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Review Article

Research advances in the translational application of anti-VEGF combined with subthreshold micropulse laser therapy for refractory diabetic macular edema

Degong Wang, Dongdong Wei, Fenfen Zhang, Changhui Liu

Department of Ophthalmology, Qilu Hospital of Shandong University Dezhou Hospital (Dezhou People' s Hospital), Dezhou 253014, Shandong, China

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Abstract: Diabetic macular edema (DME) is a leading cause of visual decline in patients with diabetic retinopathy (DR). While intravitreal anti-vascular endothelial growth factor (VEGF) agents have become the first-line treatment, some patients fail to achieve complete resolution or experience recurrent fluid accumulation despite ongoing treatment regimens. This therapeutic resistance defines the difficult entity known as refractory DME, which remains a significant management dilemma in clinical practice. Subthreshold micropulse laser (SML) selectively targets retinal pigment epithelium (RPE) cells, inducing heat shock protein (HSP) expression and modulating inflammatory cytokine release. It exerts a biomodulatory effect while avoiding the photocoagulation scars associated with conventional laser. Translational research on combining anti-VEGF therapy with SML has attracted increasing attention. This narrative review covers the disease characteristics and treatment dilemmas of refractory DME, the therapeutic mechanism of SML, clinical evidence for combination therapy, and related translational research. Future directions, including optimization of individualized treatment strategies and exploration of novel biomarkers, are also discussed.

Keywords: Anti-vascular endothelial growth factor, subthreshold micropulse laser, refractory diabetic macular edema

Introduction

Central vision loss in patients with diabetic retinopathy (DR) arises principally from diabetic macular edema (DME), and a notable proportion of affected patients experience persistent or relapsing disease [1]. Given the prevalence of diabetes continues to rise worldwide, the overall health burden attributable to DME is growing. Epidemiological data indicate that the prevalence of DME ranges from 5.2% to 14.3% among people with diabetes, with projections indicating that approximately 28.61 million people worldwide will be affected by 2045. DR may emerge at any stage of diabetes, and its occurrence is strongly associated with glycemic status, blood pressure, lipid levels, and disease duration [1].

Over the past several years, anti-vascular endothelial growth factor (VEGF) therapies have supplanted traditional laser photocoagulation as the first-line treatment for DME. However, in clinical practice, some patients show persistent macular edema after the initial loading dose, or experience recurrent edema during follow-up, failing to achieve complete resolution even with intensive monthly injections, a condition defined as refractory DME [2, 3]. Persistent DME has been defined as macular edema that remains despite anti-VEGF therapy, with reported incidence rates varying according to different definitions. About 18% to 40% of DME patients do not respond well to initial anti-VEGF treatment [2]. In addition to the epidemiological burden, the socio-economic impact of DME is substantial. Quality of life in DME patients decreases significantly, impairing reading, driving, and occupational functions. The direct medical expenses associated with anti-VEGF treatment, coupled with the indirect costs of frequent clinic visits and lost productivity, place

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considerable pressure on global healthcare systems. In addition, the psychological burden of chronic treatment and fear of vision loss lead to anxiety and depression in affected individuals. These factors underscore the urgent need for therapeutic regimens that can simultaneously improve visual acuity while reducing injection frequency and associated healthcare costs [1].

Subthreshold micropulse laser (SML) is an established laser modality that converts standard continuous-wave beams into brief, repeated pulses. These pulses act preferentially on the retinal pigment epithelium (RPE) while avoiding thermal injury to the neural retina. This action elicits both anti-inflammatory activity and regenerative modulation. SML thus offers a novel strategy to overcome the therapeutic impasse in refractory DME [4, 5]. Over the past few years, the translation of combined anti-VEGF and SML regimens from experimental investigations toward real-world clinical practice has accelerated, making this approach a prominent area of interest within vitreoretinal research. Multiple systematic reviews and meta-analyses have recently synthesized the accumulating evidence, further supporting the clinical value of this combination strategy [6-8].

Therapeutic dilemmas in refractory DME

Definition and clinical features of refractory DME

Currently, no globally accepted standard definition exists for refractory DME. In clinical practice, the term typically denotes a condition in which, following three to six consecutive anti-VEGF injections, central macular thickness (CMT) either remains above 300 μm or falls by less than one-fifth from baseline, while best-corrected visual acuity (BCVA) shows no meaningful improvement or even progressive decline. Optical coherence tomography (OCT) commonly reveals macular abnormalities including persistent diffuse retinal thickening, cystoid spaces, or serous detachment in these cases [9]. For instance, a recent study reported that in a group of refractory DME patients who received pars plana vitrectomy combined with subretinal dexamethasone implant, the mean baseline CMT was 504.8 ± 160.0 μm, illustrating the severe anatomical disruption that may ultimately warrant surgical intervention in this population [10].

From a pathophysiological perspective, the mechanisms underlying refractory DME are highly heterogeneous. In addition to sustained activation of the VEGF signaling pathway, chronic low-grade inflammation, Müller cell dysfunction, impaired RPE pump function, and mechanical traction at the vitreoretinal interface may all contribute [11]. Müller glia are the predominant glial cells in the retina, and their distinctive morphology and metabolic properties enable extensive interactions across all retinal layers. In diabetes, a hyperglycemic environment prompts these cells to secrete VEGF along with various inflammatory cytokines, which compromise blood-retinal barrier (BRB) integrity and promote macular edema. Müller cells also regulate retinal water balance through aquaporin-4 (AQP4) channels; impairment of this transport system under chronic hyperglycemia plays a key role in sustaining abnormal fluid accumulation. Meanwhile, persistent low-grade inflammation is a fundamental feature of DR, characterized by elevated pro-inflammatory factors, activation of intracellular inflammatory cascades, and subsequent BRB disruption that precipitates edema [11]. Recent data indicate that certain OCT-derived parameters-such as ellipsoid zone status and the abundance of hyperreflective intraretinal spots-could serve as useful predictors of therapeutic outcomes and assist in refining management approaches for patients with treatment-resistant DME [12].

Stratifying DME by OCT morphology is important for both predicting disease course and guiding clinical decisions. This approach typically distinguishes three main subtypes: diffuse retinal thickening (DRT), characterized by neurosensory thickening and reduced reflectivity due to inner BRB compromise; cystoid macular edema (CME), defined by distinct hyporeflective cystoid lesions predominantly affecting the outer plexiform and inner nuclear layers, resulting from outer BRB failure at the RPE; and serous retinal detachment (SRD), which occurs when impaired RPE pumping permits subretinal fluid collection [10, 11]. Patients with CME or SRD generally present with poorer initial visual acuity and often demand intensified therapeutic regimens. Notably, the SRD pattern has been implicated as a negative prognostic indicator for visual recovery, even with anti-VEGF administration. Consequently, OCT-based subtyping offers clinically actionable information

for selecting appropriate interventions and forecasting visual prognosis in DME [12].

Limitations of anti-VEGF monotherapy

Despite the substantial anatomical and functional benefits of anti-VEGF treatment in most DME cases, a considerable number of patients exhibit suboptimal responses to monotherapy. Evidence indicates that a notable subset of DME patients fails to attain maximal benefit from anti-VEGF alone; moreover, the requirement for repeated injections often compromises adherence and overall care quality [13]. Pivotal trial data suggest that approximately 40% of DME cases do not respond to monthly anti-VEGF monotherapy [2], whereas other studies report nonresponse rates between 18% and 30% [12].

The etiology of anti-VEGF resistance involves multiple intersecting pathways, including persistent hyperglycemia-driven chronic inflammation, impaired Müller cell homeostasis, and compromised RPE pumping activity, all of which collectively undermine therapeutic efficacy. In vitrectomized eyes, the therapeutic benefit of anti-VEGF agents for DME may be attenuated due to accelerated drug washout from the vitreous space. A case series of three vitrectomized eyes with DME refractory to prior anti-VEGF therapies reported that switching to 8 mg aflibercept yielded substantial anatomical and functional improvement, suggesting that altered pharmacokinetics in such eyes may require escalated dosing or alternative drug selection [14].

