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Evolving Anti-VEGF Therapy For Diabetic Retinopathy: Current Evidence, Durability Strategies, And Future Directions

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Abstract

Diabetic retinopathy (DR) remains one of the leading causes of vision impairment and blindness among working-age adults worldwide. The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has significantly transformed the management of DR by effectively reducing retinal vascular permeability, inhibiting neovascularization, and improving visual outcomes. This article reviews the evolving role of anti-VEGF agents in the treatment of diabetic retinopathy, highlighting current clinical evidence regarding their efficacy, safety, and comparative performance. Particular attention is given to durability strategies designed to reduce treatment burden, including treat-and-extend regimens, high-dose formulations, sustained-release delivery systems, and emerging long-acting therapeutic approaches. The review also discusses the limitations of existing therapies, such as the need for frequent intravitreal injections, patient adherence challenges, and variability in treatment response. Furthermore, future directions are explored, including novel molecular targets, gene-based therapies, combination treatments, and advancements in personalized medicine supported by artificial intelligence and predictive biomarkers. The findings indicate that while anti-VEGF therapy remains the cornerstone of contemporary diabetic retinopathy management, ongoing innovations aimed at enhancing treatment durability and individualized care have the potential to improve long-term outcomes and reduce the global burden of diabetic eye disease.

Keywords: Diabetic Retinopathy; Diabetic Macular Edema; Anti-Vegf; Ranibizumab; Bevacizumab; Aflibercept; Brolucizumab; Faricimab; Aflibercept 8 Mg; Port Delivery System; Sustained Drug Delivery.

INTRODUCTION

Diabetic retinopathy (DR) remains a major microvascular complication of diabetes mellitus and a leading cause of preventable visual impairment in working-age adults. The global diabetes epidemic is expanding rapidly. The International Diabetes Federation estimates 589 million adults aged 20-79 years live with diabetes in 2024, a number projected to reach 853 million by 2050. Within this population, estimates suggest that approximately one in five adults with diabetes has DR; consequently, vision-threatening diabetic retinopathy will likely remain a substantial public health challenge through 2045. The implications of these trends are particularly significant in low- and middle-income countries, wherein the provision of comprehensive screening, continuous care, and economically accessible repeated intravitreal injections may be constrained.

The historical progression of DR treatment may be delineated into several distinct phases. Initial investigations, notably the Early Treatment Diabetic Retinopathy Study and the Diabetic Retinopathy Study, elucidated the efficacy of laser photocoagulation for the management of diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). However, laser therapy does not directly address the underlying biological mechanisms contributing to vascular leakage and neovascularization. Subsequently, the advent of the modern therapeutic era introduced intravitreal injections designed to inhibit vascular endothelial growth factor (VEGF), a pivotal protein. This intervention mitigates vascular leakage, enhances macular architectural integrity, induces regression of aberrant neovascularization, and diminishes the overall severity of DR. Currently, optical coherence tomography (OCT) serves as a critical diagnostic modality for the monitoring of DME and the evaluation of treatment efficacy. Currently, anti-VEGF therapy is considered the primary therapeutic option for the majority of individuals presenting with DME that compromises central vision and induces visual acuity deficits.

Despite its transformative impact, conventional anti-VEGF therapy encounters practical limitations. The necessity of monthly or near-monthly visits presents challenges for sustained long-term adherence. patients with diabetes frequently present with systemic comorbidities, including renal disease, cardiovascular risk factors, mobility impediments, and concurrent medical appointments. Consequently, clinical trial outcomes often appear more favorable than those observed in routine clinical practice. Undertreatment, delayed retreatment, and loss to follow-up may predispose to complications such as edema, persistent neovascularization, vitreous hemorrhage, tractional complications, and ultimately, irreversible visual loss. These limitations suggest the necessity for novel therapeutic strategies that offer extended duration of action, enhanced intraocular efficacy, or broader pathway targeting.

This narrative review examines the evolution of anti-VEGF (vascular endothelial growth factor) therapy for DR and DME. This review will highlight drug-specific trial data, their safety profiles, durations of efficacy, and integration within contemporary clinical practice. The focus encompasses established agents: ranibizumab, bevacizumab, and aflibercept. Additionally, a detailed exposition of newer agents developed for extended duration of action is provided: brolucizumab, faricimab, and aflibercept 8 mg. Sustained delivery using the port delivery system with ranibizumab is also discussed.

Evidence identification and scope of review

This article offers a narrative, current review; it does not constitute a formal systematic review. The methodology primarily focused upon evidence derived from pivotal phase 2 and phase 3 randomized clinical trials, long-term extension analyses, major comparative effectiveness studies, recent device trials, clinical guideline documents, and high-quality reviews relevant to anti-VEGF therapy in DR and DME. Emphasis was placed on landmark studies that have demonstrably altered therapeutic paradigms, elucidated comparative treatment effectiveness, established durability, or underscored critical safety considerations.

This review focuses on intravitreal pharmacologic therapy for DME, nonproliferative DR (NPDR), and PDR. We discuss corticosteroid implants, laser photocoagulation, vitrectomy, and systemic diabetes management only when they directly influence anti-VEGF decision-making. This review aims to provide a clinically useful, journal-ready synthesis for retina specialists and ophthalmologists, whether they are in high-resource or resource-variable environments.

