Clinical Ophthalmology

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COMMENTARY

Anti-VEGF Therapies in Retinal Disorders: Current Landscape and Future Directions

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Abstract: Anti-vascular endothelial growth factor (anti-VEGF) therapy has transformed the management of macular neovascularization and other retinal vascular disorders; however, treatment burden, variable response, and cost continue to limit real-world outcomes. This Commentary presents an evidence synthesis from a curated collection of articles, focusing on three intersecting priorities: expanding access through biosimilars with comparable efficacy and safety profiles; optimizing treatment through individualized agent selection and faricimab switching paradigms; and leveraging quantitative multimodal imaging biomarkers, including advanced en-face optical coherence tomography fluid metrics, to refine disease monitoring and retreatment decisions. Emerging structural and angiographic biomarkers, including advanced en-face optical coherence tomography metrics, offer opportunities for earlier risk stratification and personalized care. In parallel, patient-centered considerations and pragmatic treatment algorithms remain essential to enhance adherence and durability of response. Together, these themes underscore a shift toward precision-guided, accessible, and evidence-based retinal care. Prospective validation and implementation research will be critical to translate these advances into sustainable clinical practice.

Keywords: anti-vascular endothelial growth factor, macular neovascularization, optical coherence tomography, biosimilars

Introduction

Anti-vascular endothelial growth factor (anti-VEGF) therapy has transformed the management of macular neovascularization and other retinal vascular disorders, with pivotal multicenter trials demonstrating that ranibizumab (MARINA, ANCHOR), aflibercept (VIEW 1, VIEW 2), and brolucizumab (HAWK, HARRIER) preserve and improve vision in neovascular age-related macular degeneration (nAMD), while RISE/RIDE and VIVID/VISTA established the superiority of anti-VEGF over laser in diabetic macular edema (DME).[1–3] However, treatment burden, variable response, and cost continue to limit real-world outcomes, as long-term cohorts such as SEVEN-UP and the 5-year CATT follow-up have shown that many eyes experience gradual visual decline, persistent fluid, and progressive atrophy despite initially strong treatment responses.[1–6] Newer agents like high-dose aflibercept (8 mg) and faricimab are now emerging as concurrent strategies aimed at extending treatment intervals and improving durability, particularly in eyes requiring frequent injections, although real-world data on their long-term benefit and comparative effectiveness are still evolving.[1]

This Commentary presents an evidence synthesis from a curated collection of articles, focusing on three intersecting priorities: expanding access through biosimilars with comparable efficacy and safety profiles; optimizing treatment through individualized agent selection and faricimab-based switching paradigms; and leveraging quantitative multimodal imaging biomarkers, including advanced en-face optical coherence tomography fluid metrics, to refine disease monitoring and retreatment decisions. Emerging structural and angiographic biomarkers, including advanced en-face optical coherence tomography metrics, offer opportunities for earlier risk stratification and personalized care. In parallel, patient-centered considerations and pragmatic treatment algorithms remain essential to enhance adherence and durability of response. Together, these themes underscore a shift toward precision-guided, accessible, and evidence-based retinal

https://doi.org/10.2147/OPTH.S603279
Received: 17 February 2026
Accepted: 28 March 2026
Published: 1 April 2026

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Evolving Clinical Strategies and Biosimilars

A major theme is optimizing treatment efficacy and access. Two systematic reviews reinforce that emerging biosimilars can match branded anti-VEGF efficacy. Aljuhani et al[7] performed a meta-analysis of 2039 eyes in nAMD and found no significant differences between aflibercept biosimilars and reference aflibercept in improving visual acuity or reducing retinal thickness. Their conclusion that biosimilar aflibercept offers comparable outcomes and safety while lowering cost supports broader use of these drugs in practice. Similarly, Sheth et al[8] evaluated a ranibizumab biosimilar (Razumab) in eyes with macular neovascularization (MNV; nAMD and polypoidal choroidal vasculopathy [PCV]). After three monthly loading doses, mean visual acuity improved significantly, and en-face OCT metrics showed marked reduction in fluid area and perimeter.[8] Importantly, nearly all treated eyes improved vision (91.7% had acuity gains) and no adverse events were noted.[8] These findings echo previous reports that ranibizumab biosimilars achieve outcomes equivalent to the original drug.[9,10] By confirming that biosimilars can deliver robust vision gains and fluid resolution, the study highlights their role in reducing treatment costs and expanding access, especially in resource-limited settings.[11,12]

