Published in final edited form as:

Curr Ophthalmol Rep. 2016 March ; 4(1): 38–47. doi:10.1007/s40135-016-0091-2.

Update in the Management of Macular Edema Following Retinal Vein Occlusions

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Abstract

Retinal vein occlusion (RVO) is a common retinal vascular disease classified according to the anatomical location of the occlusion in central (CRVO) or branch (BRVO) retinal vein occlusion. RVO is an important cause of visual loss worldwide and frequently results in visual impairment and ocular complications. Major causes of vision loss in BRVO and CRVO include macular edema (ME), capillary non-perfusion, and neovascularization, causing glaucoma, vitreous hemorrhage and/or tractional retinal detachment.[1–4] Macular edema is the leading cause of decreased central visual acuity in RVO.[5]

Recently, there was a paradigm shift in the treatment of ME due to RVO with the advent of new pharmacotherapy treatment strategies and combination therapies. This paper reviews the current thinking and discusses the evidence behind the emerging treatment options for ME following RVO, including laser photocoagulation, intravitreal anti-vascular endothelial growth factor (VEGF), intravitreal corticosteroid-based pharmacotherapies, and surgical management.

Keywords

Retinal Vein Occlusion; Macular Edema; Intravitreal Injections; Vascular Endothelial Growth Factors; Steroids

Introduction

Retinal vein occlusion (RVO) is the second most common cause of vision loss due to retinal vascular disease, staying behind only the diabetic retinopathy.[5,6] The prevalence of RVO

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Mariana R. Thorell and Raquel Goldhardt declare that they have no conflict of interest.

increases with age, varies with race or ethnicity, and does not differ with gender.[6] Risk factors include systemic vascular diseases such as hypertension, diabetes and cardiovascular diseases. The disease presentation is divided into central (CRVO) or branch (BRVO) retinal vein occlusion, according to the anatomical location of the occlusion. Macular edema (ME) is a frequent complication and an important cause of visual impairment in both ischemic and nonischemic RVO.[7,8]

Over the past years, the standard of care for the treatment of ME due to RVO has shifted and pharmacotherapy has supplanted the concept of watch and wait. One of the main factors in the development of ME apart from increased venous pressure is the elevated level of vascular endothelial factor (VEGF) with subsequent break down of the blood-retinal barrier and leakage.[9] Before the development of anti-VEGF therapy, there was no effective treatment for CRVO.[10] For a long time, the treatment of choice for ME associated with BRVO was grid laser photocoagulation. Goals of the treatment is to improve or to maintain visual acuity (VA).

There has been a revolution in the treatment of RVO over the past couple of years. The first studies defining the standards of management for RVO limited the treatment options to observation, laser photocoagulation, or corticosteroids. More recent studies have shown evidences that vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of ME following RVO. Anti-VEGF agents are currently between the most effective and frequently the first choice of treatment for RVO cases. Corticosteroids remain one of the treatment options for ME secondary to RVO and the drug is available under intravitreal injection or sustained-release intravitreal implant. Surgical management with vitrectomy is not considered as primary therapy given associated surgical risks and lack of controlled trials showing benefit, unless persistent vitreous hemorrhage or traction retinal detachments. The purpose of this review article is to summarize the most scientific relevant data on ME due to RVO.(Tables 1 and 2) In clinical practice, it is important to initiate early treatment for ME secondary to RVO that results in better visual outcomes and limits irreparable retinal damage.[11,12]

1. Anti-VEGF Drugs

Intravitreal anti-VEGF drugs have become the standard treatment for ME following RVO. Bevacizumab (Avastin®; Genentech Inc., San Francisco, CA, USA) is not US Food and Drug Administration (FDA) approved for intraocular use. However, bevacizumab is widely off-label used for different retinal diseases, including BRVO and CRVO. Ranibizumab (Lucentis®; Genentech, San Francisco, CA, USA) was first approved in the US for the treatment of neovascular age-related macular degeneration in 2006 and later received approvals for the treatment of BRVO and CRVO in 2010. Aflibercept (Eylea®; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) was approved for CRVO in September 2012 and for BRVO in 2014.[13,14]

1.1. Ranibizumab—Ranibizumab is a recombinant, humanized monoclonal antibody Fab fragment for intraocular use that neutralizes all active forms of VEGF-A. The use of

ranibizumab for intravitreal injection encouraged the tests to investigate the effects of neutralizing VEGF in eyes with RVO.[9]

From the results of BRAVO (Branch Retinal Vein Occlusion) and CRUISE (Central Retinal Vein Occlusion) studies completed in 2009 we have learned that Ranibizumab works well to treat ME due to BRVO[15] and CRVO.[16,17] The BRAVO and CRUISE clinical trials were the first trials to evaluate the use of Ranibizumab as treatment for patients with BRVO and CRVO respectively. The investigation of treatment strategies and response to ranibizumab treatment continued in following studies.