Furthermore, repeated intravitreal injections increase patient discomfort and carry potential hazards including endophthalmitis, ocular hypertension, and retinal detachment; the high cost also imposes a substantial financial burden on patients and healthcare systems [15]. Anti-VEGF compounds vary in molecular structure and pharmacokinetic behavior. For instance, brolucizumab - a small, single-chain antibody fragment - delivers a molar dose per injection approximately 2-fold higher than aflibercept (2 mg) and roughly 22-fold greater than ranibizumab. On the contrary, faricimab combines the effects of anti-VEGF and anti- angiopoietin-2 (Ang-2). This pharmacological difference can regulate its efficacy on incurable DME [4]. The treat-and-extend (T&E) strategy has attracted attention as a practical approach to reduce treatment burden without compromising visual outcomes. Under this protocol, injection intervals are gradually extended based on disease stability, aiming to determine the longest feasible interval that maintains adequate disease suppression. Several large-scale randomized controlled trials have shown that T&E is noninferior to monthly fixed injections for DME results. However, for patients with incurable DME who still have fluid after monthly administration, T&E alone may be insufficient. These patients often need adjuvant treatment, such as switching to a different anti-VEGF agent, adding corticosteroids, or combining with SML. The optimal sequence and timing of these combination strategies remain under active investigation [2, 12, 13].

Determining reliable predictors of treatment response is also crucial for guiding early decision-making and avoiding long-term ineffective treatment. Adherence to anti-VEGF therapy represents another major challenge. The high treatment burden, including frequent outpatient visits, injection-related anxiety, and economic costs, leads to suboptimal adherence in real-world. Studies estimate that up to 40-50% of patients do not comply with recommended injection regimens [12, 13]. Poor adherence is associated with poor visual outcomes and increased medical expenses. Strategies to improve compliance, such as patient education, T&E programs and combined therapies that reduce injection frequency, are key components of optimal DME management [12, 13, 15].

Against this background, combined treatment strategies are gradually attracting attention. Studies show that some combined therapies, such as conbercept plus SML or anti-VEGF plus conventional laser photocoagulation, outperform their respective monotherapies. These methods can restore macular anatomy, effectively reduce edema, improve visual function to a certain extent, and reduce the number of treatments, thus solving the limitations of monotherapy [16, 17]. Accumulating evidence from real-world studies and clinical trials consistently shows that adding SML to anti-VEGF treatment can significantly reduce injection frequency while maintaining comparable or even better anatomical and functional results [18]. A comparative overview of the molecular struc-

Table 1. Molecular structure comparison of anti-VEGF agents

Agent	Molecular Type	Molecular Weight	Target	Vitreous Half-life	Relative Molar Dose per Injection	Reference
Ranibizumab	Monoclonal antibody fragment	~48 kDa	VEGF-A	~9 days	1×	[4]
Aflibercept (2 mg)	VEGF receptor-Fc fusion protein	~115 kDa	VEGF-A/B, PlGF	~11 days	~2×	[4]
Aflibercept (8 mg)	VEGF receptor-Fc fusion protein	~115 kDa	VEGF-A/B, PlGF	Prolonged	~8×	[14]
Brolucizumab	Single-chain Fv fragment	~26 kDa	VEGF-A	~10 days	~22×	[4]
Faricimab	Bispecific antibody	~150 kDa	VEGF-A, Ang-2	~13 days	~4×	[12]

Note: Ang-2: angiopoietin-2; PlGF: placental growth factor; VEGF: vascular endothelial growth factor.

tures, pharmacokinetic properties, and relative molar doses of different anti-VEGF agents is provided in **Table 1**.

Mechanism of action and biological effects of SML

Technological development from traditional laser to SML

Traditional macular grid laser photocoagulation was once the standard treatment for DME. However, despite its therapeutic benefits, the continuous wave lasers used in routine practice produce unavoidable lateral and axial heat diffusion, which leads to permanent photoreceptor damage and retinal scar formation. These changes cause visual defects, including central scotomas and weakened contrast sensitivity.

SML represents a significant technological advance over traditional lasers. It works by dividing the continuous-wave beam into a series of microsecond-level, brief, repetitive pulses, allowing interpulse cooling intervals that limit total heat accumulation. Evidence shows that, compared with traditional lasers, the micropulse mode delivers energy intermittently, reducing unnecessary damage to adjacent structures while still achieving effective treatment of target tissue [19]. Since 2009, the yellow micropulse variant with a wavelength of 577 nm has been available clinically. The navigated version of yellow SML is also used to treat refractory cystoid macular edema. However, substantial differences exist across studies in the clinical parameters used (e.g., power setting, duty ratio and beam diameter), which may limit direct comparability of reported results [19].

A large-scale randomized noninferiority trial called diamonds further confirmed that SML can achieve visual improvement and macular thickness reduction equivalent to standard threshold lasers, with a more favorable safety profile [20]. The dosing basis of SML differ fundamentally from those of traditional continuous wave lasers. Key parameters determining SML treatment include beam diameter (usually 100-200 μm), duty ratio (defined as the fraction of active emission in the pulse sequence, typically 5-15%), power output in watts, duration of each exposure, and total number of applications. Among these, the duty ratio is particularly important because it establishes a balance between active irradiation and subsequent heat-dissipation intervals. A lower duty ratio allows more complete cooling between pulses, reducing the risk of heat accumulation and retinal damage.

"Subthreshold" means that laser power is titrated below the visible retinal burn threshold. Typically, power is adjusted upwards from an invisible test spot until a barely visible burn appears, then reduced by 20-50% for therapeutic application [19]. However, considerable differences exist in the specific parameters used across different laser platforms and clinical studies, including 577-nm yellow, 810-nm infrared diode, and 532-nm green lasers. This heterogeneity in treatment parameters complicates cross-study comparisons and efforts to establish standardized protocols. Work to develop consensus guidelines for SML parameter selection is ongoing [20, 21]. The histological and cellular differences between conventional continuous-wave laser and SML are illustrated in **Figures 1** and **2**. **Figure 1** demonstrates the superior tissue preservation achieved with micropulse delivery at the tissue level, while **Figure 2** shows the cellular protective effect of SML, with viable cells preserved within the laser spot area after micropulse delivery at equivalent energy levels, in contrast to the cell

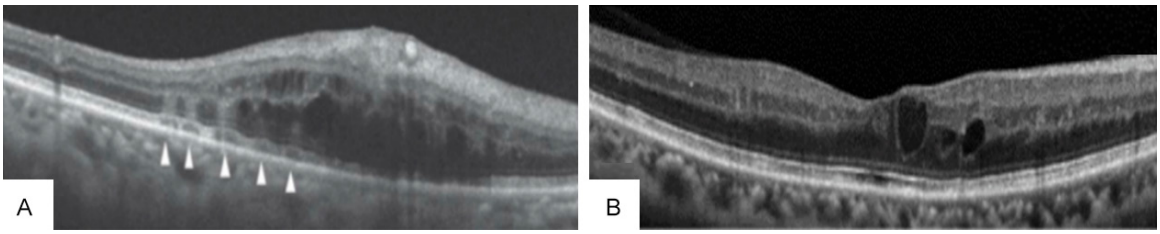

Figure 1. Histological comparison of conventional continuous-wave laser and SML effects on retinal pigment epithelium (RPE) and retinal tissue. A: Continuous-wave laser causes RPE disruption (arrowheads), fluid peaks adjacent to the laser site, and hyperreflective bands, indicating irreversible tissue damage. B: SML treatment results in 100% tissue preservation with no morphological changes in the retina throughout the observation period, demonstrating the safety and biomodulatory nature of micropulse delivery.

