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Beyond Traditional Treatment: A Holistic Approach to Managing Retinal Vein Occlusion with Macular Edema

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Abstract: *Retinal vein occlusion (RVO) ranks as the second most prevalent retinal vascular disease, representing a significant cause of vision loss globally. The development of macular edema (ME) secondary to RVO is a major complication that severely impairs central visual acuity and quality of life. As a chronic condition often linked to systemic factors, its clinical management demands a multifaceted and proactive strategy. This article provides a systematic review of the contemporary clinical management of RVO-ME. It elucidates how current principles have shifted from traditional, reactive interventions toward a comprehensive model. This modern paradigm emphasizes precise baseline assessment, individualized treatment regimens leveraging anti-VEGF therapy and steroids, integrated systemic management of risk factors, and structured long-term follow-up. This systematic discussion aims to consolidate current evidence and offer practical guidance for optimizing patient care and visual outcomes.*

Keywords: *Retinal vein occlusion, macular edema, precision medicine multi-disciplinary management, precision medicine, full-cycle disease management*

1. Introduction

Retinal vein occlusion (RVO) is an ocular disease affecting the retinal vessels, caused by thrombosis that obstructs blood flow and leads to vision loss. Different types of the disease often result from emboli blocking different locations, such as central retinal vein occlusion (CRVO) caused by obstruction of the central retinal vein, or branch retinal vein occlusion (BRVO) caused by obstruction of a branch retinal vein[1]. RVO induces hemodynamic changes and inflammatory responses, damaging the vascular endothelium and causing capillary leakage around the fovea centralis, leading to macular edema (ME) that severely impairs visual perception[2]. A study by Song Peiqi et al. found that the 2015 global prevalence rates among individuals aged 30-89 were 0.77% for RVO, 0.64% for BRVO, and 0.13% for CRVO[3]. In China, the incidence rate is approximately 1.9%, with a rising prevalence each year. Consequently, the prevention and treatment of RVO-ME present a formidable and demanding challenge [4].

According to the treatment guidelines for RVO, common therapies for ME associated with this condition include laser photocoagulation, intravitreal steroid injections, and anti-VEGF drug therapy [5]. While laser photocoagulation and intravitreal steroid injections can alleviate edema to some extent, they are often accompanied by side effects such as impaired peripheral vision, elevated intraocular pressure, and an increased risk of cataract development. Prior to anti-VEGF therapy, early management typically involves observation, with symptomatic treatment initiated only after clinical manifestations appear. This approach often misses the optimal treatment window, leading to chronic, refractory ME and suboptimal visual quality improvement. Furthermore, anti-VEGF therapy in the early stages frequently employs an “on-demand” treatment regimen, resulting in unstable visual outcomes during therapy. Combined with poor patient compliance, difficulties in effective follow-up and assessment contribute to suboptimal treatment outcomes under this traditional model.

A number of studies indicate that RVO-ME is closely associated with systemic conditions such as hypertension, dyslipidemia, cardiovascular disease, and diabetes. However, we often overlook systemic factors and focus solely on the eye, which contributes to the poor long-term outcomes of RVO-ME

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treatment[6]-[9]. Our treatment for RVO-ME frequently remains at the macro level of reducing edema, neglecting the damage to the retinal inner layer structures. This is also a key reason for the suboptimal improvement in visual quality among RVO-ME patients. Consequently, as expectations for treatment outcomes continue to rise, new clinical management concepts have emerged to address the lagging and one-sided nature of this traditional treatment model.

Four key changes are included in this paradigm shift: from isolated ocular therapy to comprehensive systemic care; from standardized procedures to precision customized medicine; from short-term interventions to lifetime health stewardship; and from passive treatment to proactive maintenance. This new paradigm emphasizes developing individualized treatment plans based on precise assessments and dynamically adjusting approaches through structured long-term follow-up while concurrently managing systemic risk factors. This paper aims to systematically outline and elaborate on this new model for RVO clinical management. It delves into core dimensions, including precision assessment systems, personalized treatment strategies, comprehensive disease pathway management, and collaborative support systems. The goal is to provide ophthalmologists with clear, comprehensive theoretical foundations and practical guidance for clinical practice, ultimately enhancing the long-term visual prognosis and quality of life for RVO patients.