BRAVO: The clinical trial called BRAVO enrolled 397 patients to one of the three treatment arms: ranibizumab 0.3 mg, ranibizumab 0.5 mg, and sham for six months, followed by PRN ranibizumab 0.5 mg for all eyes until month 12. After three months of study entry, patients of all groups have grid-pattern laser photocoagulation rescue therapy allowed.[1]

After 6 months, monthly ranibizumab resulted in a gain of 16.6 and 18.3 letters in the 0.3 mg and 0.5 mg ranibizumab respectively, compared to 7.3 letters in the sham group. At month 12, mean improvement in VA was 16.4 and 18.3 letters in the 0.3 mg and 0.5 mg ranibizumab respectively, compared to 12.1 letters in the sham/0.5 mg group. From study entry, 56% and 60.3% of ranibizumab-treated eyes 0.3- and 0.5-mg, respectively gained 15 letters compared to 43.9% in the sham group followed by ranibizumab 0.5 mg for months 6–12.[18] The benefits of ranibizumab for eyes with BRVO observed in the first 6-month period were generally maintained at one year.[16,18]

CRUISE: A Phase III, multicenter, randomized controlled trial, the CRUISE study,[16] randomized 392 patients with ME due to CRVO for treatment with ranibizumab (0.3 mg or 0.5 mg) or sham injections for 6 months. This period was followed by additional 6-month observation period in which patients from all groups were evaluated monthly and received a PRN ranibizumab injection if met the pre-specified re-treatment criteria.[16,19]

At 6 months, the mean gain in BCVA was 12.7 letters in the 0.3 mg ranibizumab group, 14.9 letters in the 0.5 mg ranibizumab group and 0.8 letters in the sham group ($P < 0.0001$ for each ranibizumab group vs. sham).[19] At 12 months, BCVA improvements from baseline were 13.9 letters in both 0.3 mg and 0.5 mg groups, compared to 7.3 letters in the sham/0.5 mg group. Of the ranibizumab treated eyes, 46.2% (0.3/0.5 mg) and 50.8% (0.5/0.5 mg) gained 15 letters compared to 33.1% in the sham/0.5 mg group.[16]

In general, the benefits of ranibizumab for CRVO observed in the first six months were maintained at one year with low rate of ocular and non-ocular safety events.

A post-hoc analysis of data from BRAVO and CRUISE studies offered clues regarding who will have better visual outcomes. They found out that if you are an early ranibizumab responder; meaning, having a central retinal thickness (CRT) on optical coherence tomography (OCT) of 250µm or less at month 3, you would have an excellent final VA outcome.[20] Those who had residual ME at month 3 had worse visual outcomes at month 6.

HORIZON (Ranibizumab for macular edema due to retinal vein occlusion): The HORIZON trial[17] was an extension of the BRAVO and CRUISE studies and highlights the divergence in patients with CRVO. The open-label, multicenter study was design to determine the long-term effects of ranibizumab in patients with ME due to BRVO and CRVO. The same number of patients (304 patients from each study) who completed the BRAVO and CRUISE studies were included in the HORIZON study. Eligible patients received an intravitreal injection of 0.5 mg ranibizumab if they met pre-specified criteria. Reinjections were performed if intraretinal fluid was identified. Macular grid laser was permitted as well in the BRVO eyes. Patients were evaluated every 3 months or more frequently when necessary.

In the BRVO group, the mean change from baseline BCVA letter score at month 12 was -2.3 letters (0.3/0.5 mg), -0.7 letters (0.5 mg/0.5 mg), and +0.9 (sham/0.5 mg). The mean change in BCVA score between baseline and month 24 was +14.9 letters (0.3/0.5 mg), +17.5 letters (0.5 mg/0.5 mg), and +15.6 (sham/0.5 mg). Despite less frequent follow-up and fewer ranibizumab injections in the second year, VA in BRVO patients remained stable. However, the use of macular grid laser may have contributed to the stability of these eyes.