Another innovative approach is combination therapy for DME. Hubayni et al[13] systematically reviewed trials comparing intravitreal bevacizumab (IVB) alone vs IVB plus topical glaucoma drugs (timolol–dorzolamide or dorzolamide alone) in DME. The pooled results showed no meaningful difference in central macular thickness (CMT) or visual acuity (VA) improvements among the groups.[13] In other words, adding topical therapy did not enhance the retina outcomes of IVB. An interesting secondary finding was that IOP decreased more in the combined groups, as expected from the glaucoma drops.[13] Clinically, this suggests that concurrent ocular hypotensive drops can be used when needed (eg, if IOP is elevated) without compromising DME efficacy, but they do not augment the anti-VEGF effect on macular edema.[13]

The collection also addresses resistant or refractory AMD. One study examined switching to faricimab (a bispecific anti-VEGF/Ang-2 antibody) in patients with nAMD who were "low responders" to monthly aflibercept.[14] Rothbächer et al[14] found that after a loading series of faricimab, treatment intervals could be significantly extended (mean ~5.4 weeks vs 4 weeks before; $p < 0.001$) and central retinal thickness (CRT) fell markedly (from ~268 μm to ~249 μm after one month). The number of eyes with intraretinal or subretinal fluid (IRF/SRF) also declined significantly.[14] Notably, eyes with serous or drusenoid pigment epithelial detachments (PEDs) responded especially well to switching, whereas eyes with fibrovascular PEDs were less likely to allow interval extension.[14] These results demonstrate that faricimab can provide additional fluid resolution in cases where prior anti-VEGF therapy plateaued, consistent with faricimab's known ability to target both VEGF-A and Ang-2.[14–16] As one review notes, faricimab's prolonged activity often permits dosing every 3–4 months, relieving treatment burden.[16] The current study shows this benefit even in a real-world refractory cohort, underscoring faricimab as a valuable option for "suboptimal" responders.[14]

Imaging Advances and Objective Metrics

Assessing treatment response is critical. Sheth et al[8] introduced a novel use of en-face OCT minimum-intensity (MI) imaging to quantify fluid objectively. This method collapses each OCT A-scan to its darkest voxel, highlighting fluid pockets as black regions. After three loading doses of ranibizumab biosimilar, the median fluid area on en-face OCT fell from 0.90 to 0.32 mm^2 (a 65% reduction; $p = 0.007$) and the fluid perimeter also shrank significantly.[8] The authors argue that such quantitative maps could complement conventional OCT measures (like central thickness) by capturing the extent and spread of edema across the macula. In practice, these en-face MI images might help clinicians detect subtle residual fluid or complex fluid patterns that cross multiple B-scans. As technology and AI advance, objective fluid metrics (area, perimeter) could refine "treat-and-extend" or PRN decisions: persistent small fluid on MI maps may justify maintaining intervals, whereas new fluid might prompt earlier re-treatment. While still investigational, this approach highlights the trend toward more precise, quantitative monitoring in anti-VEGF therapy.

Patient Burden and Perceptions

Equally important are the patient-centered aspects of chronic injection therapy. Robinson et al[17] surveyed 101 patients (with nAMD or DME) and 100 retina specialists to compare experiences and expectations. The study reveals the significant logistical and psychological burden of frequent injections.[17] For example, 66% of DME and 86% of nAMD patients needed injections at least every 8 weeks, and 82% required a caregiver or public transport to attend appointments.[17] Patients reported major symptoms like worsening vision, blurred vision, and difficulty in low light, which affect daily life.[17] Importantly, one-third of nAMD patients felt they received inadequate counseling about their disease (vs 11% of DME patients).[17] The study also found gaps between doctor and patient perceptions: clinicians tended to overestimate how necessary patients thought the injections were and underestimated how hard it was for patients to get to the clinic.[17] These discordances suggest a need for better communication. The authors conclude that ophthalmologists should be aware of the multidimensional burden (physical, emotional, financial) on patients and provide targeted education to align expectations and improve adherence.[17]

Collectively, these findings remind us that treatment success is not just anatomical improvement but also patient satisfaction and quality of life. Reducing visit frequency (via longer-acting drugs like faricimab or sustained-delivery systems) and addressing practical barriers (transportation, costs) are as critical as the injections themselves.

