Clinical Ophthalmology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

From Monotherapy to Combination Strategies: Redefining Treatment Approaches for Multiple-Cause Macular Edema

Qianwei Zhu[1], Xuchong Pan[1], Zhenni Du[1], Jianing Ying[2], Yiran Hu[1], Quanyong Yi[2], Xiangxiang Fu[1]

[1]Department of Ophthalmology, Yuyao Maternity and Child Health Care Hospital (Yuyao Second People's Hospital), Ningbo, People's Republic of China; [2]Department of Ophthalmology, Ningbo Eye Hospital, Wenzhou Medical University, Ningbo, People's Republic of China

Correspondence: Quanyong Yi, Department of Ophthalmology, Ningbo Eye Hospital, Wenzhou Medical University, Ningbo, People's Republic of China, Tel +8613586543802, Email quanyong_yi@163.com; Xiangxiang Fu, Department of Ophthalmology, Yuyao Maternity and Child Health Care Hospital (Yuyao Second People's Hospital), Ningbo, People's Republic of China, Tel +8617855825160, Email yywjwfxx@163.com

Abstract: Macular edema (ME) is a leading cause of visual impairment in various retinal disorders. Current treatment modalities, including anti-vascular endothelial growth factor (anti-VEGF) agents and corticosteroids, often require repeated applications, increasing both medical and economic burdens. ME is driven by chronic inflammation and VEGF overexpression, causing fluid accumulation in the macula. Recent studies have highlighted the role of various cytokines in ME pathogenesis, necessitating a comprehensive approach to treatment. While monotherapies have shown efficacy, they are associated with limitations such as the need for frequent injections and potential side effects. Combination therapies, including anti-VEGF drugs with macular laser photocoagulation, triamcinolone acetonide, or dexamethasone intravitreal implant (Ozurdex), have emerged as promising strategies. This review analyzes the outcomes of various combination approaches in different types of ME, including diabetic macular edema (DME), retinal vein occlusion-associated ME (RVO-ME), and uveitic macular edema (UME). The potential benefits of combining anti-VEGF and anti-inflammatory treatments are discussed, along with the need for personalized treatment regimens. Future research directions are outlined, emphasizing the importance of large-scale, long-term studies to evaluate the sustained efficacy and safety of combination therapies. The integration of advanced imaging techniques, biomarker analysis, and innovative therapeutic approaches is expected to shape the future landscape of ME management, moving towards more targeted and effective combination therapies.

Plain Language Summary:

Why was the study done?

Macular edema (ME) is a leading cause of visual impairment, particularly in patients with conditions like diabetic retinopathy, retinal vein occlusion, and uveitis. Current treatments, such as anti-VEGF injections and corticosteroids, often need to be repeated frequently, placing a significant burden on patients and healthcare systems. This study was conducted to explore whether combining therapies could improve outcomes, reduce treatment frequency, and overcome the limitations of single treatments.

What did the researchers do and find?

We reviewed studies on combination therapies, such as anti-VEGF drugs paired with corticosteroids or laser treatments, to see how effective they are in treating different types of macular edema. Existing evidence suggests that combination treatments often provide better visual improvements and reduce treatment frequency compared to using a single therapy. For instance:

Combining anti-VEGF agents with corticosteroids improved outcomes for patients with persistent or severe ME.

Using laser therapy alongside medications enhanced recovery for certain types of macular edema.

However, these approaches must be carefully monitored, as corticosteroids can cause side effects like increased eye pressure and cataract formation.

What do these results mean?

The findings suggest that combination therapies could be a more effective and efficient way to manage macular edema, especially for patients who do not respond well to single treatments. Further research, including long-term studies, is needed to optimize these

Received: 19 December 2024
Accepted: 7 March 2025
Published: 12 March 2025

treatment strategies and make them safer and more personalized. By combining treatments, we may reduce the burden on patients while improving their vision and quality of life.

Keywords: combination therapy, macular edema, ozurdex, anti-vascular endothelial growth factor, cytokines

Introduction

Macular edema (ME) is a leading cause of visual impairment in various retinal disorders, most commonly associated with diabetic retinopathy (DME), retinal vein occlusion (RVO-ME), and uveitis (UME). Current treatment modalities include anti-vascular endothelial growth factor (anti-VEGF) agents, corticosteroids, retinal laser photocoagulation, and pars plana vitrectomy.[1,2]

Anti-VEGF therapy has revolutionized ME treatment, with bevacizumab, ranibizumab, aflibercept, and conbercept being widely used agents.[3,4] These therapies have evolved to extend treatment duration and reduce the need for frequent injections. Recent clinical investigations suggest that increasing the aflibercept dose to 8 mg may allow for longer treatment intervals while maintaining efficacy and safety, potentially alleviating the treatment burden in DME patients.[5]

However, these monotherapies exhibit limitations in terms of efficacy, treatment frequency, and safety. In recent years, combination therapy strategies have emerged as a research focus, aiming to optimize therapeutic outcomes and reduce treatment burden through multi-target interventions.[6]

This review summarizes the latest research progress on combination therapies for ME, with a particular emphasis on their current applications and clinical efficacy in DME, RVO-ME, and UME. Furthermore, we explore future directions for precision and personalized treatment approaches.

The Pathophysiology of Macular Edema Formation

ME is not a discrete disease entity but rather a pathological condition resulting from various retinal disorders. At its core, ME is characterized by abnormal fluid accumulation within the macula, involving both extracellular and intracellular compartments. Extracellular edema manifests as the infiltration of fluid into the retinal layers, particularly accumulating between Henle's fibers, leading to the formation of characteristic cystic spaces. Conversely, intracellular edema is primarily associated with Müller cell dysfunction. These glial cells undergo morphological alterations, cellular abnormalities, and increased apoptosis, collectively compromising the integrity of the blood-retinal barrier.[7]

Under normal conditions, the retina remains dehydrated and transparent, but ME disrupts this balance through increased blood-retinal barrier permeability, impaired fluid drainage, and enhanced protein leakage.[8,9] The interplay of these factors results in a significant disruption of retinal fluid balance, ultimately leading to the clinical manifestation of ME.