Pathobiological rationale for anti-VEGF and beyond-VEGF therapy

The pathogenesis of Diabetic Retinopathy (DR) may involve the synergistic interplay of multiple factors: high blood sugar, cell damage, harmful protein buildup, inflammation, loss of key support cells, thickened blood vessel walls, poor blood vessel function, occlusion of microvasculature, and a compromised blood-retinal barrier. Collectively, these alterations may induce retinal hypoxia, extravasation of fluid, and a gradual decrement in perfusion (progressive ischemia). Hypoxia, in turn, may result in the upregulation of Vascular Endothelial Growth Factor A (VEGF-A), which subsequently induces vascular permeability and aberrant neovascularization. This cascade may culminate in significant pathological sequelae, including intraretinal fluid accumulation, macular edema, hard exudates, retinal neovascularization, vitreous hemorrhage, fibrovascular proliferation, and tractional retinal detachment.

Given the pivotal role of VEGF, the efficacy of anti-VEGF agents administered intravitreally for Diabetic Macular Edema (DME) and Proliferative Diabetic Retinopathy (PDR) is comprehensible; however, VEGF alone may not represent the singular pathway implicated. Angiopoietin-2 (Ang-2), operating in conjunction with the angiopoietin-Tie pathway, appears to induce vascular destabilization, promote pericyte loss, incite inflammatory responses, and facilitate vascular leakage. The demonstrated significance of this pathway, therefore, provides a mechanistic rationale for faricimab, a bispecific antibody engineered to inhibit both VEGF-A and Ang-2. This paradigm shift from a sole focus on VEGF blockade toward comprehensive vascular stabilization via dual pathway inhibition may represent a significant advancement in the contemporary management of retinal pathologies.

Persistent Diabetic Macular Edema (DME), despite extensive anti-VEGF interventions, may indicate chronic pathology, characterized by diminished perfusion, inflammatory processes, Müller cell dysfunction, VEGF-independent vascular leakage, or retinal neurodegeneration. Similarly, while regression of Proliferative Diabetic Retinopathy (PDR) following anti-VEGF therapy may be expeditious, recurrence is possible upon treatment discontinuation. Consequently, current therapeutic strategies necessitate considerations beyond mere anti-VEGF agent selection; a judicious alignment of drug durability, mechanism of action, and individualized monitoring protocols with each patient's unique characteristics and risk profile is warranted.

Established anti-VEGF agents

Ranibizumab

Ranibizumab constitutes a specialized antibody fragment exhibiting high affinity for Vascular Endothelial Growth Factor A (VEGF-A). It may be conceptualized as a truncated antibody, devoid of its Fc region, specifically engineered for intravitreal administration. Early clinical investigations involving ranibizumab demonstrated that VEGF blockade could effectuate visual acuity improvements in Diabetic Macular Edema (DME), rather than merely arresting disease progression. This observation represented a pivotal advancement.

The RISE and RIDE phase 3 trials investigated the efficacy of interventions for diabetic macular edema (DME). Participants received either monthly sham injections or monthly ranibizumab (0.3 mg or 0.5 mg). In RISE, 44.8% of patients receiving ranibizumab 0.3 mg and 39.2% receiving ranibizumab 0.5 mg gained at least 15 ETDRS letters at 24 months, compared with 18.1% in the sham group[8]. In RIDE, the corresponding proportions were 33.6% and 45.7% for ranibizumab 0.3 mg and 0.5 mg, respectively, compared with 12.3% in the sham group[8]. Ranibizumab also effected a reduction in the necessity for macular laser and an enhancement of ocular structural integrity. After 36 months, the persistence of early ranibizumab benefits was observed. However, the deferral of treatment initiation, even with subsequent ranibizumab administration, did not fully restore the visual acuity gains associated with earlier intervention. This observation underscores a critical implication: delayed initiation of DME treatment may culminate in irreversible retinal damage, notwithstanding subsequent management of edema.

DRCR Retina Network Protocol I facilitated a comprehensive understanding of the optimal integration of ranibizumab with laser photocoagulation. Ranibizumab with prompt or deferred laser produced better visual outcomes than laser alone in center-involved DME. Even following a five-year observation period, the combination of ranibizumab with deferred laser treatment demonstrated considerable efficacy. Consequently, it was ascertained that anti-VEGF treatment should assume a central role, and that immediate macular laser application was not consistently requisite for center-involved DME.

In PDR, DRCR Protocol S compared ranibizumab with panretinal photocoagulation (PRP). Thus, ranibizumab appears most efficacious for individuals capable of consistent attendance, concurrently experiencing DME, necessitating rapid regression of neovascularization, or seeking to avert the visual field constriction associated with PRP. Nevertheless, PRP retains its critical importance when patient adherence to follow-up regimens is uncertain.

Bevacizumab

Bevacizumab is a full-length monoclonal antibody against VEGF-A. Its off-label utilization for DME and PDR is widespread, attributable to its economical cost and extensive accessibility. Although not initially sanctioned for intraocular administration, bevacizumab maintains a crucial role within numerous healthcare systems, particularly in contexts where the affordability or accessibility of branded anti-VEGF therapeutics presents significant challenges.

The BOLT study randomly compared bevacizumab to macular laser for persistent, clinically significant DME. At 24 months, the bevacizumab group gained a median of nine ETDRS letters, compared with 2.5 letters in the laser group. Furthermore, 49% of bevacizumab-treated eyes gained at least ten letters, while only seven percent in the laser group. These results suggested the notable

efficacy of bevacizumab for DME, indicating that VEGF suppression may be superior to laser monotherapy for a substantial proportion of patients with center-involved disease.

