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REVIEW

Pharmacological Treatment for Diabetic Macular Edema: A 2025 Update on Durability and Multi-Target Therapies

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Abstract: Diabetic macular edema (DME) remains a leading cause of vision loss in the working-age population, yet its management is undergoing a fundamental paradigm shift from high-frequency anti-VEGF monotherapy toward more durable and multi-mechanism therapeutic strategies. This narrative review provides an up-to-date overview of the pharmacological landscape of DME as of 2025, synthesizing evidence from pivotal clinical trials, recent regulatory approvals, and available real-world outcomes. We examine the transition toward injection-sparing approaches and discuss the clinical rationale for targeting alternative biological pathways beyond VEGF inhibition, including angiopoietin-2 (eg, faricimab), the plasma kallikrein–kinin system, and tyrosine kinase–mediated signaling. Collectively, emerging evidence suggests that the future management of DME will be defined by a paradigm shift toward injection-sparing, multi-pathway therapeutic strategies, extending beyond short-term fluid suppression toward a more personalized, precision-medicine framework that prioritizes long-term durability, safety, and functional outcomes.

Keywords: diabetic macular edema, pharmacological treatment, anti-VEGF, corticosteroids, long-acting therapy, multi-target, gene therapy

Introduction

Diabetic macular edema (DME) is one of the most common microvascular complications of diabetes mellitus (DM) and a leading cause of vision loss among individuals with diabetes, posing a particular burden on the working-age population.[1] It is estimated that approximately 19 million people worldwide were affected by DME in 2020, and the number is expected to rise in parallel with the global increase in DM prevalence, underscoring DME as a growing public health challenge.[2,3] This review aims to provide a comprehensive overview of the pathophysiology of DME, current therapeutic options, and advances in emerging pharmacologic treatments.

Methods

This narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA)[4] to ensure methodological rigor, balance, and transparency.

Literature Search and Data Sources

A structured literature search was performed using PubMed, Embase, and the Cochrane Library, covering publications from January 1, 2010, to October 31, 2025. Search terms included Medical Subject Headings and free-text keywords related to diabetic macular edema, anti-VEGF therapy, corticosteroids, angiopoietin-2, tyrosine kinase inhibitors, and gene therapy. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were additionally searched to identify ongoing or unpublished studies, particularly for emerging therapeutic agents.

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Study Selection and Narrative Synthesis

Priority was given to Phase III randomized controlled trials for approved therapies and Phase I/II studies for investigational agents. Real-world and retrospective studies were included where available to contextualize long-term safety, durability, and treatment burden. Studies were selected based on predefined criteria, including stage of clinical development, relevance to therapeutic pathways, and availability of efficacy and safety data, while preclinical studies without clear translational relevance were not prioritized.

Given substantial heterogeneity in mechanisms of action, trial design, outcome measures, and development stages, quantitative meta-analysis was not performed. Instead, a critical narrative synthesis was applied, incorporating thematic grouping by mechanism of action, contextual comparison with established clinical benchmarks, and focused assessment of safety signals and reasons for trial discontinuation.

Pathophysiology of DME

The pathogenesis of DME involves a complex network of metabolic, vascular, and inflammatory disturbances driven by chronic hyperglycemia. A key event is dysfunction of the retinal microcirculation leading to breakdown of the blood–retinal barrier (BRB). Compromise of the BRB permits leakage of plasma fluid and macromolecules into the neurosensory retina, resulting in macular thickening and cystoid edema. Early hyperglycemia-induced alterations include transient vasodilation and hemodynamic changes,[5] followed by structural damage[6] such as pericyte loss,[7,8] endothelial apoptosis, and basement membrane thickening,[9,10] all of which collectively weaken capillary integrity.

Hyperglycemia activates several pathological pathways[11]— including the polyol pathway,[12] accumulation of advanced glycation end products (AGEs),[13,14] protein kinase C (PKC) activation, and increased hexosamine flux[15–17] — which amplify oxidative stress, promote inflammation, and impair cellular function. Additional dysregulation of the renin–angiotensin–aldosterone system (RAAS),[18] the kallikrein–kinin system (KKS),[19] and aquaporins (AQPs)[20] further contributes to BRB disruption and fluid imbalance.

