CASE REPORT

Anti-Vascular Endothelial Growth Factor (VEGF) in Central Retinal Vein Occlusion : Are Loading Doses Necessary ?

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ABSTRACT

Background : Ranibizumab (anti-VEGF) given monthly for six doses, is effective in central retinal vein occlusion (CRVO). However, the cost and adherence to complete Ranibizumab regiment is a burden for developing countries.
Aim : To present two CRVO cases with satisfactory outcome after partial regiment of ranibizumab injections.
Case presentation : A 52-year old male came with sudden, painless visual decline of the left eye (LE). Best corrected visual acuity (BCVA) was 0.4. Relative afferent pupillary defect (RAPD) was positive on LE. Anterior segment was normal. Fundus examination revealed a cup-disc ratio (CDR) of 0.4, macular edema (ME), scattered hemorrhages, dilated and tortuous retinal veins. Patient was diagnosed with CRVO and was given two monthly injections before stopping treatment. Patient came with worsened VA, was then given another injection. After 6 months, his BCVA was 0.8. Similarly, a 32-year old male came with sudden painless decline of vision of LE (BCVA 0.15). Anterior segment was normal. Fundus examination showed CDR of 0.3, ME, multiple scattered pre-retinal hemorrhages, dilated and tortuous retinal veins. Patient was similarly diagnosed with CRVO of LE and given two monthly injections. Final BCVA after six months follow-up was 0.9.
Conclusion : Both cases showed improvement in VA despite having partial regiment of ranibizumab injections.

Keywords : anti-VEGF, CRVO, loading dose, ranibizumab, retina

Central retinal vein occlusion (CRVO) is a sight threatening condition which requires prompt treatment. It is regarded as the second most common abnormality in the retina after diabetic retinopathy. Visual deterioration due to macular edema occurs in 5-15% cases of branch retinal vein occlusion (BRVO) and almost all cases of CRVO.[1] This is mainly due rising level of vascular endothelial growth factor (VEGF). VEGF disrupts blood-retinal barrier, stimulates neovascularization and increases vascular permeability leading to macular edema.[2]

When left untreated, visual acuity will worsen over time. A meta-analysis showed a pooled mean decrease in VA of 10 letters from baseline to six months and

three letters from baseline to ≥ 12 months in non-ischemic CRVO. In ischemic CRVO, pooled mean decrease was 15 letters from baseline in 6 months and 35 letters from baseline ≥ 12 months.[3] The final outcome is affected by presenting VA, degree of retinal ischemia, age, female gender and absence of hypertension.[4] Patients who had good initial VA (6/12) or better are more likely to stay in this range of VA. From those in intermediate group (6/15 – 6/60), 19% experienced improvement of VA, 44% had the same range of VA, 37% had worsened VA to <6/60.[5] Unfortunately, for those presenting with <6/60 VA, there is 80% chance of deteriorating VA.

Current treatment of CRVO include anti-VEGF agents, bevacizumab, ranibizumab and aflibercept, which have been proven safe and effective in reducing macular edema as well as preserving visual functional and anatomical outcomes.[1,6] These agents work by blocking extracellular VEGF dimer hence blocking its attachment to the receptor.[7] Previous well-known randomised controlled trials (RCTs), such as CRUISE and BRAVO used six months treatment regimen for treating BRVO and CRVO, respectively by using ranibizumab. These RCTs have proven the efficacy and safety of ranibizumab. Guideline by Royal College of Ophthalmologists also recommends the use of monthly anti-VEGF injection for six months. However, recent data suggested that lower number of anti-VEGF injections may similarly lead to satisfactory outcomes.[8] This is useful especially in low- to middle-income countries and for patients with low compliance. Here, we would like to present two cases of retinal vein occlusions with satisfying results after partial regiments of anti-VEGF treatment.

CASE SERIES

Case 1

A 52-year old man presented to ophthalmology clinic with sudden and painless decrease of vision on the left eye. Patient had history of uncontrolled dyslipidemia. Vital signs were within normal limits. Upon ophthalmologic examinations, best corrected visual acuity (BCVA) was 0.4 on the left eye while 1.0 on the right eye. Relative afferent pupillary defect (RAPD) was positive on the left eye. Intraocular pressure and anterior segment were within normal limits. Fundus examination on the left eye showed cup disc ratio (CDR) of 0.4, macular edema, scattered hemorrhages, dilated and tortuous retinal veins (Fig. 1). Patient was diagnosed with CRVO and ranibizumab injections were initiated (Fig. 2).