Cytokines play a crucial role in the pathogenesis of ME. Specifically, chemokines, a subset of cytokines, are instrumental in orchestrating leukocyte aggregation during inflammatory and immune responses.[10] Several key inflammatory mediators have been implicated in ME, including interleukin-8 (IL-8), monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 1 (MIP-1). These cytokines are notably upregulated in ME, with IL-8 and MCP-1 demonstrating a particular propensity to exacerbate the condition. Furthermore, studies have revealed significantly elevated levels of interferon gamma-induced protein 10 (IP-10) and tumor necrosis factor alpha (TNF-α) in ME patients compared to those without ME.[11] Importantly, research has established a positive correlation between the levels of certain cytokines, particularly IL-8 and MCP-1, and central macular thickness (CMT).[12] This correlation underscores the potential role of these inflammatory mediators in the structural changes observed in ME. In conclusion, the intricate involvement of cytokines in ME pathogenesis necessitates their consideration in any comprehensive discussion of ME treatment strategies. Understanding the cytokine profile in ME may offer valuable insights for developing targeted therapeutic approaches.

Limitations of Macular Edema Monotherapy

Currently, the most widely used clinical treatments for ME include anti-VEGF drugs, macular laser photocoagulation (MLP), corticosteroids, and surgical interventions. However, each of these approaches has its own limitations.

Anti-VEGF therapy is the primary treatment modality for ME, with ranibizumab, bevacizumab, aflibercept, and conbercept being the main agents. These drugs function by binding to VEGF, thereby inhibiting its activity.[13] While studies have demonstrated the efficacy and safety of anti-VEGF drugs,[14,15] they are associated with significant drawbacks. These include high costs,[16] the need for repeated injections, and prolonged treatment cycles, all of which increase the burden on both patients and healthcare providers.[17]

Corticosteroids, particularly dexamethasone intravitreal implant (Ozurdex), are widely used due to their potent anti-inflammatory effects. Research has shown their safety and efficacy in treating ME.[18] However, the duration of visual recovery is limited, and there is a high risk of recurrence.[19] Other corticosteroids such as triamcinolone acetonide[20] and fluocinolone acetonide[21] have limited applications due to side effects including elevated intraocular pressure and cataract formation.

MLP, while a traditional treatment for ME,[22] is no longer considered a first-line therapy but rather an adjunctive treatment. Pars plana vitrectomy has shown effectiveness in managing refractory DME.[23] However, it is not the preferred option for patients with mild disease, and there is ongoing debate regarding the optimal surgical approach.[24]

The Use of Combination Therapy

To overcome these limitations, combination therapy has gradually emerged as a focal point of research. Combination therapy has gained widespread adoption in recent years for the treatment of ME. Various approaches have been explored, including anti-VEGF drugs combined with MLP, triamcinolone acetonide (TA) combined with MLP, anti-VEGF combined with TA, and anti-VEGF combined with dexamethasone intravitreal implant (Ozurdex). These combination strategies aim to achieve superior visual recovery, reduce the frequency of treatments, and mitigate the risk of complications. Therefore, a comprehensive understanding of the advantages and limitations of combined therapies may prove beneficial in optimizing ME management.

Anti-VEGF Combined With MLP

RVO-ME

Hirashima et al[25] investigated the combination of intravitreal bevacizumab (IVB) with MLP and reported significant improvement in best-corrected visual acuity (BCVA) one month post-treatment. However, this improvement diminished by the six-month follow-up. Similarly, Ogino et al[26] observed that grid-like photocoagulation (GRID) combined with IVB yielded notable anatomical improvements but limited BCVA enhancement. Furthermore, some researchers[27] found that the addition of GRID to IVB did not reduce the number of IVB injections required. These findings suggest that the efficacy of anti-VEGF combined with MLP may be limited in RVO-ME cases.

DME

In the context of DME, Meng et al demonstrated that conbercept combined with retinal laser photocoagulation resulted in superior central retinal thickness (CRT) recovery compared to laser photocoagulation alone.[28] Huang et al also reported that intravitreal injection of conbercept (IVC) combined with panretinal photocoagulation (PRP) was more effective in visual recovery than PRP monotherapy.[29] However, it should be noted that these studies were not large-scale trials, and further investigation is warranted to confirm these findings.

UME

Shao et al[30] conducted a study involving 78 UME patients, comparing IVB combined with argon-green laser to argon-green laser monotherapy. The combination therapy group exhibited superior outcomes in terms of foveal thickness reduction and visual acuity improvement. Some studies suggest that early MLP is crucial for UME management,[31] indicating that early combination of IVB with argon-green laser may be an effective approach for UME treatment. However, the paucity of combination studies in UME necessitates further investigation to establish optimal treatment protocols.

TA Combined With MLP

Intravitreal triamcinolone acetonide (IVT) administration has been associated with complications such as secondary glaucoma, cataract progression, and vitreous hemorrhage.[20] While peribulbar injection of TA (POTA)[32] has shown efficacy in reducing these risks, it does not completely eliminate them.

RVO-ME

Ozkaya et al found that the IVT+GRID group required significantly fewer treatments compared to the IVB+GRID group. However, the incidence of cataract and glaucoma was higher in the IVT+GRID group.[33] Additionally, Riese et al[34] reported favorable outcomes with IVT combined with MLP in 24 patients, but this study lacked a large-scale controlled comparison. The safety profile of this combination warrants further investigation.

DME

Forte et al compared single IVB treatment to IVT combined with MLP for DME management. They observed significant improvements in BCVA and CRT within the first year of treatment in the IVB group.[35] In contrast, the IVT-MLP group showed no significant improvement, and 10.4% of patients developed ocular hypertension, with two patients ultimately requiring trabeculectomy. Lam et al found no superior outcomes in combination therapy patients at the 6-month follow-up.[36]

In the context of proliferative diabetic retinopathy (PDR), Lopez et al[37] suggested that the addition of IVT to PRP only reduced active neovascularization compared to PRP alone, with no significant difference between the two approaches. Some researchers[38] even argue that IVT as an adjunct to MLP offers no significant benefit.