Synthesis and Outlook

This collection paints a balanced picture: anti-VEGF therapies remain the cornerstone of retinal disease management, but the field is actively evolving to address unmet needs. On one hand, biosimilars are proving their worth, potentially alleviating economic barriers without sacrificing outcomes, although heterogeneity in real-world settings and variability in study designs underscore the need for cautious interpretation and context-specific application.[7,8] Regulatory pathways for biosimilars require rigorous analytical similarity, pharmacokinetic-pharmacodynamic equivalence, and confirmatory clinical trials demonstrating comparable efficacy and safety versus the reference product, yet post-approval pharmacovigilance remains critical to detect rare or delayed events, differences in manufacturing batches, and local- or system--specific safety signals, particularly in regions where distinct products such as Razumab are available only in limited markets and full regulatory "interchangeability" is not yet uniformly established.[2,7,8] In clinical practice, switching from innovator to biosimilar agents or between biosimilars has generally shown similar visual and anatomical outcomes, but a subset of eyes can experience modest VA- or fluid-related fluctuations, underscoring the importance of individualized risk-benefit assessment and close monitoring after transition.[18,19] In this context, attention to the "nocebo effect" is also important: patient- or physician-level expectations and negative perceptions around biosimilars can influence reported symptomatology and treatment satisfaction even in the absence of objective changes, highlighting the need for clear communication, education, and shared decision-making to support confident and comfortable biosimilar adoption.

Combination approaches (eg, anti-VEGF plus adjunctive treatments) are explored, but not all yield extra benefit, and the incremental gain often depends on patient-specific and disease-specific factors.[4,14,20] On the other hand, newer agents like faricimab are changing paradigms by tackling non-responders and enabling longer treatment intervals, although available data are still limited by relatively short follow-up, predominantly selected trial populations, and evolving real-world experience.[4,14,20] In cases with fibrovascular PEDs where faricimab fails to allow further interval extension, management might include consideration of higher-dose aflibercept (8 mg) to intensify VEGF suppression, closer monitoring of OCT biomarkers of non-response (such as persistent subretinal fibrosis, outer retinal atrophy, or persistent sub-RPE irregularity), or shortening/stabilizing the injection interval to maintain anatomical control while still balancing treatment burden and vision-preserving durability.[4,14,20]

In routine practice, most clinics still base retreatment decisions on standard B-scan volume maps, with qualitative and quantitative assessment of IRF and SRF. Advances in imaging, such as en-face OCT fluid mapping and related quantitative minimum-intensity metrics, are currently available on only some commercial OCT platforms, most notably as minimum-intensity slabs on ZEISS CIRRUS systems, but typically as research-oriented or export functions that require additional post-processing, so their practical accessibility and integration into routine retreatment algorithms remain limited in many clinics.[8] As such, MI-based en-face imaging is best regarded as an emerging, experimental

adjunct that may in future support more precise monitoring and personalized retreatment criteria, yet these biomarkers face important technical constraints,[8] yet these biomarkers face important technical constraints: reproducibility can vary across devices and software versions, segmentation algorithms are highly dependent on underlying retinal-layer delineation, and small changes in scan quality or segmentation thresholds can alter apparent fluid volumes and thus influence "objective"-appearing treatment decisions.