Compared with CRUISE baseline, at 24 months, BCVA changed +16.2 letters (0.5/0.5 mg), +14.9 letters (0.3/0.5 mg), and +9.4 letters (sham/0.5 mg). Over the 12 months of the HORIZON, BCVA worsened by 4.1, 5.2, and 4.2 letters in the 0.3/0.5 mg, in the 0.5/0.5 mg, and in the sham/0.5 mg treatment groups, respectively. Conclusions of the authors stated that reduced follow-up and fewer injections of ranibizumab during the second year were associated with a VA decrease in patients with ME due to CRVO.[21]

The study also found that repeated long-term injections of ranibizumab did not lead to new safety events. In addition, the rates of serious adverse events were similar to prior ranibizumab trials.

RETAIN (Extended Follow-up of Patients With Macular Edema Due to Retinal Vein Occlusion): The RETAIN study[22] continued to follow 32 CRVO patients and 34 BRVO patients from the HORIZON trial for another two years of treatment. Patients were seen every month during the first year and at least every 3 months during the second year of the study. Patients were treated with intravitreal injection of ranibizumab in the presence of intraretinal fluid. If the patient required injections on consecutive visits they were treated with ranibizumab plus scatter laser photocoagulation.

Seventeen of 34 BRVO patients (50%) presented resolution of the ME defined by the absence of intraretinal fluid for a 6-month period or more after the last injection. The last injection was given within 2 years of treatment initiation in 76% of patients. The mean BCVA in patients with resolved ME improved 25.9 letters while in patients with unresolved ME improved 17.1 letters (P = 0.09). Considering both these groups, approximately 80% of patients had a final BCVA of 20/40 or better.

Following long-term treatment with ranibizumab, BRVO patients presented excellent response. However, they required occasional injections after 4 years treatment, patients maintained good visual potential even if they had chronic, recurrent edema.

Fourteen of the 32 CRVO patients (44%) had ME resolution and 71% received the last injection within two years of treatment initiation. Patients with resolved CRVO had greater improvement in BCVA compared with unresolved disease (25.2 vs. 4.3 letters; $P = 0.002$). A greater percentage of final BCVA of 20/40 or better was also observed in the resolved CRVO patients compared to the unresolved disease group (64.3% vs. 27.8%; $P = 0.04$).

In the CRVO group, 44% of patients had edema resolution and a good outcome within 4 years. However, most of the CRVO ranibizumab-treated patients (56%) still required frequent injections and presented reduced visual potential.

SHORE (Monthly versus as-needed Ranibizumab injections in patients with retinal vein occlusion): A randomized and open-label 15-month study, the SHORE trial, was designed to compare PRN and monthly 0.5 mg ranibizumab in BRVO and CRVO patients stabilized by monthly injections.[19] Two hundred two subjects received monthly ranibizumab during 7 months. After this period until month 14, patients meeting stability criteria (84.7%) were randomized (1:1) to PRN treatment versus continued monthly injections. At month 15, results concluded that visual outcomes were excellent. In this study they showed that in patients with RVO, after monthly injections of ranibizumab for at least 7 months and provided there is resolution of edema and stable vision, switching to PRN dosing didn't compromise visual outcomes at month 15 compared with continued monthly injections.

1.2. Bevacizumab—Bevacizumab is a recombinant humanized monoclonal antibody against all isoforms of VEGF-A and is one of the most closely watched drugs in the world today. The widespread use of bevacizumab remains off-label for intravitreal injection treatment. However, there are numerous studies with levels II and III of evidence demonstrating the safety and efficacy of the use of bevacizumab for RVO-associated ME. [23–30]