Vascular endothelial growth factor (VEGF), particularly VEGF-A, is a central mediator of DME.[21] Capillary nonperfusion and tissue hypoxia activate hypoxia-inducible factor-1 (HIF-1), which markedly upregulates VEGF expression.[22,23] VEGF increases vascular permeability by inducing phosphorylation and degradation of tight-junction proteins via VEGF receptor (VEGFR)-2, promotes endothelial proliferation, and possesses pro-inflammatory activity— all of which exacerbate BRB compromise.[24–26] The pivotal role of VEGF forms the basis for anti-VEGF therapy as the first-line treatment for DME in most guidelines/clinical practice.[27]

Inflammation also plays a crucial role.[28] Elevated intraocular cytokines such as TNF-α, IL-1β, IL-6, IL-8, IL-17A, and MCP-1[29,30] enhance vascular permeability and promote leukostasis, further damaging the BRB.[31] Activation of microglia and Müller cells in a hyperglycemic and inflammatory milieu sustains a vicious cycle of cytokine release, oxidative stress, and VEGF overproduction.[32,33]

Finally, dysfunction of the retinal neurovascular unit—comprising neurons, glia, endothelial cells, and pericytes—contributes to disease progression.[34] Diabetic retinal neurodegeneration, characterized by neuronal apoptosis and reactive gliosis, often precedes microvascular damage,[35] highlighting the need to consider neuroprotection in DME management.

Current Pharmacologic Therapies for DME

Anti-VEGF Agents

Anti-VEGF agents inhibit the binding of VEGF to its receptors, thereby reducing VEGF-mediated vascular permeability and neovascularization. They remain the first-line therapy for DME.[36] Currently approved or commonly used anti-VEGF agents include ranibizumab, aflibercept, conbercept, brolucizumab, and bevacizumab (Table 1).

Ranibizumab

Ranibizumab (Lucentis) is a humanized recombinant Fab fragment (48 kDa) that specifically binds VEGF-A and blocks its interaction with VEGFR-1/2, thus suppressing endothelial proliferation, vascular leakage, and neovascularization.[37] It was the first FDA-approved anti-VEGF agent for DME.[38] Several biosimilars, including Byooviz (ranibizumab-nuna) and Cimerli (ranibizumab-eqrn), have also received FDA approval for retinal vascular diseases.[39]

Table 1 Overview of Current Pharmacological Therapies for Diabetic Macular Edema

Category	Agent (Trade Name)	Molecular Characteristics	Clinical Trials	Durability	Clinical Status
Anti-VEGF	Ranibizumab (Lucentis)	Fab fragment (48 kDa)	RISE, RIDE	Monthly or PRN	FDA approval (DME): 2012
	Aflibercept 2mg (Eylea)	Fusion protein (115 kDa)	VIVID, VISTA	Q8W	FDA approval (DME): 2014
	Aflibercept 8mg (Eylea HD)	High-dose fusion protein (115 kDa)	PHOTON	Q8-16W	FDA approval (DME): 2023
	Conbercept (Lumitin)	Fusion protein (143 kDa)	SAILING (China)	PRN regimen	NMPA Approved (China): 2018 Not FDA-approved
	Brolucizumab (Beovu)	scFv fragment (26 kDa)	KESTREL, KITE	Q8-12W	FDA approval (DME): 2022
	Bevacizumab (Avastin)	Full-length humanized monoclonal IgG1 antibody (149 kDa)	DRCR.net Protocol T	Similar to other anti-VEGF	Off-label
Multi-target with VEGF Inhibition	Faricimab (Vabysmo)	Bispecific IgG1 antibody (VEGF-A and Ang-2)	YOSEMITE, RHINE	Up to 16W	FDA approval (DME): 2022
Corticosteroids	Triamcinolone Acetonide	Intravitreal suspension	DRCR.net Protocol B&I	PRN	Largely superseded by intravitreal steroid implants
	Dexamethasone Implant (Ozurdex)	Biodegradable implant	MEAD	Q3-6M	FDA approval (DME): 2014
	Fluocinolone Acetonide (Iluvien)	Non-biodegradable implant	FAME, PALADIN	Up to 36M	FDA approval (DME): 2014

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Aflibercept

Aflibercept (Eylea) is a 115-kDa recombinant fusion protein comprising the extracellular domains of VEGFR-1 and VEGFR-2 fused to the Fc portion of human IgG1. It binds VEGF-A, VEGF-B, and placental growth factor (PLGF).[40] The PHOTON trial demonstrated that high-dose Eylea HD (8 mg) effectively extended treatment intervals while maintaining outcomes compared with the 2-mg formulation, reducing treatment burden.[41] Multiple aflibercept biosimilars, including Yesafili, Opuviz, Ahzantive, Enzeevu, and Pavblu, have also gained FDA approval.

Conbercept

Conbercept (Lumitin) is a 143-kDa recombinant fusion protein developed in China. It contains the second extracellular domain of VEGFR-1 and the third and fourth domains of VEGFR-2 fused to human IgG1 Fc, enabling high-affinity binding to VEGF-A/B/C and PLGF.[42] It received the China National Medical Products Administration approval for DME in 2018. However, global Phase III trials (PANDA-1/2) were terminated early in 2021 due to the inability to meet the primary endpoint, limiting regulatory approval to specific regions outside the United States and Europe.