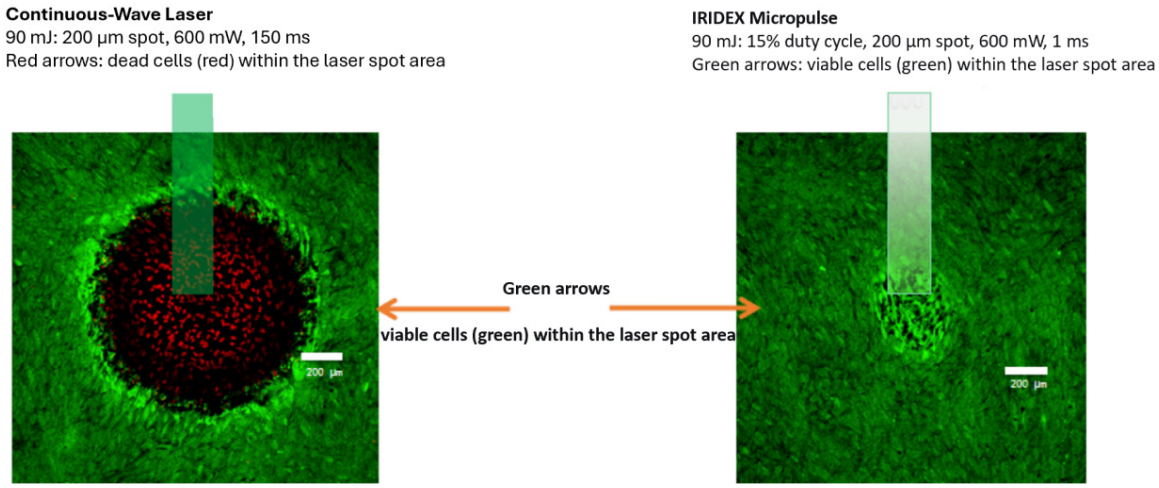

Figure 2. Comparative cellular effects of conventional continuous-wave laser and IRIDEX Corporation (IRIDEX) micropulse laser on retinal tissue at equivalent energy (90 mJ). Left panel: Continuous-wave laser (600 mW, 150 ms) induces cell death (red arrows) within the laser spot area. Right panel: IRIDEX micropulse laser (15% duty cycle, 600 mW, 1 ms) preserves viable cells in the laser spot area (green arrow). Micropulse delivery allows tissue cooling between pulses to prevent thermal damage and maintain cell vitality.

death observed with continuous-wave laser [21].

Selective RPE targeting and biological effects

The core feature of SML is its tissue selectivity, with RPE cells as the primary target. It provides laser energy in a short pulse sequence, allowing the tissue cooling during each pulse interval. This maintains the temperature rise in RPE cells at a sublethal level, avoiding photoreceptor damage and laser scar formation associated with conventional continuous-wave photocoagulation [21].

At a molecular level, the modest thermal stimulus elicited by SML enhances HSP production in RPE cells, an effect that underpins its therapeutic action. A growing body of evidence indicates that following SML application, aqueous humor concentrations of pro-inflammatory mediators-including VEGF-decline markedly in DME patients. Moreover, this laser modality not only reduces inflammatory factor expression and facilitates macular fluid clearance but also achieves results comparable to conventional laser therapy [22]. In addition, reports suggest that SML may foster long-term correction of retinal neuroinflammatory metabolic disturbances, thereby contributing to re-establish retinal homeostasis and constrain local inflammatory activity [23].

In vitro evidence shows that SML exposure reduces the expression of factors promoting choroidal neovascularization within RPE cells, while simultaneously enhancing secretion of pigment epithelium-derived factor (PEDF) - an endogenous anti-angiogenic and neuroprotective agent produced by the RPE [24]. Never-

Table 2. Molecular, transcriptomic, cellular, and tissue-level biological effects of SML

Level of Effect	Specific Effect	Mechanism/Outcome	Reference
Molecular	HSP upregulation	Mild thermal effect induces HSP expression in RPE cells	[22]
Molecular	Pro-inflammatory cytokine downregulation	Significant reduction of VEGF and other cytokines in aqueous humor	[22]
Molecular	PEDF upregulation	Upregulation of PEDF secreted by RPE cells	[24]
Molecular	Inflammatory pathway modulation	Long-term modulation of retinal neuroinflammatory biomarkers	[23]
Molecular	PEDF and erythropoietin (EPO) unchanged	No significant changes in aqueous PEDF and EPO after SML	[25]
Transcriptomic	Differential gene expression	Distinct gene expression profiles after SML vs. continuous-wave laser	[26]
Cellular	Intercellular junction remodeling	Potential involvement in junction remodeling and cytoskeletal rearrangement	[43]
Tissue	Microcirculatory improvement	Reduced foveal avascular zone (FAZ) area on optical coherence tomography angiography (OCTA), improved superficial capillary plexus	[41]

Note: EPO: erythropoietin; FAZ: foveal avascular zone; HSP: heat shock protein; OCTA: optical coherence tomography angiography; PEDF: pigment epithelium-derived factor.

theless, a study by Midena et al. found no significant changes in aqueous PEDF or erythropoietin (EPO) levels when comparing pre- and post-SML samples from DME patients. This suggests that fluctuations in soluble cytokine concentrations in the anterior chamber may not accurately reflect local biological effects at the RPE level; alternatively, additional, as-yet-unidentified effector molecules may participate in the regulatory network activated after laser treatment [25].

An RNA sequencing study by Shiraya et al. [26] revealed fundamental differences in gene expression profiles between SML and continuous-wave laser. Beyond regulating inflammatory cytokines, SML may also be involved in remodeling intercellular junctions and rearranging the cytoskeleton. Research on the impact of SML on RPE tight junction protein expression remains in its early stages. Furthermore, SML may improve vascular stability by restoring the physiological balance between VEGF and PEDF [24, 26]. Recent transcriptomic studies have further elucidated the molecular differences between SML and continuous-wave laser, revealing distinct gene expression profiles that may underlie the unique biomodulatory effects of SML [26]. The molecular, transcriptomic, cellular, and tissue-level biological effects of SML on RPE cells and retinal tissue are summarized in **Table 2**.

The RPE plays a central role in maintaining retinal homeostasis through multiple functions: absorption of scattered light, transport of nutrients and waste between the choroid and photoreceptors, phagocytosis of shed photoreceptor outer segments, secretion of growth factors, and maintenance of the outer blood-retinal barrier through tight junctions. Dysfunction of any of these RPE functions can contribute to the development and persistence of DME. The selective targeting of RPE by SML is therefore mechanistically rational, as it aims to restore RPE function without damaging the overlying photoreceptors or neurosensory retina [22, 23].

The SML-induced heat shock protein response encompasses both HSP70 and HSP90, which function as molecular chaperones that preserve protein conformational integrity, prevent aggregation, and assist in refolding under stress. Specifically, increased HSP70 expression in RPE cells is related to the cytoprotective effects of SML, because HSP70 inhibits activation of the nuclear factor kappa-B (NF-κB) pathway, a key inflammatory regulatory factor - thus reducing the release of inflammatory mediators. This partner-mediated anti-inflammatory effect is considered the main mechanism by which SML plays a role in DME [24, 25].

Clinical evidence for combination therapy

Biological basis for synergistic effects of combination therapy

The theoretical basis for combining anti-VEGF agents and SML lies in the mechanistic comple-

mentarity of the two treatments [27, 28]. Anti-VEGF agents primarily inhibit neovascularization and reduce vascular permeability by rapidly neutralizing excess VEGF in the vitreous cavity and retinal tissue, thus quickly alleviating macular edema [29]. In contrast, SML exerts a slower-onset but more lasting and stable therapeutic effect by long-term regulation of RPE cell secretory function. At the molecular level, SML has been proven to down-regulate pro-inflammatory and angiogenic factors while up-regulating protective factors such as PEDF, thus restoring the physiological balance between VEGF and PEDF and potentially improving vascular stability [24].