Treatment with bevacizumab demonstrated improvement in best-corrected visual acuity (BCVA) and reduction of central macular thickness (CMT) when compared to sham injection in CRVO,[31,32] or when compared to steroid[33] or grid-pattern laser photocoagulation[34] in BRVO. The MARVEL group from India published a prospective, head-to-head study comparing bevacizumab with ranibizumab in the treatment of ME due to BRVO and their results suggest that both bevacizumab and ranibizumab can be given to patients on an as needed (PRN) basis and still lead to excellent improvement in VA.[35] The CRAVE study was the first randomized, multicenter study comparing effectiveness of bevacizumab and ranibizumab in reducing ME from CRVO and BRVO. They used mostly treatment-naïve patients mirroring previous CRUISE and BRAVO protocols. Their 6-month data showed no difference between both drugs, even when they stratified by BRVO and CRVO.[36]

1.3. Aflibercept—Aflibercept is a fusion protein that binds multiple isoforms of human VEGF-A, VEGF-B, and placental-derived growth factor (PDGF) and presents higher affinity than bevacizumab or ranibizumab.[37,38] The intravitreal injection of aflibercept was approved by the FDA in 2012 for the treatment of ME following CRVO based on two Phase III, randomized, multicenter, clinical trials, the COPERNICUS and GALILEO studies. [20,39–42] Following this approval and based on positive results from the phase 3 VIBRANT trial, Aflibercept was approved by the FDA for the treatment of ME following BRVO in 2014.

COPERNICUS (Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion): In the COPERNICUS study,[39,41] a randomized, multicenter, double-masked, phase 3 trial, 188 patients with ME secondary to CRVO were randomized (3:2 ration) to 2 mg aflibercept injection treatment (n=114) vs sham injection (n=74) every 4 weeks for a 24-week interval. Following the initial 6-month interval, all patients followed an as needed or pro re nata (PRN), during the next 6 months including an extension of unmasked treatment for 1 year.

During the PRN phase, patients in the aflibercept monthly/PRN group were given an average of 2.5 injections. The aflibercept group did not appear to have an increased incidence of ocular and nonocular adverse events compared to the sham group. However, the two-year results showed that the visual and anatomic improvements observed at the end of the fixed dosing period were diminished after continued PRN dosing, when monitoring frequency was reduced from week 52 to 100. Eyes receiving sham/ PRN aflibercept did not have visual and anatomic improvement as important as those receiving aflibercept monthly from the start, suggesting a benefit from initiating early treatment.[41]

GALILEO (Vascular Endothelial Growth Factor Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion): The GALILEO study[43] was a randomized, double-masked, phase 3 trial, designed to evaluate aflibercept for the treatment of ME secondary to CRVO. During the first 6 months, randomized patients received 2 mg intravitreal aflibercept (n=106) or sham injection (n=71) every four weeks. From weeks 24 to 48, patients were monitored every 4 weeks and maintained their original randomization, receiving aflibercept or sham through week 52. From weeks 52 to 76, patients were monitored every 8 weeks, and both groups received intravitreal aflibercept PRN. Panretinal laser photocoagulation was allowed at any time during the study for treatment of neovascularization.

As observed in the COPERNICUS study, in the GALILEO trial, there was a significantly greater anatomic improvement at six months in the aflibercept group compared to sham group. However, in the GALILEO study, in which patients continued their assigned treatment up to 12 months, this difference was maintained over time. In addition, the visual improvements were maintained when treatment intervals extended, demonstrating a benefit from early intravitreal aflibercept injection treatment and a need for long-treatment to control ME in many CRVO eyes.

Copernicus (US) and Galileo (Europe) showed that about 55% of subjects had improvement of 3 lines or more. Overall the results were strikingly similar with previous Lucentis trials. The advantage of aflibercept is based on the higher affinity and durability that it may provide.

VIBRANT (Study to Assess the Clinical Efficacy and Safety of Intravitreal Aflibercept Injection in Patients With Branch Retinal Vein Occlusion): The phase 3 VIBRANT trial[44] was a double-masked, randomized study of 183 patients to compare aflibercept with grid laser in patients with ME following BRVO. Patients in the aflibercept group received 2 mg intravitreal aflibercept every 4 weeks for 24 weeks and every 8 weeks through week 48 with rescue grid laser at week 36 when needed. Patients in the grid laser group received grid laser at baseline visit and 1 additional laser from week 12 to 20 (if met prespecified criteria) and 2mg intravitreal aflibercept every 8 weeks from week 24 after 3 monthly doses.

