

Managing patients with retinal vein occlusions: Is there any real step forward?

Whenever I examine and manage a patient with retinal vein occlusion/s (RVO), I am reminded of the excellent editorials written by Neil M. Bressler and Andrew P. Schachat^[1] in 2010 in the *Ophthalmology* and Francis Char Decroos and Sharon Fekrat^[2] in 2011 in the *American Journal of Ophthalmology*. Bressler and Francis neat and methodical analysis of the intrigues involved in the management of a case of central or branch retinal vein occlusion (CRVO or BRVO) in their respective articles is commendable.

Down the timeline role of various newer agents have been investigated or are being investigated in the management of RVO cases, as I am scripting this editorial. The most important alternatives available today to us for managing macular edema (ME) associated with retinal vein occlusions could be listed as:

1. Observation
2. Macular grid laser
3. Intravitreal triamcinolone acetonide (IVTA)
4. Intravitreal ranibizumab
5. Intravitreal implant of dexamethasone

Newer additions:

6. Intravitreal bevacizumab
7. Intravitreal aflibercept
8. Intravitreal flucinolone acetonide implant
9. Intravitreal tissue plasminogen activator (tPA)

Intravitreal bevacizumab is still not being evaluated by any large randomized, controlled trial. Intravitreal flucinolone implant has failed to get FDA approval owing to safety concerns at present but shown promising results in trials. Intravitreal tPA is still the subject of pilot studies. Intravitreal aflibercept has been evaluated in recently published COPERNICUS trial.

Results of various combination therapies of above mentioned agents are increasingly being reported, though none of the combination therapies has yet been evaluated by relevant large controlled, randomized clinical trials. Results of one such trial investigating ranibizumab vs. ranibizumab plus grid laser for ME associated with RVO, by Azad *et al* is reported in this issue.

This is not an all exhaustive list of the interventions tried upon the patients of RVO and reported in the literature in past few years. Ehlers *et al*,^[3] McIntosh *et al*^[4] and Mohamed *et al*^[5] have summarized and analysed these interventions in their respective articles.

I may earnestly look forward to the coming decade for further novel therapies targeting those growth factors, cytokines, interleukins other than vascular endothelial growth factors (VEGF), likely to have a role in the pathogenesis of the condition, especially platelet-derived growth factor, pigment epithelium-derived growth factor) and erythropoietin.^[6-8]

So, looking back to the questions of the most optimal therapeutic choice in a given patient of vein occlusion (not only for ME but also for other conditions associated with RVO), timing and duration of such an intervention and, most importantly, outcome expected after application of one such agent, what answers do we have today and what could we look forward to?

We are at the same point where Bressler^[1] was 2 years ago facing scarcity of concrete management guidelines for managing cases of RVO amid plethora of therapeutic choices.

We are still struggling for clear directions and answers for above-said questions in the deluge of new therapeutic options and floodgates are still open with some more in the pipeline. The past decade has created a paradoxical ocular pharmacological landscape where development of drugs outpaced the indications for use. Some of the most potent therapeutic agents are at our disposal but without any clear cut guidelines vis-à-vis their use or assured outcome expectations. Interestingly, our conventional mechanism of clinical trials, to settle these issues has been unyielding so far for clear answers.

Why could we not draw a generally applicable conclusion from various trials while they all address the problem of retinal venous occlusion!

As pointed out time and again, the diverse study designs and methodological disparity including primary outcome measures, among different trials have baffled the attempts to trace a common thread across the studies.

Look at the following summary of the definitions of duration of disease i.e., RVO taken into consideration by different trials:

1. The Central Retinal Vein Occlusion Study (CRVOS)^[9]
The time of diagnosis to the entry in the study. Natural history data of only 187 patients with 1 month or less disease duration.
2. The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) trials^[10]
Disease onset to the date of first treatment, minimum 6 weeks of disease duration needed while some patients of BRVO in standard care group were observed for additional 4 months before grid photocoagulation performed.