Brolucizumab

Brolucizumab (Beovu) is a 26-kDa single-chain variable fragment (scFv) with high molar concentration per injection due to its small size.[43] It binds VEGF-A and inhibits its biological activity. The KESTREL and KITE trials showed non-inferior visual and anatomical outcomes to aflibercept in DME, with the possibility of extending dosing intervals to 3–4 months.[44,45] Beovu received FDA approval for DME in 2022.

Bevacizumab

Bevacizumab (Avastin) is a 149-kDa full-length monoclonal antibody initially approved for metastatic solid tumors.[46] Although not formally approved for ophthalmic use, its low cost has led to widespread off-label use in retinal diseases.[47] In 2024, the European Commission approved Lytenava, the first ophthalmic bevacizumab formulation, for age-related macular degeneration (AMD).[48]

Limitations of Anti-VEGF Agents

Despite their effectiveness, anti-VEGF agents have notable limitations:

- High treatment burden: Monthly injections during initiation and long-term frequent dosing result in substantial time, financial, and logistical burdens, contributing to reduced adherence and poorer real-world outcomes;[49]
- Suboptimal responders: A significant proportion of patients exhibit persistent or refractory DME despite adequate anti-VEGF therapy,[50–52] highlighting that VEGF is not the only pathway driving DME and underscoring the need for additional targets;
- Potential complications: Ocular adverse events are primarily related to the intravitreal injection procedure, while severe complications such as endophthalmitis or retinal detachment are rare. Because these ocular events are attributable to the route of administration rather than to specific pharmacological targets, similar procedural safety considerations apply across intravitreal therapies and are addressed where applicable in this review. Systemic adverse events are uncommon; however, caution is warranted in patients with cardiovascular risk factors due to the theoretical risk of arterial thromboembolic events associated with anti-VEGF therapy.[42,53]

Multi-Target Agents Combined with VEGF Inhibition

Faricimab (Vabysmo) is a bispecific IgG1 antibody that inhibits both VEGF-A and angiopoietin-2 (Ang-2),[54] a stress-induced cytokine elevated in DME that destabilizes retinal vasculature by antagonizing the Ang-1/Tie2 pathway, promoting endothelial dysfunction, and enhancing VEGF-mediated leakage.[55] Dual inhibition provides broader vascular stabilization than targeting VEGF alone.

In the YOSEMITE and RHINE trials,[56,57] faricimab achieved visual and anatomical outcomes comparable to aflibercept while enabling extended dosing intervals of up to 12–16 weeks for many patients, substantially reducing treatment burden with a similar safety profile. Approved by the FDA in 2022, faricimab introduces a novel dual-pathway

strategy for DME, with the potential to improve adherence and long-term disease control. Further real-world data and phenotype-specific analyses remain needed.

Corticosteroids

Corticosteroids exert potent anti-inflammatory, anti-permeability, and anti-proliferative effects, making them an important therapeutic option for DME,[58] particularly in cases with suboptimal or transient response to anti-VEGF therapy.[59] Currently available corticosteroids for DME include triamcinolone acetonide (TA), dexamethasone, and fluocinolone acetonide (FA), administered via intravitreal injection or sustained-release implants.

Triamcinolone Acetonide

TA is a potent corticosteroid with strong anti-inflammatory and anti-edematous activity and was one of the earliest intravitreal agents used for DME. DRCR.net Protocol B[60] demonstrated that intravitreal TA provided more rapid visual improvement than focal/grid laser photocoagulation, although with higher rates of cataract formation and intraocular pressure (IOP) elevation. Due to its suspension nature, limited duration, and relatively high complication rate, TA has largely been replaced by anti-VEGF therapy and newer steroid implants. However, TA remains valuable in resource-limited settings or in patients who require rapid reduction of inflammation or cannot afford long-term anti-VEGF therapy.

Dexamethasone Implant

The dexamethasone intravitreal implant (Ozurdex) encloses 0.7 mg of dexamethasone within the NOVADUR biodegradable polymer system, allowing sustained release for up to 6 months and reducing the need for frequent injections. The MEAD trials[61,62] demonstrated significant improvements in retinal thickness and visual acuity. However, adverse events—particularly cataract progression (65% vs 20% in phakic eyes) and IOP elevation (40% vs 10%)—were markedly more common.[63] Given its long-acting profile, Ozurdex is particularly suitable for pseudophakic eyes, vitrectomized eyes, patients intolerant to anti-VEGF therapy, or those unwilling to undergo monthly injections.

Fluocinolone Acetonide Implant

The FA implant (Iluvien) is a non-biodegradable device containing 0.19 mg FA that delivers 0.25 μg/day over 36 months. The FAME and PALADIN trials showed sustained anatomical and visual gains with significant reduction in treatment burden—76% of eyes required no additional therapy during the study.[64,65] However, IOP elevation and cataract formation remain major considerations. The FDA approved FA implants in 2014 for DME patients previously exposed to corticosteroids without significant IOP response.