In terms of kinetic characteristics, anti-VEGF agents have a limited half-life in the vitreous cavity and require repeated injections to maintain an effective concentration, and they are ineffective against inflammatory pathways other than VEGF [30]. Meanwhile, the therapeutic effect of SML has a slower onset but lasts longer, and reprogramming of RPE cell biological functions after a single treatment can persist for several months [31].

In terms of tissue targets, anti-VEGF agents mainly act on VEGF receptors on vascular endothelial cells, inhibiting increased vascular permeability and neovascularization, whereas SML primarily targets RPE cells, improving RPE barrier and pump function and promoting active transport and absorption of subretinal fluid [21]. Improved RPE function also helps restore oxygen supply and metabolic support to the outer retina, creating a microenvironment favorable for photoreceptor survival [20]. Quantitative synthesis from recent meta-analyses has confirmed the added value of combining therapies. In a 12-month comparison with anti-VEGF alone, Ma et al. found that combined treatment yielded better BCVA outcomes (MD: -0.05, 95% CI: -0.10 to -0.01) and greater CMT reduction (MD: -18.27 μm, 95% CI: -27.36 to -9.18) [27]. Separately, a meta-analysis by Hosoya et al., pooling 8 studies totaling 493 eyes, revealed that combination regimens significantly reduced anti-VEGF injection counts (MD: -2.22, 95% CI: -3.02 to -1.42, $P < 0.0001$) [18]. Accordingly, integrating these two therapeutic approaches is expected to deliver rapid yet durable synergistic effects targeting both inner and outer retinal layers.

A detailed understanding of the time course of each treatment modality is essential for designing optimal combination regimens. Anti-VEGF agents reach peak vitreous concentrations within 1-2 days after intravitreal injection and maintain therapeutic levels for approximately 4-6 weeks, depending on the specific agent and dose. This rapid onset makes anti-VEGF therapy ideal for quickly reducing macular edema, particularly in patients with severe vision loss. In contrast, the biological effects of SML take weeks to months. The upregulation of HSP and anti-inflammatory mediators occurs within days, but the full therapeutic effect - including regulation of RPE secretory function and improved fluid transport, may take 3-6 months to appear. This time difference shows that combined treatment should start with anti-VEGF injection to quickly reduce edema, followed by SML to provide continuous maintenance and reduce the need for ongoing injections [20, 21, 27, 28, 31].

The spatial complementarity of these two modalities further supports their combined use. Anti-VEGF agents are delivered through the vitreous and diffuse throughout the vitreous cavity, reaching the inner retina and vascular endothelium. Their effects are mainly limited to the inner retina, where VEGF is most abundant in DME. In contrast, SML acts primarily at the RPE and outer retinal levels, improving outer blood-retinal barrier function and enhancing subretinal fluid absorption. By simultaneously targeting both internal and external retinal barriers, combination therapy addresses the full spectrum of DME pathophysiology [21, 27, 28].

Furthermore, the combination of anti-VEGF and SML may reduce the risk of the “rebound phenomenon” observed after discontinuation of anti-VEGF therapy. Rapid cessation of anti-VEGF can lead to a surge in VEGF expression and rebound edema. SML may help stabilize the retina during tapering or withdrawal of anti-VEGF therapy, facilitating successful transition to less intensive maintenance regimens [31].

Efficacy and safety of combination therapy

In recent years, a growing number of clinical studies have evaluated the therapeutic value of combining anti-VEGF agents with SML for DME. Furashova et al. reported that adding micropulse diode laser to ranibizumab injections not only produced meaningful visual acuity gains

and lowered the total number of required injections among DME patients, but also demonstrated noninferiority to ranibizumab monotherapy [32]. Koushan et al. found that aflibercept combined with SML significantly reduced CMT and injection frequency in DME patients compared with aflibercept alone, with no serious laser- or injection-related complications [33]. Furthermore, studies have found that combination therapy significantly improves perfusion in the deep retinal capillary plexus and restores macular microcirculation [34]. Collectively, these studies confirm that the combination regimen is safe and effective.

A comprehensive meta-analysis by Wijeweera et al., including 563 eyes from 10 studies, demonstrated that combination therapy was associated with significantly fewer anti-VEGF injections and better BCVA and CMT reduction at both 6 and 12 months compared with anti-VEGF monotherapy [6, 7]. Consistent with this, Hosoya et al. observed that combining SML with anti-VEGF treatment led to a substantial reduction in injection frequency, while yielding similar improvements in both BCVA and CMT [18].

Jiang et al. [5] performed a systematic review and meta-analysis incorporating 13 eligible studies, comprising 405 eyes receiving combined SML and anti-VEGF therapy and 400 eyes treated with anti-VEGF alone as controls. Across all follow-up timepoints, the two cohorts showed no significant difference in either Early Treatment Diabetic Retinopathy Study (ETDRS) letters or LogMAR acuity ($P > 0.05$), except at the 6- and 12-month timepoints, where the combination arm exhibited a statistically significant improvement in both measures ($P < 0.05$). On subgroup analysis, for patients with baseline CMT below 400 μm, combined therapy yielded superior CMT reductions at every assessed interval ($P < 0.05$). In contrast, among patients with baseline CMT of 400 μm or higher, the two groups did not differ significantly ($P > 0.05$). The combination group also required significantly fewer annual anti-VEGF injections ($P < 0.05$), while SML session frequency ranged from 1.41 ± 0.37 to 3.4 ± 1.4 annually.

In a retrospective design, Han et al. [16] enrolled 72 DME patients to compare conbercept plus 577-nm SML against conbercept monotherapy. At the 3- and 6-month assessments, the combination cohort demonstrated statistically better BCVA, CMT, deep capillary plexus density, and mean retinal sensitivity compared with the monotherapy group (all $P < 0.05$). Moreover, injection counts were lower in the combined group (3.33 ± 0.68 vs. 4.06 ± 0.96, $P < 0.05$).

Long-term outcomes of anti-VEGF combined with SML are worthy of attention. Most published trials provide follow-up data of up to one year, and evidence beyond 24 months remains limited. In a five-year longitudinal evaluation, Zavorkova et al. observed that DME patients receiving SML maintained lasting efficacy in both BCVA and CMT, with adverse events within an acceptable range [5, 18]. A significant advantage of SML is its prolonged therapeutic effect, as its regulatory effect on the RPE can last for years after a single treatment [5, 18].

However, due to disease progression or recurrence, some patients may require retreatment with SML. The safety of combined treatment is an important consideration. SML is considered safe, with no reports of retinal scars, scotomas, or significant visual field defects in properly treated patients. The absence of visible retinal damage distinguishes SML from traditional photocoagulation and supports its use in the macula, where even small injuries can have significant functional consequences. When combined with anti-VEGF treatment, the safety profile is additive rather than synergistic, and no unique or unexpected safety signals have been identified in clinical trials. However, the long-term impact of repeated SML on RPE function and retinal health requires ongoing monitoring [5, 20, 32].

Comparison of different anti-VEGF drugs in the combination scheme

Many studies have evaluated the relative effectiveness of various VEGF inhibitors in combination with SML for DME. In a retrospective analysis, Liu et al. included 64 DME patients and compared the efficacy of intravitreal conbercept plus micropulse laser (MPL) versus monotherapy. Six months after treatment, the combined treatment group showed a higher overall remission rate, fewer required injections, better BCVA, and lower CMT values compared with the monotherapy group [36]. Recently, another study evaluating conbercept combined with

577-nm SML for DME also found that dual therapy produced more favorable clinical outcomes and reduced the number of intravitreal injections [37]. In a prospective study, Fang et al. also investigated conbercept combination therapy for DME and confirmed that at months 2, 3 and 4, the combination group showed statistically significant BCVA improvement and greater CMT reduction compared with the monotherapy group [38].

