. The spectral-domain OCT (**C**) also illustrates the corresponding fluid pockets (indicated by yellow and blue arrows in both A and C). Notably, the foveal A-scan of the OCT (**C**) reveals that the fluid pocket located nasally (yellow arrow) appears larger than the temporal fluid pocket (blue arrow). In contrast, the en-face OCT-MI (**A** and **B**) indicates that the extent of the temporal fluid is markedly greater than that of the nasal fluid pocket.

The method provides objective, reproducible measures of fluid burden. Because each pixel in the MI image represents the minimum reflectivity along its A-scan,[14,15] quantitative analysis of these maps yields repeatable fluid metrics that are not subject to subjective grader interpretation. In practice, this means we could track global changes in fluid that span multiple B-scans, rather than relying on limited cross-sections (eg central subfield thickness). Moreover, quantifying the perimeter of fluid regions offers insight into the complexity or fragmentation of the fluid information lost in simple volumetric measures.

Objective fluid mapping carries significant clinical implications. In nAMD and PCV management, both the volume and distribution of OCT-detected fluid serve as key biomarkers of disease activity.[1,9] Coulibaly et al recently demonstrated that accurately measuring and mapping fluid on OCT is essential for assessing disease activity and guiding treatment decisions in nAMD.[28] Many researchers are actively studying automated fluid quantification (using artificial intelligence [AI]) to guide individualized therapy.[29,30] In line with this, our en-face OCT-MI approach could serve as a practical tool for monitoring. For example, after each injection, an MI map could reveal residual or recurrent fluid that might not be obvious on B-scans. Automated or semi-automated calculations of fluid area and perimeter would help determine whether disease activity has truly resolved or if retreatment is needed. Coulibaly et al propose that automated fluid quantification could provide an objective basis for scheduling retreatments, thereby minimizing variability in treatment intervals.[28] By providing a standardized, quantitative endpoint, en-face OCT-MI biomarkers could thus refine PRN/treat-and-extend strategies: small stable fluid on MI may allow extending intervals, whereas any new black areas on MI might prompt reinjection.

In addition, en-face OCT-MI metrics may become valuable as longitudinal biomarkers of anti-VEGF response. For instance, the degree of baseline fluid area or its rate of shrinkage might correlate with visual prognosis or recurrence risk: a question for future study. Because MI maps capture the spatial distribution of fluid, they could reveal patterns (eg multilobular fluid, eccentric spread) associated with more aggressive disease. Overall, adopting en-face OCT-MI moves fluid assessment toward the