To understand how bevacizumab compared to other treatments, Protocol T assigned eyes with center-involved DME and visual impairment at random to aflibercept, bevacizumab, or ranibizumab. After one year, all three pharmacotherapies demonstrated an improvement in visual acuity. Crucially, the efficacy of each treatment appeared contingent upon the patient's baseline visual acuity. In eyes with baseline visual acuity of approximately 20/50 or worse, aflibercept evinced a superior visual outcome compared to both bevacizumab and ranibizumab. Conversely, for eyes exhibiting superior baseline visual acuity, the outcomes appeared largely commensurate among all three agents. At two years, all groups maintained visual improvement, with aflibercept remaining superior to bevacizumab in the worse-vision subgroup, though it wasn't statistically better than ranibizumab anymore. The five-year follow-up data indicated the maintenance of improved visual acuity in a substantial proportion of eyes; however, this sustained benefit typically necessitated continued therapeutic intervention and ophthalmic surveillance subsequent to the trial's conclusion.

Consequently, in clinical practice, bevacizumab may represent a judicious initial therapeutic consideration, particularly when budgetary constraints are paramount. This pragmatic approach appears especially pertinent for eyes presenting with mild to moderate visual impairment and where expedited treatment initiation is feasible. However, in instances where an eye manifests inferior baseline visual acuity, substantial macular edema, a high treatment burden, or an suboptimal early response, a transition to aflibercept, ranibizumab, faricimab, or aflibercept 8 mg may be warranted. A DRCR study examined a smart, cost-effective strategy: starting with aflibercept, versus starting with bevacizumab and then switching if needed. This phased therapeutic strategy appears capable of yielding comparable visual improvements for numerous patients, whilst concomitantly reducing the utilization of more costly pharmacological agents. This type of evidence is particularly relevant for Indonesia and other resource-variable settings.

Aflibercept 2 mg

Aflibercept is a recombinant VEGF-trap fusion protein that binds VEGF-A, VEGF-B, and placental growth factor (PlGF). Its broader ligand-binding profile and high affinity suggest its potential as a pivotal agent in DME treatment. The VIVID and VISTA trials compared intravitreal aflibercept with laser photocoagulation in DME. At week 52, aflibercept led to significantly superior visual acuity than laser, with VISTA reporting mean gains of 12.5 letters with every-4-week dosing and 10.7 letters with every-8-week dosing after loading, compared with 0.2 letters for laser. In VIVID, visual gains were similarly favorable for aflibercept compared with laser [20]. Patients maintained these visual improvements and demonstrated beneficial effects on the severity of DR through 100 and 148 weeks.

Protocol T placed aflibercept in direct comparison with bevacizumab and ranibizumab. Its advantage was most evident in eyes with poorer baseline vision, while eyes with relatively good baseline vision showed similar outcomes across agents. The clinical implications of these findings suggest a preference for aflibercept 2 mg when baseline visual acuity is substantially reduced, macular edema is prominent, or a rapid anatomical response is deemed critical. However, its designation as a universal first-line therapy for all cases of DME may warrant further consideration.

Aflibercept also has evidence in NPDR without DME. PANORAMA enrolled eyes with moderately severe to severe NPDR and found that aflibercept elicited a significant amelioration in DRSS levels, thereby mitigating the incidence of vision-threatening complications and center-involved DME over a 100-week period. DRCR Protocol W similarly observed that prophylactic administration of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up; however, subsequent longer-term follow-up did not demonstrate a superior visual acuity outcome when eyes underwent close observation and prompt intervention upon disease progression. These results might suggest a degree of clinical sobriety. Anti-VEGF can improve DR anatomy and reduce progression risk. Nonetheless, the prophylactic treatment of NPDR without DME necessitates careful

consideration, weighing the associated treatment burden and cost against the practicality of close observation with rescue treatment.

Table 1. Landmark evidence for established anti-VEGF agents in diabetic retinopathy and diabetic macular edema.

Agent / study	Population and regimen	Key trial data	Clinical interpretation
Ranibizumab: RISE/RIDE	DME; monthly sham vs ranibizumab 0.3 mg or 0.5 mg.	At 24 months, ≥15-letter gain in RISE: 44.8% with 0.3 mg and 39.2% with 0.5 mg vs 18.1% sham; in RIDE: 33.6% and 45.7% vs 12.3% sham	These trials indicated that ranibizumab may ameliorate visual acuity in patients with DME. It was observed that delayed initiation of therapy did not fully restore visual function, even at 36 months.
Ranibizumab: Protocol I	Center-involved DME; ranibizumab with prompt or deferred laser.	Five-year data supported ranibizumab with deferred laser; fewer eyes needed macular laser treatment	Findings suggested that anti-VEGF treatment for DME may obviate the immediate requirement for macular laser photocoagulation.
Ranibizumab: Protocol S	PDR; ranibizumab vs PRP.	Five-year visual acuity was similar between ranibizumab and PRP	Ranibizumab appears efficacious for PDR, contingent upon consistent patient adherence to follow-up protocols. However, Panretinal Photocoagulation (PRP) retains its significance in instances where adherence may be a clinical concern.
Bevacizumab: BOLT	Persistent clinically significant DME; bevacizumab vs macular laser.	At 24 months, median gain was 9 ETDRS letters with bevacizumab vs 2.5 letters with macular laser; a mean gain of 8.6 letters for bevacizumab versus a mean loss of 0.5 letters for macular laser	Bevacizumab appears to be an effective therapeutic option for DME, particularly in resource-constrained environments, largely due to its enhanced accessibility and reduced cost relative to other anti-VEGF agents.
Protocol T	Center-involved DME; aflibercept vs bevacizumab vs ranibizumab.	All agents improved vision; aflibercept showed greatest advantage over ranibizumab in eyes with baseline VA 20/50 or worse, especially at year 1.	Baseline visual acuity may inform the selection of the optimal pharmacotherapeutic agent, rather than presuming a singular, universally applicable first-line intervention.
Aflibercept: VIVID/VISTA	DME; aflibercept vs laser.	At week 52, VISTA showed +12.5 and +10.7 letters with aflibercept regimens vs +0.2 letters with laser; benefits persisted through long-term follow-up.	These findings suggest aflibercept constitutes a viable therapeutic modality for DME.