2. The Cornerstone of New Concepts: Precise Evaluation and Diagnosis

2.1 Multi-Dimensional Diagnostic Assessment

2.1.1 Optical Coherence Tomography (OCT)

OCT provides high-resolution images enabling anatomical analysis of each retinal layer. It can distinguish morphological features such as retinal edema, subretinal edema, and hyperreflective lesions, as well as perform differential retinal layer analysis to indicate whether these layers are thickened, thinned, or disrupted within the photoreceptive layer[10]. OCT can be used to evaluate the diagnosis and staging of retinal vein occlusion, monitor ME, and assess retinal imaging biomarkers[11]. The Ottawa study revealed a strong correlation between central macular thickness(CMT) and macular sensitivity, with significantly reduced macular sensitivity observed in cases of markedly thickenss CMT[12]. Ozer et al. demonstrated that the outer limiting membrane and ellipsoid zone serve as prognostic factors for ME resolution and visual acuity improvement[2].

2.1.2 Optical Coherence Tomography Angiography (OCTA)

OCTA is a novel imaging technique based on OCT that visualizes functional blood vessels within the eye. OCTA operates by utilizing changes in OCT signals caused by moving particles such as red blood cells (RBCs) as the contrast mechanism for blood flow imaging[13]. Koulisis et al. demonstrated that a combination of OCTA metrics describing retinal capillary density and morphology correlates closely with the clinical severity of retinal vein occlusion (RVO)[14]. OCTA images are based on variable backscatter from retinal vessels and neurosensory tissue, providing reliable, high-resolution, noninvasive retinal vasculature imaging in a clinically feasible manner. They effectively display areas of impaired perfusion, microaneurysms, capillary remodeling, certain types of intraretinal fluid accumulation, and intraretinal neovascularization, making them valuable for RVO diagnosis and management[15].

2.1.3 Fundus fluorescein angiography (FFA)

FFA serves as the gold standard for diagnosing retinal vein occlusion (RVO) and plays a crucial role in assessing non-perfused areas, neovascularization, and leakage in retinal vessels[16],[17]. These findings are vital indicators for evaluating RVO progression, treatment efficacy, and post-treatment resolution. Interpretation of FFA is highly dependent on “stages.” Vascular leakage manifests in the early or mid-phase of FFA, while cystoid cavity filling appears in the late phase[11]. Considering the primary manifestations of RVO in FFA, the condition is categorized into five “lesion” labels: nonperfused areas, macular tortuosity, hemorrhage, microaneurysms, and ME. Neovascularization correlates with large nonperfused areas on FFA. Both CRVO and BRVO can be broadly classified as ischemic or non-ischemic based on capillary nonperfusion areas[18].

2.1.4 Fundus photography

Fundus photography is another imaging technique that provides a more direct visualization of retinal hemorrhages, exudates, neovascularization, and peripheral retinal conditions. It holds significant

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reference value in the assessment, treatment, and follow-up of retinal vein occlusion (RVO)[19]. The EURETINA guidelines do not specify which imaging method is more suitable for documenting and monitoring retinal lesions[11]. The Royal College of Physicians guidelines recommend including fundus photography as part of the baseline assessment, and the American Academy of Ophthalmology also advises its use[5],[20].

2.2 Full-body assessment

The pathogenesis of RVO involves multiple contributing factors. Chronic endothelial stress induced by hypertension, diabetes, and hyperlipidemia leads to arterial sclerosis. Mechanical obstruction of the crossing retinal veins causes venous stasis, turbulent blood flow, endothelial injury, intimal thickening, and intravascular thrombosis. Retinal vascular endothelial injury and subsequent disruption of the blood-retinal barrier result in hyperpermeability, leading to retinal edema[21].