Recent studies have also explored the combination of brolucizumab with SML, showing promising results in achieving stable DME resolution through the combined anti-proliferative and duration-prolonging effects of the dual-modal approach [39]. In addition to combination approaches, brolucizumab monotherapy has also been evaluated in refractory DME. Hansraj et al. [35] conducted a prospective interventional study involving 19 eyes from 13 patients with refractory DME, all of whom received 6 mg/0.05 mL intravitreal brolucizumab injections. Over a course averaging 3.3 injections given every 11.1 weeks, median LogMAR acuity improved from 0.40 (20/50) to 0.35 (20/44) ($P = 0.004$), while central retinal thickness decreased from 517 μm to 237 μm ($P = 0.001$), a relative reduction of 54.1%. Intraocular inflammation occurred in 5.2% of cases, and no patient experienced sustained visual impairment. These findings indicate that brolucizumab monotherapy may be an effective option for selected patients with treatment-resistant DME, although direct comparisons with combination strategies require further study.

Currently, direct, large-scale, face-to-face randomized controlled trial evidence comparing the effectiveness of various anti-VEGF agents (including ranibizumab, aflibercept, conbercept and brolucizumab) in combined regimens is lacking. Therefore, further investigation is needed to determine which agent is most suitable for use with SML. In daily clinical practice, switching to another anti-VEGF agent may offer additional therapeutic benefits for some patients. Real-world data from the SWIRL research show that in DME patients who do not respond to bevacizumab, changing to ranibizumab or aflibercept can still improve functional outcomes. For patients who remain refractory to anti-VEGF monotherapy, combining intravitreal corticosteroids with anti-VEGF agents may produce significant anatomical and functional improvements. A 2025 review suggests that timely switching to different anti-VEGF agents or adopting corticosteroid-based therapies is a promising strategy for treating incurable DME [15].

Several clinical factors guide the selection of specific anti-VEGF agents for combination with SML. Ranibizumab is a Fab fragment with a relatively short elimination half-life, requiring more frequent intravitreal administration; nevertheless, its long-term safety has been well documented. In contrast, aflibercept is characterized by enhanced receptor affinity and prolonged duration of action, allowing extended treatment intervals for most patients. The recently approved 8 mg aflibercept formulation for DME further extends its duration of activity, which may be particularly beneficial when the goal is to minimize injection frequency in combination regimens. Conbercept, a VEGF receptor Fc fusion protein developed in China, has shown encouraging results in Asian populations and may provide a more economical alternative in resource-limited healthcare settings [4, 14, 15, 27].

Owing to its compact molecular structure and high molar concentration per dose, brolucizumab achieves potent resolution of intraretinal fluid; nonetheless, its use has been linked to a somewhat elevated incidence of intraocular inflammatory events compared with other agents. Faricimab, the first bispecific antibody designed to simultaneously neutralize VEGF and Ang-2, has met noninferiority criteria versus aflibercept in phase III trials. Its additional blockade of Ang-2 - a pathway implicated in vascular destabilization-may confer supplementary benefits.

In clinical practice, switching to a different anti-VEGF agent in patients with an inadequate initial response is a valuable management strategy. Because different agents have distinct molecular characteristics, transitioning from one type to another - for example, from an antibody fragment to a fusion protein, or vice versa - may effectively overcome resistance or suboptimal efficacy. Current data suggest that patients who fail to derive sufficient benefit from a first agent may still achieve meaningful improvement after switching to a second drug. Whether adding SML enhances the efficacy of drug

Table 3. Summary of clinical studies on anti-VEGF combined with SML for DME

Study (Author, Year)	Study Design	Sample Size (Eyes)	Anti-VEGF Agent	Follow-up	Key Findings	Reference
Furashova et al., 2020	randomized controlled trial (RCT), non-inferiority	61	Ranibizumab	12 months	Combination non-inferior to monotherapy, fewer injections	[32]
Koushan et al., 2022	Prospective	54	Aflibercept	12 months	Greater CMT reduction, lower injection frequency	[33]
Altınel et al., 2021	Retrospective	68	Anti-VEGF	6 months	Improved deep capillary plexus perfusion	[34]
Liu et al., 2023	Retrospective	64	Conbercept	6 months	Higher response rate, better BCVA, thinner CMT	[36]
Fang et al., 2020	Prospective	42	Conbercept	4 months	Superior BCVA and CMT at 2, 3, 4 months	[38]
Han et al., 2025	Retrospective	72	Conbercept	6 months	Improved deep capillary plexus (DCP) density and retinal mean sensitivity (RMS), fewer injections	[16]
Giyasova et al., 2023	Prospective	153	Brolucizumab	12 months	68.5% no additional injection needed, superior to monotherapy	[39]

Note: BCVA: best-corrected visual acuity; CMT: central macular thickness; DCP: deep capillary plexus; RCT: randomized controlled trial; RMS: retinal mean sensitivity.

switching, or whether drug switching and SML addition should be considered sequential versus simultaneous strategies, requires further investigation [14, 15, 17]. A summary of key clinical studies comparing different anti-VEGF agents combined with SML for DME is presented in **Table 3**.

Translational research on combination therapy

From molecular mechanisms to biomarkers

In-depth analysis of SML mechanisms of action has opened new directions for translational research. A transcriptomic study by Shiraya et al. revealed fundamental differences in gene expression profiles between SML and continuous-wave laser, laying the foundation for developing molecular markers to predict laser therapy response [26]. Regarding the regulation of inflammatory cytokines, SML has demonstrated the ability to alter levels of major pro-inflammatory molecules, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Vujosevic et al. provided additional evidence that SML diminishes OCT-detectable signs of inflammation, such as hyperreflective foci, microvascular abnormalities, and inner retinal layer disorganization. These observations imply an anti-inflammatory effect of SML that may aid in re-establish retinal equilibrium and constrain local inflammatory responses [40].

OCT biomarkers - including retinal thickness, intraretinal cystoid spaces, hyperreflective dots, and disorganization of retinal inner layers (DRIL) - provide important information on disease severity and treatment response. Suspended scattering particles in motion (SSPiM) are observed in approximately one-third of DME patients and may adversely affect treatment response. Optical coherence tomography angiography (OCTA) microaneurysm analysis can provide additional microcirculatory information. Integration of OCT and OCTA can help clinicians optimize DME management. Brolucizumab treatment has also been shown to improve macular ischemia, as evidenced by improvements in foveal capillary anatomy and perfusion density [6, 40].

The biomodulatory effects of SML on RPE cells extend beyond regulating cytokine secretion and may also involve remodeling of intercellular junctions and cytoskeletal rearrangement. These structural changes may directly enhance RPE barrier function and fluid transport efficiency, forming the anatomical basis for the sustained anti-edema effect of SML. However, research on the impact of SML on RPE tight junction protein expression is still in its early stages and requires further experimental validation. Sabal et al. recently used OCTA to demonstrate that SML can improve macular microvasculature in mild DME by reducing foveal avascular zone (FAZ) size in the superficial capillary plexus, providing new imaging-based evidence for the vascular effects of SML [41].

The development of pharmacogenomic markers represents the frontier of personalized DME treatment. Genetic variations in the VEGF gene,

its receptor and related inflammatory pathway genes may affect individual response to VEGF-targeted therapy. Studies have found that polymorphisms in the VEGF-A gene (rs833061, rs699947, rs2010963) and VEGFR2 gene (rs2071559, rs1870377) are associated with differential treatment responses in DME patients [11, 12]. However, these findings have not been consistently replicated across populations, and the clinical use of genetic testing in DME treatment remains to be determined. Integrating genetic data with clinical and imaging biomarkers may improve the accuracy of response prediction and enable truly individualized treatment selection [11, 12].