3. The Branch Retinal Vein Occlusion (BRAVO) study^[11] and Central Retinal vein occlusion (CRUISE) study^[12] - Time since diagnosis to the screening for the study (9 months and 12 months with 28 days of screening for BRVO and CRVO, respectively), no restriction of minimum disease duration to enter the study.
4. The Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion with Macular Edema (GENEVA) trials^[13] Disease duration 9 months in eyes with CRVO and 12 months in eyes with BRVO with minimum of 6 weeks duration for both groups, before initiation of therapy
5. The Controlled Phase III Evaluation of Repeated Intravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety (COPERNICUS) study^[14] CRVO with macular edema diagnosed within 9 months of study initiation, no minimum disease duration required.
6. The General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye (GALILEO) study^[15] Same as COPERNICUS but results not published.
7. The Randomized study comparing ranibizumab to sham in patients with macular edema secondary to central Retinal vein Occlusion (ROCC) study^[16] Symptom duration equal to or less than 6 months, no minimum disease duration required.

These studies also have not highlighted the mode of disease recognition by the patients. It is unclear whether patients noticed visual problem in affected eye on the day of actual occlusion or later incidentally (as incidental closure of good eye or during vision screening). This point is especially important in Indian context where many a patient noticed vision decrease incidentally days or months after the actual onset of occlusion. Patients with longer duration of disease would not behave the same as those with shorter duration. Similarly patients with macular edema have not been evaluated across the studies for presence or absence of serous subfoveal detachment, a condition with significance in determining outcome after intervention.

Likewise look at the primary outcome measures analysed by the studies:

1. SCORE trials: gain of 15 or more letters from baseline to month 12 with 4-monthly intravitreal triamcinolone compared to grid photocoagulation for BRVO and 4-monthly intravitreal triamcinolone compared to observation for CRVO
2. BRAVO and CRUISE: mean change in BCVA from baseline at month 6 compared with sham with monthly ranibizumab intravitreal injections for 6 months
3. Twin GENEVA trials: time to achieve 15 or more letter improvement in visual acuity at 6 month following only 1 treatment with dexamethasone intravitreal implant at baseline compared with sham
4. COPERNICUS - gain of 15-letter or more in best-corrected visual acuity (BCVA) at week 24 with monthly intravitreal injections of VEGF Trap-Eye compared with sham
5. GALILEO – same as COPERNICUS but results not published
6. ROCC - mean change from baseline in BCVA score and central macular thickness at 6 month with monthly intravitreal ranibizumab injections for 3 months (thereafter as and when needed) compared with sham.

These studies are incomparable and unmatched in their design and evaluation of different treatment options. As suggested by Bressler,^[1,17] to look at the same clinically relevant outcomes reported in each study such as numbers gaining or losing 15 or more letters at a clinically relevant time point such as the primary outcome time point chosen for each of the studies (12 months for IVTA and 6 months for both dexamethasone and ranibizumab) may be a way forward, but it is still not the correct answer we are looking for in a given scenario of vein occlusion.

There exists a wide disparity in the sham group of various studies. This turns out to be an important consideration since natural history data has largely been drawn from the observations made on sham group. Discrepancies in natural history data have been recently highlighted by Decroos and Fakrat^[2] as well as Yeh *et al.*^[18,19] Yeh *et al* in a post hoc analysis of pooled data from twin GENEVA trials concluded that every 1-month increase in duration of ME significantly lowered the odds of achieving 15 or more letters at 6 month in both CRVO and BRVO (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.83–0.94; $P < 0.001$). At 12 months this was still significant for BRVO cases (OR, 0.86 [CI] 0.77–0.97, $P < 0.005$) but not for CRVO cases. However, one should remember that in GENEVA trials patients with wide range of disease duration were clubbed together, with 10% of patients having ME of 90 days or less or 391 days or more duration. A small number of patients had already received laser treatment before study entry. On the other hand patients with spontaneous resolution would have been automatically excluded from all the studies, as the cases that might have even slightly better vision than study's requirement. Therefore, number of patients with spontaneous improvement has been grossly underestimated across the studies. Natural histories of BRVO and CRVO have also been reviewed by Rogers *et al*^[20] and MacItosh *et al*,^[21] respectively.