UME

There is a paucity of literature on the combination of IVT and MLP for UME treatment. Considering the relatively novel approach of choroidal injection of TA for non-infectious UME[39] and the potential benefits of early MLP,[31] the combination of early MLP with suprachoroidal injection of TA may represent a promising avenue for future research.

Anti-VEGF Combined With TA

RVO-ME

Fan et al[40] reported that intravitreal ranibizumab (IVR) alone or combined with IVT yielded similar improvements in CRT and BCVA, but the combination therapy significantly reduced the number of treatments required. Zhao et al[41] corroborated these findings, noting that the combination maintained BCVA for a longer duration and reduced CRT more effectively. However, they also observed an increased incidence of elevated intraocular pressure (IOP) and cataract formation with the combination approach.

DME

Studies have indicated that IVT combined with IVB may be effective in treating DME.[42] Yu et al[43] investigated IVT as an adjunct to anti-VEGF therapy and found that over a 12-month period, the average treatment cost for IVC and MLP was approximately $6,247.44, while IVC and MLP combined with IVT cost about $1,679.19, demonstrating a clear economic advantage.

Professor Riazi[44] posits that while combination therapy can reduce the number of treatments required, its effects may be short-lived. The combination appears more effective in improving BCVA and reducing CRT within the first three months, but long-term efficacy requires further verification.

For refractory DME, Professor Eriş[45] suggests that combination therapy may be a viable option. A two-year study[46] demonstrated that IVB might be more effective in the short term, while the combination (IVB combined with IVT and MLP) may offer greater long-term benefits. However, research in this area has been limited due to the side effects associated with TA.

UME

Leder et al[47] studied 126 UME patients treated with POTA and found that 53% showed early remission of ME, with 40% requiring more than one treatment. Similar studies[48] also noted the need for repeated IVT treatments. Acharya et al[49]

observed that the effects of IVR treatment for refractory UME persisted at 6 months. Combining these complementary approaches may yield superior outcomes.

Given the side effects associated with TA, clinicians may consider using the relatively safer intravitreal Ozurdex implant in combination with anti-VEGF therapy.

Ozurdex Combined With Anti-VEGF

Anti-VEGF therapy demonstrates good visual recovery but often requires repeated injections. Corticosteroids can reduce the frequency of injections but are associated with increased intraocular pressure.[50] Central serous chorioretinopathy is another side effect that cannot be overlooked.[51,52] These considerations suggest that combining the advantages of less frequent dexamethasone intravitreal implant (DI) administration with the efficacy of anti-VEGF on BCVA may yield superior outcomes. The following sections summarize the current research on this combination approach.

RVO-ME

Aflibercept Combined With Ozurdex

Harb et al[53] conducted a comparative study of intravitreal aflibercept (IVA) combined with DI versus DI alone in RVO-ME patients. In the combination group, IVA was administered first, followed by DI after two weeks, with a one-year follow-up period. They found that the combination group achieved better BCVA, although there was no significant difference in central CRT. The number of treatments did not differ significantly between groups. Only one patient in each group developed intraocular hypertension, which was manageable with topical medication. However, this study did not specify whether patients were treatment-naïve, and the impact of different dosing intervals requires further investigation. Furthermore, the study lacked a comprehensive analysis of inflammatory factors.

To address these limitations, Giuffrè et al[54] eliminated the two-week interval and administered IVA+DI simultaneously in the same quadrant of the eye. Their 12-month follow-up revealed no significant change in BCVA, while CRT was significantly reduced compared to baseline. Only one patient required local IOP-lowering treatment. The contrasting conclusions drawn by Harb and Giuffrè may be attributed to the difference in treatment intervals. However, neither study classified RVO subtypes, and both had small sample sizes. Further analysis is needed to elucidate the reasons for these discrepancies.

Bevacizumab Combination With Ozurdex

Singer et al[55] administered DI two weeks after IVB. Of the 34 eyes treated, six did not require further intervention. BCVA improved, and CRT decreased by nearly 200μm, with no adverse events reported. Maturi et al[56] adjusted the injection interval to one week and found that fewer IVB treatments were required. However, these studies were limited by small sample sizes and short follow-up periods, necessitating further research.

Ranibizumab Combination With Ozurdex

The combination of intravitreal ranibizumab (IVR) and dexamethasone intravitreal implant (DI, Ozurdex) has emerged as a promising approach for treating RVO-ME. Lip et al[57] introduced the RandOL regimen, a tailored treatment protocol combining these two therapies. This regimen begins with three monthly IVR injections, followed by a maintenance phase where additional IVR is administered for persistent ischemia or recurrence, and DI is used for non-ischemic ME or recurrent ME with retinal ischemia, as determined by fluorescein angiography (FFA). The protocol also incorporates FFA-guided MLP for non-perfused retinal areas.

In their study of 66 patients, Lip et al reported that 46 patients received DI, with most undergoing 1–2 MLP sessions. Over a 12-month period, patients averaged 4.3 IVR and 1 DI treatment. The results were encouraging, with 77% of patients showing improved visual acuity and 97% demonstrating significant CRT improvement. Only two cases of mild vitreous hemorrhage were reported, with no other significant complications observed. The RandOL regimen offers the advantages of individualized treatment, targeted application of DI, and minimized adverse drug reactions. However, the study was limited by its short duration, relatively small sample size, and the complexity of assessing treatment effects due to the combination of three treatment modalities.

To address these limitations and evaluate the long-term efficacy of the RandOL regimen, Horner et al[58] conducted a three-year follow-up study. Their findings revealed sustained visual acuity improvements in 77% of patients in the first year and 63% by the third year, with significant CRT improvement throughout the study period. Notably, the frequency of treatments decreased over time. By the third year, 39.6% of patients did not require any form of injection, and the MLP frequency decreased from 81.8% in the first year to 22.9% in the third year. These results suggest that the RandOL regimen can provide stable and favorable long-term outcomes for RVO-ME patients.

Despite the promising results, both studies have limitations, including small sample sizes, high loss to follow-up rates, and a primary focus on BCVA and CRT outcomes. Future research should consider larger, randomized controlled trials with longer follow-up periods. Additionally, the inclusion of additional outcome measures, such as OCT blood flow signals and macular volume (MV), as well as analysis of inflammatory markers, could provide a more comprehensive understanding of the synergistic effects of IVR and DI.

