Retinal Vein Occlusion- A Review

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Abstract: *Retinal vein occlusions are the second most common form of retinal vascular disease after diabetic retinopathy. They are divided into two major groups: Branch retinal vein occlusion and Central retinal vein occlusion. With newer advances in intravitreal drug therapy, the management of RVO has shifted from laser to pharmacotherapy. This has also improved the visual recovery in cases that previously ended in permanent visual damage. We discuss the epidemiology, risk factors and the current practice in management of RVO and how it has changed from the traditional management.*

Retinal vascular occlusions are the second most common form of retinal vascular disease after diabetic retinopathy[1]. There are two major anatomic forms of retinal vascular occlusions branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Furthermore, retinal vein occlusions (RVOs) can be classified as ischemic and non-ischemic occlusions, depending on the degree of non-perfusion based on the fluorescein angiogram[2].

If the occlusion occurs within or posterior to the optic nerve head, it is labeled CRVO, occlusion at the major bifurcation is determined to be HRVO (Hemi-retinal vein occlusion), and any obstruction within a tributary is a BRVO. Often, HRVO is considered as a separate condition that behaves intermediately between BRVO and CRVO[3].

EPIDEMIOLOGY AND RISK FACTORS

BRVO is more common than CRVO; worldwide prevalence of BRVO is estimated at 0.4% and CRVO around 0.08% with equal ratio between men and women and increased risk with older age[4].

The Blue Mountains Eye Study reported a 10-year incidence of RVOs at 1.6%[5]. The Beaver Dam Eye Study reported a 15-year cumulative incidence of 2.3% for RVOs, with 1.8% for BRVO and 0.5% for CVRO[6].

The greatest risk factor predicting development of RVO is a RVO in the contralateral eye. Individuals with BRVO in 1 eye have a 10% risk of any RVO in the contralateral eye within 3 years[7]. The estimated risk of contralateral involvement in people with CRVO is ~1% per year, which increases to 7% at 5 years[8].

Typical atherosclerosis risk factors like increasing age, hypertension, diabetes mellitus, race and hyperlipidemia are commonly associated with all types of RVO[9], but vein occlusions can also be secondary to other processes such as inflammation, vasospasm, compression or thrombophillia. Close association with glaucoma has also been seen. Local anatomic variations may play a role in formation of all types of vein occlusion, but BRVO are most often due to venous compression by a thickened arteriole at an arteriovenous crossing site[10] while the etiology of CRVO is thought to be secondary to thrombus formation in the central retinal vein at the level of or posterior to the lamina cribosa.

Overall the visual prognosis of CRVO is worse than that of BRVO, particularly of the ischemic type, and largely depends on vision at presentation.

CLINICAL FEATURES

The most common symptom is decreased vision that may be caused due to macular edema or vitreous haemorrhage. Other causes of decreased vision include macular ischemia, optic neuropathy, tractional retinal detachment or even combined retinal detachment.

The increased intravenous pressure results in vascular tortuosity, retinal hemorrhages, cotton wool spots, and optic nerve edema. Congestion of normal capillary bed can result in macular edema, thereby causing metamorphopsia and decreased vision. However, macular edema can resolve in up to 30% of patients in the nonischemic subtype CRVO[11].

Eyes with more capillary nonperfusion have a greater risk of ocular neovascularization both retinal and iris, that may lead to neovascular glaucoma. In a study by Hayreh and colleagues they found in their series of patients with ischemic CRVOs that the cumulative incidence of any neovascularization and neovascular glaucoma at 9 months was 52% and 34%, respectively[12].

With time, collateralization (retina-retina and retina-choroid anastomosis) can bypass the obstruction and improve clinical signs such as hemorrhages, cotton wool spots, and nerve edema.

MANAGEMENT

Diagnostic tests

Retinal vein occlusion is a clinical diagnosis. However, when a patient presents with RVO, a baseline systemic and ocular evaluation is required. A systemic metabolic profile including complete haemogram, blood sugar, glycosylated haemoglobin, lipid profile, coagulation profile, serum homocysteine levels and kidney function tests are required. Also, a full cardiac evaluation

that may include echocardiography and carotid Doppler is recommended.