In a study by Ponto K A et al. on risk factors for RVO, hypertension was associated with an odds ratio (OR) of 1.81 for retinal vein occlusion. Cardiovascular disease contributes to the development of retinal vein occlusion, increasing the risk of occurrence by 40%[6]. Homocysteine, a significant risk factor for cardiovascular disease, is associated with an increased risk of RVO when elevated[7]. Pan M et al., through a retrospective study of 127 RVO patients, identified triglycerides as a risk factor for RVO, while high-density lipoprotein was found to be a protective factor[9]. Kazantzis D's research indicates systemic inflammatory factors play a significant role in the pathogenesis of RVO[22]. Age, hypertension, dyslipidemia, and elevated homocysteine levels constitute risk factors for retinal vein occlusion. Therefore, comprehensive systemic examinations are recommended after a patient's initial visit, particularly including blood pressure, lipid profile, complete blood count, and neck Doppler ultrasound.

3. The Core of the New Concept: Individualized Treatment

3.1 Treatment Options

Patients with RVO should undergo comprehensive medical history collection, ocular examination, and ophthalmic imaging as needed prior to treatment.

According to the American Academy of Ophthalmology's care guidelines and the European Retina Association (EURETINA) guidelines for managing retinal vein occlusion, RVO is a chronic disease requiring individualized monitoring. Management should emphasize addressing patients' systemic risk factors. The primary treatment goals for RVO are improving vision and quality of life, managing neovascular complications and ME, and controlling blood pressure, diabetes, blood glucose, and other systemic risk factors through communication and coordination with healthcare providers[11],[20].

Patients benefit from treatment while minimizing unnecessary vitreous injections. Consequently, personalized treatment plans reduce the risk of overtreatment and undertreatment, optimizing the risk-benefit profile and ensuring efficient utilization of National Health Service resources[23].

3.2 Dynamic Adjustment

3.2.1 Anti-VEGF

Anti-VEGF agents demonstrate significant therapeutic advantages in RVO management and represent the preferred treatment for RVO-ME. Currently, anti-VEGF drugs used for RVO include ranibizumab, aflibercept, bevacizumab, faricizumab, and conbercept.

Ranibizumab is a recombinant humanized monoclonal antibody fragment specifically designed to bind and inhibit VEGF subtypes. It is indicated for the treatment of visual impairment due to ME associated with BRVO or CRVO[24],[25]. Aflibercept binds to VEGF-A, VEGF-B, and PlGF. It effectively isolates these growth factors, thereby inhibiting angiogenesis and regulating vascular permeability[26]. Bevacizumab is a humanized monoclonal antibody containing two binding sites capable of interacting with VEGF-A[25]. Faricimab is a bispecific IgG1 antibody that simultaneously binds and inhibits VEGF-A and angiopoietin-2. By binding to the Tie2 receptor on endothelial cells, it acts as an antagonist to Ang-1, disrupting Ang-1's stabilizing effect. This disruption leads to increased vascular permeability and inflammation, thereby promoting pathological angiogenesis. By inhibiting angiopoietin-2, Faricimab restores vascular stability and reduces pathological neovascularization[27],[28].

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Conbercept is a recombinant anti-angiogenic fusion protein structurally similar to apivastatin, capable of binding to placental growth factor and all subtypes of VEGF-A and VEGF-B[29]. These anti-VEGF biosimilars demonstrate significant efficacy in treating ME associated with RVO. Conbercept, an independently developed Chinese anti-VEGF drug, contains fusion proteins targeting VEGF-A, VEGF-B, and PlGF receptors; it was initially used to inhibit neovascularization in exudative age-related macular degeneration[30]. Conbercept improves visual acuity and reduces ME thickness in both BRVO and CRVO. Compared to ranibizumab, intravitreal injections of aflibercept or conbercept yield superior mean visual acuity changes and greater reduction in ME thickness[31],[32].