Limitations of Corticosteroids

The use of corticosteroids in DME requires balancing efficacy and safety. While they offer important benefits for patients with inadequate anti-VEGF response and significantly reduce treatment frequency through sustained-release formulations, their risk of cataract and IOP elevation restricts use mainly to second-line therapy or carefully selected patient populations.

Emerging Therapies for DME

Despite major advances, current DME treatments remain limited by high injection burden, suboptimal response in a substantial proportion of patients, and long-term risks. To address these challenges, multiple new therapeutic strategies are under active investigation (Table 2).

Next-Generation Anti-VEGF Therapies

Ranibizumab Port Delivery System (Susvimo)

Susvimo is a small, refillable intraocular implant comprising a 0.02 mL drug reservoir and a titanium release-control element that regulates passive diffusion of ranibizumab (100 mg/mL) into the vitreous cavity. This system maintains therapeutic drug concentrations while substantially reducing the frequency of conventional intravitreal injections.[66,67] The PAGODA study[68] compared Susvimo refilled every six months with monthly intravitreal ranibizumab injections,

Table 2 Emerging and Investigational Therapies for Diabetic Macular Edema

Category	Agent	Molecular Characteristics & Delivery	Development Stage
Next-generation Anti-VEGF Therapies	Ranibizumab Port Delivery System (Susvimo)	Refillable ocular implant for continuous passive diffusion of ranibizumab	FDA Approved (2025); PAGODA Trial: Non-inferior to monthly injections with refills every 6 months (Q24W)
	KSI-301 (Tarcocimab Tedromer)	Anti-VEGF antibody–biopolymer conjugate (intravitreal)	Phase III (DR, GLOW1) showed a reduced risk of DME
	OPT-302 (Sozinibercept)	Soluble VEGFR-3 Fc fusion inhibiting VEGF-C/D, adjunct to anti-VEGF-A (intravitreal)	Phase II DME study reported positive signals
Multi-Target Biologics	IBI-302 (Efdamrofusp)	Bispecific fusion protein targeting VEGF and C3b/C4b (intravitreal)	Phase II DME program ongoing with 2025–2026 updates
	RC28-E (Tanvudepcimab)	Bispecific fusion protein targeting VEGF and FGF-2 (intravitreal)	Phase III trial versus aflibercept is ongoing
	AG-73305	Bispecific fusion protein blocking VEGF and integrin receptors (intravitreal)	Phase II dose-escalation study in DME (early safety/efficacy signals reported)
	KSI-501 (Tabirafusp Tedromer)	Bispecific antibody–biopolymer conjugate targeting VEGF and IL-6 (intravitreal)	Phase I multiple-ascending-dose study in DME reported
Tyrosine Kinase Inhibitors (TKIs)	GB-102 (Sunitinib Malate)	Intravitreal biodegradable sustained-release sunitinib formulation (pan-VEGFR/PDGFR)	Phase II DME/RVO study terminated
	OTX-TKI (Axpaxli)	Hydrogel implant for sustained release of axitinib (pan-VEGFR/PDGFR)	Phase I (DR, HELIOS) showed reduced DME incidence
	EYP-1901 (Duravyu)	Bioerodible insert for sustained release of vorolanib (pan-VEGFR/PDGFR)	Phase II (VERONA) reported durability signals
	PAN-90806 (PanOptica)	Topical small-molecule eye drops (VEGFR TKI)	Early clinical data in PDR; DME use remains exploratory
	KHK4951 (Tivozanib)	Topical tivozanib eye drops (VEGFR TKI)	Phase II trial in DME is ongoing
	D-4517.2 (Migaldendranib)	Targeted nanomedicine migaldendranib administered subcutaneously (systemic delivery)	Phase II reported a reduced need for rescue anti-VEGF injections in DME
Next-generation Corticosteroids	OXU-001	Suprachoroidal sustained-release dexamethasone microspheres delivered via microcatheter	Phase II (OXEYE) trial compares OXU-001 with Ozurdex aiming to extend durability
	IBE-814 IVT	Fully degradable intravitreal dexamethasone prodrug implant delivering low sustained dose	Phase II dose-ranging study completed
	OCS-01 (Oculis)	Topical high-concentration dexamethasone suspension targeting posterior segment (eye drop)	Phase III (DIAMOND-1/2) trials are ongoing
Gene Therapy	ADVM-022 (Ixo-vec)	AAV2.7m8 vector encoding aflibercept	Terminated in DME (INFINITY) due to dose-limiting toxicity (severe hypotony/inflammation)
	ABBV-RGX-314	AAV8 vector encoding anti-VEGF antibody fragment (suprachoroidal/subretinal delivery)	Phase II (ALTITUDE / ELAAVATE) trials are ongoing
	4D-150	AAV vector (dual transgene) encoding aflibercept and a miRNA targeting VEGF-C	Phase II (SPECTRA) received FDA RMAT designation in 2025; follow-up is ongoing
	FT-003	AAV vector encoding an aflibercept-like protein	Phase II trial was cleared by the FDA in 2024
Other Therapies	Fenofibrate	Oral PPAR-α agonist; systemic lipid/metabolic control	Included in the 2025 ADA Standards of Care to reduce DR progression and DME risk (LENS trial)
	BCX4161 (Avoralstat)	Plasma kallikrein inhibitor delivered suprachoroidally to target VEGF-independent leakage/inflammation	Phase I trial listed, with authorization to proceed in Australia reported
	RZ402	Oral plasma kallikrein inhibitor (systemic)	Phase II proof-of-concept top-line results were reported
	UBX1325 (Foselutoclax)	Senolytic small molecule (BCL-xL inhibitor) given intravitreally	Phase II (BEHOLD / ASPIRE) trials are ongoing