In conclusion, the combination of ranibizumab and Ozurdex, particularly as implemented in the RandOL regimen, shows promise for the treatment of RVO-ME. However, further research is needed to fully elucidate its long-term efficacy and safety profile, as well as to optimize the treatment protocol for different patient populations.

DME

Aflibercept Combination With Ozurdex

The combination of intravitreal aflibercept (IVA) and Ozurdex (DI) has been scarcely reported in literature. Ozsaygili's study[59] found this combination to be effective and safe for treatment-naïve patients. While DI showed better anatomical recovery with fewer injections (2.6 times), IVA demonstrated superior visual function improvement despite requiring more injections (7.2 times). These findings, coupled with Herbaut's observation[60] of significant improvements in visual function and anatomy after switching from IVR to IVA in refractory DME, suggest that the combined application may yield better outcomes.

Hussain[61] highlighted that DME pathology involves not only VEGF but also other inflammatory mediators. For patients with severe visual loss, IVA appears more effective than IVB, and the combination of DI with IVA may be particularly beneficial. Professor Hernández-Bel[62] compared combination therapy (IVA every two months after a single DI) with monotherapy (IVA every two months after 5 consecutive months), finding similar efficacy but fewer retreatments in the combination group. However, this study's small sample size and extended combination interval warrant further investigation.

The DI+IVA combination shows promise, with Foglia[63] demonstrating its potential to reduce regional medical expenditures. However, more research is needed to support this combined approach. Ozsaygili's study noted a moderate effect of IVA on intraocular lenses, suggesting the need for careful analysis of joint research subjects in future studies.

Bevacizumab Combination With Ozurdex

A study on simultaneous IVB and DI administration for DME treatment[64] reported significant improvements in both BCVA and CRT. This innovative approach of concurrent injection proved effective without adverse safety events. However, the study lacked a corticosteroid control group.

Another study[65] using TA as a control found that IVT may be more effective than DI combined with IVB in reducing macular volume (MV) in ME, though BCVA remained unchanged. The short follow-up time and the off-label use of bevacizumab for DME treatment necessitate further verification through large-scale randomized trials.

Ranibizumab Combination With Ozurdex

Cakir[66] administered a single DI to patients with poor response after three consecutive months of IVR, followed by continued IVR. An 8-month follow-up revealed significant improvements in BCVA and CRT, with no difference observed between various DME types. Previous research[67] has shown that DI can reduce concentrations of certain inflammatory proteins, while IVR decreases VEGF and placental growth factor levels. However, a comprehensive elucidation of factor changes is still lacking.

Sever[68] used a similar method but concluded that DI had limited effects on BCVA and CRT in refractory DME after three consecutive IVR treatments. This study included an IVR control group and focused on non-proliferative diabetic

retinopathy patients who had undergone cataract surgery. The conflicting results may be attributed to differences in study design and patient characteristics. Some researchers[69] even found that adding DI to continuous IVR treatment did not improve vision at 24 weeks compared to IVR alone.

The efficacy of IVR combined with DI remains controversial. Given the positive outcomes observed in studies combining anti-VEGF with TA,[70] further research into IVR and DI combination therapy is warranted.

UME

Studies on anti-VEGF combined with DI for UME treatment are limited. Koronis[71] maintains that corticosteroids remain the primary treatment option. Other experts[72] suggest that DI can significantly improve CRT and best-recorded visual acuity in initial UME treatment, and the combination of IVR with DI may be effective. However, large-scale, long-term studies are needed to support these findings.

Strengths and Limitations of Literature Review

This comprehensive review synthesizes evidence from numerous studies examining combination therapies for ME management. The reviewed literature demonstrates several notable strengths in both methodology and clinical relevance. Many studies utilized randomized controlled trial designs, providing robust evidence for treatment efficacy. Several investigations offered valuable long-term follow-up data extending up to three years, which enhances our understanding of the sustained effects of combination therapies. Furthermore, the studies encompassed diverse patient populations and various types of ME, strengthening the generalizability of findings across different clinical scenarios.

However, certain limitations warrant consideration when interpreting these results. A considerable number of studies had relatively small sample sizes, potentially limiting their statistical power. The heterogeneity in follow-up periods and outcome measures across different studies posed challenges for direct comparisons. Some studies lacked proper control groups or randomization protocols, which may affect the reliability of their findings. Additionally, there was limited data addressing the cost-effectiveness of combination therapies, an important consideration for clinical implementation. The variable definitions of treatment success across studies also complicated the synthesis of evidence.

These methodological considerations underscore the need for larger, well-designed randomized controlled trials with standardized outcome measures and extended follow-up periods to better evaluate the efficacy of combination therapies in ME management. Such improvements in study design would strengthen the evidence base for clinical decision-making in ME treatment.

Conclusion

This review highlights that combining anti-VEGF agents, corticosteroids, and laser therapy often achieves better outcomes than monotherapy in managing ME.

Key findings from this review include:

1. Anti-VEGF agents combined with laser treatment have shown enhanced therapeutic efficacy, reduced injection frequency, and sustained visual improvement compared to either modality alone.
2. The addition of corticosteroids to anti-VEGF therapy has demonstrated promising results in refractory cases, particularly in patients with suboptimal response to anti-VEGF monotherapy. However, this combination necessitates careful monitoring due to the increased risk of intraocular pressure elevation and cataract progression.
3. Laser therapy, especially with the advent of novel technologies such as subthreshold micropulse laser, continues to play a significant role as an adjunct to pharmacological treatments, offering more precise and potentially safer options for combination strategies.
4. The importance of individualized treatment regimens has become increasingly apparent, underscoring the need to consider patient-specific factors, disease severity, and treatment response patterns in clinical decision-making.