3.2.2 Steroid hormones

Intravitreal steroid injections (such as triamcinolone, dexamethasone, and other corticosteroids) have been demonstrated to be effective for RVO-ME, particularly in cases dominated by inflammatory factors. However, they carry associated risks of cataract and glaucoma, necessitating cautious clinical application[5],[33]. Steroid therapy is generally considered a second-line adjunctive treatment for RVO.

3.2.3 Lasers

Retinal laser photocoagulation serves as an adjunctive treatment for RVO complicated by neovascularization[5]. For patients with iris neovascularization or retinal neovascularization following RVO, the optimal therapeutic approach is dense peripheral panretinal photocoagulation.

3.2.4 Treatment options

For anti-VEGF therapy under the PRN regimen, weekly monitoring for the first 4–8 weeks is recommended to achieve optimal visual outcomes. During the second year, visual acuity continued to improve at 4–8 week follow-ups with timely treatment[34]. The SCORE2 trial comparing monthly fixed injections, PRN, and the treat-and-extend (TER) regimen in patients responding well to 6 months of aflibercept showed no significant difference in visual gain at 12 months but significantly reduced injection frequency in the TER and PRN groups. Thus, these three regimens (monthly fixed, PRN, and TER) provide comparable visual outcomes. The risk associated with monthly injections in the fixed monthly regimen and the requirement for 4–8 weekly appointments in the PRN regimen make the treat-and-extend regimen the preferred option[35]. Volkmann et al. found that TER may lead to high patient persistence and visual improvement comparable to large prospective clinical trials. The advantages of TER include face-to-face communication with patients to explain the necessity of continued treatment and strict management protocols[36]. TER may serve as an active tool to avoid undertreatment or overtreatment and can be considered a primary tool in daily practice, aiding in the development of individualized treatment plans for patients[37].

4. The Core of the New Concept: Comprehensive Disease Management

4.1 Staged Management

4.1.1 CRVO

For patients diagnosed with CRVO-ME, anti-VEGF therapy is recommended using a 3+PRN treatment regimen. If no visual improvement occurs after the first three injections, discontinuation may be considered. It is advised to terminate treatment after completing six injections. Patients achieving stable vision may transition to a TER regimen. If vision remains stable without recurrent ME, the interval for TER injections may be extended by 2–4 weeks compared to the previous cycle. If vision decline occurs due to ME secondary to CRVO, the interval may be shortened. Once a recurrence interval is established, it is recommended to maintain this interval for 6 months before considering extension. Patients on the PRN regimen should be followed monthly (or bimonthly). Immediate reinitiation of treatment is indicated when vision decline occurs due to MO secondary to CRVO[5].

If anti-VEGF therapy proves ineffective, switching to another anti-VEGF agent is permissible, with monthly injections for 3 months to evaluate the efficacy of the switch. In SCORE2, patients with poor response to bevacizumab demonstrated significant visual improvement after switching to aflibercept [5],[35]. Retrospective case series showed marked visual gain at 30 days following Ozurdex use after anti-VEGF treatment failure; Ozurdex may also replace anti-VEGF agents[38].

4.1.2 BRVO

For patients with BRVO-ME, anti-VEGF therapy is recommended. The RETAIN study suggests

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continuous treatment with ranibizumab for 6 months, followed by selection of an appropriate treatment regimen based on individual circumstances once the condition stabilizes[39]. No significant difference was observed between aflibercept and ranibizumab; the treatment regimen is the same as above. Once the condition stabilizes, an individualized plan can be developed. The most common treatment regimen for bevacizumab involves 2 to 3 injections within the first 5-6 months[40].

The GENEVA study evaluated the safety and efficacy of intravitreal dexamethasone (Ozurdex) in participants with ME secondary to RVO. Results demonstrated superior outcomes in participants with ME caused by BRVO compared to control participants. The incidence and progression of glaucoma and cataracts represent significant complications associated with Ozurdex therapy[41].