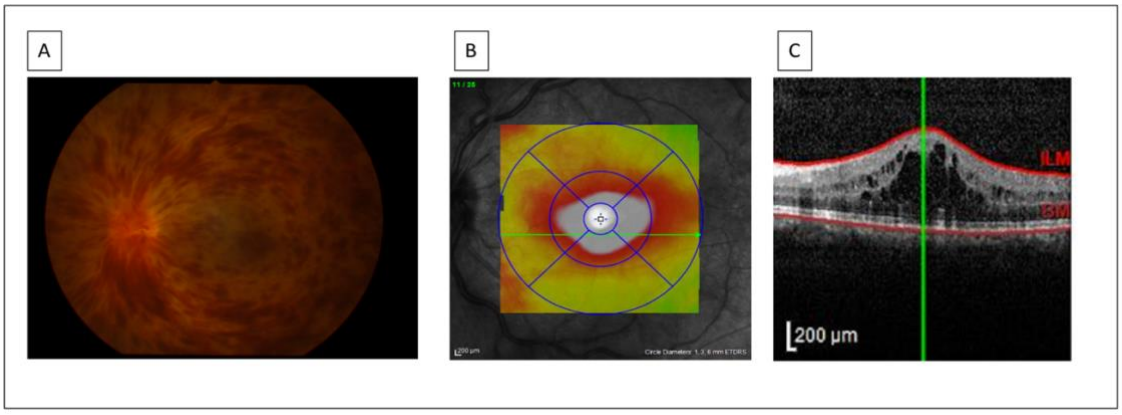

Fig 1. Patient condition prior to treatment. (A) Fundus picture (B-C) Optical Computed Tomography (OCT) result of patient 1

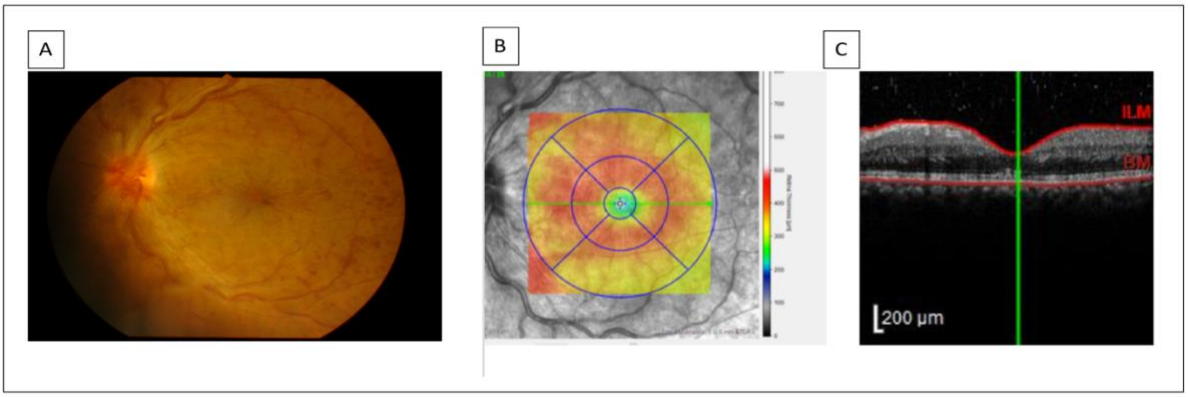

Fig 2. Patient condition after 1st injection (A) Fundus picture (B-C) OCT result of patient 1

After second injection, patient's BCVA was 0.9 on left eye and 1.0 on right eye. Since then, fundus examination showed improved retina (Fig. 3). However, patient did not come back for routine eye examination and came back after two months without injections with worsened VA (0.6 on the left eye and 1.0 on the right eye) and macular edema (Fig. 4). Patient was then given another single dose ranibizumab injection. Patient's macular edema was resolved and final BCVA was 0.8 on the left eye. Patient was then monitored monthly for the next six month with final BCVA of and improvement of retinal condition.

