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Research Progress on Drug Therapy for Retinal Vein Occlusion Combined with Macular Edema

Junhan Xu[1], Ning Zhang[2]*
Beijing Luhe Hospital, Capital Medical University, Beijing 100069, China
**Author to whom correspondence should be addressed.*

Abstract: As a common cause of blindness in retinal vascular diseases, retinal vein occlusion (Retinal vein occlusion, RVO) often leads to macular edema (macular edema, ME), which is the core pathological link causing central vision loss in patients. In recent years, with the innovative application of anti-vascular endothelial growth factor (anti-vascular endothelial growth factor, VEGF) agents, breakthroughs in sustained-release glucocorticoid technology, and the promotion of multimodal combined therapy strategies, clinical management of RVO-associated ME has entered a new phase of precision treatment. This review is based on evidence from evidence-based medicine, systematically analyzing the latest advancements in the pharmacological treatment system for RVO-ME, and proposes new directions for exploration from a translational medicine perspective, addressing current research gaps.

Keywords: Retinal vein occlusion; Macular edema; Combined treatment; Drug therapy

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1. Introduction

Retinal vein occlusion is the second most common retinal vascular disease globally, following diabetic retinopathy, with an annual incidence of about 0.5–2.0% [1]. Among these, approximately 30% of RVO patients develop macular edema, leading to severe central vision loss [2]. Additionally, RVO-ME is closely associated with systemic diseases (such as hypertension and atherosclerosis), with about 60% of patients also having cardiovascular metabolic abnormalities [3], indicating that it is not only an ophthalmic emergency but also a warning sign for overall vascular health.

The core mechanism of RVO-ME is ischemia and hypoxia caused by venous blood flow obstruction, along with vascular leakage. The upregulation of VEGF is the primary driving factor, which promotes fluid leakage [4] by increasing vascular permeability. At the same time, local inflammatory responses (such as elevated IL-6 and TNF-α)

exacerbate the disruption of the blood-retinal barrier [5]. Additionally, oxidative stress and apoptosis signals (such as downregulated Sirtuin-1 expression) further damage the retinal neuroepithelium [6]. Recent studies have found that plasma von Willebrand levels are significantly elevated in patients with RVO-ME, suggesting a tendency towards platelet activation and thrombosis. These mechanisms collectively lead to macular edema and loss of photoreceptor function.

Traditional treatments, such as grid laser photocoagulation, can reduce leakage but do not improve vision and may damage retinal structure [7]. Current drug development focuses on dual inhibition of VEGF and inflammation. Anti-VEGF drugs (such as ranibizumab and bevacizumab) can rapidly reduce macular central foveal thickness (Central Macular Thickness, CMT), but require frequent injections (averaging 4–6 times per year), and 30% of patients develop resistance or recurrence of [8,9]; corticosteroids (such as dexamethasone implants) have long-lasting effects, but increased intraocular pressure (15–30%) and cataract progression (20–40%) limit their long-term use [10]. Additionally, about 20% of refractory ME cases show no response to monotherapy [11], necessitating more effective strategies.

Therefore, many people have begun to study the effectiveness of combination therapies, including anti-VEGF drugs combined with laser phototherapy, corticosteroids combined with laser phototherapy, anti-VEGF drugs combined with corticosteroids, and triple therapy. These have significantly improved the clinical outcomes of RVO-ME, but their widespread use has also exposed new issues: there are significant differences in treatment responses among different patients. Some patients still face the risk of recurrence or cumulative side effects despite receiving combination therapy, while others may incur unnecessary economic and health burdens due to overtreatment. Therefore, how to precisely select the optimal combination therapy based on patient characteristics (such as RVO classification, ischemic degree, and comorbidities) has become a core challenge in personalized treatment. This article reviews the advantages and disadvantages of various combination therapy regimens through a search of domestic and international literature and provides feasible directions for future research.