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demonstrating comparable one-year visual gains. While offering durability, the implant requires vigilance for device-related adverse events such as endophthalmitis, which have been observed in the broader PDS program. In 2025, the FDA approved Susvimo for DME patients previously responsive to at least two anti-VEGF treatments, offering an innovative option to reduce treatment burden while maintaining visual benefits.

KSI-301 (Tarcocimab Tedromer)

KSI-301 is a 950 kDa antibody-biopolymer conjugate combining a humanized IgG1 anti-VEGF antibody with a phosphorylcholine polymer. The antibody binds VEGF-A with high affinity, blocking VEGFR-1/2 interactions, while the large hydrophilic polymer prolongs intravitreal half-life, enabling 4–6 month dosing intervals for sustained inhibition.[69] The GLOW1 study[70] demonstrated that KSI-301 significantly slows diabetic retinopathy (DR) progression and reduces the risk of vision-threatening complications, including DME, although its specific efficacy in DME requires further evaluation.

OPT-302 (Sozinibercept)

OPT-302 is a 150 kDa fusion protein composed of human IgG1-Fc and extracellular domains 1–3 of VEGFR-3. It binds VEGF-C/D with high affinity, preventing VEGFR-2/3 activation, and is designed to complement anti-VEGF-A therapy for comprehensive VEGF pathway inhibition.[71] Phase II trials in DME patients showed that OPT-302 combined with aflibercept provided significant improvements in BCVA and retinal thickness compared with aflibercept monotherapy, suggesting that VEGF-C/D blockade may confer additional anatomical and functional benefits.[72]

Multi-Target Biologics Combined with Anti-VEGF Activity

IBI-302 (Efdamrofusp Alfa)

IBI-302 is a dual-specific fusion protein targeting VEGF and complement components C3b/C4b. Its N-terminal includes VEGFR-1/2 extracellular domains, and its C-terminal comprises human complement receptor-1 (CR1) fused to an IgG1-Fc. CR1 selectively binds C3b/C4b, inhibiting both classical and alternative complement pathways, reducing complement-mediated inflammation, while neutralizing all VEGF isoforms to decrease vascular permeability and neurovascular damage.[73] Phase I studies demonstrated favorable safety, significant improvement in visual acuity and macular edema, and the potential to extend dosing intervals to 12–16 weeks. A Phase II trial is ongoing to directly compare IBI-302 (4 mg and 8 mg) with faricimab (6 mg) in DME treatment.[74]

RC28-E (Tanvudepcimab)

RC28-E is a fusion protein targeting VEGF and fibroblast growth factor (FGF), comprising VEGFR-1 domain 2, VEGFR-2 domain 3, FGFR1 domain 3, and IgG1-Fc.[75] FGF2 binding to FGFR extracellular domains promotes angiogenesis and alters vascular permeability.[76] Phase II trials indicated that RC28-E provides superior outcomes in DME patients, particularly those with suboptimal glycemic control, with fewer injections during maintenance and comparable safety to conbercept.[77] A Phase III trial comparing RC28-E (2 mg) with aflibercept (2 mg) is underway.

AG-73305

AG-73305 is a fusion protein targeting VEGF and integrins.[78] Integrins are transmembrane receptors mediating cell-cell and cell-matrix adhesion, influencing vascular leakage, inflammation, neovascularization, and fibrosis.[79] Phase II intravitreal studies (0.5–4 mg) demonstrated good safety and tolerability, with over 50% of DME patients showing significant BCVA and CST improvements after a single injection, maintained for 12–24 weeks.[80]

KSI-501 (Tabirafusp Tedromer)

KSI-501 targets VEGF and IL-6, conjugated to a phosphorylcholine polymer, binding one VEGF and two IL-6 molecules simultaneously.[81] IL-6, produced by monocytes, macrophages, and microglia, disrupts the BRB, induces VEGF, and increases vascular permeability, contributing to macular edema.[29] Phase I studies indicated potential for visual and structural improvement with sustained effect.[82]

Tyrosine Kinase Inhibitors (TKIs)

GB-102 (Sustained-Release Sunitinib Malate)

GB-102 is a biodegradable intravitreal sustained-release formulation of sunitinib. By inhibiting multiple receptor tyrosine kinases (RTKs), including VEGFR and platelet-derived growth factor receptor (PDGFR), it suppresses both angiogenesis and inflammatory responses. This multi-targeted mechanism positions GB-102 as a potential therapy for ocular neovascular diseases such as DME.[83] The sustained-release design aims to extend injection intervals up to six months. However, clinical trials in AMD patients showed inferior visual outcomes compared with aflibercept, and subsequent studies in DME have been discontinued.