Apart from ME associated with RVO other facets of retinal venous occlusions are, sadly, very scantily studied.

Concurrent systemic abnormalities as systemic arterial hypertension, cardiovascular disease, diabetes mellitus, hyperhomocysteinemia, and obesity are well-proven risk factors for the development of CRVO or BRVO but still we have no robust evidence as to how they affect the course and consequences of retinal venous occlusions with or without intervention. There is a convincing clinical insight that strict control of these systemic associations is fundamental in the management of retinal vein occlusions. One must ensure strict control of these conditions well before planning any intervention for the cases of CRVO or BRVO. In Indian context this issue assumes wider proposition since in a majority of patients with RVO, the issue of systemic condition control takes a back seat owing to regrettable lack of proper health infrastructure as well as poor access to the health facilities.

Ocular neovascularization in RVO has neither been investigated properly nor its natural history been established as of now.

Although recently COPERNICUS^[13] and SCORE trials^[21] have studied the ocular neovascularization associated with retinal vein occlusions. The results of Phase 1 RAVE trial^[22] investigating the efficacy of ranibizumab in preventing neovascular glaucoma are yet to be published.

Central to the ambiguity surrounding retinal venous occlusive disorders is our scant understanding of the disease pathophysiology. Hayreh^[23] has provided some very important clues to decode the underlying pathophysiology of RVO. Whereas anti-VEGF agents are being used increasingly in the management of ME with RVO, role of VEGFs in the development of ME or neovascularization in the eyes with RVO is not entirely clear. On the other hand experimental studies as well as clinical studies, with limited data, also suggest a protective role of VEGFs for retinal hemodynamics and a direct role in retinal neuroprotection, especially in hypoxic condition.^[24,25] The BOLT study is the randomized trial where a detailed, FFA-based, quantitative, statistical evaluation of macular perfusion before and after anti-VEGF treatment was provided in the cases of diabetic retinopathy.^[24,26]

Restoration of venous flow in vein occlusion is established by recanalization or development of collaterals across the site of occlusion or both.^[24] In a retrospective study reperfusion was characterized by recanalization in only 22 (34%) of the 65 eyes, whereas intraretinal neovascularization was the main mechanism of reperfusion in 54 (83%) of the 65 eyes. Intraretinal neovascularization was the main mechanism of reperfusion in larger nonperfusion areas.^[27] VEGF promote formation of collateral vessels to overcome the effects of ischemic injuries and establish reperfusion of the retina.^[27,28] VEGF blockade in pre-existing retinal hypoxia has been shown to induce vasoconstriction in macular capillary bed thereby further increasing hypoxic damage.^[29,30] Anti-VEGF treatment also reduces choriocapillary endothelial cell fenestrations in primate retina that might further damage the already ischemic inner retina.^[31]

VEGFs are only a small link in the biochemical cascade involved in the pathogenesis of retinal vascular disorders. Our understanding about the role of other factors involved in this cascade is rudimentary at best. Recently, it is indicated that maintaining a normal balance between antiangiogenic and proangiogenic VEGFs (VEGF 165/VEGF165b) would be more suitable approach instead of only targeting proangiogenic VEGFs.^[32,33]

Based on the above discussion I treat RVO patients on individual basis and observe the patients of RVO monthly for first 3 months from the date of onset of symptoms, ensuring strict systemic control of associated systemic abnormalities. In my personal experience, majority of these patients improved spontaneously after 3 months if strict control of associated systemic conditions is assured. As discussed above, 3-months time gives our biochemistry and physiology ample time to heal and to establish collaterals. If patient does not satisfactorily recover vision and significant ME still persists, appropriate intervention is planned after obtaining a fundus fluorescein angiography (FFA). We favor intravitreal dexamethasone implant in all patients except in cases of steroid responder or glaucoma. All RVO patients are examined at regular intervals including those having spontaneous resolution to detect any neovascularization at the earliest and to ensure strict systemic control.