2. Joint treatment strategy

2.1. Anti-VEGF combined with laser photocoagulation

Laser photocoagulation inhibits VEGF secretion by reducing ischemic areas, and when used in combination with anti-VEGF drugs, it can enhance therapeutic effects. A systematic review by Weijie *et al.* [12]. showed that the combined anti-VEGF and laser group had a 27% greater reduction in CST compared to the single anti-VEGF treatment group ($p < 0.001$), and a 33% lower cumulative risk of recurrence over 12 months. This synergistic advantage may stem from the regional regulation of ischemic sources by laser therapy and the molecular-level inhibition of microvascular leakage by anti-VEGF drugs, forming a complementary mechanism. Additionally, 577 nm micro-pulsed lasers can reduce the risk of thermal damage, making them suitable for non-ischemic CRVO treatment [13].

2.1.1. Lezhu monoclonal antibody

Ranibizumab combined with laser photocoagulation improves RVO-ME by inhibiting VEGF and reducing ischemic areas synergistically. After 3 months of combined treatment, BCVA increased by an average of 12.5 to 16.3 letters (ETDRS visual acuity chart), and CST decreased by 230 to 298 μm [14,15]. After 6 to 12 months of combined treatment, the BCVA in the combined group maintained an improvement of 14.8 to 18.2 letters, with CST stabilizing at 280 to 320 μm [16]. The BCVA improvement was 4.7 letters greater than in the monotherapy group ($p = 0.01$), and

the number of injections decreased by 1.8 per year [17,18], with a recurrence rate reduced by 35% to 48% compared to monotherapy. Ranibizumab + laser had a lower recurrence rate than ranibizumab + triamcinolone acetonide (18% vs. 32%, $p = 0.04$), but there was no difference in CST reduction [19]. In ischemic BRVO patients, the CST reduction after combined treatment was greater (-315 μm vs. non-ischemic-265 μm, $p = 0.02$), but there was no significant difference in visual acuity improvement [20]. For those who received intervention within 3 months of onset, BCVA improved more significantly (+17.5 letters vs. +12.1 letters after 3 months, $p = 0.03$) [21]. The incidence of intraocular pressure elevation (≥ 25 mmHg) was 8% to 12%, significantly lower than in the combined treatment of ranibizumab + triamcinolone acetonide (22% to 35%) [22]. The incidence of retinal fibrosis was ≤ 2%, and there were no drug-related systemic side effects [23].

2.1.2. Conbercept

Conbercept, as a multi-target fusion protein, has shown significant efficacy in Chinese populations through the inhibition of multiple targets on VEGF and the reduction of ischemic areas. Studies have indicated that the clinical treatment effectiveness rate of [24,25] combined with laser photocoagulation therapy is 92.31-96.77%, higher than the photocoagulation group (76.92–80.65%). The peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistance index (RI) of the central retinal artery (CRA), as well as BCVA, were all higher in the conbercept group compared to the photocoagulation group. However, CMT, macular volume CV, and serum VEGF levels were lower in the conbercept group. The incidence of adverse reactions was not different from the photocoagulation group.

After 3 months of combined therapy, BCVA improved by an average of 12.8–16.5 letters (ETDRS visual acuity chart), and CST decreased by 225–312 μm. At 6–12 months of treatment, the combined group maintained an improvement in BCVA of 14.2-18.0 letters, with CST stabilizing at 280-330 μm, and the recurrence rate was reduced by 42–55% [26,27] compared to monotherapy. In BRVO patients, BCVA improvement was more significant (+16.5 letters vs. central retinal vein occlusion (CRVO) +13.2 letters, $p = 0.02$), with CST decreasing by 312 μm [28]. For ischemic BRVO patients, the improvement in vision after combined therapy was even greater (+15.3 letters vs. non-ischemic +13.1 letters, $p = 0.04$). The incidence of elevated intraocular pressure (≥ 25 mmHg) was 7%-13%, significantly lower than that of combination therapy with conbercept + triamcinolone acetonide. The incidence of retinal fibrosis was ≤ 1.5%, and there were no severe systemic adverse reactions.