Routine ocular examination includes assessment of intraocular pressure, slit lamp exam with undilated gonioscopy, and dilated funduscopy to detect glaucoma, ocular neovascularization, and/or macular edema.

Optical coherence tomography (OCT) is helpful in confirming the presence of macular edema and provides a quantitative assessment of the thickening. It also provides additional information such as presence of vitreoretinal surface abnormalities, neurosensory detachments, and/or loss of outer/inner retinal integrity that may further[15] guide therapy and prognostication of the patient. Hence, OCT is required in all eyes with RVO irrespective of duration.

Fundus Fluorescein angiography (FFA) allows visualization of the peripheral capillary nonperfusion areas (CNP), macular ischemia/leakage, collateral formation and subtle neovascularization that may not be clinically apparent. It also helps in categorising the RVO as ischemic or non-ischemic. Five or more disc areas of capillary nonperfusion were used in the Branch Vein Occlusion Study (BVOS), and 10 or more disc areas in the Central Vein Occlusion Studies (CVOS), to categorize RVO into perfused, nonperfused, or indeterminate[13,14]. FFA is not done in fresh cases of RVO as in most cases, the retinal haemorrhages cause blocked fluorescence and CNP areas are not determined. It is recommended to do FFA once retinal haemorrhages resolve (Figure 1).

ERG - both standard and multifocal - also show abnormalities in RVO and are a direct indicator of the amount of ischemia and eventual prognosis. However, ERG changes do not direct the management and may not be required in all cases of RVO.

Treatment

Treatment Before Anti-Vegf Therapy

Before the anti-VEGF era, 2 landmark multicenter randomized clinical trials helped guide management of ME and neovascularization secondary to RVO.

The Branch Vein Occlusion Study (BVOS) established the standard of care for nearly 25 years in the treatment of ME secondary to BRVO. Patients with perfused BRVO and visual acuity of 20/40 or worse and angiographic CME were randomized to grid laser or observation. The results of this study demonstrated

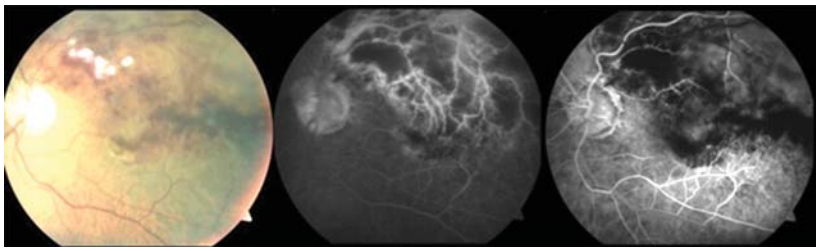


Figure 1: *A case of Superotemporal fresh BRVO (duration of decreased vision for 1 week) with retinal haemorrhages in superotemporal quadrant. FFA shows blocked fluorescence throughout the affected area. At this stage, FFA cannot define the ischemic area or leakage at macula.*

nearly twice as many patients in the treatment arm i.e. grid laser (65%) gaining 2 or more lines of vision in comparison to the control arm (37%) in 3 years of follow-up[15]. The recommendation from this trial suggested waiting 3 months after diagnosis (for possible spontaneous improvement), followed by grid laser if there was presence of persistent ME and vision worse than 20/40. This study also recommended that scatter peripheral laser should be applied after development of retinal neovascularization to decrease rates of vitreous hemorrhage.

The CVOS (central vein occlusion study) evaluated the benefits of laser- both PRP and grid laser, in CRVO. The authors recommended careful observation of ischemic CRVOs, as the preventative PRP group still had 20% of patients developing iris neovascularization, which needed more treatment. In regards to ME, the CVOS did not demonstrate a benefit for grid laser on visual acuity in patients with CRVO and vision 20/50 or worse secondary to ME[16].