Aflibercept: PANORAMA / Protocol W	Moderately severe to severe NPDR without center-involved DME.	Aflibercept improved DRSS and reduced progression risk, but Protocol W did not demonstrate superior visual acuity with prophylaxis when immediate rescue treatment was available.	The prevention of anatomic changes does not necessarily imply the routine administration of prophylactic injections for all patients with Non-Proliferative Diabetic Retinopathy (NPDR).

Limitations of conventional anti-VEGF therapy

While anti-VEGF treatments are effective, a primary impediment pertains to patient adherence to therapeutic regimens over time. In randomized trials, strict visit schedules, retreatment following strict rules, and close monitoring yield optimal outcomes. In routine practice, many patients receive fewer injections than trial participants. This undertreatment may then lead to poorer clinical outcomes, including diminishing functional gains, compared to trial results.

These frequent injections are also pose considerable burdens for patients, creating mental, practical, and financial challenges. Many patients with diabetes need care from several specialists. Some also deal with chronic kidney disease, heart problems, nerve damage, mobility impairments, or work limitations. For patients traveling long distances, a monthly retina visit may be unrealistic. These barriers are especially important in places like island nations or regions with large tertiary care centers, where patients often have to travel between cities for scans, laser treatment, or injections.

Another limitation is incomplete response. Some eyes show persistent intraretinal fluid or disorganization of retinal inner layers despite repeated injections. Others dry anatomically but fail to gain vision because of chronic edema, ischemic maculopathy, photoreceptor disruption, or neurodegeneration. Development of longer-acting agents and dual-pathway strategies improves real-world disease control under imperfect adherence.

Durability-oriented and newer pharmacologic strategies

Brolucizumab

Brolucizumab is a single-chain antibody fragment that blocks VEGF-A. Its diminutive size permits the incorporation of a substantial quantity of therapeutic agent into a standard injection. This characteristic is posited to facilitate enhanced binding affinity to VEGF and greater tissue penetration. In the KESTREL and KITE phase 3 trials for DME, brolucizumab 6 mg showed visual outcomes equivalent to aflibercept 2 mg, alongside concomitant robust anatomical ameliorations. One hundred-week results showed sustained visual and anatomical outcomes. In KESTREL, patients demonstrated an increase of 8.8 letters with brolucizumab 6 mg and 10.6 letters with aflibercept by week 100. In KITE, the respective increases measured 10.9 and 8.4 letters. A subset of patients receiving brolucizumab demonstrated an extended duration between therapeutic administrations, thereby indicating a prolonged therapeutic effect in specific individuals.

However, it is incumbent upon researchers to modulate the enthusiasm surrounding brolucizumab with an acknowledgment of safety considerations. In the 100-week KESTREL/KITE analysis, intraocular inflammation occurred with greater frequency in the brolucizumab cohort compared to aflibercept in KESTREL. Although incidence rates were comparable in KITE, this phenomenon nevertheless constituted a notable concern. Retinal vasculitis and retinal vascular occlusion were rare, but still serious events[10]. Post-marketing experience in neovascular age-related macular degeneration illuminated the specific safety concerns pertaining to intraocular inflammation, retinal vasculitis, and occlusive vasculitis associated with this therapeutic agent. Consequently, the consideration of brolucizumab may be warranted for select patients requiring potent desiccation or extended duration of action. Nevertheless, its routine substitution for more established and ostensibly safer therapeutic options is not advised without due diligence. Careful ascertainment of any prior

inflammatory history, procurement of informed consent, and prompt evaluation of post-injection symptomatology are imperative requisites.

Faricimab

Faricimab is a bispecific antibody that blocks both Ang-2 and VEGF-A. This bispecificity confers a dual mechanism of action: the attenuation of vascular permeability via VEGF-A blockade and the restoration of vascular stability through Ang-2 inhibition. The phase 2 BOULEVARD trial indicated the therapeutic efficacy of this approach for DME. In that study, treatment-naive patients who received faricimab 6 mg demonstrated superior average vision gains at week 24 compared to those administered ranibizumab 0.3 mg. Furthermore, anatomical improvement, DRSS improvement, and an extended interval to re-treatment were observed, with all outcomes exhibiting dose-dependency.