OTX-TKI (Axpaxli)

OTX-TKI is an intravitreal implant of axitinib developed using the biodegradable Elutyx hydrogel platform.[84] Axitinib inhibits VEGFR-1/2/3 and PDGFR, among other RTKs, and the hydrogel enables stable intraocular release for 6–12 months, markedly reducing injection frequency.[85] The HELIOS study in DR patients demonstrated that OTX-TKI delays DR progression and lowers DME incidence, though dedicated trials targeting DME are yet to be conducted.

EYP-1901 (Duravyu)

EYP-1901 is a sustained-release TKI implant based on the Durasert E biodegradable platform, with vorolanib as the active ingredient. Vorolanib simultaneously inhibits VEGFR-1/2/3 and PDGFR-β, providing broad-spectrum anti-VEGF /PDGF effects for 6–9 months following a single injection.[86] The mid-term report of the VERONA study indicated that a higher proportion of EYP-1901-treated eyes did not require supplemental injections at 16 weeks compared with aflibercept (82% vs 50%), with stable BCVA and CST improvements. These results support progression to Phase III trials to further evaluate the feasibility of a "half-yearly" dosing regimen in terms of efficacy and safety.

PAN-90806 (PanOptica)

PAN-90806 is a small-molecule TKI eye drop administered once daily. It diffuses through the sclera and choroid to reach the retina and inhibit RTKs.[87] Phase I/II studies in AMD and proliferative DR patients demonstrated biological activity, and reversible punctate keratopathy reported as an adverse event has been mitigated by reformulation as a particulate suspension. Whether PAN-90806 can ultimately provide an injection-free option for DME patients awaits results from ongoing Phase II/III trials.

KHK4951 (Tivozanib)

KHK4951 is a nanocrystalline TKI eye drop containing tivozanib, which inhibits VEGFR-1/2/3 and PDGFR. Tivozanib is a clinically approved, safe agent, with an oral formulation already FDA-approved for renal cell carcinoma.[88] Phase I studies have demonstrated its efficacy and favorable safety profile in AMD patients.[89] Phase II trials in DME are currently ongoing, with outcomes yet to be reported.

D-4517.2 (Migaldendranib)

D-4517.2 is a hydroxyl dendrimer therapeutic formulation delivering the small-molecule TKI migaldendranib. It can cross the blood-retinal barrier via subcutaneous or oral administration and is selectively taken up by macrophages, microglia, and hypertrophic RPE cells, maintaining therapeutic levels in target tissues for at least one month after a single dose.[90] Interim Phase II data indicate significant improvements in visual acuity and retinal edema in DME patients, with overall good safety and tolerability.

Next-Generation Corticosteroids

OXU-001

OXU-001 is a long-acting dexamethasone microsphere (Dexaspheres) formulation delivered via the Oxulumis luminescent microcatheter into the suprachoroidal space (SCS). This approach maintains sustained drug concentrations in the retina/choroid while markedly minimizing exposure to anterior segment structures such as the lens and trabecular meshwork. The OXEYE study is comparing the safety, tolerability, efficacy, and durability of OXU-001 with intravitreal dexamethasone implants (Ozurdex). Designed as a "once-yearly" therapy, it aims to reduce frequent intravitreal injections and short-acting steroid implant limitations, offering a next-generation long-acting corticosteroid strategy for DME.

IBE-814 IVT

IBE-814 IVT is a long-acting dexamethasone prodrug implant based on the Epidel platform, composed entirely of dexamethasone dimer prodrug. Following a single intravitreal injection, it undergoes surface erosion at a zero-order rate, releasing active dexamethasone continuously for 6–9 months. The RIPPLE-1 study demonstrated significant BCVA and CST improvements at 6 and 9 months, with an 82% reduction in treatment burden, and a safety profile comparable to other corticosteroids.[91,92] Phase III trials are ongoing to further establish its clinical potential in DME.

OCS-01 (Oculis)

OCS-01 is a high-concentration dexamethasone ocular suspension formulated via the OPTIREACH nanonization technology, using cyclodextrins as solubilizing excipients. Administered topically to the conjunctival sac, it penetrates the blood-retinal barrier to reach the posterior retina.[93] Preliminary Phase I results from the DIAMOND-1 trial demonstrated statistically significant BCVA and CST improvements. Phase III DIAMOND-1/2 trials are ongoing, with topline data expected in 2026.