4.2 Collaborative Management of Systemic Risk Factors

Based on the comprehensive examination results from the initial admission, ophthalmologists should proactively collaborate with internists or general practitioners to jointly manage patients' underlying conditions such as hypertension, diabetes, and hyperlipidemia, which form the foundation of treatment[5],[20].

4.3 Management of RVO Complications：Treatment of Neovascularization

At each follow-up visit, visual acuity, macular thickness, and intraocular pressure should be assessed, and the presence of neovascularization should be examined. Retinal neovascularization is an indication for ischemic retinal photocoagulation, although evidence suggests that delaying laser treatment until vitreous hemorrhage occurs does not adversely affect visual prognosis. New vessels appear only when capillary closure occurs in at least one quadrant, typically 6 months after occlusion [5].

4.4 Management of Special Types of RVO: Treatment of Ischemic RVO-ME

Capillary nonperfusion is a key clinical feature of RVO that may influence its clinical course[42]. In the RAVE study, the ischemic RVO-diagnosed eye met at least 3 of 4 high-risk criteria: best-corrected visual acuity ≤6/60; Goldmann perimetry loss of 1–2 e-deopters; relative afferent pupillary defect ≥0.9 log; electrophysiological electroretinogram B-wave amplitude reduced to ≤60% of corresponding A-wave; and reported visual acuity improvement with anti-VEGF therapy[43]. The COPERNICUS and GALILEO studies demonstrated visual acuity gains following anti-VEGF injections in ischemic RVOs with capillary nonperfusion >10 DA[44].

Anti-VEGF therapy may mask the progression of neovascularization, as neovascularization in ischemic CRVO shows no improvement with anti-VEGF treatment but merely delays it. In an analysis of 231 eyes with CRVO-ME, 4.5% developed neovascularization, with a median interval of 9.6 months between the most recent intravitreal anti-VEGF treatment and the observation of neovascularization [45]. Therefore, close monitoring (1-2 times monthly) is recommended during the first year after discontinuing anti-VEGF therapy in ischemic CRVO eyes. Age and glaucoma history are risk factors for capillary nonperfusion progression. It is recommended to initiate anti-VEGF therapy at the earliest signs of iris or corneal neovascularization, followed by adequate panretinal photocoagulation on the same day (prior to anti-VEGF treatment) or within 1–2 weeks[5].

5. New Concepts Provide the Foundation: Building a Support System

5.1 New technologies offer the backing

Artificial intelligence (AI) plays a significant role in the diagnosis and treatment of retinal diseases. This emerging technology offers substantial advantages in automated screening and diagnosis while mitigating biases associated with manual measurements and counting. By adopting AI visualization and quantification techniques, biomarkers commonly observed in imaging studies can be accurately analyzed[46]. AI has emerged as a clinical tool for early RVO screening.

Nagasato et al. proposed combining deep learning algorithms with ultra-wide-field fundus photography to accurately diagnose early-stage BRVO, offering assistance in regions with limited access to ophthalmic care centers. This facilitates early intervention for BRVO patients in remote areas, thereby improving their visual quality[47]. Furthermore, OCT proves highly effective in diagnosing and

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managing RVO. Accurate segmentation of hyperreflective foci (HRF) using U-Net reveals that patch-based methods enhance computational capacity for HRF pixels, delivering optimal segmentation accuracy for identifying HRF across various retinal pathologies[48]. Computational TER can predict individual long-term requirements for anti-VEGF therapy in patients with neovascular age-related macular degeneration, DME, and RVO-associated ME undergoing TER. Low treatment demand can be identified with reasonable accuracy at the baseline stage before treatment initiation, demonstrating the potential for optimizing treatment individualization at the earliest possible stage[37].