Studies have shown that the clinical outcomes of lecanemab combined with photocoagulation and conbercept combined with photocoagulation are similar, with reductions in BCVA, CMT, VEGF, monocyte chemotactic protein-1 (MCP-1), and interleukin-6 (IL-6). However, other studies indicate that the conbercept group showed a 3.2 letter improvement in BCVA over 6 months compared to the lecanemab group ($p = 0.03$), and the number of injections decreased by 1.5 times per year.

2.1.3. Abecip

Abepristone combined with laser photocoagulation for CRVO-ME can significantly improve vision and anatomical structure. At 3 months, BCVA in the combined group increased by 15.2–17.8 letters (ETDRS), CST decreased by 285–318 μm, and the recurrence rate at 6 months was only 8–12%, better than the monotherapy group. Abepristone combined with threshold-limited laser therapy for ischemic BRVO-ME increased BCVA by 18.5 letters at 6 months, decreased CST by 315 μm, and the recurrence rate was only 8%; the CST reduction for CRVO-ME treatment reached 298 μm, significantly better than monotherapy.

2.2. Anti-VEGF combined with corticosteroids

For the treatment of refractory edema, combination therapy can break through the bottlenecks faced by monotherapy. Relevant studies show that combination therapy has a certain synergistic effect in improving BCVA and reducing CMT. Treatment with lecanemab combined with dexamethasone implant can accelerate edema absorption, with

BCVA improving by 14.2 to 15.2 letters (ETDRS standard) and CMT decreasing by 248.6 to 329 μm; in contrast, BCVA in the lecanemab monotherapy group only improved by 9.5 to 10.8 letters, and CMT decreased by 194.3 to 241 μm. A recent one-year study (n = 45) showed that the BCVA in the dexamethasone combined with lecanemab treatment group maintained +12.8 letters, with the number of injections reduced to an average of 3.5 times per year. Additionally, triamcinolone acetonide combined with anti-VEGF drugs (such as lecanemab and conbercept) can reduce the frequency of injections, with the average number of injections per 6 months being 2.3 times, significantly lower than the 4.1 times in the monotherapy group, although combination therapy may increase the risk of elevated intraocular pressure (15.6% vs. 5.2%) and cataract incidence (8.3% vs. 0%). Meta-analyses have confirmed that lecanemab combined with triamcinolone acetonide improves CMT by 42.7 μm over 6 months compared to monotherapy. In addition, the incidence of local inflammatory response in combination therapy was 1.5 times higher than that in the monotherapy group, but abecipumab combined with dexamethasone did not significantly increase systemic side effects.

2.3. Triple therapy (anti-VEGF + hormone + laser)

Triple therapy (anti-VEGF + hormone + laser) has advantages in improving microcirculation and can significantly improve RVO-ME through multi-mechanism synergy. After 1–3 months of treatment, BCVA improves by an average of 14.5–18.2 letters (ETDRS visual acuity chart), CST decreases by 285–352 μm, and BCVA improves by 4.8 letters more than in the dual therapy (anti-VEGF + laser) group (p = 0.01), significantly outperforming dual or monotherapy. After 3 months of treatment with lecanemab + triamcinolone acetonide + laser, CST decreases by 352 μm, while BCVA improves by 18.2 letters in the anti-VEGF + dexamethasone implant + laser group. Triple therapy can also extend the duration of efficacy, with a recurrence rate of only 12–18% over 12 months, significantly lower than the dual therapy (28–35%) and reduced injection frequency by 1.5 times per year. The incidence of increased intraocular pressure (≥ 25 mmHg) in triple therapy is 22–30%, requiring medication control, and the rate of cataract progression (18–25%) is comparable to that of corticosteroids used alone, but without additional systemic side effects.

2.4. Combined treatment of traditional Chinese and Western medicine

Many traditional Chinese medicines, such as Compound Blood Thrombosis and Astragalus Clear Granules, can enhance their efficacy by improving microcirculation. A meta-analysis conducted by Xiaojuan *et al.* in 2022 showed that the combination of traditional Chinese medicine with anti-VEGF drugs increased BCVA by 6.2 letters (95% CI: 3.1–9.3) compared to baseline levels, and also reduced the average number of injections by 1.8 per year. For patients with Qi deficiency and blood stasis syndrome, the combined use of traditional Chinese medicine can significantly improve the score, providing a basis for precise stratified treatment. Additionally, studies have suggested that the lipid-lowering drug atorvastatin may enhance the efficacy of anti-VEGF therapy through its anti-inflammatory mechanisms.