The pivotal YOSEMITE and RHINE trials compared faricimab with aflibercept in DME using fixed every-8-week and personalized treat-and-extend dosing up to every 16 weeks. At one year, faricimab achieved vision improvements similar to aflibercept while allowing extended dosing intervals in many patients. Two-year results demonstrated the potential for extended duration of effect: a reduction in median injection frequency was observed within the faricimab treat-and-extend arms than in fixed faricimab every-8-week or aflibercept every-8-week arms, and more than 60% of patients in faricimab treat-and-extend arms achieved every-16-week dosing at week 96, with approximately 80% at every-12-week or longer intervals.

Faricimab also appears to facilitate effective retinal fluid resolution. A systematic literature review and network meta-analysis suggested that faricimab treat-and-extend may facilitate superior retinal fluid resolution and necessitate a reduced frequency of injections than other anti-VEGF treatments. Nonetheless, prudence is advisable regarding indirect comparisons, given the potential variability across trials concerning critical parameters such as patient baseline characteristics, retreatment protocols, and optical coherence tomography utilization methodology. Consequently, in clinical practice, faricimab may represent an optimal therapeutic option when durability is paramount, when macular edema persists despite alternative treatments, or when its dual-action mechanism could confer additional ocular benefits. Its implementation does not, however, obviate the necessity for optical coherence tomography-guided monitoring, particularly throughout the transition from loading to extension phases.

Aflibercept 8 mg

Aflibercept 8 mg is a high-dose formulation developed to extend VEGF suppression while preserving the familiar aflibercept molecular mechanism. The mechanistic underpinning is straightforward: the administration of an augmented dosage facilitates a protracted maintenance of therapeutic drug concentrations, thereby enabling an extension of treatment intervals while preserving its fundamental mechanism of action. The PHOTON trial evaluated aflibercept 8 mg in DME using every-12-week and every-16-week regimens after loading, compared with aflibercept 2 mg every 8 weeks. At 48 weeks, aflibercept 8 mg met noninferiority criteria for visual acuity compared with standard aflibercept 2 mg.

The 96-week PHOTON results further supported durability. Such an outcome may hold considerable clinical significance for patients who exhibit a favorable response to aflibercept but necessitate frequent injections for sustained retinal fluid resolution. In such eyes, aflibercept 8 mg may provide a smoother escalation than switching mechanism, particularly when the physician wants to maintain VEGF-trap biology while reducing injection frequency.

The relative positioning of aflibercept 8 mg and faricimab merits consideration. Both aim to reduce treatment burden. Faricimab offers dual Ang-2/VEGF-A inhibition; aflibercept 8 mg offers higher exposure to an established VEGF-trap. Large head-to-head trials in DME designed to demonstrate superiority appear to be lacking. Selection may therefore rest upon prior response, OCT phenotype, availability, reimbursement, safety profile, and physician experience. One class cannot be assumed to be superior.

Table 2. Newer durability-oriented anti-VEGF and delivery strategies.

Strategy	Mechanistic rationale	Key data	Main caution / clinical positioning
Brolucizumab	Small single-chain antibody fragment; binds a lot of VEGF-A with each injection.	KESTREL/KITE showed vision that was just as good vs aflibercept in DME and showed sustained 100-week results; some patients could go longer between treatments[30]	Inflammatory safety signal, including intraocular inflammation, retinal vasculitis, and vascular occlusion, suggests that careful patient selection and monitoring may be warranted.
Faricimab	It blocks both Ang-2 and VEGF-A; helps reduce leakage and makes blood vessels in the retina more stable.	YOSEMITE/RHINE clearly showed vision was just as good as aflibercept and allowed for durable, personalized dosing; specifically, more than 60% got injections every 16 weeks, and about 80% got them every 12 weeks or less often at week 96 in T&E arms	It lasts a long time for persistent edema; individual patient response means we need to use OCT to watch patients closely.
Aflibercept 8 mg	Higher dose of familiar VEGF-trap; longer intraocular exposure and keeps VEGF levels low for longer.	PHOTON was just as good at week 48; 96-week data showed many patients could go 12 weeks or more between treatments, with some even able to go 20 weeks or more	It may be considered when standard aflibercept exhibits insufficient durability; its precise positioning relative to faricimab appears to require further investigation.
Port delivery system with ranibizumab	It's a device we implant surgically that provides a continuous flow of ranibizumab.	PAGODA looked at whether vision (BCVA) was just as good as monthly ranibizumab for DME. And in PAVILION, assessed improvements in DRSS scores and reductions in NPDR progression among eyes without DME.	It lessens the need for frequent injections, yet does come with surgical and device-related risks, so you'll need specialized procedures for implantation and refills.

Sustained drug delivery: port delivery system with ranibizumab

Sustained delivery is different from longer-acting injections. The approach relies upon continuous release rather than prolongation of a discrete administration. The port delivery system (PDS) delivers ranibizumab continuously from a surgically implanted, refillable reservoir inside the eye. This tiny implant holds the drug, controls how it's released, has a special cap for refills, and an anchor to keep it in place. This design directly targets one of the major weaknesses of anti-VEGF therapy: repeated injections and frequent visits.