Gene Therapy

ADVM-022 (Ixo-Vec)

ADVM-022 uses an intravitreal AAV2.7m8 vector encoding aflibercept under proprietary promoter/enhancer elements, enabling long-term retinal ganglion and RPE cell secretion of aflibercept. This continuous VEGF and PLGF blockade reduces capillary permeability and macular edema.[94] The INFINITY trial evaluated its efficacy in newly diagnosed DME patients.[95] Early data suggested reduced treatment frequency; however, dose-limiting toxicities, including severe intraocular inflammation and hypotony at higher doses, led to discontinuation of further DME development. ADVM-022 illustrates a "single injection, long-acting aflibercept" paradigm, but the INFINITY findings highlight the critical importance of safety in high-inflammation-prone populations. Research has pivoted to low-dose AMD strategies, which, if successful, may reopen the potential for DME applications.

ABBV-RGX-314

ABBV-RGX-314 employs a NAV-AAV8 vector carrying a gene encoding a ranibizumab-like anti-VEGF Fab fragment under a retina-specific promoter. Following subretinal or SCS injection, transduced retinal cells continuously secrete the antibody, providing durable VEGF neutralization and BRB stabilization.[96] The ALTITUDE trial in DR patients demonstrated significant slowing of disease progression and reduced vision-threatening events with good tolerability.[97] Based on these findings, the ELAAVATE study in DME patients began enrollment in 2025, aiming to deliver up to one year of therapeutic effect from a single administration.

4D-150

4D-150 utilizes an engineered AAV R100 vector carrying two gene sequences: aflibercept and a miRNA targeting VEGF-C, aiming to inhibit VEGF-A/B/C and PLGF simultaneously with a single intravitreal injection, reducing injection burden while preserving vision.[98] Interim results from the SPECTRA study demonstrated favorable visual, anatomical, and safety outcomes, with an 86% reduction in injection frequency compared to aflibercept. Consequently, 4D-150 received FDA Regenerative Medicine Advanced Therapy designation, accelerating further clinical development.

FT-003

FT-003, developed by a Chinese research team, employs a modified AAV vector encoding an aflibercept-like protein. After intravitreal administration, transduced retinal cells stably express the anti-VEGF protein.[99] Phase I data in China indicated good safety and preliminary efficacy in DME patients, with more than 80% reduction in supplemental anti-VEGF injection frequency.[100] Building on these results, the FDA has approved Phase II trials in AMD and DME, to be conducted in both China and the US.

Other Therapies

Fenofibrate

Fenofibrate, a widely used oral fibrate, improves triglyceride and high density lipid-cholesterol levels more effectively than statins.[101] It activates PPAR-α, suppressing pro-inflammatory cytokines (IL-1β, TNF-α), downregulating VEGF, and inhibiting retinal neuronal apoptosis.[102] Large trials (FIELD, ACCORD-Eye, LENS) demonstrated its protective effect in diabetic eyes, reducing DR progression, need for laser therapy, and DME risk.[102–105] Accordingly, the 2025 ADA Standards of Care recommend fenofibrate as a therapeutic option for type 2 diabetic patients with DR to mitigate disease progression.[106]

BCX4161 (Avoralstat)

BCX4161 is a plasma kallikrein inhibitor (PKI) initially developed for hereditary angioedema.[107] The plasma kallikrein-kinin system promotes retinal vascular leakage and inflammation independently of VEGF. BCX4161 inhibits plasma kallikrein activity, reducing bradykinin production and downstream inflammation.[108] Preclinical studies show that SCS administration achieves sustained high tissue concentrations with minimal systemic exposure.[109] In 2025, an I/IIa clinical trial commenced in Australia to evaluate efficacy and tolerability in DME patients.

RZ402

RZ402, another PKI, demonstrated in animal studies that oral administration suppresses retinal vascular leakage and leukostasis without exposure-related adverse effects.[110,111] Phase II topline data indicate that daily oral RZ402 significantly improves CST with good tolerability.[112] Larger studies are needed to optimize dosing and confirm efficacy, potentially offering a non-invasive, bilateral therapy for patients with suboptimal anti-VEGF response.

UBX1325 (Foselutoclax)

UBX1325 is a BCL-xL small-molecule inhibitor, administered intravitreally, which selectively eliminates senescent cells in retinal microvasculature via a senolytic mechanism, thereby reducing inflammation and vascular leakage.[113] Single injections showed durable 48-week visual benefits in the BEHOLD study.[114] In the ASPIRE trial for refractory DME, UBX1325 provided visual gains comparable to aflibercept with favorable safety and tolerability.[115]

Discussion

Pharmacological management of DME is shifting from frequent, burden-intensive anti-VEGF monotherapy toward strategies that prioritize durability and multi-pathway inhibition. The therapies reviewed here are not simply incremental additions; collectively, they point to a restructuring of care delivery centered on sustained disease control with fewer interventions.