The visual improvements in the aflibercept group were maintained at week 52, while the gains in vision in the laser group were attributable to aflibercept rescue treatment. Likewise, anatomical improvements were also significantly greater in the aflibercept group with the laser group at week 24, and after that, the laser group had a significant anatomical improvement resulting from aflibercept rescue therapy. Furthermore, intravitreal aflibercept injections were generally well tolerated by patients with the most common adverse events those typical associated with intravitreal injections. The vibrant study results were no surprise that patients receiving aflibercept were twice as likely to gain 15 letters or more compared to laser.

2. Corticosteroids

Intravitreal corticosteroids are effective for treating ME in RVO eyes as a result of the potent anti-inflammatory properties of the steroids, inhibiting many cytokines involved in the disease process including VEGF, interleukin-6, intercellular adhesion molecule-1 and monocyte chemoattractant protein-1.[45] However, due to potential side effects, including development of cataract[46] and high intraocular pressure,[47] intravitreal steroids are most frequently used in cases that do not respond or become recalcitrant with time to anti-VEGF therapy.[48,49]

Currently, the triamcinolone acetonide is the treatment choice in some settings because of its greater availability and the lower cost of the drug.[50,51] However, the introduction of the sustained-release intravitreal corticosteroid implants, has demonstrated some advantages as longer duration of action and decreased toxicity. Several ongoing studies are evaluating different slow-release intravitreal corticosteroids implants and only one commercially available implant is approved by the FDA for the treatment of ME associated with CRVO and BRVO, which will be discussed in the dexamethasone implant topic.[52]

2.1. Intravitreal Triamcinolone Acetonide—Triamcinolone acetonide intravitreal injection has been shown to improve vision and decrease ME in eyes with RVO.[53,54]

About 15 years ago, we had the first breakthrough for CRVO with the SCORE study because it showed that steroids provided improvement in VA and reduction of visual loss compared with the observation group.

SCORE (Standard Care vs. Corticosteroid for Retinal Vein Occlusion): The SCORE-BRVO[55] randomized 411 patients to compare 1-mg (n=136) and 4-mg (n=138) of intravitreal triamcinolone acetonide (IVTA; Kenalog, Bristol-myers Squibb, New York, NY) with grid-pattern laser photocoagulation (n=137) in eyes with ME secondary to BRVO.

At 12 months there was no difference observed in VA for the standard care group compared with the triamcinolone groups. The mean gain in BCVA was 4 to 5 letters in all groups with a mean of 2.2 injections for the 1-mg IVTA, 2.2 injections for the 4-mg IVTA, and 1.5 grid-pattern laser applications for the laser treatment group. However, the IVTA groups were more likely to develop adverse events as elevated intraocular pressure and cataract than the laser treatment group.

The SCORE-CRVO trial[56] compared the efficacy and safety of 1-mg and 4-mg of preservative free-IVTA to observation in eyes with vision loss due to ME secondary to perfused CRVO.

After one year, 27% of the patients in the 1-mg IVTA group and 26% in the 4-mg IVTA group presented a visual improvement of 15 letters, while only 7% of the observation group experienced the same gain. The SCORE-CRVO study results provided the first level I evidence to support intervention for visual improvement in ME secondary to CRVO, besides the increased rates of cataract surgery at 12–24 months and higher rates of intraocular lowering needed at 12 months for the IVTA groups.[56,57] In addition, the 1-mg dose has shown a superior safety profile when compared to the 4-mg dose.[56]

2.2. Dexamethasone Implant—The commercially available intravitreal dexamethasone (DEX) implant for the treatment of ME secondary to BRVO and CRVO, Ozurdex (Allergan, Inc., Irvine, CA, USA), is a biodegradable dexamethasone (DEX) 0.7 mg slow-release implant composed of a copolymer of lactic acid and glycolic acid that progressively dissolves in the vitreous gel. The preservative-free DEX implant was also FDA approved for noninfectious posterior uveitis, and, most recently, diabetic macular edema.[58]

GENEVA (Global Evaluation of implantable dEXamethasone in retinal Vein occlusion with macular edema): The prospective, multicenter GENEVA study[59] compared 0.35mg vs 0.7 mg intravitreal dexamethasone implant (DEX) (Ozurdex, Allergan, Irvine, CA) vs sham injection in RVO eyes. The BRVO and CRVO groups were randomized to a 6-month, double-masked sham-controlled phase followed by a 6-month open-label extension of the studies. Patients included were randomized to 0.7 mg DEX implant (n=421), 0.35 mg DEX implant (n=412), or sham injection (n=423). At 6 months, patients could receive DEX implant 0.7 mg if met pre-specified criteria and they were followed for a 12 months period.