3. Emerging drugs

Plasma von Willebrand factor (vWF) levels are associated with the severity of RVO-ME. Hiromasa et al. found that patients whose vWF levels decreased by more than 30% after receiving anti-VEGF treatment showed more significant visual improvement (p = 0.01), suggesting that vWF has the potential to serve as a marker for treatment efficacy. Additionally, hypoxia-related markers such as HIF-1α (hypoxia-inducible factor-1α) also have the potential to predict the effectiveness of anti-VEGF therapy, which means that patients with higher HIF-1α levels may be prioritized for combined anti-inflammatory treatments in the future. Furthermore, plasma kininase inhibitors (such as

KVD001) can block the production of bradykinin by targeting plasma kallikrein (PK). When the PK-bradykinin pathway is activated, vascular leakage and inflammatory cell infiltration occur. Therefore, plasma kininase inhibitors can reduce vascular permeability, alleviate inflammatory responses, and decrease retinal edema, offering a promising new treatment option for resistant patients. However, the efficacy data of KVD001 did not reach statistical significance, which may be due to the limitation of small sample size or single-dose administration. Therefore, a rigorous phase II/III clinical trial is needed to confirm its efficacy on RVO-ME.

Bispecific antibodies (such as Faricimab) can simultaneously target VEGF-A and angiogenic factor-2 (Angiopoietin-2, Ang-2), two inflammatory mediators. According to the results of phase II trials, the injection interval can be extended to 16 weeks, which can effectively reduce the frequency of injections. In addition, gene therapy represented by ADVM-022 has been shown to have a therapeutic effect for up to 12 months in animal models by using adeno-associated virus (adeno-associated virus, AAV) vectors to continuously express anti-VEGF protein.

4. Treatment challenges and future directions

Patients who initiated anti-VEGF treatment within 3 months of diagnosis showed significantly better BCVA improvement compared to those who delayed treatment (+11.5 vs. +6.3 letters, $p < 0.001$). However, the awareness of diabetic eye disease among middle-aged and elderly individuals still needs to be improved. A cohort study by Woldetensaye *et al.* showed that low-income patients were more likely to choose cheaper TA over anti-VEGF drugs (OR = 2.4, $p = 0.03$), leading to a difference in visual prognosis (a 4.7-letter reduction in BCVA improvement), indicating that social factors influence the treatment outcomes of this condition.

Individualized dose adjustment (such as the “Treat-and-Extend” protocol) can balance efficacy and safety, which we need to promote. In addition, OCTA-based quantitative analysis of the avascular zone (FAZ) in the macula can dynamically assess treatment response. AI models can integrate imaging and genomic data, so in the future, AI is expected to achieve precise prediction of treatment regimens.

5. Conclusion

Combination therapy, through the synergistic effects of different drugs, can significantly improve ocular structure and function in the short term. For example, anti-VEGF drugs can reduce abnormal angiogenesis, while hormonal drugs can repair retinal barrier function. However, long-term use may lead to side effects, such as increased intraocular pressure and worsening cataracts caused by hormonal drugs. Therefore, we need to dynamically assess the risks of drug therapy based on the patient’s treatment response. Additionally, when formulating individualized treatment plans, multiple factors must be considered comprehensively, including the degree of macular damage shown by eye examinations (such as retinal outer layer tears), the optimal treatment timing (such as early ischemia intervention), and the management of systemic diseases (such as hypertension). Future research should focus on developing precise treatment strategies based on molecular characteristics, improving existing treatment models that rely on clinical experience through analyzing data on vascular growth factors, inflammatory factors, and genetic differences.

Disclosure statement

The author declares no conflict of interest.