Lipidomics and metabolomics approaches are also being used to identify novel biomarkers in DME. Studies have detected changes in the lipid profile of aqueous humor and vitreous in DME patients, including changes in sheath lipids and phospholipids [42]. These lipid changes may reflect potential cellular stress and inflammation and could serve as biomarkers of disease activity. Whether SML treatment regulates these lipid profiles and whether such changes correlate with clinical outcomes are areas for future exploration [42].

The role of complement activation in DME pathogenesis has also gained attention. Dysregulation of the complement system, including elevated levels of complement factors C3a and C5a, has been observed in the vitreous of diabetic patients. These complement components may contribute to vascular permeability and inflammation in DME. Whether SML treatment affects complement activation and whether complement biomarkers predict response to combination therapy remain to be investigated [11, 12].

Biomarkers and precision stratification

Refractory DME exhibits considerable heterogeneity, and the effectiveness of combination strategies can differ widely among patient subgroups. A primary aim of translational research is to identify biomarkers that can both forecast therapeutic efficacy and enable precise patient classification. Preliminary studies have revealed several candidate indicators associated with anti-VEGF responsiveness. In peripheral blood, systemic inflammatory measures - including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) - have been linked to treatment sensitivity in DME, suggesting that overall inflammatory state may shape clinical outcomes [42]. At the ocular level, baseline aqueous or vitreous concentrations of inflammatory cytokines such as IL-6, interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1) may predict the magnitude of response to anti-VEGF monotherapy. One study proposed that inflammation-induced redistribution of claudin-5 can lead to anti-VEGF resistance, indicating that tight junction proteins may serve as important molecular markers to distinguish anti-VEGF-sensitive from -resistant patients [43].

Patients with baseline CMT < 400 μm derive greater benefit from combination therapy. OCT biomarker profiles differ between persistent and resolving DME, and these differences correlate with vision-related quality of life measures such as reading function. Ultrastructural imaging biomarkers-including external limiting membrane integrity and ellipsoid zone integrity-are associated with treatment response in DME [6, 12]. The PULSE study is a randomized pseudo-control trial that provides important insights into the role of SML in eyes with good vision and emphasizes the need for careful patient selection in clinical practice [44].

Treatment response prediction models are becoming increasingly sophisticated, integrating multiple data types to improve prognostic accuracy. Machine learning algorithms have been applied to OCT images to predict visual outcomes and treatment responses in DME. These algorithms can extract quantitative imaging features imperceptible to the human eye, such as subtle changes in retinal reflectivity, texture patterns, and fluid space distribution. Deep learning methods may ultimately enable automated prediction of treatment response at the individual patient level, thereby guiding clinical decision-making [6, 12].

The correlation between therapeutic response and quality of life indicators is increasingly regarded as an important result in clinical trials. Although BCVA and CMT remain traditional primary endpoints, patient-reported outcomes-such as visual function questionnaires (such as NEI-VFQ-25, retinal disease treatment satisfaction questionnaire) provide additional information on the practical impact of treatment.

Table 4. Biomarkers and predictors in refractory DME

Biomarker Category	Specific Marker	Clinical Significance	Reference
Peripheral blood	NLR (neutrophil-to-lymphocyte ratio)	Correlates with anti-VEGF treatment sensitivity	[42]
Peripheral blood	PLR (platelet-to-lymphocyte ratio)	Correlates with anti-VEGF treatment sensitivity	[42]
Aqueous/vitreous	IL-6, IL-8, MCP-1	Baseline levels predict response to anti-VEGF monotherapy	[42]
Tight junction proteins	Claudin-5 redistribution	Inflammation-induced redistribution leads to anti-VEGF resistance	[43]
OCT structural	Ellipsoid zone integrity	Predicts treatment response and guides therapeutic decisions	[12]
OCT structural	Intraretinal hyperreflective dots	Predicts treatment response	[12]
OCT structural	DRIL (disorganization of retinal inner layers)	Suggests anti-inflammatory effect	[40]
OCTA parameters	FAZ (foveal avascular zone) area	SML reduces FAZ area	[41]
OCT novel	SSPiM (suspended scattering particles in motion)	Observed in ~1/3 of DME patients, may affect treatment response	[6]

Note: DRIL: disorganization of retinal inner layers; FAZ: foveal avascular zone; IL-6: interleukin-6; IL-8: interleukin-8; MCP-1: monocyte chemoattractant protein-1; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SSPiM: suspended scattering particles in motion.

Studies show that improvement in OCT biomarkers, especially the resolution of cystoid spaces and restoration of retinal structure, is associated with improved reading speed, contrast sensitivity, and activities of daily living [42]. These patient-centered outcomes are crucial for assessing the real-world benefits of combination treatment.

Future research should focus on establishing a consensus definition of "response" and "nonresponse" for combination therapy. The lack of standardized response criteria hinders cross-study comparison and the development of evidence-based treatment algorithms. A consensus framework integrating anatomical parameters (CMT reduction, intraretinal fluid resolution) and functional parameters (BCVA improvement, quality of life) will facilitate clinical decision-making and research integration [6, 12].

Table 4 summarizes the currently identified biomarkers and predictive factors associated with treatment response in refractory DME, encompassing peripheral blood indices, intraocular cytokines, and imaging parameters.

Challenges and future perspectives

Although anti-VEGF combined with SML shows promising clinical prospects for refractory DME, several challenges remain in its translational application. Vitreous corticosteroid implants (such as dexamethasone implants) show good salvage therapeutic effects in anti-VEGF-resistant patients by comprehensively inhibiting inflammatory pathways, but the risk of increased intraocular pressure and cataract progression limits their widespread use [45].

The combination of SML with new treatments may represent an important future direction. Theoretically, SML can be combined with corticosteroid implants, bispecific antibodies, and even vitrectomy to form multi-target treatment regimens tailored to different pathophysiological mechanisms. However, increasing the number of combination components also adds complexity and uncertainty, requiring rigorous clinical research to gradually identify optimal regimens. In addition, the lack of unified parameters limits the comparability of study results and the feasibility of clinical translation. The lack of international consensus on the definition of incurable DME and different inclusion criteria across studies also affect the generalizability of findings. Although many clinical studies on combined treatment have been carried out, most are single-center, small-sample, short-term follow-up studies, and long-term efficacy and safety data are still insufficient. The best indications and individualized regimens for combination therapy need further clarification. Long-term data from the DME and Diode Subthreshold Micropulse Laser (DIAMONDS) trial and other prospective studies have begun to address some of these gaps, providing evidence for the sustained efficacy and cost-effectiveness of SML in DME management [20, 46].

The PULSE study provides key data on the application of SML in specific patient subgroups. This prospective, single-blind, pseudorandomized controlled trial recruited 27 eyes of 19 participants diagnosed with center-involving DME and good baseline visual acuity (20/25 or better). During the 24-month observation period, SML failed to delay the vision loss threshold that would trigger initiation of anti-VEGF; the mean time to reaching the endpoint was similar between the treatment and sham groups (5 months). These results emphasize that careful patient selection is crucial when considering SML in DME patients with relatively preserved vision.

Cost-effectiveness analysis from the DIAMONDS trial shows that, compared with standard lasers, SML provides favorable economic benefits for center-involving DME with baseline CMT less than 400 μm. The reduction in injection frequency achieved through combination therapy significantly reduces patients' direct financial expenditure and the indirect time-related burden associated with repeated outpatient visits [44, 46]. As healthcare systems seek to optimize resource allocation, the pharmacoeconomic considerations of anti-VEGF combined with SML are becoming increasingly important. The high cost of anti-VEGF agents, especially when administered monthly, accounts for a large proportion of DME treatment costs. By reducing the number of anti-VEGF injections required, SML can generate substantial savings over the treatment course. Cost-benefit analysis from the DIAMONDS trial shows that for DME with baseline CMT < 400 μm, SML is more cost-effective than standard lasers, mainly by reducing subsequent anti-VEGF drug use [20, 46].