Quantifying the Shift in Durability

The most immediate impact of emerging therapies is the extension of treatment intervals. Clinical practice is transitioning from a standard of 8–12 injections in the first year (typical of ranibizumab or aflibercept 2 mg monotherapy)[116] toward a realistic expectation of approximately 3–4 treatments per year with high-dose aflibercept 8 mg[41] and faricimab[56] during maintenance phases. Delivery innovations, including the ranibizumab port delivery system (Susvimo)[68] and potentially one-time gene therapies (eg, ABBV-RGX-314),[96,97] further advance this trajectory, offering the goal of reducing treatment to 1–2 interventions annually or even zero maintenance injections in selected responders. By alleviating injection fatigue, this durability paradigm may finally narrow the well-documented gap between clinical trial efficacy and real-world visual outcomes.[117]

Systemic and Non-Pharmacological Factors

The pursuit of potent intraocular therapy should not obscure systemic drivers of disease. Apparent pseudoresistance to anti-VEGF therapy is frequently observed in patients with uncontrolled systemic risk factors, and durable control is unlikely when poor glycemic control, hypertension, and dyslipidemia continue to compromise the blood–retinal barrier.[118,119] Higher HbA1c and poorer renal function have also been associated with less favorable anti-VEGF responses, reinforcing the need for systemic optimization as part of routine DME care.[120,121]

In parallel, pharmacotherapy is not sufficient for all DME phenotypes. Vitreoretinal interface abnormalities can limit the efficacy of pharmacologic inhibition; in eyes with vitreomacular traction or epiretinal membrane, pars plana vitrectomy remains the definitive option, particularly when injections or laser are inadequate.[122] Although laser photocoagulation is no longer first-line for most cases, subthreshold micropulse laser retains an adjunctive role in extrafoveal edema and non–center-involving DME, with potential to reduce injection burden without permanent retinal injury.[123,124] Future management will likely follow a hybrid model integrating systemic control, targeted pharmacotherapy, and phenotype-specific mechanical or laser interventions.

Critical Appraisal of Safety

Innovation must be matched by rigorous safety appraisal. High-dose or molecularly engineered anti-VEGF agents have introduced rare but serious adverse events, including retinal vasculitis and occlusive inflammation.[125] Similarly, implant-based durability may be offset by device-related complications such as implant-associated endophthalmitis.[126] Clinicians must weigh low-frequency, high-severity risks against the clinical value of reduced injection burden, particularly in monocular patients or in settings with limited access to urgent ophthalmic care. As efficacy gains converge across therapies, safety, tolerability, and delivery reliability are likely to become the principal determinants of adoption.

Towards Precision Medicine

The one-drug-fits-all approach to DME is increasingly untenable. Growing evidence supports phenotype-guided therapy, with treatment selection informed by biomarkers and disease characteristics. A central priority is to define clinically meaningful DME endotypes and to identify imaging or molecular biomarkers that indicate which pathways are dominant in an individual patient, thereby guiding selection of pathway-targeted therapies.[127,128] Such an approach can maximize efficacy, reduce avoidable risk, and lower costs by minimizing trial-and-error treatment.

Conclusion

The therapeutic landscape for DME has evolved from simple VEGF blockade into a complex system of durability and precision. This review leads to three critical conclusions:

- Durability is the New Benchmark: The primary clinical goal has shifted from maximizing visual gains to maintaining those gains with a sustainable frequency (moving from monthly to quarterly or bi-annual dosing).
- Safety Dictates Adoption: As efficacy plateaus across agents, the distinct safety profiles of novel drugs and delivery systems will drive therapeutic selection.
- Holistic Integration is Essential: Pharmacotherapy cannot succeed in isolation. Optimal visual preservation requires integrating advanced therapeutics with strict systemic metabolic control and timely surgical intervention for mechanical pathology.

By embracing these principles, clinicians can navigate the expanding array of DME treatment options and deliver care that is not only cutting-edge but also patient-centered and sustainable for the long term.

Abbreviations

AGEs, advanced glycation end products; AMD, age-related macular degeneration; Ang-2, angiopoietin-2; AQPs, aquaporins; BRB, blood – retinal barrier; CR1, complement receptor-1; DM, diabetes mellitus; DME, diabetic macular edema; DR, diabetic retinopathy; FA, fluocinolone acetonide; FGF, fibroblast growth factor; HIF-1, hypoxia-inducible factor-1; IOP, intraocular pressure; KKS, kallikrein–kinin system; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; PKI, plasma kallikrein inhibitor; PLGF, placental growth factor; RAAS, renin–angiotensin–aldosterone system; RTKs, receptor tyrosine kinases; scFv, single-chain variable fragment; SCS, suprachoroidal space; TA, triamcinolone acetonide; TKIs, Tyrosine Kinase Inhibitors; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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