The BRVO and CRVO patient populations treated with a single DEX implant with a more predictable release profile showed some evidence of benefit at two months, when there was a

peak effect of the drug. When compared to the sham group, the time to achieve a 15-letter improvement in BCVA was significantly short in the treatment groups. However, there was a substantial drop-off between two and three months and the benefits were reduced at six months.

Patients receiving a second DEX implant presented a 15-letter improvement in BCVA 60 days after the second injection in 32% of cases. The ocular adverse events were similar to in patients receiving one or two DEX implants, except for cataract, which had a higher incidence in the repeated injection group. Besides the 10.3% increase in number of patients initiating IOP-lowering medications after the second treatment, the IOP increases were usually transient and well controlled.

The study provided limited information regarding the safety and efficacy of a single implant injection at 12 months since most of the patients in the study were treated with open-label 0.7 mg implant at day 180, reporting cataract (4–7%) and elevated intraocular pressure (30%). In addition, the GENEVA trial did not express the optimal retreatment interval for the 0.7 mg implant.

3. Laser

3.1. Grid Laser—The use of laser for RVO was controversial long before the anti-VEGF era. In the 80's the Branch Vein Occlusion Study (BVOS) helped to establish grid-pattern laser photocoagulation as the standard of care for the appropriate patients with perfused ME and laser was the only option for this patients. A decade later, the Central Vein Occlusion Study Group (CVOS) confirmed that grid laser did in fact decrease ME, but was of no visual benefit in patient with ME due to CRVO.[1,60]

Since the conclusion of these studies, grid laser photocoagulation is being an effective option for treatment of ME due to BRVO. However, due to irreversible damage to the retinal tissue, risk of developing iatrogenic paracentral scotoma and the advent of anti-VEGF options, the laser is having a limited use.[61]

Various results with grid-pattern laser photocoagulation for treatment of ME in eyes with BRVO have been reported in the following years. Combination therapy with grid-pattern laser and anti-VEGF therapy may increase efficacy in incomplete responders to anti-VEGF monotherapy. In the same manner, a combination of intravitreal steroid injection with grid-pattern laser may also result in a more potent effect.[62]

3.2. Scatter photocoagulation—Initially, it was believed that intravitreal anti-VEGF injections would be needed in patients with RVO for a relatively short period of time until recanalization or collateral formation was established. The vein occlusion is merely the initiating event and high levels of VEGF cause additional capillary closure and worsening ischemia. Scatter photocoagulation reduces retina ischemia, suggesting that it may promote resolution of ME and/or reduce the need for anti-VEGF injections. The RELATE (Ranibizumab DosE Comparison and the Role of Laser in Retinal Vein Occlusions) study demonstrated no long-term benefit in improving VA, resolution of edema, or number of ranibizumab injections obtained by addition of laser treatment to ranibizumab.[63]

4. Vitrectomy

There has been a rise and fall in the surgical management of venous occlusions. Pars plana vitrectomy has been explored to treat ME secondary to RVO.[64][65] However, in most studies a significant improvement in BCVA has not been observed.[66] Time has proven that vitrectomy with radial optic neurotomy for CRVO or arteriovenous sheathotomy for BRVO are not very robust treatment approaches.

Sato et al.[67] investigated the impact in VA of microincisional vitrectomy with ILM peeling for ME due to BRVO. However six eyes (6%) presented recurrent or persistent ME at 12 months after surgery, the BCVA was significantly improved as well as central retinal thickness decreased.

The investigation of the vitrectomy results requires more controlled, masked, prospective studies to evaluate if there is a real long-term benefit performing the surgical procedure. In addition to drying the retina, anti-VEGF agents reduce the risk of complications requiring surgery such as neovascularization, vitreous hemorrhage and tractional retinal detachment.