However, the cost-effectiveness of SML depends on multiple factors, including the cost of laser procedures, retreatment frequency, the specific anti-VEGF drug used, and regional differences in drug pricing and healthcare delivery. From a healthcare system perspective, adoption of combined treatment requires careful consideration of infrastructure, training, and patient access. SML requires specialized laser equipment and operator training, which may not be available in all retina practices [20, 46].

Patient-centered outcomes extend beyond visual acuity to include treatment satisfaction, quality of life, and mental health. Combined treatment reduces injection frequency, which may improve patient satisfaction and reduce treatment-related anxiety. Patients requiring fewer clinic visits may experience fewer disruptions to daily activities and work, contributing to improved overall well-being. Future studies should incorporate validated patient-reported outcome measures to capture these benefits [44, 45].

The future landscape of DME treatment includes emerging therapies that may be combined with SML. Gene therapy, continuous release drug delivery system and cell-based therapy are at different stages of development. In patients receiving these new therapies, SML can be used as an auxiliary or salvage treatment, particularly when efficacy is suboptimal or when treatment-free intervals are desired. The optimal integration of SML with emerging therapies will require careful investigation in the coming years [45].

Future efforts should include large-scale, multicenter, long-term prospective randomized controlled trials using standardized laser parameters and injection protocols to provide higher-level evidence for combination therapy. Multimodal evaluation tools, such as OCTA, multispectral imaging, and aqueous humor/serum biomarkers, should be used to establish a predictive model of the combined treatment response and achieve truly precision medicine. For specific subtypes of incurable DME, such as edema with prominent hard exudates, post-vitrectomy DME, or DME with epiretinal membrane, targeted clinical studies should be carried out to determine the best time and suitable population for combined treatment.

Conclusion

Anti-VEGF combined with SML for refractory DME represents a combination treatment strategy that is both mechanistically complementary and clinically practical. While achieving comparable or superior visual function outcomes and anatomical improvements, combination therapy significantly reduces the number of anti-VEGF injections, lowers treatment burden, and alleviates patient pain and financial pressure. With the standardization of laser parameters, optimization of treatment protocols, refinement of biomarker-guided individualized

treatment strategies and accumulation of more high-quality clinical evidence, the combination strategy is expected to become an important component of standardized treatment systems for refractory DME, thereby occupying a clearer position in the landscape of individualized treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Changhui Liu, Department of Ophthalmology, Qilu Hospital of Shandong University Dezhou Hospital (Dezhou People' s Hospital), No. 1166 Dongfanghong West Road, Dezhou 253014, Shandong, China. E-mail: changhui2988@163.com

References

[1] Sakini ASA, Hamid AK, Alkhuzaie ZA, Al-Aish ST, Al-Zubaidi S, Tayem AA, Alobi MA, Sakini ASA, Al-Aish RT, Al-Shami K, Hanifa H and Khunda SS. Diabetic macular edema (DME): dissecting pathogenesis, prognostication, diagnostic modalities along with current and futuristic therapeutic insights. Int J Retina Vitreous 2024; 10: 83.

[2] Lee SH, Lee GW, Lee SJ and Kim SG. Association between the response of intravitreal antivascular endothelial growth factor injection and systemic factors of diabetic macular edema. BMC Ophthalmol 2024; 24: 166.

[3] Dugel PU, Bandello F and Loewenstein A. Dexamethasone intravitreal implant in the treatment of diabetic macular edema. Clin Ophthalmol 2015; 9: 1321-1335.

[4] Yao CS and Paulus YM. Advances in minimally traumatic retinal laser therapy. Expert Rev Med Devices 2025; 22: 1293-1302.

[5] Jiang Y, He W and Qi S. Evaluating the efficacy of subthreshold micropulse laser combined with anti-VEGF drugs in the treatment of diabetic macular edema: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2025; 16: 1553311.

[6] Wijeweera C, Ni J, Petocz P, Preda V and Jabbour J. Efficacy of anti-VEGF monotherapy versus anti-VEGF therapy with subthreshold micropulse laser (SML) in the management of diabetic macular oedema (DMO): a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol 2024; 262: 2733-2749.

[7] Xu D, Zhu T, Huang L, Wang X and Chen M. Clinical efficacy of subthreshold micropulse laser combined with anti-VEGF drugs in the treatment of diabetic macular edema: a meta-analysis. Medicine (Baltimore) 2024; 103: e34583.

[8] Lubis PM, Prabaniswara MP and Victor AA. Comparison of micropulse subthreshold laser plus anti-VEGF versus anti-VEGF alone in diabetic macular edema: systematic review. Indian J Ophthalmol 2023; 71: 3448-3453.

[9] Haydinger CD, Ferreira LB, Williams KA and Smith JR. Mechanisms of macular edema. Front Med (Lausanne) 2023; 10: 1128811.

[10] Zhong YY, Tang C, Zhang LY, Zhang XD and Liu SL. Dexamethasone implant for refractory macular edema secondary to diabetic retinopathy and retinal vein occlusion. Int J Ophthalmol 2024; 17: 1837-1842.

[11] Zhang J, Zhang J, Zhang C, Zhang J, Gu L, Luo D and Qiu Q. Diabetic macular edema: current understanding, molecular mechanisms and therapeutic implications. Cells 2022; 11: 3362.

[12] Sorour OA, Levine ES, Baumal CR, Elnahry AG, Braun P, Girgis J and Waheed NK. Persistent diabetic macular edema: definition, incidence, biomarkers, and treatment methods. Surv Ophthalmol 2023; 68: 147-174.

[13] Rennie C, Lotery A, Payne J, Singh M and Ghanchi F. Suboptimal outcomes and treatment burden of anti-vascular endothelial growth factor treatment for diabetic macular oedema in phakic patients. Eye (Lond) 2024; 38: 215-223.

[14] Kashiwagi I, Nonaka R, Sasaki S, Yamamoto T, Yasuda K and Shimura M. Efficacy of aflibercept (8 mg) for diabetic macular edema in vitrectomized eyes refractory to the other anti-VEGF drug therapies: a report of three cases. Int Med Case Rep J 2025; 18: 465-471.

[15] Egger D, Heger KA, Bolz M, Brinkmann MP, Krepler K, Vecsei-Marlovits PV, Wedrich A and Waldstein SM. Intravitreal therapy-success stories and challenges. Wien Med Wochenschr 2025; 175: 162-174.

[16] Han Y, Yang MY, Wang HL, Meng J, Zhu ML, Ma SY, Wang SH and Li XJ. Conbercept combined with 577 nm subthreshold micropulse laser for diabetic macular edema. Int J Ophthalmol 2025; 18: 2122-2129.

[17] Chen J, Wang H and Qiu W. Intravitreal antivascular endothelial growth factor, laser photocoagulation, or combined therapy for diabetic macular edema: a systematic review and network meta-analysis. Front Endocrinol (Lausanne) 2023; 14: 1096105.

[18] Hosoya H, Ueta T, Hirasawa K, Toyama T and Shiraya T. Subthreshold micropulse laser combined with anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol 2024; 262: 3073-3083.