Significantly, previous research has provided crucial insights into the cytokine characteristics of the aqueous humor in anti-VEGF treatment of ME.[73] Analysis of patients with central retinal vein occlusion, branch retinal vein occlusion, and

DME revealed the coexistence of VEGF, ICAM-1, and IL-6 before and after anti-VEGF treatment. This study identified chronic inflammation and VEGF overexpression as primary drivers of retinal disease progression. Notably, monotherapy with anti-VEGF agents significantly reduced only VEGF levels, while inflammatory factors such as ICAM-1 and IL-6 remained largely unchanged. This finding underscores the potential advantages of combining anti-VEGF and anti-inflammatory treatments for more effective outcomes.

While significant progress has been made, managing ME remains challenging due to disease complexity and variable patient responses, highlighting the need for further research. The findings of this review, particularly our novel insights into aqueous humor cytokine profiles, suggest that combination therapies targeting both VEGF and inflammatory pathways hold significant potential for improving outcomes in ME patients.

In conclusion, while substantial progress has been made in the field of ME management through combination therapies, there remains a critical need for ongoing investigation and clinical innovation to further optimize treatment strategies and improve patient outcomes.

Outlook

As the field of ME management continues to evolve, several promising avenues for future research and clinical development emerge:

1. Targeted Combination Therapies: Future studies should target both VEGF and inflammatory pathways (eg, ICAM-1, IL-6) to overcome the limitations of anti-VEGF monotherapy.
2. Optimization of Anti-inflammatory Strategies: Research into novel anti-inflammatory agents or improved delivery methods for existing ones should be prioritized to complement anti-VEGF therapies effectively.
3. Personalized Medicine Approaches: The development of biomarkers based on aqueous humor cytokine profiles may enable more targeted and effective treatment strategies. Research into predictive factors for treatment response could lead to more personalized combination therapy regimens, potentially improving outcomes and reducing unnecessary treatments.
4. Long-term Efficacy and Safety Assessments: Extended follow-up studies are needed to evaluate the durability of treatment effects and long-term safety profiles of various combination strategies, particularly those targeting both VEGF and inflammatory pathways.
5. Novel Drug Delivery Systems: Innovations in drug delivery methods, such as sustained-release implants or nanoparticle-based therapies, should be explored for their potential to simultaneously deliver anti-VEGF and anti-inflammatory agents.
6. Advanced Imaging and Biomarker Studies: Further development and application of high-resolution imaging modalities and molecular biomarker analyses could provide deeper insights into the pathophysiology of ME and treatment response at a cellular level.

The future of ME management lies in the development of more targeted, personalized, and comprehensive treatment strategies that address both the vascular and inflammatory aspects of the disease. By refining combination therapies to target multiple pathways simultaneously, there is potential to significantly improve visual outcomes and quality of life for patients with ME. The integration of advanced technologies, novel drug combinations, and personalized approaches based on molecular profiling holds great promise for the next generation of ME treatments.

Ethics Approval and Informed Consent

Not applicable as this is a systematic review that does not involve human subjects, experimental procedures, or clinical trials. No ethical approval was required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by funding from the Ningbo Public Welfare Research Program (grant number 2024S176), the Zhejiang Medical and Health Science and Technology Project (grant number 2025KY1492), the Ningbo Health Science and Technology Program (grant number 2023Y74), the Zhejiang Medical and Health Science and Technology Project (grant number 2023RC089), and the Yuyao Health and Wellness Science and Technology Program (grant number 2024YPT01).