In the PAGODA trial, researchers compared continuous ranibizumab 100 mg/mL via PDS (with refills every 24 weeks) against monthly ranibizumab 0.5 mg for DME. The trial, with 634 participants, reported that the adjusted mean BCVA gain averaged over weeks 60 and 64 was 9.6 letters with PDS Q24W and 9.4 letters with monthly ranibizumab, suggesting comparable efficacy to a limited extent.

However, some specific side effects were more frequent with PDS than monthly ranibizumab, and patients had a temporary drop in vision after the implant was put in, which later recovered.

The PAVILION trial looked at PDS (with refills every 36 weeks) compared to just monitoring patients with moderately severe to severe NPDR, but without center-involved DME.

We need to be cautious about the device itself. The PDS had a voluntary recall in 2022 due to worries that the septum might dislodge. The manufacturer subsequently updated the device and the refill needles to address these concerns. Even with better device design, we still need to discuss complications like conjunctival erosion, conjunctival retraction, vitreous hemorrhage, retinal detachment, and endophthalmitis during informed consent. And we must monitor them closely. The PDS can be a good option for certain patients who face a lot of treatment. The intervention therefore constitutes a surgical treatment platform rather than a simple injection.

Emerging investigational directions

Exploration focuses upon strategies aimed at the amelioration of treatment burden or the achievement of broader disease control. Tyrosine kinase inhibitors exert their effect through the blockage of signals from many angiogenic receptors. They might offer a longer effect inside the eye when delivered through sustained-release methods. Earlier interest in VEGF-C and VEGF-D inhibition suggested that other VEGF ligands might cause ongoing fluid leakage, although development in adjacent retinal indications has been challenging. Such approaches remain conceptually important but necessitate robust DME-specific evidence prior to their consideration for integration into routine clinical practice.

Gene therapy is another attractive but complex strategy. The objective involves the sustained intraocular delivery of anti-angiogenic proteins following a singular administration. This could turn chronic injection therapy into a durable, one-time biologic solution. RGX-314 and related approaches have been studied in retinal vascular disease, including DR. However, numerous unresolved inquiries persist regarding gene therapy: specifically, the optimal methodology for vector delivery, the management of intraocular inflammation, the regulation of dosage, the assurance of reversibility and durability, the potential systemic ramifications, and its suitability for diabetic eyes complicated by ischemia. Gene therapy appears promising; however, its investigational status indicates that it does not yet constitute a standard, near-term therapeutic modality.

Artificial intelligence may also influence future anti-VEGF care. Automated OCT fluid quantification, DR severity grading, ischemic risk assessment, and the prediction of recurrence could support personalized retreatment and referral pathways. In health systems with limited retina specialist density, AI-assisted screening could identify high-risk patients earlier, while durability-focused drugs could reduce visit burden after referral. The value of AI may depend not only on algorithm performance but also, crucially, on its integration with existing treatment capacity, reimbursement structures, and patient navigation pathways.

How Do We Compare Treatments and Position Them Clinically?

The establishment of a simplistic hierarchy of therapeutic agents ought to be circumvented. The evidence supports a more nuanced framework: first, an understanding of the disease phenotype; second, an assessment of baseline visual acuity and OCT features; third, an evaluation of patient adherence to treatment regimens; fourth, a consideration of cost and accessibility; and fifth, an adjustment of treatment predicated upon early response. By way of illustration, a patient presenting with mild center-involved DME and favorable visual acuity may necessitate a distinct therapeutic approach. Conversely, individuals exhibiting dense edema, diminished baseline visual acuity, bilateral disease, concomitant chronic kidney disease, considerable geographical barriers to care, or active PDR coupled with unreliable follow-up, may warrant a substantially divergent therapeutic strategy.

In instances of DME coupled with preserved visual acuity, close observation, focal/grid laser photocoagulation for discrete extrafoveal leaks, or anti-VEGF therapy may constitute viable considerations. The selection among these modalities often hinges upon symptomatic presentation, optical coherence tomography (OCT) findings, and the patient's risk tolerance. Protocol V, which is

beyond the current scope of this discourse, suggests that immediate intravitreal injections may not invariably be requisite for all instances of center-involved DME with favorable visual acuity, particularly where meticulous follow-up can be ensured. For DME presenting with visual impairment, anti-VEGF therapy typically represents the initial therapeutic consideration. Bevacizumab, for example, may serve as an effective, cost-efficient first-line agent. Aflibercept may be preferentially utilized in cases of more pronounced baseline visual compromise, while ranibizumab demonstrably possesses robust evidentiary support. Faricimab and aflibercept 8 mg present as appealing alternatives when prolonged therapeutic durations are desired or in the management of refractory macular edema.

For Proliferative Diabetic Retinopathy (PDR), Ranibizumab and other anti-VEGF agents may induce rapid regression of neovascularization. These agents are particularly beneficial in the presence of concomitant DME or as a preoperative measure prior to surgical interventions such as vitrectomy for intraocular hemorrhage or tractional retinal detachment. However, in scenarios where patient adherence to follow-up appointments may be compromised, panretinal photocoagulation (PRP) remains an indispensable intervention. The judicious combination of therapeutic modalities is often warranted. For severe Non-Proliferative Diabetic Retinopathy (NPDR) without DME, the application of prophylactic anti-VEGF therapy may mitigate the risk of disease progression. Nevertheless, Protocol W indicates that visual acuity may not invariably improve with such intervention, particularly if rigorous patient monitoring and timely rescue treatment can be implemented. Consequently, the reservation of prophylactic treatment for meticulously selected, high-risk patients, rather than its universal application in severe NPDR, is generally advocated.