[19] Bodea F, Bungau SG, Bogdan MA, Vesa CM, Radu A, Tarce AG, Purza AL, Tit DM, Bustea C and Radu AF. Micropulse laser therapy as an integral part of eye disease management. Medicina (Kaunas) 2023; 59: 1388.
[20] Lois N, Campbell C, Waugh N, Azuara-Blanco A, Maredza M, Mistry H, McAuley D, Acharya N, Aslam TM, Bailey C, Chong V, Downey L, Eleftheriadis H, Fatum S, George S, Ghanchi F, Groppe M, Hamilton R, Menon G, Saad A, Sivaprasad S, Shiew M, Steel DH, Talks JS, Doherty P, McDowell C and Clarke M; DIAMONDS Study Group. Diabetic macular edema and diode subthreshold micropulse laser: a randomized double-masked noninferiority clinical trial. Ophthalmology 2023; 130: 14-27.
[21] Iovino C, Iodice CM, Pisani D, Rosolia A, Testa F, Giannaccare G, Chhablani J and Simonelli F. Yellow subthreshold micropulse laser in retinal diseases: an in-depth analysis and review of the literature. Ophthalmol Ther 2023; 12: 1479-1500.
[22] Midena E, Micera A, Frizziero L, Pilotto E, Esposito G and Bini S. Sub-threshold micropulse laser treatment reduces inflammatory biomarkers in aqueous humour of diabetic patients with macular edema. Sci Rep 2019; 9: 10034.
[23] Frizziero L, Calciati A, Midena G, Torresin T, Parrozzani R, Pilotto E and Midena E. Subthreshold micropulse laser modulates retinal neuroinflammatory biomarkers in diabetic macular edema. J Clin Med 2021; 10: 3134.
[24] Li Z, Song Y, Chen X, Chen Z and Ding Q. Biological modulation of mouse RPE cells in response to subthreshold diode micropulse laser treatment. Cell Biochem Biophys 2015; 73: 545-552.
[25] Midena E, Bini S, Frizziero L, Pilotto E, Esposito G and Micera A. Aqueous humour concentrations of PEDF and Erythropoietin are not influenced by subthreshold micropulse laser treatment of diabetic macular edema. Biosci Rep 2019; 39: BSR20190328.
[26] Shiraya T, Araki F, Nakagawa S, Ueta T, Totsuka K, Abe H, Naito Y, Toyama T, Sugimoto K and Kato S. Differential gene expression analysis using RNA sequencing: retinal pigment epithelial cells after exposure to continuous-wave and subthreshold micropulse laser. Jpn J Ophthalmol 2022; 66: 487-497.
[27] Ma CC, Chen PH and Hsieh YH. Optimizing diabetic macular edema treatment: a meta-analysis of subthreshold micropulse laser and anti-vascular endothelial growth factor combination therapy. J Clin Med 2024; 13: 4782.
[28] Tai F, Nanji K, Garg A, Zeraatkar D, Phillips M, Steel DH, Garg SJ, Kaiser PK, Guymer RH, Wykoff CC, Sivaprasad S and Chaudhary V. Subthreshold compared with threshold macular photocoagulation for diabetic macular edema: a systematic review and meta-analysis. Ophthalmol Retina 2024; 8: 223-233.
[29] Cheema AA and Cheema HR. Diabetic macular edema management: a review of anti-vascular endothelial growth factor (VEGF) therapies. Cureus 2024; 16: e52676.
[30] Holekamp N, Gentile B, Giocanti-Aurégan A, García-Layana A, Peto T, Viola F, Kertes PJ, Mirt M, Kotecha A, Lambert J, Lewis HB and Chi GC. Patient experience survey of anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration and diabetic macular edema. Ophthalmic Res 2024; 67: 311-321.
[31] Kanar HS, Arsan A, Altun A, Akı SF and Hacısalihoglu A. Can subthreshold micropulse yellow laser treatment change the anti-vascular endothelial growth factor algorithm in diabetic macular edema? A randomized clinical trial. Indian J Ophthalmol 2020; 68: 145-151.
[32] Furashova O, Strassburger P, Becker KA and Engelmann K. Efficacy of combining intravitreal injections of ranibizumab with micropulse diode laser versus intravitreal injections of ranibizumab alone in diabetic macular edema (ReCaLL): a single center, randomised, controlled, non-inferiority clinical trial. BMC Ophthalmol 2020; 20: 308.
[33] Koushan K, Eshtiaghi A, Fung P, Berger AR and Chow DR. Treatment of diabetic macular edema with aflibercept and micropulse laser (DAM study). Clin Ophthalmol 2022; 16: 1109-1115.
[34] Altınel MG, Acikalin B, Alis MG, Demir G, Mutibayraktaroglu KM, Totuk OMG and Ardagil A. Comparison of the efficacy and safety of anti-VEGF monotherapy versus anti-VEGF therapy combined with subthreshold micropulse laser therapy for diabetic macular edema. Lasers Med Sci 2021; 36: 1545-1553.
[35] Hansraj S, Narula R, Raval VR, Narayanan R and Tyagi M. Real world outcomes of intravitreal brolucizumab for persistent diabetic macular edema. Int J Retina Vitreous 2025; 11: 101.
[36] Liu J, Li R, Han K, Yu X, Tang Y and Zhao H. Intravitreal injection of Conbercept combined with micropulse laser therapy enhances clinical efficacy in patients with diabetic macular edema. Am J Transl Res 2023; 15: 531-538.
[37] Sun GL, Zhang S, Qin X, Liu YY, Zhao YJ and Xu Y. 577 nm subthreshold micropulse laser combined with conbercept for diabetic macular edema after vitrectomy. Guoji Yanke Zazhi 2023; 23: 996-1000.
[38] Fang LJ and Wei WB. Clinical study of intravitreal conbercept injection combined with subthreshold micropulse laser for diabetic ma-

cular edema. Zhonghua Yanke Yixue Zazhi (Dianziban) 2020; 10: 90-96.
[39] Giyasova AO and Yangieva NR. Comparing the effectiveness of brolucizumab therapy alone versus that combined with subthreshold micropulse laser exposure in the treatment of diabetic macular edema. Oftalmologicheskii Zhurnal 2023; 2: 16-20.
[40] Vujosevic S, Toma C, Villani E, Brambilla M, Torti E, Leporati F, Muraca A, Nucci P and De Cilla S. Subthreshold micropulse laser in diabetic macular edema: 1-year improvement in OCT/OCT-angiography biomarkers. Transl Vis Sci Technol 2020; 9: 31.
[41] Sabal B, Wylęgała E and Teper S. Impact of subthreshold micropulse laser on the vascular network in diabetic macular edema: an optical coherence tomography angiography study. Biomedicines 2025; 13: 1194.
[42] Gu W, Wang M, Li Z and Xu T. The association between peripheral blood inflammatory markers and anti-VEGF treatment response in patients with type 2 diabetic macular edema. Front Med (Lausanne) 2025; 12: 1653753.
[43] Arima M, Nakao S, Yamaguchi M, Feng H, Fujii Y, Shibata K, Wada I, Kaizu Y, Ahmadieh H, Ishibashi T, Stitt AW and Sonoda KH. Claudin-5 redistribution induced by inflammation leads to anti-VEGF-resistant diabetic macular edema. Diabetes 2020; 69: 981-999.
[44] Feldman S, Basra J, Lawani A, Ren Y, Wilson M, Moshiri A, Park SS and Yiu G. Subthreshold micropulse laser for eyes with center involving diabetic macular edema with good visual acuity: the pulse study, a randomized clinical trial. Ophthalmic Surg Lasers Imaging Retina 2025; 56: 86-93.
[45] Wei Q, Chen R, Lou Q and Yu J. Intravitreal corticosteroid implant vs intravitreal ranibizumab for the treatment of macular edema: a meta-analysis of randomized controlled trials. Drug Des Devel Ther 2019; 13: 301-307.
[46] Mistry H, Maredza M, Campbell C and Lois N; DIAMONDS Study Group. Subthreshold micropulse laser versus standard laser for the treatment of central-involving diabetic macular oedema with central retinal thickness of < 400 μ: a cost-effectiveness analysis from the DIAMONDS trial. BMJ Open 2023; 13: e067684.