Yet challenges persist. A significant minority of patients remain refractory (as reported in earlier literature, 15–40% of AMD and DME eyes respond inadequately), highlighting the need for alternative pathways.[6] Immunological and inflammatory factors beyond VEGF (eg, Ang-2, cytokines) are under investigation, and emerging data suggest that mechanistic heterogeneity across diseases may influence response patterns.[20,21] Clinical strategies such as adding steroids, laser therapy, or new gene-based approaches are being tested for resistant cases, but many of these remain experimental and heterogeneous in design and endpoints.[20,21] Additionally, the healthcare community must continue to address patient-centric issues: simplifying regimens, improving clinic access, and ensuring clear, consistent communication, particularly as imaging-driven protocols become more complex and potentially more reliant on algorithmic outputs.

Looking ahead, the retina field is poised to refine anti-VEGF care in several ways. First, longer-duration therapies such as port-delivery systems and gene-based approaches are being developed to vastly reduce injection frequency, though long-term safety and real-world effectiveness remain to be fully established.[20–23] Second, combination biologics and agents targeting pathways beyond VEGF-A (eg, Ang-2, complement, or inflammatory mediators) are in development to overcome resistance, but their additive value over existing regimens is still being evaluated in heterogeneous trial populations and across diverse healthcare systems.[16,17,20,21] Third, patient selection and monitoring will become more sophisticated, possibly integrating AI-driven analysis of imaging biomarkers (such as en-face–based metrics) to tailor treatment intervals; here again, external validation, standardization across devices and segmentation pipelines, and explicit reporting of reproducibility measures are essential to avoid overinterpreting apparent "precision." The insights from this collection underscore both how far anti-VEGF therapy has advanced and how much remains to be done: extending benefits to every patient, minimizing burdens, and preserving vision in an aging population. In the spirit of innovation and collaboration, the ophthalmic community should continue to push these frontiers, guided by evidence--based advances, robust regulatory and pharmacovigilance frameworks, and a commitment to patient-centered care.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Aldokhail LS, Alhadlaq AM, Alaradi LM, Alaradi LM, AlShaikh FY. Outcomes of anti-VEGF therapy in eyes with diabetic macular edema, vein occlusion-related macular edema, and neovascular age-related macular degeneration: a systematic review. *Clin Ophthalmol*. 2024;18:3837–3851. doi:10.2147/OPTH.S489114
2. Narayanan R, Hariprasad SM, Sheth J. Biosimilars for the treatment of retinal diseases. *Ophthalmic Surg Lasers Imaging Retina*. 2021;52 (5):242–246. doi:10.3928/23258160-20210429-01
3. Sheth JU, Stewart MW, Narayanan R, et al. Macular neovascularization. *Surv Ophthalmol*. 2025;70(4):653–675. doi:10.1016/j. survophthal.2024.08.003
4. Chakraborty D, Das S, Maiti A, et al. Clinical evaluation of faricimab in real-world diabetic macular edema in India- a multicenter observational study. *Clin Ophthalmol*. 2025;19:269–277. doi:10.2147/OPTH.S502033
5. Chakraborty S, Sheth JU. Contralateral effect following intravitreal brolucizumab injection in diabetic macular edema. *Case Rep Ophthalmol Med*. 2022;2022:3755249. doi:10.1155/2022/3755249
6. Wallsh JO, Gallemore RP. Anti-VEGF-resistant retinal diseases: a review of the latest treatment options. *Cells*. 2021;10(5):1049. doi:10.3390/ cells10051049
7. Aljuhani HS, Hubayni RA, Qedair J, et al. Efficacy and safety of aflibercept biosimilars relative to reference aflibercept therapy for neovascular age-related macular degeneration: a systematic review and meta-analysis. *Clin Ophthalmol*. 2025;19:1911–1918. doi:10.2147/OPTH.S524395
8. Sheth JU, Bhopalka AK, Meshram B, Karande S. Quantitative assessment of en-face OCT-derived minimum intensity fluid changes following ranibizumab biosimilar therapy in macular neovascularization secondary to nAMD and PCV. *Clin Ophthalmol*. 2025;19:2505–2512. doi:10.2147/ OPTH.S542496
9. Soman M, Nair I, Sheth JU, Nair U. Innovator Versus Biosimilar Ranibizumab in Polypoidal Choroidal Vasculopathy: real-World Evidence. *Ophthalmol Ther*. 2022;11(3):1175–1186. doi:10.1007/s40123-022-00507-w
10. Chakraborty D, Stewart MW, Sheth JU, et al. Real-world safety outcomes of intravitreal ranibizumab biosimilar (Razumab) therapy for chorioretinal diseases. *Ophthalmol Ther*. 2021;10(2):337–348. doi:10.1007/s40123-021-00345-2