Treatment of RVO markedly changed with the advent of anti-VEGF therapy in the mid-2000s.

TREATMENT WITH ANTI-VEGF AGENTS

Three different anti-VEGF agents are routinely given via intravitreal injection in clinical practice; both ranibizumab and aflibercept are FDA-approved. Although bevacizumab is off-label for RVO-associated macular edema, it is much less expensive than the alternatives and is frequently used all over the world.

Ranibizumab

The BRAVO study (Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety) explored the use of ranibizumab for BRVO-associated CME in 2 monthly intravitreal doses (0.3 mg and 0.5 mg) and compared it with sham injection. Monthly injections were administered for 6 months followed by a 6-month observation period in which treatment on PRN basis was applied with 0.5 mg ranibizumab. Patients in the control group were also eligible for 0.5 mg ranibizumab in the observation period. The results showed a marked improvement in vision and decrease in CMT in both ranibizumab treatment groups. Percentage of 3 or more visual acuity lines gained was higher in the treated groups as well, with 55% in the 0.3 mg group and 61% in the 0.5 mg group compared with 29% in the sham group. The need for rescue laser was also low in treated groups, needed in about 19% in the ranibizumab group and 55% in sham group[17].

The CRUISE (Ranibizumab for treatment of macular edema following CRVO) trial compared the effectiveness of 6 consecutive months of intravitreal ranibizumab with observation for adults with CRVO and macular edema. It demonstrated robust anatomic and visual improvement in the ranibizumab group[18].

Other studies of significance included an open-label extension (HORIZON) of these 2 studies with 205 and 181 patients who completed BRAVO and CRUISE, respectively. This was a 12-month study with at least 3-month follow-up intervals with retreatment criteria of BCVA of at least 20/40 or CFT greater than 250 µm. This study demonstrated that for BRVOs the visual gains were largely retained but that there was a definite worsening of visual outcomes in patients with CRVOs under this study's treatment protocol[19] (Figure 2).

Bevacizumab

Numerous early studies have demonstrated the improvement in visual acuity, regression of neovascularization, decrease in central retinal thickness (CRT), and cystoid macula edema (CME) in BRVO patients treated with bevacizumab[20-23].

Thapa et al reported a large

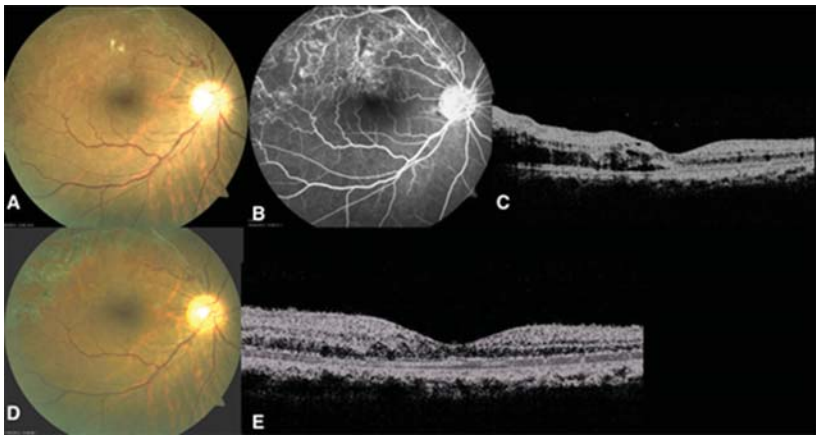


Figure 2: A) *Fundus photograph showing an superotemporal BRVO in the right eye with CME and VA of 20/200.* ***B)*** *FFA showing perfused macula with mild leakage and peripheral CNP areas.* ***C)*** *SD-OCT of inital presentation before treatment reveals significant CME.* ***D,E)*** *Fundus photo and SD-OCT at 1-year follow-up with near resolution of CME after sectoral laser and 5 anti-VEGF injections, with the last injection administered 5 months before this SD-OCT. Final visual acuity was 20/30.*

prospective study that included 63 untreated eyes with BRVO-related ME that were treated if VA was less than 20/40 or CRT was greater than 250 µm. Results showed improvement of logarithm of the minimum angle of resolution (logMAR) BCVA from 0.82 at baseline to 0.40 at 12 months (P < 0.001) and CRT of 515.3 µm at baseline to 233.6 µm at 12 months (P < 0.001)[24].