Table 3. Practical treatment positioning for diabetic retinopathy and diabetic macular edema.

Clinical scenario	Evidence-informed option	Escalation / switch consideration	Comments for resource-variable settings
Center-involved DME with visual impairment and moderate vision loss	Start anti-VEGF. Bevacizumab may demonstrate efficacy, particularly when cost or access represents the primary consideration. Otherwise, ranibizumab or aflibercept constitute efficacious and established therapeutic alternatives.	Escalation or a therapeutic switch may be warranted upon evidence of a suboptimal early response, persistent intraretinal or subretinal fluid, or frequent disease recurrences.	The initial deployment of bevacizumab may permit the reservation of higher-cost agents for patients who demonstrate an inadequate response, thereby enhancing treatment accessibility for a broader patient demographic.
DME with worse baseline VA (approximately 20/50 or worse)	Aflibercept 2 mg represents a robust therapeutic option, substantiated by rigorous clinical investigations such as Protocol T. Should the clinical presentation necessitate an extended therapeutic duration, faricimab or aflibercept 8 mg constitute viable alternatives.	An early therapeutic modification may be considered if central macular thickness (CST) persists at an elevated level, or if visual acuity improvement remains insufficient following an adequate course of initial therapy.	The determination of the optimal therapeutic agent, particularly one possessing enhanced potency or a prolonged duration of action, is based upon baseline visual acuity and optical coherence tomography (OCT) scans, especially when resource allocation is constrained.
Frequent recurrence on standard anti-VEGF	Faricimab or aflibercept 8 mg may reduce injection frequency while preserving disease control.	Prior to determining treatment inefficacy, a comprehensive assessment is typically conducted, encompassing patient adherence to the therapeutic regimen, the appropriateness of injection intervals, the findings of optical coherence tomography	Longer-acting treatments may mitigate travel burdens; however, consideration must also be given to drug availability and insurance coverage.

		(OCT) scans, and the stability of the patient's systemic health.	
Active PDR with reliable follow-up	Consideration may be given to anti-VEGF therapy, particularly in the concomitant presence of DME; ranibizumab has demonstrated efficacy in investigations such as Protocol S.	Panretinal photocoagulation (PRP) is typically supplemented if neovascularization recurs, if consistent patient follow-up cannot be reliably ensured, or if there is a discernible risk of retinal detachment.	Often, a combination of anti-VEGF and PRP may represent a judicious therapeutic approach, particularly within larger referral centers.
Active PDR with poor follow-up reliability	Panretinal photocoagulation (PRP) maintains a pivotal role in this context. Anti-VEGF agents may be utilized adjunctively to facilitate the rapid regression of neovascularization and achieve disease stabilization prior to surgical intervention.	Sole reliance on anti-VEGF therapy is generally contraindicated if patients frequently fail to attend scheduled follow-up appointments.	This represents a prevalent challenge across numerous clinical settings and should inform the strategic formulation of patient communication protocols.
Severe NPDR without DME	Observational management may be a reasonable approach for these patients, emphasizing the maintenance of systemic health and prompt intervention as warranted. For certain high-risk patients, aflibercept might preclude disease progression.	Therapeutic intervention is indicated if disease progression occurs, or if the emergence of central DME, proliferative diabetic retinopathy (PDR), neovascularization, or other high-risk indicators is observed.	It may often prove challenging to advocate for routine preventive treatment given the frequency of required patient visits and the associated elevated costs.
High treatment burden despite good response	Should the objective be extended therapeutic duration, viable options include faricimab, aflibercept 8 mg, and the consideration of PDS for suitably selected patients.	It is imperative to recognize that the PDS implant necessitates surgical intervention and device implantation. Its application is typically reserved for specific patient populations following the provision of comprehensive, detailed counseling.	In numerous contexts, longer-acting injections may often present a more pragmatic alternative than PDS implant surgery.

Safety considerations

Safety considerations necessitate the delineation of injection risks, drug-specific risks, and those associated with the device or surgical procedure. All intravitreal injections carry small but serious risks of endophthalmitis, retinal tear, rhegmatogenous retinal detachment, traumatic cataract, intraocular pressure rise, and sterile inflammation. Systemic safety considerations for diabetic patients also arise, owing to concomitant vascular morbidities. Large trials do not appear to have demonstrated substantial disparities in systemic risk among anti-VEGF agents. The application of judicious clinical judgment is warranted for patients presenting with recent cerebrovascular accidents, myocardial infarctions, uncontrolled hypertension, renal impairment, or pregnancy.

An examination of drug-specific safety directs attention toward brolucizumab, given its established association with ocular inflammation and retinal complications. Faricimab and aflibercept 8 mg showed similar eye safety compared to other tested treatments in key studies. Ongoing surveillance of drug safety remains imperative as these treatments gain broader real-world utilization. The Port Delivery System (PDS) introduces a novel category of risk, given that its implantation and

refill procedures necessitate surgical device involvement. The PAGODA and PAVILION trials show promise. However, adverse events manifested with greater frequency in device-treated eyes; consequently, protracted monitoring is essential to ascertain the extent of this platform's potential clinical application.