References

[1] Ciulla T, Pollack J, Williams D, 2021, Visual Acuity Outcomes and Anti-VEGF Therapy Intensity in Macular Oedema Due to Retinal Vein Occlusion: A Real-World Analysis of 15613 Patient Eyes. Br J Ophthalmol, 105(12): 1696–1704.

[2] Zhu X, Yu Y, Zhuoga S, et al., 2022, Real-World Outcomes of Anti-Vascular Endothelial Growth Factor Therapy for Retinal Vascular Vein Occlusion in Tibet, China. Int J Ophthalmol, 15(11): 1814–1820.

[3] Hirai H, Yamashita M, Matsumoto M, et al., 2022, Alteration of Plasma von Willebrand Factor in the Treatment of Retinal Vein Occlusion with Cystoid Macular Edema. PLoS One, 17(9): e0264809.

[4] Avery R, Castellarin A, Steinle N, et al., 2017, Systemic Pharmacokinetics and Pharmacodynamics of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab. Retina, 37(10): 1847–1858.

[5] Qin H, Shi F, Zhang C, et al., 2022, Anti-VEGF Reduces Inflammatory Features in Macular Edema Secondary to Retinal Vein Occlusion. Int J Ophthalmol, 15(8): 1296–1304.

[6] Hwang D, Chang Y, Lin T, et al., 2020, Changes in the Systemic Expression of Sirtuin-1 and Oxidative Stress after Intravitreal Anti-Vascular Endothelial Growth Factor in Patients with Retinal Vein Occlusion. Biomolecules, 10(10): 1414.

[7] Hattenbach L, Chronopoulos A, Feltgen N, 2022, Retinal Vein Occlusion: Intravitreal Pharmacotherapies and Treatment Strategies for the Management of Macular Edema. Ophthalmologie, 119(11): 1100–1110.

[8] Narayanan R, Kelkar A, Abbas Z, et al., 2021, Sub-Optimal Gain in Vision in Retinal Vein Occlusion Due to Under-Treatment in the Real World: Results from an Open-Label Prospective Study of Intravitreal Ranibizumab. BMC Ophthalmol, 21(1): 33.

[9] Zhou H, Sun Z, Zhao M, et al., 2022, Prognostic Factor Study of Macular Edema Recurrence in Retinal Vein Occlusion after Conbercept Treatment: A Post Hoc Analysis of the FALCON Study. Comput Math Methods Med, 2022: 3616044.

[10] Carnevali A, Bacherini D, Metrangolo C, et al., 2024, Long Term Efficacy and Safety Profile of Dexamethasone Intravitreal Implant in Retinal Vein Occlusions: A Systematic Review. Front Med (Lausanne), 11: 1454591.

[11] Giuffrè C, Cicinelli M, Marchese A, et al., 2020, Simultaneous Intravitreal Dexamethasone and Aflibercept for Refractory Macular Edema Secondary to Retinal Vein Occlusion. Graefes Arch Clin Exp Ophthalmol, 258(4): 787–793.

[12] Weijie Z, Yuanyuan D, Xiaoyan J, et al., 2022, Comparison of the Efficiency of Anti-VEGF Drugs Intravitreal Injections Treatment with or without Retinal Laser Photocoagulation for Macular Edema Secondary to Retinal Vein Occlusion: A Systematic Review and Meta-Analysis. Frontiers in Pharmacology, 13: 948852.

[13] Li L, Qian R, Zhaohui S, et al., 2022, Clinical Efficacy of Conbercept Plus Micropulse Laser (577 nm) Treatment in Macular Edema Secondary to Non-Ischemic Central Retinal Vein Occlusion. Pakistan Journal of Medical Sciences, 38(5): 1366–1370.

[14] Li X, Chen Z, Liu X, 2024, Comparison of the Efficacy of Kangbepic and Lezumab Combined with Laser Photocoagulation in Treating Retinal Vein Occlusion Combined with Macular Edema. Chinese Journal of Drug and Clinical Practice, 24(24): 1595–1600.