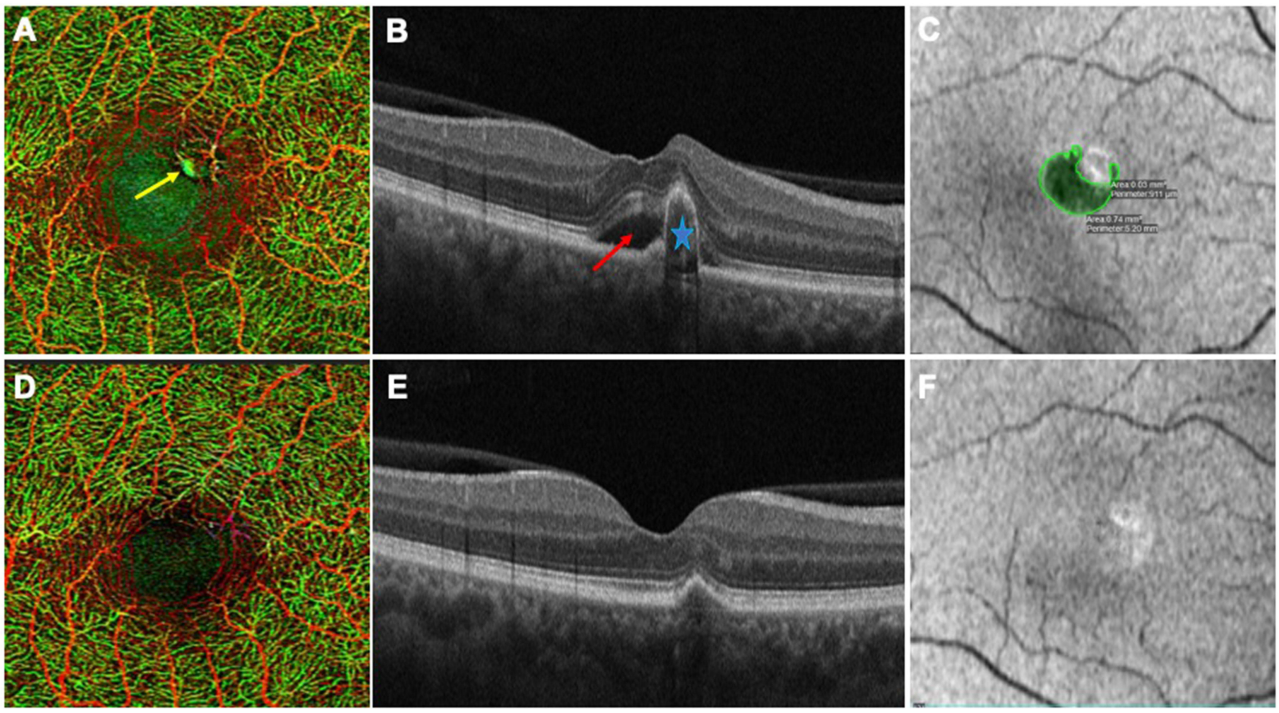

Figure 2 Baseline optical coherence tomography angiography (OCTA) (**A**) of a patient demonstrates macular neovascularization (MNV) (yellow arrow), along with a corresponding pigment epithelial detachment (PED) (blue asterisk; (**B**) and subretinal fluid (SRF) (red arrow; (**B**) on spectral domain OCT (SD-OCT). The Minimum-intensity en-face optical coherence tomography (en-face OCT-MI) at baseline provides detailed metrics of the fluid, including its area and perimeter (**C**). Following three intravitreal injections of the ranibizumab biosimilar, the patient's best-corrected visual acuity improved from 20/40 to 20/20, with complete resolution of the MNV observed on OCTA (**D**). Additionally, at 12 weeks, there was complete resolution of the SRF on both the SD-OCT (**E**) and en-face OCT-MI (**F**).

quantitative paradigm now seen in other specialties. In combination with deep learning or automated segmentation, MI maps promise to enhance disease monitoring by providing sensitive, reproducible readouts of exudation.

Our results underscore the growing importance of biosimilars in ophthalmology. High costs of anti-VEGF injections pose a heavy burden, especially in countries like India.[8] To address this, Razumab was developed as a more affordable alternative to innovator ranibizumab without sacrificing efficacy or safety, and real-world data show its outcomes match Lucentis across multiple indications.[19,26] Biosimilars also offer substantial savings: in India, Razumab costs about $125 per dose versus $320 for branded ranibizumab, and other agents like aflibercept remain even pricier.[8,23,24] Single-use vials and familiar handling make these products easy to integrate into practice. By lowering costs, biosimilars can reach patients who might otherwise forgo treatment, broadening access in nAMD and PCV care, conditions with a high risk of vision loss. As clinical evidence mounts and regulators (including the FDA) approve ophthalmic biosimilars like SB11, the retinal community's confidence is growing: these agents promise to reduce drug expenditure while maintaining outcomes and advancing public health.[20–26]

Key strengths of our study include the novel use of en-face OCT-MI and the focused real-world evaluation of a ranibizumab biosimilar in nAMD/PCV. By quantifying fluid area and perimeter changes, we demonstrated objective metrics that correlated with treatment effect. However, several limitations must be acknowledged. The study's retrospective design carries inherent biases (eg lack of randomization and potential selection bias). The sample size was modest and not powered to allow a meaningful comparison between nAMD and PCV subgroups. Additionally, the analysis was conducted by a single grader, which may introduce subjective variability. The lack of a parallel control group (such as patients receiving innovator ranibizumab) limits the ability to draw direct comparative conclusions. The follow-up period was short (12 weeks), so longer-term efficacy, durability of fluid resolution, and safety could not be assessed. Additionally, while en-face OCT-MI offers quantitative data, manual steps in image processing could introduce variability; future work should assess reproducibility explicitly. Finally, the MI technique is proprietary to certain OCT

platforms, which may affect generalizability. Nevertheless, this study provides a proof of concept for OCT-MI use in exudative AMD/PCV and generates hypotheses for further research.

Moving forward, prospective longitudinal studies are needed to validate OCT-MI fluid metrics as a biomarker of anti-VEGF response. It would be valuable to track how MI-derived fluid area/perimeter evolve over longer treatment courses and whether they predict re-treatment intervals or visual outcomes. Comparative trials of biosimilar versus originator ranibizumab using en-face OCT-MI as an endpoint could further elucidate any subtle differences in fluid dynamics. In summary, our findings open a new avenue for objective OCT-based monitoring in MNV and underscore the promise of cost-effective biosimilars in managing retinal disease.

Conclusion

In this proof-of-concept study, loading doses of the RzB, resulted in significant visual improvement and a reduction in fluid in MNV secondary to nAMD or PCV, as objectively measured by en-face OCT-MI. These findings support the use of en-face OCT-MI as a quantitative biomarker for fluid exudation and treatment response. Given the lower cost profile of biosimilars, their adoption may broaden access to effective therapy in resource-limited settings. To establish external validity and inform routine clinical use, multicenter, randomized trials with extended follow-up are now warranted. Overall, the findings highlight the potential of biosimilars and advanced imaging in shaping the future of MNV management.

Disclosure

J.S., B.M., S.K.: Shantilal Shanghvi Foundation (SSF) (not relevant to the work under consideration). The authors declare that they have no competing interests in this work.

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