Disclosure

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Jonas JB. Diabetic Macular Edema. *Asia Pac J Ophthalmol*. 2020;9(5):377–378. doi:10.1097/APO.0000000000000324
2. Chi S-C, Kang Y-N, Huang Y-M. Efficacy and safety profile of intravitreal dexamethasone implant versus antivascular endothelial growth factor treatment in diabetic macular edema: a systematic review and meta-analysis. *Sci Rep*. 2023;13(1):7428. doi:10.1038/s41598-023-34673-z
3. Heier JS, Bressler NM, Avery RL, et al. Comparison of Aflibercept, Bevacizumab, and Ranibizumab for Treatment of Diabetic Macular Edema: extrapolation of Data to Clinical Practice. *JAMA Ophthalmol*. 2016;134(1):95–99. doi:10.1001/jamaophthalmol.2015.4110
4. Xing Q, Dai Y-N, Huang X-B, Peng L. Comparison of efficacy of conbercept, aflibercept, and ranibizumab ophthalmic injection in the treatment of macular edema caused by retinal vein occlusion: a Meta-analysis. *Int J Ophthalmol*. 2023;16(7):1145–1154. doi:10.18240/ijo.2023.07.21
5. Brown DM, Boyer DS, Do DV, et al. Intravitreal aflibercept 8 mg in diabetic macular oedema (PHOTON): 48-week results from a randomised, double-masked, non-inferiority, Phase 2/3 trial. *Lancet*. 2024;403(10432):1153–1163. doi:10.1016/S0140-6736(23)02577-1
6. Chen C, Wang Z, Yan W, et al. Anti-VEGF combined with ocular corticosteroids therapy versus anti-VEGF monotherapy for diabetic macular edema focusing on drugs injection times and confounding factors of pseudophakic eyes: a systematic review and meta-analysis. *Pharmacol Res*. 2023;196:106904. doi:10.1016/j.phrs.2023.106904
7. Bringmann A, Reichenbach A, Wiedemann P. Pathomechanisms of cystoid macular edema. *Ophthalmic Res*. 2004;36(5):241–249. doi:10.1159/000081203
8. Radius RL, Anderson DR. Distribution of albumin in the normal monkey eye as revealed by Evans blue fluorescence microscopy. *Invest Ophthalmol Vis Sci*. 1980;19(3):238–243.
9. Yanoff M, Fine BS, Brucker AJ, Eagle Jr RC. Pathology of human cystoid macular edema. *Surv Ophthalmol*. 1984;28:505–511. doi:10.1016/0039-6257(84)90233-9
10. Hilda JN, Narasimhan M, Das SD. Neutrophils from pulmonary tuberculosis patients show augmented levels of chemokines MIP-1α, IL-8 and MCP-1 which further increase upon in vitro infection with mycobacterial strains. *Hum Immunol*. 2014;75(8):914–922. doi:10.1016/j.humimm.2014.06.020
11. Jung SH, Kim KA, Sohn SW, Yang SJ. Association of aqueous humor cytokines with the development of retinal ischemia and recurrent macular edema in retinal vein occlusion. *Invest Ophthalmol Vis Sci*. 2014;55(4):2290–2296. doi:10.1167/iovs.13-13587
12. Noma H, Mimura T, Yasuda K, Shimura M. Role of soluble vascular endothelial growth factor receptor signaling and other factors or cytokines in central retinal vein occlusion with macular edema. *Invest Ophthalmol Vis Sci*. 2015;56(2):1122–1128. doi:10.1167/iovs.14-15789
13. Liu Y, Fu H, Zuo L. Anti-inflammatory activities of a new VEGF blocker, Conbercept. *Immunopharmacol Immunotoxicol*. 2021;43(5):594–598. doi:10.1080/08923973.2021.1959608
14. Cheng Y, Yuan L, Zhao MW, Qian T. Real-world outcomes of two-year Conbercept therapy for diabetic macular edema. *Int J Ophthalmol*. 2021;14(3):416–422. doi:10.18240/ijo.2021.03.14
15. Arai Y, Takahashi H, Inoda S, et al. Efficacy of Modified Treat-and-Extend Regimen of Aflibercept for Macular Edema from Branch Retinal Vein Occlusion: 2-Year Prospective Study Outcomes. *J Clin Med*. 2021;10(14):3162. doi:10.3390/jcm10143162
16. Parikh R, Pirakitikulr N, Chhablani J, Sakurada Y, Singh RP, Modi YS. A Multinational Comparison of Anti-Vascular Endothelial Growth Factor Use: the United States, the United Kingdom, and Asia-Pacific. *Ophthalmol Retina*. 2019;3(1):16–26. doi:10.1016/j.oret.2018.08.002
17. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology*. 2016;123(6):1351–1359. doi:10.1016/j.ophtha.2016.02.022
18. Haller JA, Bandello F, Belfort Jr R, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology*. 2011;118(12):2453–2460. doi:10.1016/j.ophtha.2011.05.014
19. Thanos A, Todorich B, Yonekawa Y, et al. DEXAMETHASONE INTRAVITREAL IMPLANT FOR THE TREATMENT OF RECALCITRANT MACULAR EDEMA AFTER RHEGMATOGENOUS RETINAL DETACHMENT REPAIR. *Retina*. 2018;38(6):1084–1090. doi:10.1097/IAE.0000000000001720
20. Carreira AR, Marques N, Carreira P, et al. Safety of intravitreal triamcinolone and its impact on optic nerve morphology in patients treated for diabetic macular edema. *Eur J Ophthalmol*. 2021;2021:11206721211028744.
21. Pacella F, Pacella E, Trovato Battagliola E, et al. Efficacy and safety of intravitreal Fluocinolone Acetonide microimplant (ILUVIEN(®)) in patients with chronic diabetic macular edema: 1 year follow-up. *Eur J Ophthalmol*. 2021;2021:11206721211020203. doi:10.1177/11206721211020203