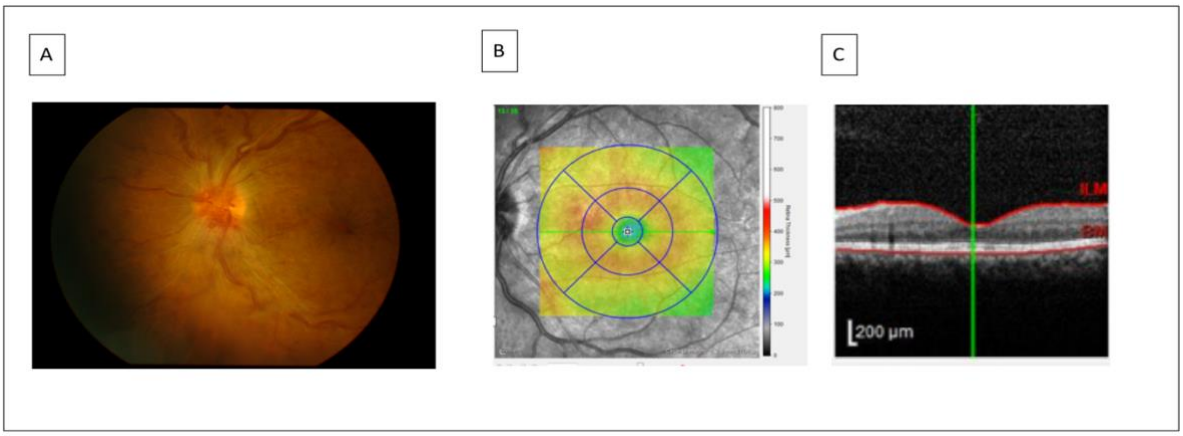

Fig 3. patient condition after 2nd injection. (A) Fundus picture (B-C) OCT result of patient 1

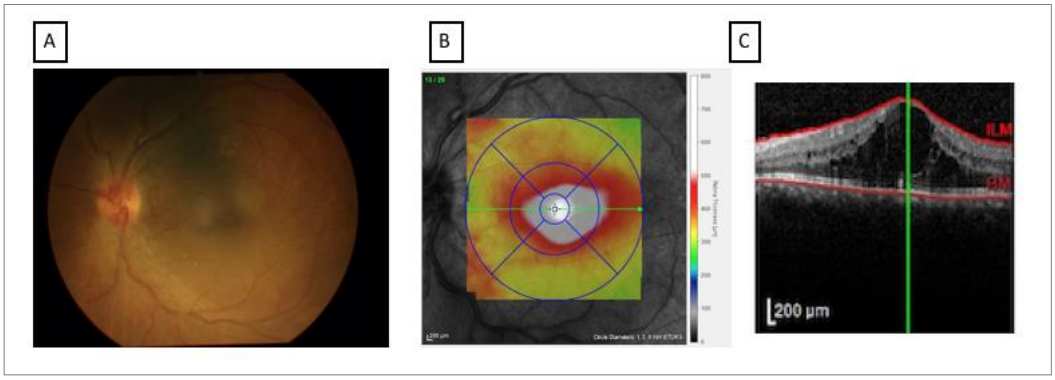

Fig 4. Patient condition after two months loss to follow-up. (A) Fundus picture (B-C) OCT result of patient 1.

Case 2

A 32 year old male presented to ophthalmology clinic with chief complaint of painless and sudden decrease of vision on the left eye. Patient was without risk factors. Upon initial assessment, BCVA was 0.15 on the left eye and 1.0 on the right eye. RAPD was positive on the left eye. Intraocular pressure and anterior segment were within normal limits. Fundus examination showed CDR of 0.3, fundus examination showed dilated and tortuous retinal veins, multiple scattered pre-retinal hemorrhages, and macular edema (Fig. 5). Patient was diagnosed with CRVO and was treated with two monthly injections of intravitreal ranibizumab (Fig. 6-7). Patient came for routine follow up monthly for the next six months with final BCVA of 0.9 on left eye with improvement of retinal conditions.

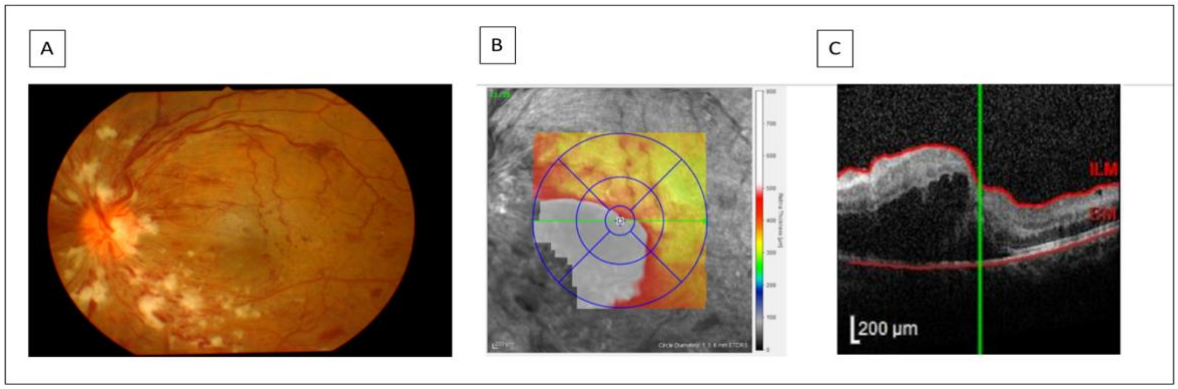

Fig 5. Patient condition prior to injection. (A) Fundus picture (B-C) OCT result of patient 2