Conclusions

Currently, the intravitreal anti-VEGF pharmacotherapy is the treatment choice in most of the RVO cases and clinical practices. The emergence of sustained-release corticosteroids implants has proven the efficacy of the intravitreal injection in ME due to RVO, since the implant allows high intraocular concentration with minimal systemic absorption. The implants are an interesting option in patients who are pseudophakic and had vitrectomy since they no longer have a vitreous gel to sustain the release of an intravitreal injection. It should be used with caution in vitrectomized eyes with an open or absent posterior capsule because they can be swept into the anterior chamber by the aqueous fluid dynamics inside the eye.

Treatment strategies for RVO continue to evolve. Strategies for sustained intraocular delivery of anti-VEGF agents or combination therapy are being extensively investigated and long-term results will determine the prognosis. Furthermore, studies exploring options for treatment of eyes with persistent ME despite intravitreal injections are the goals for the near future. There is no compelling evidence to date to support the use of combination therapy as a primary treatment. Combination therapy is an option with the possible advantage of using different mechanisms of action. While possibly not as good as monthly anti-VEGF monotherapy in RVO, it does provide an option for patients who need more flexibility in their dosing schedules.

In conclusion, most treatment modalities still require repeated treatments and there is no optimal retreatment schedule for all cases of ME following RVO. Further studies are required to establish a treatment that reduces burden, cost, and risk of injections.

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Table 1

Anti-VEGF treatment studies

Study Name	Disease	Treatment	Duration	Outcome
BRAVO	BRVO	Intravitreal Ranibizumab	12 months	VA gains during treatment were maintained in the ranibizumab treatment groups during the observation period to 12 months.
CRUISE	CRVO	Intravitreal Ranibizumab	12 months	Benefits of ranibizumab in the first 6 months were maintained after an observation period to 12 months.
HORIZON	BRVO	Intravitreal Ranibizumab	24 months	VA was maintained stable with reduced follow-up and fewer injections in the second year.
HORIZON	CRVO	Intravitreal Ranibizumab	24 months	VA decreased with reduced follow-up and fewer injections in the second year.
RETAIN	BRVO	Intravitreal Ranibizumab	49 months	Excellent results and maintained VA with long-term treatment with ranibizumab.
RETAIN	CRVO	Intravitreal Ranibizumab	49 months	Most patients required frequent injections, had reduced VA, and present a guarded prognosis after long-term treatment.
SHORE	BRVO and CRVO	Intravitreal Ranibizumab	15 months	Excellent VA results after monthly injections for at least 7 months followed by PRN treatment.
COPERNICUS	CRVO	Intravitreal Aflibercept	24 months	VA and anatomical improvements at the end of fixed dosing period decreased after changing to PRN from year 1 to 2.
GALILEO	CRVO	Intravitreal Aflibercept	18 months	VA and anatomical improvements after fixed, monthly dosing at week 24 were maintained with treatment intervals extended.
VIBRANT	BRVO	Intravitreal Aflibercept	12 months	VA and anatomical improvements maintained with injections every 8 weeks after 6 monthly injections.

Abbreviations: BRVO= branch retinal vein occlusion, CRVO= central retinal vein occlusion, VA= visual acuity.

Table 2

Steroids and laser treatment studies

Study Name	Disease	Treatment	Duration	Outcome
SCORE	BRVO	Intravitreal Triamcinolone Acetonide	12 months	No difference in VA between standard care treatment and triamcinolone group at 1 year.
SCORE	CRVO	Intravitreal Triamcinolone Acetonide	12 months	Triamcinolone groups had greater VA improvements compared to observation group.
GENEVA	BRVO	Intravitreal Dexamethasone Implant	12 months	Repeated DEX implant had a favorable safety profile. Treatment group had a shorter time to achieve a 15-letter improvement in VA.
GENEVA	CRVO	Intravitreal Dexamethasone Implant	12 months	Repeated DEX implant had a favorable safety profile. Treatment group had a shorter time to achieve a 15-letter improvement in VA.
BVOS	BRVO	Grid laser	36 months	Lesser reduced development of neovascularization and occurrence of vitreous hemorrhage.
CVOS	CRVO	Grid laser	36 months	Laser did not show benefits.
RELATE	BRVO and CRVO	Laser photocoagulation in addition to Ranibizumab	33 months	VA did not improve and macular edema did not reduce significantly with laser in addition to Ranibizumab.

Abbreviations: BRVO= branch retinal vein occlusion, CRVO= central retinal vein occlusion, VA= visual acuity, DEX= dexamethasone.