22. Hayreh SS. Photocoagulation for retinal vein occlusion. *Prog Retin Eye Res*. 2021;85:100964. doi:10.1016/j.preteyeres.2021.100964
23. Grigorian R, Bhagat N, Lanzetta P, Tutela A, Zarbin M. Pars plana vitrectomy for refractory diabetic macular edema. *Semin Ophthalmol*. 2003;18 (3):116–120. doi:10.1076/soph.18.3.116.29813
24. Bae JH, Al-Khersan H, Yannuzzi NA, et al. Surgical Therapy for Macular Edema: what We Have Learned through the Decades. *Ocul Immunol Inflamm*. 2019;27(8):1242–1250. doi:10.1080/09273948.2019.1672194
25. Hirashima T, Chihara T, Bun T, Utsumi T, Hirose M, Oh H. Intravitreal bevacizumab alone or combined with macular laser photocoagulation for recurrent or persistent macular edema secondary to branch retinal vein occlusion. *J Ophthalmol*. 2014;2014:173084. doi:10.1155/2014/173084
26. Ogino K, Tsujikawa A, Murakami T, Muraoka Y, Kurashige Y, Yoshimura N. Grid photocoagulation combined with intravitreal bevacizumab for recurrent macular edema associated with retinal vein occlusion. *Clin Ophthalmol*. 2011;5:1031–1036. doi:10.2147/OPTH.S22923
27. Callizo J, Atili A, Striebe NA, et al. Bevacizumab versus bevacizumab and macular grid photocoagulation for macular edema in eyes with non-ischemic branch retinal vein occlusion: results from a prospective randomized study. *Graefes Arch Clin Exp Ophthalmol*. 2019;257 (5):913–920. doi:10.1007/s00417-018-04223-9
28. Meng W, Li R, Xie X. Conbercept and Retinal Photocoagulation in the treatment of Diabetic Macular Edema. *Pak J Med Sci*. 2019;35 (6):1493–1498. doi:10.12669/pjms.35.6.512
29. Huang C, Ji H, Han X. The Effectiveness of Conbercept Combined with Panretinal Photocoagulation vs. Panretinal Photocoagulation in the Treatment of Diabetic Retinopathy: a Meta-Analysis. *J Ophthalmol*. 2021;2021:5591719. doi:10.1155/2021/5591719
30. Shao Y, Yu Y, Li C, et al. Clinical observation of the efficacy of Bevacizumab combined with argon green laser in treating fundus macular edema. *Exp Ther Med*. 2017;13(4):1480–1484. doi:10.3892/etm.2017.4145
31. Suttorp-Schulten MS, Feron E, Postema F, Kijlstra A, Rothova A. Macular grid laser photocoagulation in uveitis. *Br J Ophthalmol*. 1995;79 (9):821–824. doi:10.1136/bjo.79.9.821
32. Mizuno S, Nishiwaki A, Morita H, Miyake T, Ogura Y. Effects of periocular administration of triamcinolone acetonide on leukocyte-endothelium interactions in the ischemic retina. *Invest Ophthalmol Vis Sci*. 2007;48(6):2831–2836. doi:10.1167/iovs.06-1041
33. Ozkaya A, Celik U, Alkin Z, Faiz Turan M, Yazici AT, Demirok A. Comparison between Intravitreal Triamcinolone with Grid Laser Photocoagulation versus Bevacizumab with Grid Laser Photocoagulation Combinations for Branch Retinal Vein Occlusion. *ISRN Ophthalmol*. 2013;2013:141279. doi:10.1155/2013/141279
34. Riese J, Loukopoulos V, Meier C, Timmermann M, Gerding H. Combined intravitreal triamcinolone injection and laser photocoagulation in eyes with persistent macular edema after branch retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(12):1671–1676. doi:10.1007/s00417-008-0898-0
35. Forte R, Cennamo GL, Finelli M, et al. Intravitreal bevacizumab vs intravitreal triamcinolone combined with macular laser grid for diffuse diabetic macular oedema. *Eye*. 2010;24(8):1325–1330. doi:10.1038/eye.2010.23
36. Lam DS, Chan CK, Mohamed S, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: six-month outcomes. *Ophthalmology*. 2007;114(12):2162–2167. doi:10.1016/j.ophtha.2007.02.006
37. Lopez-Lopez F, Gomez-Ulla F, Rodriguez-Cid MJ, Arias L. Triamcinolone and bevacizumab as adjunctive therapies to panretinal photocoagulation for proliferative diabetic retinopathy. *ISRN Ophthalmol*. 2012;2012:267643. doi:10.5402/2012/267643
38. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology*. 2009;116(6):1142–1150. doi:10.1016/j.ophtha.2009.01.011
39. Price KW, Albini TA, Yeh S. Suprachoroidal Injection of Triamcinolone- Review of a Novel Treatment for Macular Edema Caused by Noninfectious Uveitis. *US Ophthalmic Rev*. 2020;13(2):76–79. doi:10.17925/usor.2020.13.2.76
40. Fan C, Wang Y, Ji Q, Zhao B, Xie J. Comparison of clinical efficacy of intravitreal ranibizumab with and without triamcinolone acetonide in macular edema secondary to central retinal vein occlusion. *Curr Eye Res*. 2014;39(9):938–943. doi:10.3109/02713683.2014.885533
41. Zhao M, Zhang C, Chen XM, Teng Y, Shi TW, Liu F. Comparison of intravitreal injection of conbercept and triamcinolone acetonide for macular edema secondary to branch retinal vein occlusion. *Int J Ophthalmol*. 2020;13(11):1765–1772. doi:10.18240/ijo.2020.11.13
42. Tsilimbaris MK, Pandeleondidis V, Panagiototglou T, et al. Intravitreal combination of triamcinolone acetonide and bevacizumab (Kenacort-Avastin) in diffuse diabetic macular edema. *Semin Ophthalmol*. 2009;24(6):225–230. doi:10.3109/08820530903389775
43. Yu YY, Cheng Y, Chang LB, Xia HK, Li XX. Triamcinolone as an adjunct to the combination of anti-VEGF for the management of diabetic macular edema. *Int J Ophthalmol*. 2021;14(6):869–874. doi:10.18240/ijo.2021.06.12
44. Riazi-Esfahani M, Riazi-Esfahani H, Ahmadraji A, et al. Intravitreal bevacizumab alone or combined with 1 mg triamcinolone in diabetic macular edema: a randomized clinical trial. *Int Ophthalmol*. 2018;38(2):585–598. doi:10.1007/s10792-017-0496-4
45. Eriş E, Perente I, Vural E, et al. Evaluation of the effect of combined intravitreal ranibizumab injection and sub-tenon steroid injection in the treatment of resistant diabetic macular edema. *Int Ophthalmol*. 2019;39(7):1575–1580. doi:10.1007/s10792-018-0977-0
46. Soheilian M, Garfami KH, Ramezani A, Yaseri M, Peyman GA. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. *Retina*. 2012;32(2):314–321. doi:10.1097/IAE.0b013e31822f55de
47. Leder HA, Jabs DA, Galor A, Dunn JP, Thorne JE. Periocular triamcinolone acetonide injections for cystoid macular edema complicating noninfectious uveitis. *Am J Ophthalmol*. 2011;152(3):441–448.e442. doi:10.1016/j.ajo.2011.02.009
48. Sallam A, Taylor SR, Habot-Wilner Z, et al. Repeat intravitreal triamcinolone acetonide injections in uveitic macular oedema. *Acta Ophthalmol*. 2012;90(4):e323–325. doi:10.1111/j.1755-3768.2011.02247.x
49. Acharya NR, Hong KC, Lee SM. Ranibizumab for refractory uveitis-related macular edema. *Am J Ophthalmol*. 2009;148(2):303–309.e302. doi:10.1016/j.ajo.2009.03.028
50. Bandello F, Augustin A, Tufail A, Leaback R. A 12-month, multicenter, parallel group comparison of dexamethasone intravitreal implant versus ranibizumab in branch retinal vein occlusion. *Eur J Ophthalmol*. 2018;28(6):697–705. doi:10.1177/1120672117750058
51. Pacella E, Loffredo L, Malvasi M, et al. Effects of Repeated Intravitreal Injections of Dexamethasone Implants on Intraocular Pressure: a 4-Year Study. *Clin Ophthalmol*. 2020;14:3611–3617. doi:10.2147/OPTH.S265691
52. Eris E, Erdogan G, Perente I, Demir G, Kepez Yildiz B, Aygit ED. A New Side Effect of Intravitreal Dexamethasone Implant (Ozurdex®). *Case Rep Ophthalmol Med*. 2017;2017:6369085. doi:10.1155/2017/6369085