Although significant vision improvement occurs in most cases, presence of macular ischemia continues to be a negative prognostic factor[25].

Various studies have also shown an improvement in vision and reduction in CMT after use of bevacizumab in CRVO related ME[26-28]. However, many have also reported a decrease in CMT without an improvement in vision[29]. The BERVOLT (Bevacizumab for RVO-long term) study evaluated 65 patients with CRVO-related ME and stratified patients into presenting BCVA of less than 1.25 and more than 1.25 logMAR units[30]. With a mean of 9.7 injections, there was no significant change in either of the subgroups despite a significant improvement in CRT in both groups that was sustained through 24 months. The authors concluded the high incidence of poor VA at baseline (suggestive of ischemic CRVO) may have contributed to the lack of improvement seen.

Aflibercept

Aflibercept is a 115 kD fusion VEGF trap with high affinity for VEGF-A along with VEGF-B and placental growth factor. It is FDA approved for use in ME due to RVO.

A phase 3 randomized, double masked trial (VIBRANT:VEGF trap in patients with macular edema in BRVO) compared monthly aflibercept with focal photocoagulation in a 52-week period in patients with ME secondary to BRVO[31]. A total of 183 patients were randomized 1:1 to receiving either 6 injections of 2 mg of aflibercept every 4 weeks and maintenance injections every 8 weeks from weeks 24 to 48 or photocoagulation at baseline with sham injections up until week 48.

The primary outcome was the percentage of patients with at least 15 letter BCVA gain at the 24-week time point, which was 52.7% in the aflibercept group and 26.7% in the photocoagulation group. At the 52-week time point, 57.1% and 41.1% in the aflibercept and the photocoagulation groups, respectively, gained at least 15 letters in BCVA. Also, 80.7% of the photocoagulation group received rescue injections at a mean of 4.4 injections from weeks 24 to 48. The results tended to favor the early treatment of BRVO with aflibercept as opposed to grid photocoagulation as patients in the photocoagulation group with rescue aflibercept still had inferior visual outcomes at 52 weeks compared with the initial aflibercept cohort.

Two parallel phase 3, randomized, clinical trials (COPERNICUS and GALILEO) evaluated the use of aflibercept versus sham in the treatment of ME secondary to CRVO[32,33]. Both the trials compared 2 mg aflibercept injections every 4 weeks for 24 weeks and as needed afterwards according to prespecified study criteria. After the 24-week endpoint, sham group patients in the COPERNICUS study could also receive aflibercept if they fit retreatment criteria. At the primary endpoint of 24 weeks, the COPERNICUS study demonstrated that 56.1% of patients in the aflibercept group versus 12.3% of the sham group achieved at least 15 letter gain as compared to baseline.

In the GALILEO study, at 24 weeks, 60.2% and 22.1% of treatment and sham patients had at least 15 letter gain. At week 52, this proportion was unchanged in the treatment group but increased to 32.4% in the sham group. Additionally, these studies helped show the benefits of treatment compared with natural history but also superior outcomes with early treatment of CRVO-related ME with aflibercept.

All the studies till date evaluating the effect of Anti-VEGFs in RVOs have shown a significant difference as compared with sham injections. They have also found a better visual recovery in eyes treated early, hence emphasising the importance of early treatment.