[15] Wang N, 2022, Comparison of the Efficacy of Laser Coagulation Combined with Intravitreal Injection of Conbercept or Lezumab for Retinal Branch Vein Occlusion and Macular Edema. Practical Anti-Blindness Technology, 17(4):

141–144.

[16] Chen X, 2022, Long-Term Efficacy Observation and Predictive Factor Analysis of Laser Photocoagulation Combined with Leucovirin for Ischemic Retinal Branch Vein Occlusion Complicated with Macular Edema, thesis, Tongfang Knowledge Network (Beijing) Technology Co., Ltd.

[17] Wang Y, Du Z, Wang T, et al., 2022, Observation on Efficacy and Safety of Lezhu Monoclonal Antibody Combined with Laser Photocoagulation for Treatment of Macular Edema Secondary to Retinal Branch Vein Occlusion. Guizhou Medical, 46(6): 947–948.

[18] Yang D, Li L, 2019, Observation on the Efficacy of Lezhu Monoclonal Antibody Combined with Laser Photocoagulation in Treating Retinal Branch Vein Occlusion (BRVO) Secondary Macular Edema. New Progress in Ophthalmology, 39(4): 369–372.

[19] Jiao W, Ma N, Wang S, et al., 2018, Observation on the Efficacy of Lezhu Monoclonal Antibody Combined with Triamcinolone Acetonide Intravitreal Injection in Treating Retinal Branch Vein Occlusion with Macular Edema. Clinical Medical Literature Electronic Journal, 5(12): 34–35 + 37.

[20] Cao Z, Yang Y, Liu Y, 2022, Clinical Efficacy of Intravitreal Injection of Bevacizumab Combined with Laser Photocoagulation for Ischemic Retinal Branch Vein Occlusion Macular Edema. Journal of Rational Clinical Drug Use, 15(15): 155–158.

[21] Li S, Gao R, Chen H, 2016, Efficacy of Lezhu Monoclonal Antibody Combined with Argon Laser Retinal Photocoagulation in Treating Macular Edema Caused by Retinal Branch Vein Occlusion at Different Periods. New Progress in Ophthalmology, 36(12): 1161–1164.

[22] Wang X, 2017, Observation on the Efficacy of Intravitreal Injection of Lezumab Combined with Triamcinolone or Laser Photocoagulation in Treating Macular Edema Secondary to Retinal Branch Vein Occlusion. Chinese Journal of Practical Medicine, 12(2): 110–112.

[23] Shi H, Ma K, Zheng C, 2022, Efficacy of Lezhu Monoclonal Antibody Combined with Photocoagulation in Treating Macular Edema Secondary to Central Retinal Vein Occlusion. Journal of North Sichuan Medical College, 37(2): 252–255.

[24] Lantu C, Xie L, Luo C, et al., 2024, Efficacy of Combretastine Combined with Laser Photocoagulation in Treating Retinal Branch Vein Occlusion with Macular Edema. Journal of Clinical Ultrasound in Medicine, 26(12): 1016–1020.

[25] Liu J, Yue S, 2024, The Effect of Intravitreal Injection of Conbercept Combined with Laser Photocoagulation on the Treatment of Retinal Vein Occlusion Combined with Macular Edema. Medical Frontiers, 14(31): 47–49.

[26] Xu F, 2020, Clinical Observation on the Efficacy of Combined Retinal Photocoagulation and Kangbepic for Retinal Vein Occlusion with Macular Edema, thesis, Tongfang Knowledge Network (Beijing) Technology Co., Ltd.

[27] Zhao Q, 2021, The Efficacy of Kangbepic Combined with Retinal Laser Photocoagulation in the Treatment of Retinal Vein Occlusion with Macular Edema. Clinical Medicine, 41(10): 79–81.

[28] Shi Y, Xu Y, Zhang H, et al., 2020, Efficacy and Safety of Intravitreal Injection of Conbercept Combined with Selective Photocoagulation for the Treatment of Central Retinal Vein Occlusion Complicated by Macular Edema. Journal of Guangxi Medical University, 37(12): 2241–2245.