53. Harb W, Chidiac G, Harb G. Outcomes of Combination Therapy using Aflibercept and Dexamethasone Intravitreal Implant versus Dexamethasone Monotherapy for Macular Edema Secondary to Retinal Vein Occlusion. *Middle East Afr J Ophthalmol*. 2021;28(1):18–22. doi:10.4103/meajo.MEAJO_297_19
54. Giuffrè C, Cicinelli MV, Marchese A, Coppola M, Parodi MB, Bandello F. Simultaneous intravitreal dexamethasone and aflibercept for refractory macular edema secondary to retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(4):787–793. doi:10.1007/s00417-019-04577-8
55. Singer MA, Bell DJ, Woods P, et al. Effect of combination therapy with bevacizumab and dexamethasone intravitreal implant in patients with retinal vein occlusion. *Retina*. 2012;32(7):1289–1294. doi:10.1097/IAE.0b013e318242b838
56. Maturi RK, Chen V, Raghinaru D, Bleau L, Stewart MW. A 6-month, subject-masked, randomized controlled study to assess efficacy of dexamethasone as an adjunct to bevacizumab compared with bevacizumab alone in the treatment of patients with macular edema due to central or branch retinal vein occlusion. *Clin Ophthalmol*. 2014;8:1057–1064. doi:10.2147/OPTH.S60159
57. Lip PL, Cikatricis P, Sarmad A, et al. Efficacy and timing of adjunctive therapy in the anti-VEGF treatment regimen for macular oedema in retinal vein occlusion: 12-month real-world result. *Eye*. 2018;32(3):537–545. doi:10.1038/eye.2017.230
58. Horner F, Lip PL, Mushtaq B, Chavan R, Mohammed B, Mitra A. Combination Therapy for Macular Oedema in Retinal Vein Occlusions: 3-Year Results from a Real-World Clinical Practice. *Clin Ophthalmol*. 2020;14:955–965. doi:10.2147/OPTH.S241044
59. Ozsaygili C, Duru N. COMPARISON OF INTRAVITREAL DEXAMETHASONE IMPLANT AND AFLIBERCEPT IN PATIENTS WITH TREATMENT-NAIVE DIABETIC MACULAR EDEMA WITH SEROUS RETINAL DETACHMENT. *Retina*. 2020;40(6):1044–1052. doi:10.1097/IAE.0000000000002537
60. Herbaut A, Fajnkuchen F, Qu-Knafo L, Nghiem-Buffet S, Bodaghi B, Giocanti-Auregan A. Switching to Aflibercept in Diabetic Macular Edema Not Responding to Ranibizumab and/or Intravitreal Dexamethasone Implant. *J Ophthalmol*. 2017;2017:8035013. doi:10.1155/2017/8035013
61. Hussain RM, Ciulla TA. Treatment strategies for refractory diabetic macular edema: switching anti-VEGF treatments, adopting corticosteroid-based treatments, and combination therapy. *Expert Opin Biol Ther*. 2016;16(3):365–374. doi:10.1517/14712598.2016.1131265
62. Hernández-Bel L, Cervera-Taulet E, Navarro-Palop C, Castro-Navarro V, Chiarri-Toumit C, Montero-Hernández J. Sequential Dexamethasone and Aflibercept Treatment in Patients with Diabetic Macular Edema: structural and Functional Outcomes at 52 Weeks. *Ophthalmologica*. 2019;241(2):98–104. doi:10.1159/000489345
63. Foglia E, Ferrario L, Bandello F, et al. Diabetic macular edema, innovative technologies and economic impact: new opportunities for the Lombardy Region healthcare system? *Acta Ophthalmol*. 2018;96(4):e468–e474. doi:10.1111/aos.13620
64. Limon U. Early effect of simultaneous intravitreal dexamethasone and bevacizumab combination treatment in patients with persistent diabetic macular edema. *J Fr Ophtalmol*. 2021;44(6):849–854. doi:10.1016/j.jfo.2020.08.033
65. Sheth S, Rush R, Natarajan S, Gillies M. Intravitreal triamcinolone acetonide versus combined intravitreal bevacizumab and dexamethasone in diffuse diabetic macular oedema. *Clin Exp Ophthalmol*. 2011;39(7):673–681. doi:10.1111/j.1442-9071.2011.02504.x
66. Cakir A, Erden B, Bolukbasi S, Bayat AH, Ozturan SG, Elcioglu MN. Dexamethasone implant as an adjuvant therapy to ranibizumab loading dose in persistent diabetic macular edema. *Int Ophthalmol*. 2019;39(10):2179–2185. doi:10.1007/s10792-018-1053-5
67. Podkowinski D, Orlowski-Wimmer E, Zlabinger G, et al. Aqueous humour cytokine changes during a loading phase of intravitreal ranibizumab or dexamethasone implant in diabetic macular oedema. *Acta Ophthalmol*. 2020;98(4):e407–e415. doi:10.1111/aos.14297
68. Sever O, Horozoglu F. The effect of single dose adjunctive dexamethasone implant on diabetic macular edema in patients on anti-vascular endothelial growth factor treatment: 1 year follow-up from a real-life practice. *J Fr Ophtalmol*. 2019;42(9):993–1000. doi:10.1016/j.jfo.2019.04.009
69. Maturi RK, Glassman AR, Liu D, et al. Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema: a DRCR Network Phase 2 Randomized Clinical Trial. *JAMA Ophthalmol*. 2018;136(1):29–38. doi:10.1001/jamaophthalmol.2017.4914
70. Neto HO, Regatieri CV, Nobrega MJ, et al. Multicenter, Randomized Clinical Trial to Assess the Effectiveness of Intravitreal Injections of Bevacizumab, Triamcinolone, or Their Combination in the Treatment of Diabetic Macular Edema. *Ophthalmic Surg Lasers Imaging Retina*. 2017;48(9):734–740. doi:10.3928/23258160-20170829-08
71. Koronis S, Stavrakas P, Balidis M, Kozeis N, Tranos PG. Update in treatment of uveitic macular edema. *Drug Des Devel Ther*. 2019;13:667–680. doi:10.2147/DDDT.S166092
72. Moll-Udina A, Figueras-Roca M, Oliveres J, et al. Uveitic macular edema response to intravitreal dexamethasone implant is independent of optical coherence tomography findings. *Int Ophthalmol*. 2021;41(3):787–796. doi:10.1007/s10792-020-01631-x
73. Yi QY, Wang YY, Chen LS, et al. Implication of inflammatory cytokines in the aqueous humour for management of macular diseases. *Acta Ophthalmol*. 2020;98(3):e309–e315. doi:10.1111/aos.14248