TREATMENT WITH CORTICOSTEROIDS

Triamcinolone

Inflammation plays an important role in the pathogenesis of RVO, promoting vascular permeability contributing to macular edema. The effect of steroids on RVO-associated CME was evaluated first by the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study. The SCORE group examined off-label preservative-free intravitreal triamcinolone acetonide (IVTA) in 2 doses (1 mg and 4 mg) in a 1:1:1 randomization compared with standard of care. Standard of care for BRVO was grid laser, whereas standard of care for CRVO was observation. The primary efficacy endpoint was visual gain of 15 or more letters at 12 months of follow-up.

The SCORE-BRVO study showed 28.9%, 25.6%, and 27.2% of the standard care group, 1 mg, and 4 mg triamcinolone groups achieved the primary endpoint, respectively. However, the 4 mg steroid group gained vision faster than standard care and 1 mg groups, but also had high incidence of adverse effects like cataract and glaucoma. As no difference was seen in the primary outcome, the SCORE investigators recommended considering grid laser as first-line treatment for patients with BRVO associated with

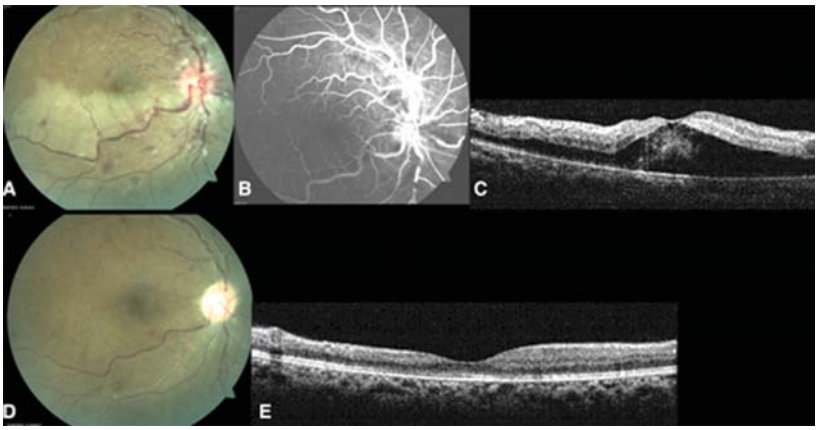


Figure 3: A,B) *Fundus photo and FFA Showing a fresh CRVO with IT branch artery occlusion with BCVA of 20/400.* ***C)*** *SD OCT showing CME with NSD.* ***D,E)*** *Fundus photo and OCT macula 6 months after single intravitreal dexamethasone implant. BVCA improved to 20/30.*

macular edema[34].

In the SCORE-CRVO study, 6.8% of the observation group, 26.5% in the 1 mg triamcinolone group, and 25.6% in the 4 mg triamcinolone group achieved a gain of ≥ 15 visual acuity letters at 12 months of follow-up. There was a statistically higher vision gain in both triamcinolone groups as compared with observation. Again, the incidence of glaucoma and cataract was significantly higher in the 4mg triamcinolone group as compared with standard care and 1 mg group. Hence, they recommended considering 1 mg triamcinolone for cases of CRVO-ME[35].

Dexamethasone implant

The Global Evaluation of implantable dexamethasone in retinal VEIN occlusion (GENEVA) trial explored 2 doses (0.7mg vs 0.35mg) of intravitreal dexamethasone implantation compared with sham for individuals with both BRVO and CRVO. Pooled data from both conditions included 34% with CRVO and 66% with BRVO. All subjects had visual acuity of 20/50 or worse and OCT central thickness greater than 299 µm. Both arms explored a 6-month outcome after single intravitreal injection of both doses (0.7 mg vs 0.35 mg) of the implant randomized 1:1:1 to sham.

The study showed a statistically significant difference in eyes achieving at least 15 letter BCVA improvement from baseline in the 2 treatment groups with the greatest response rate of 29% in treatment groups compared with 11% in the sham group at day 60. However, the statistical significance was seen in days 30–90 but was not demonstrated at the 180-day endpoint[36].