Implications for Indonesia and other resource-variable systems

In resource-constrained environments, the primary challenge transcends the mere selection of novel pharmaceutical agents; it encompasses the establishment of a sustainable, long-term treatment paradigm. A considerable proportion of patients present late, incur significant travel distances, bear out-of-pocket expenses, or rely upon circumscribed insurance coverage. Furthermore, concomitant morbidities frequently impede patient adherence to prescribed treatment regimens. These circumstances may indicate that even an optimally devised treatment plan risks suboptimal efficacy if its implementation proves unduly complex. Consequently, clinical decision-making necessitates the consideration of numerous factors: cost, access, stock reliability, optical coherence tomography (OCT) availability, injection-room capacity, and robust follow-up systems.

For many regions, a judicious approach involves the utilization of bevacizumab as an initial treatment for eyes with DME. This strategy reserves aflibercept, ranibizumab, faricimab, or aflibercept 8 mg for specific ocular presentations, including those with poorer baseline visual acuity, suboptimal treatment response, substantial bilateral disease burden, or a pronounced requirement for interval extension. PRP may nevertheless retain utility for PDR, particularly among patients exhibiting compromised follow-up adherence. Concurrently, tertiary centers must engage in strategic planning for advanced care provision, comprehensive OCT-based monitoring protocols, robust patient reminder systems, and effective referral feedback mechanisms. Such infrastructure may facilitate the avoidance of undertreatment. Longer-lasting agents are especially valuable for patients from remote islands or districts, assuming they are affordable and supplies are stable.

For the efficacious implementation of PDS or gene therapy within these contexts, requisites extend beyond mere regulatory approval, encompassing surgical training, proficiency in device management and complication resolution, robust informed consent frameworks, and dependable postoperative surveillance. In numerous centers, longer-acting injectable agents may constitute a more pragmatic intermediate progression preceding the widespread adoption of device-based delivery systems.

Limitations of the current evidence

Most pivotal clinical trials selected highly specific patient cohorts and subjected them to intensive observation. These populations may not always comprehensively represent the nuances of daily clinical practice. Trial patients may diverge from real-world patients across several dimensions, including systemic health status, renal comorbidities, socioeconomic factors, visual acuity impairment, treatment adherence, and the severity of baseline ischemia. Currently, a paucity of head-to-head evidence persists for the most recent therapeutic agents. Furthermore, indirect comparisons may present analytical complexities attributable to disparities in study design and retreatment protocols. Certain findings regarding treatment duration originate from specific trial methodologies, rather than reflecting the pragmatic application of 'treat and extend' protocols in routine clinical environments.

An additional limitation warrants consideration: Anatomical improvement doesn't always lead to better vision. PANORAMA, Protocol W, and PAVILION demonstrate substantial DRSS improvements and a reduction in the progression of disease severity. However, consideration must be given to the influence of visual outcomes, patient engagement, and the facility of rescue interventions on the prevention of NPDR in the absence of DME. Finally, the financial implications of treatments and their efficacy exhibit considerable variability across geopolitical boundaries. Consequently, interventions validated in high-income nations may not be directly transferable to regions such as Indonesia or other resource-constrained environments.

CONCLUSIONS

Clinical observations suggest that anti-vascular endothelial growth factor (Anti-VEGF) therapy has substantially ameliorated outcomes in diabetic retinopathy (DR) and diabetic macular edema (DME). Ranibizumab may demonstrate substantial efficacy in augmenting visual acuity (VA) in DME. Ranibizumab appears to present an alternative anti-VEGF therapeutic modality to panretinal photocoagulation (PRP) for selected patients with proliferative diabetic retinopathy (PDR). Bevacizumab emerged as a highly cost-effective solution, a consideration particularly pertinent in contexts of resource constraints. Aflibercept provided better visual outcomes than other drugs for DME, particularly for ocular presentations characterized by severe baseline visual impairment. Furthermore, intravitreal aflibercept injections reduced the development of PDR or center involved-DME among eyes with severe non-proliferative diabetic retinopathy (NPDR).

Consequently, the current focus of inquiry concerns the development of therapeutic modalities that offer prolonged duration of action and comprehensive disease modulation. Brolucizumab, while exhibiting robust dosing and favorable anatomical outcomes, may entail drug-specific inflammatory safety concerns. Faricimab introduces a novel mechanism of action, involving the inhibition of two distinct pathways: Angiopoietin-2 (Ang-2) and VEGF-A. It has been observed to yield sustained outcomes from a treat-and-extend regimen over a two-year period. Aflibercept 8 mg prolongs the duration of action of an established VEGF-trap mechanism. The Port Delivery System (PDS) with ranibizumab facilitates continuous intravitreal delivery, thereby substantially mitigating treatment burden; however, its implementation may entail inherent risks associated with surgical procedures and device-related complications.

A personalized treatment paradigm is often advocated for retina specialists as the optimal approach. The selection of the most efficacious anti-VEGF strategy necessitates the consideration of numerous factors, including, but not limited to, disease phenotype, initial visual acuity, optical coherence tomography (OCT) metrics, the extent of ischemic involvement, prior therapeutic response, safety profiles, patient adherence, economic implications, pharmacological availability, and systemic healthcare capacity. The future of diabetic retinopathy care is anticipated to integrate several key components: earlier detection methodologies, personalization guided by optical coherence tomography (OCT) imaging, sustained-release pharmacological interventions, selective laser modalities, and comprehensive healthcare system strategies to facilitate long-term treatment adherence and accessibility.

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