OCTA is also frequently used to assess vascular changes in RVO. Ultra-wide-field fluorescein angiography (UWF-FA) has been demonstrated to be an important tool for imaging the peripheral retinal regions in RVO[49]. Comparative evaluations of UWF-FA and wide-field optical coherence tomography angiography (WF-OCTA) indicate that WF-OCTA yields superior results to standard fluorescein angiography in RVO; UWF-FA demonstrates high concordance with standard OCTA in assessing the extent of nonperfusion areas. WF-OCTA enables precise visualization of non-perfused areas in the peripheral retina and collateral vessels. Compared to OCTA, UWF-FA visualizes a broader retinal area[50].

Xu Fabao et al. investigated the ability of an algorithm utilizing Generative Adversarial Networks to predict structural outcomes after anti-VEGF therapy for ME in RVO by analyzing post-treatment OCT images. 91.18% of synthetic OCT images possessed sufficient quality for clinical interpretation, with a mean absolute error of 26.33 ± 15.81 μm for predicting CMT. Subgroup analysis confirmed minimal impact of anti-VEGF agents (ranibizumab or conbercept) on model performance. Compared to CRVO-ME, the predictive efficacy of OCT images for BRVO-ME was comparable to that of real images[51].

Using AI to automatically detect retinal diseases from FFA images, AI-Doctor can generate detailed AI reports for FFA image interpretation. These reports include descriptions of image stages, disease diagnoses, ischemic area segmentation, and CAII calculations. This enhances the reliability of diagnosing ischemic retinal diseases and alleviates the workload of ophthalmologists[16].

The application of AI in diagnosis and follow-up has enhanced the diagnosis of retinal vein occlusion (RVO), improved the assessment of treatment efficacy, and facilitated the prediction of prognosis, thereby promoting the enhancement of visual quality in RVO treatment.

5.2 Patient Self-Management

According to guideline recommendations, patient health education also requires attention[5],[20]. Patients should understand that RVO is a chronic condition requiring lifelong monitoring. Educate them to recognize early symptoms of RVO: sudden vision loss and moving dark spots in the visual field. If these symptoms occur, prompt medical attention is essential. Healthy lifestyle practices, such as quitting smoking, abstaining from drinking, eating a low-fat diet, and engaging in regular exercise, must be emphasized in patient education.

5.3 Multidisciplinary Collaboration

RVO is a chronic condition requiring comprehensive management of systemic risk factors. Upon identifying other systemic diseases, ophthalmologists should collaborate with internists or general practitioners to jointly manage conditions such as hypertension, diabetes, and hyperlipidemia[5],[20]. Ophthalmologists can establish electronic records detailing each patient follow-up visit, conducting timely in-person or telephone follow-ups to provide psychological counseling and monitor treatment progress.

6. Challenges and Future

The standardization of RVO diagnosis and treatment faces significant hurdles. A primary challenge is the disparity in healthcare resources caused by regional economic imbalances. Patients in remote areas often lack access to advanced diagnostics and specialized ophthalmologists. Furthermore, the high cost and need for frequent administration of anti-VEGF therapy create a substantial financial and logistical burden, leading to treatment discontinuation and suboptimal outcomes. Long-term patient compliance is another critical issue, as adherence often wanes after initial improvement due to a lack of chronic disease awareness and treatment fatigue.

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In the future, the management of RVO is evolving towards more precise, intelligent, and patient-centric models. Precision medicine will utilize biomarkers and advanced imaging to tailor therapies for individual patients, moving beyond a one-size-fits-all approach. Intelligent technologies like AI for screening and telemedicine for remote consultations will help bridge the access gap. Digital health tools will improve long-term management through automated reminders and patient monitoring. Ultimately, the focus will shift towards a holistic, patient-value-oriented system that integrates education, psychological support, and quality-of-life metrics, ensuring care is both effective and compassionate.

7. Conclusion

The clinical management of RVO has entered a new phase characterized by patient-centered care, evidence-based approaches, and a focus on visual quality. By establishing a systematic evaluation framework, personalized treatment plans, and comprehensive management protocols, the quality of RVO diagnosis and treatment can be significantly enhanced, leading to improved long-term patient outcomes.

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