I hope for some real breakthrough for RVO patients in the near future.

S Natarajan

Editor, Indian Journal of Ophthalmology,
Chairman, Managing Director, Aditya Jyot Eye Hospital Pvt. Ltd.,
Wadala (W), Mumbai, Maharashtra, India.
E-mail: editor@ijo.in

References

1. Bressler N, Schachat P. Management of macular edema from retinal vein occlusions: You can never have too many choices. *Ophthalmology* 2010;117:1061-3.
2. DeCroos F, Farat S. The natural history of retinal vein occlusion: What do we really know? *Am J Ophthalmol* 2011;151:739-41e2.
3. Ehlers P, Fekrat S. Retinal vein occlusion: Beyond the acute event. *Surv Ophthalmol* 2011;56:281-99.
4. McIntosh R, Journ B, Mohamed Q, Saw S, Wong T. Interventions for branch retinal vein occlusion: An evidence-based systematic review. *Ophthalmology* 2007;114:835-46.
5. Mohamed Q, McIntosh R, Journ B, Saw S, Wong T. Interventions for cranch retinal vein occlusion: An evidence-based systematic review. *Ophthalmology* 2007;114:507-19.
6. Anti-PDGF combination agent Fovista TM demonstrated superior efficacy over Lucentis® monotherapy in large controlled wet AMD trial. Press Release: Ophthotech Corporation – Wed, Jun 13, 2012 6:00 AM EDT.
7. Barnstable C, Tombran-Tink J. Neuroprotective and antiangiogenic actions of PEDF in the eye: Molecular targets and therapeutic potential. *Prog Retin Eye Res* 2004;23:561-77.
8. Stahl A, Buchwald A, Martin G, Junker B, Chen J, Hansen LL, *et al.* Vitreal levels of erythropoietin are increased in patients with retinal vein occlusion and correlate with vitreal VEGF and the extent of macular edema. *Retina* 2010;30:1524-9.
9. The Central Vein Occlusion Study Group (COVS): Natural history and clinical management of central retinal vein occlusion. *Arch Ophthalmol* 1997;115:486-91.
10. SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study report 6. *Arch Ophthalmol* 2009;127:1115-28.

11. Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, *et al.* Ranibizumab for macular edema following branch retinal vein occlusion: Six-month primary end point results of a phase III study. *Ophthalmology* 2010;117:1102-12.
12. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, *et al.* CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: Six-month primary end point results of a phase III study. *Ophthalmology* 2010;117:1124-33.
13. Boyer D, Heier J, Brown D, Clark W, Vitti R, Berliner A, *et al.* Vascular Endothelial Growth Factor Trap-Eye for macular edema secondary to central retinal vein occlusion: Six-month results of the phase 3 COPERNICUS study. *Ophthalmology* 2012;119:1024-32.
14. ClinicalTrials.gov Identifier: NCT01012973 and Regeneron and Bayer report positive results for VEGF Trap-Eye in second phase 3 study in central retinal vein occlusion [press release]. Tarrytown, NY, and Berlin: Regeneron Pharmaceuticals, Inc., and Bayer HealthCare; 2011.
15. Kinge B, Stordahl P, Forsaa V, Fossen K, Haugstad M, Helgesen O *et al.* Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: Results from the sham-controlled ROCC study. *Am J Ophthalmol* 2010;150:310-4.
16. Wittes J, Downs M. Outcome measures to assess efficacy of treatments for age related macular degeneration. *Ophthalmology* 2009;116:S8-14.
17. Yeh W, Haller J, Lanzetta P, Kuppermann B, Wong T, Mitchell P. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. *Ophthalmology* 2012;119:1190-8.
18. Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, *et al.* Ozurdex GENEVA Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: Twelve-month study results. *Ophthalmology* 2011;118:2453-60.
19. Rogers S, McIntosh R, Lim L, Mitchell P, Cheung N, Kowalski J, *et al.* Natural history of branch retinal vein occlusion: An evidence-based systematic review. *Ophthalmology* 2010;117:1094-01.
20. McIntosh R, Rogers S, Lim L, Cheung N, Wang J, Mitchell P, *et al.* Natural history of central retinal vein occlusion: An evidence-based systematic review. *Ophthalmology* 2010;117:1113-23.
21. Chan C, Michael S, VanVeldhuisen P, Oden N, Scott I, Tolentino M, *et al.* SCORE Study Report #11: Incidences of neovascular events in eyes with retinal vein occlusion. *Ophthalmology* 2011;118:1364-72.
22. Rubeosis Anti-VEGF (RAVE) trial for ischemic central retinal vein occlusion. ClinicalTrials.gov Identifier: NCT00406471.
23. Hayreh S. Prevalent misconceptions about acute retinal vascular occlusive disorders. *Prog Retinal Eye Res* 2005;24:493-519.
24. Manousaridis K, Talks J. Macular ischaemia: A contraindication for anti-VEGF treatment in retinal vascular disease? *Br J Ophthalmol* 2012;96:179-84.
25. Nishijima K, Ng YS, Zhong L, Bradley J, Schubert W, Jo N, *et al.* Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. *Am J Pathol* 2007;171:53-67.
26. Michaelides M, Fraser-Bell S, Hamilton R, Kaines A, Egan C, Bunce C, *et al.* Macular perfusion determined by fundus fluorescein angiography at the 4-month time point in a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT Study): Report 1. *Retina* 2010;30:781-6.
27. Takahashi K, Kishi S, Muraoka K, Shimizu K. Reperfusion of occluded capillary beds in diabetic retinopathy. *Am J Ophthalmol* 1998;126:791-7.
28. Clayton JA, Chalothron D, Faber JE. Vascular endothelial growth factor-A specifies formation of native collaterals and regulates collateral growth in ischaemia. *Circ Res* 2008;103:1027-36.
29. Babiak A, Schumm AM, Wangler C, Loukas M, Wu J, Dombrowski S, *et al.* Coordinated activation of VEGFR-1 and VEGFR-2 is a potent arteriogenic stimulus leading to enhancement of regional perfusion. *Cardiovasc Res* 2004;61:789-95.
30. Papadopoulou DN, Mendrinou E, Mangioris G, Donati G, Pournaras CJ. Intravitreal ranibizumab may induce retinal arteriolar vasoconstriction in patients with age-related macular degeneration. *Ophthalmology* 2009;116:1755-61.
31. Peters S, Heiduschka P, Julien S, Ziemssen F, Fietz H, Bartz-Schmidt KU, *et al.* Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab. *Am J Ophthalmol* 2007;143:995-1002.
32. Ehlken C, Rennel E, Michels D, Grundel B, Pielen A, Junker B, *et al.* Levels of VEGF but not VEGF165b are increased in the vitreous of patients with retinal vein occlusion. *Am J Ophthalmol* 2011;152:298-303.
33. Marticorena J, Romano M, Heimann H, Stappler T, Gibran K, Groenewald C, *et al.* Intravitreal bevacizumab for retinal vein occlusion and early growth of epiretinal membrane: A possible secondary effect? *Br J Ophthalmol* 2011;95:391-5.

Access this article online	
Quick Response Code:	Website: www.ijo.in
	DOI: 10.4103/0301-4738.98698