11. Ueda-Consolvo T, Ishida M, Nakamura T, et al. Biosimilar ranibizumab (BS1) - early experience from Japan (BRIJ study). *Eye*. 2024;38 (16):3193–3196. doi:10.1038/s41433-024-03220-z
12. Sheth JU, Stewart MW, Khatri M, et al. Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: insights from the Vitreoretinal Society of India biosimilars of anti-VEGF Survey. *Indian J Ophthalmol*. 2021;69(2):352–356. doi:10.4103/ijo.IJO_2703_20
13. Hubayni RA, Qedair J, Bukhari ZM, et al. Intravitreal bevacizumab alone vs combined with topical timolol-dorzolamide or dorzolamide for diabetic macular edema: a systematic review and meta-analysis. *Clin Ophthalmol*. 2025;19:1007–1019. doi:10.2147/OPTH.S509136
14. Rothbächer J, Khalil H, Eidherr M, Bolz M. Additional effects of faricimab in aflibercept low-responders: retinal morphology and function in eyes with neovascular age related macular degeneration following a switch between two anti-VEGF agents. *Clin Ophthalmol*. 2025;19:3145–3152. doi:10.2147/OPTH.S530355
15. Agrawal V, Gupta A, Agrawal V, Sheth JU. Faricimab outcomes in chorioretinal disorders: indian real-world analysis (FOCUS Study). *Clin Ophthalmol*. 2025;19:1855–1862. doi:10.2147/OPTH.S521384
16. Biswas RK, Sheth JU, Shrivastava V, et al. Faricimab for refractory neovascular age-related macular degeneration: retrospective real-world evidence from India. *Clin Ophthalmol*. 2025;19:3881–3887. doi:10.2147/OPTH.S549584
17. Robinson K, Cooper SJ, Persaud S, Frederick JL, Singh RP. Discordance among patients and ophthalmologists regarding the burden of intravitreal injections. *Clin Ophthalmol*. 2025;19:2637–2645. doi:10.2147/OPTH.S532179
18. Chakraborty D, Sinha TK, Maiti A, et al. Transitioning from aflibercept to biosimilar ranibizumab in Diabetic Macular Edema (DME): (the TRANSFORM-DME Trial) a multicenter observational study. *Clin Ophthalmol*. 2024;18:3449–3456. doi:10.2147/OPTH.S500912
19. Sharma A, Loewenstein A, Parachuri N, Kumar N, Kuppermann BD. Biosimilar to biosimilar anti-VEGF switching for retinal diseases. *J Vitreoretin Dis*. 2023;7(6):474–476. doi:10.1177/24741264231202080
20. Guan J, Meng F, Wang C, Zhang B, Chen J, Han J. Recent advances in engineered exosome-based therapies for ocular vascular disease. *J Nanobiotechnol*. 2025;23(1):526. doi:10.1186/s12951-025-03589-3
21. Muniyandi A, Hartman GD, Song Y, Mijit M, Kelley MR, Corson TW. Beyond VEGF: targeting inflammation and other pathways for treatment of retinal disease. *J Pharmacol Exp Ther*. 2023;386(1):15–25. doi:10.1124/jpet.122.001563
22. Leferman CE, Ciubotaru AD. Ocular gene therapy as a sustained drug delivery system: pharmacokinetic and genokinetic perspectives. *J Med Life*. 2025;18(11):984–993. doi:10.25122/jml-2025-0180
23. Sharma A, Khanani AM, Parachuri N, Kumar N, Bandello F, Kuppermann BD. Port delivery system with ranibizumab (Susvimo) recall- what does it mean to the retina specialists. *Int J Retina Vitreous*. 2023;9(1):6. doi:10.1186/s40942-023-00446-z