Cataract progression differences between the groups were not statistically significant at 6 months, whereas ocular hypertension was reported in significantly more eyes in both the 0.7 mg (4.0%) and 0.35 mg (3.9%) treatment groups than the sham group (0.7%). The changes in IOP peaked, however, at day 60 and were not significantly different at day 180. During retreatment with Ozurdex, the incidence of raised IOP and cataract both were seen higher in the 0.7mg group[37].

The dexamethasone implant was approved by the US Food and Drug Administration (FDA) for RVO-associated CME in 2009.

Presently, corticosteroids are being used for RVO related ME only in cases not responding to Anti-VEGF or where Anti-VEGF are contraindicated (Figure 3).

COMPARISON OF DIFFERENT AGENTS

In recent years, several studies have been performed to compare the efficacy of the available anti-VEGF agents in the treatment of RVOs.

A large multicenter prospective randomized clinical trial (SCORE2: Study of comparative treatments of RVO-2) compared aflibercept and bevacizumab in the treatment of CRVO- or HRVO-related ME. The study showed that bevacizumab was comparable with aflibercept at the primary outcome in terms of gain in letters. However, there was a significantly lower odds of complete resolution of fluid and CME with bevacizumab when compared when aflibercept[38].

Narayanan et al[39] published a prospective randomized study comparing bevacizumab with ranibizumab, with injection at baseline followed by PRN injection based on increase in CRT or loss of vision for patients with BRVO-related ME. Although there was only a 2.5 letter difference in VA between the 2 groups at 6 months, they were not able to demonstrate the difference statistically. Rajagopal et al[40] also performed a prospective study (CRAVE:Bevacizumab Versus Ranibizumab in the Treatment of Macular Edema Due to Retinal Vein Occlusion) that randomized BRVO and CRVO patients 1:1 into 2 treatment arms with bevacizumab and ranibizumab with 6 monthly injections. The authors did not find a significant difference in final visual acuity in the two groups.

Overall, the trend in recent studies seems to favor no significant difference in visual acuity outcomes between the different anti-VEGF agents in the treatment of RVOs. There have been findings that show that aflibercept has higher likelihood of anatomical resolution of ME with potentially decreased number of injections.

FUTURE TRENDS

Recently, micropulse laser has also been used in RVO associated ME and found to be useful. It has been found to be effective without the risks of collateral retinal damage and scarring. Studies have found it to be useful in RVO-ME with BCVA both <20/40 and >20/40[41]. Recently, Buyru et al have published a study comparing Ranibizumab injection with sub threshold micro pulse laser in BRVO-ME and found them to be equally efficacious[42]. Hence micro pulse laser may be helpful in reducing the burden of injection in RVO related ME (Figure 4).

Intravitreal diclofenac has recently been used in various forms of macular edema and have been found in some studies to be comparable to other intravitreal pharmcotherapies. Seth et al have used Intravitreal Diclofenac in a case series of BRVO related ME and have found it to be effective with no side effects[43]. Its efficacy in larger groups with long follow up is still pending.

Suprachoroidal triamcinolone injection is very recently being used for macular edema. A study has found it to be effective and safe in uveitis macular edema[44]. There is an ongoing phase 2 trial - Suprachoroidal Injection of Triamcinolone Acetonide with Intravitreal Aflibercept in Subjects with Macular Edema Due to Retinal Vein Occlusion (TANZANITE) study - who are receiving either a suprachoroidal injection of TA with intravitreal aflibercept (combination arm) or only an intravitreal injection of aflibercept

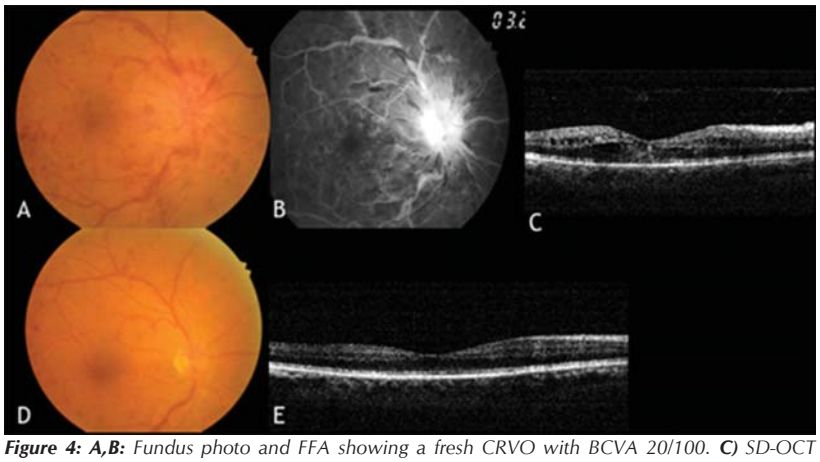
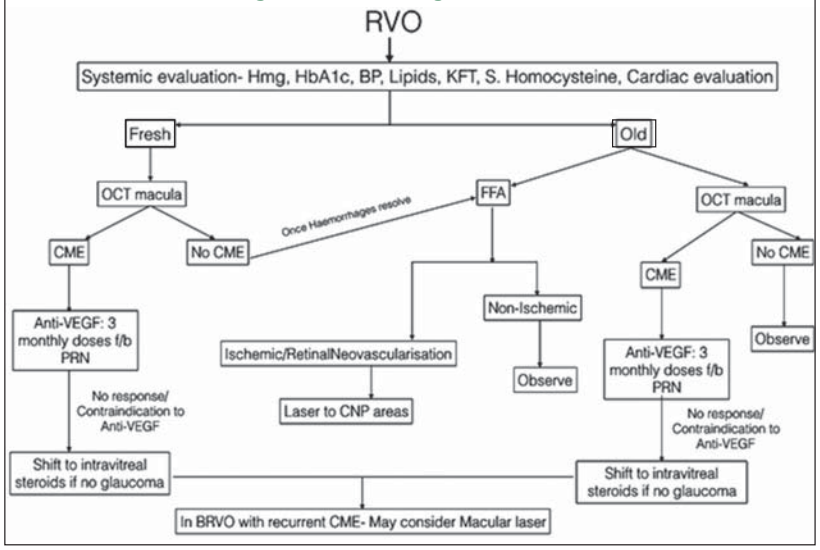


Figure 4: A,B: *Fundus photo and FFA showing a fresh CRVO with BCVA 20/100.* ***C)*** *SD-OCT showing CME.* ***D,E)*** *Fundus photo and OCT macula 2 months after yellow 577nm micropulse laser.*

Table 1: Algorithm for management of a case of RVO



(monotherapy arm), followed by monthly intravitreal aflibercept injections in both arms based on PRN criteria[45]. However, the results of this trial are not out yet. This may play an important role in the management of RVO-ME in the future.

TAKE HOME MESSAGE

1. Retinal vein occlusions are acute events with a chronic course that threaten eyesight in a spectrum of severity. No treatment has demonstrated reliable methods for directly improving the perfusion. Instead, current management focuses on minimizing vision loss from macular edema and neovascularization.
2. Anti-VEGF agents are the current standard of care for treatment of macular edema. All Anti-VEGF agents have shown equal safety and efficacy in treating RVO associated macular edema (Table 1).
3. Anti-VEGF studies have also emphasised the importance of early treatment for macular edema as visual improvement is better in early treated groups.
4. Intravitreal steroids have been established to be efficacious as well and may be considered in pseudophakic patients, patients with contraindication to Anti-VEGF and with cost-constrains.
5. Use of grid laser or micro pulse laser is reasonable in certain circumstances especially due to high cost and requirement of multiple Anti -VEGF injections, hence a combination may be able to stabilize the macular edema and hence prevent vision loss.
6. To conclude, treatment for RVO needs to be personalised and customised according to the presentation and need of the patient. Future directions for therapy will look towards improving on current practice, methods to improve perfusion, newer drugs and drug delivery methods and the role of micropulse laser. While all these advances are being gradually incorporated in our armamentarium of managing RVOs, it is important to look at underlying treatable causes and manage them appropriately.

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