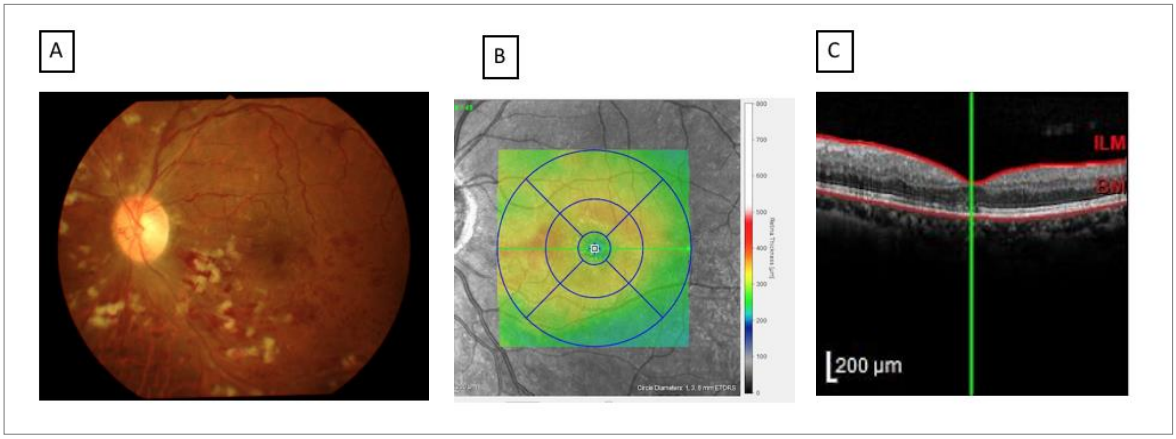

Fig 6. Patient condition after 1st injection. (A) Fundus picture (B-c) OCT result of patient 2

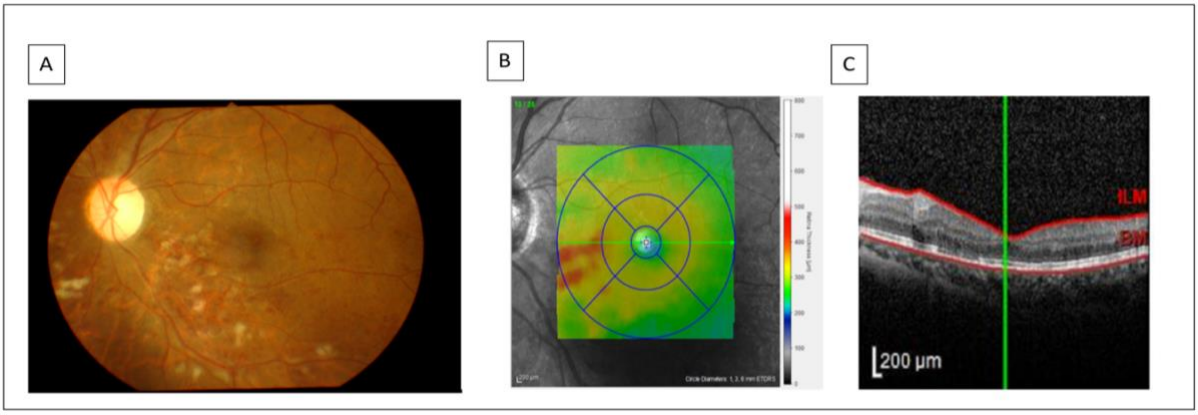

Fig 7. Patient condition after 2nd injection. (A) Fundus picture (B-C) OCT result of patient 2.

DISCUSSION

RVO is a complex multifactorial pathology, involving mainly thrombus formation and external causes of compression as well as potential vascular wall disorder. RVO, depending on the site of occurence is classified as BRVO and CRVO. BRVO occurs mainly at the AV crossings while CRVO occurs at the central retinal vein, at the level of lamina cribosa.

CRVO is classified into ischemic and non-ischemic CRVO by several criterias; 1) presenting visual acuity, 2) clinical findings and 3) results of supportive examinations. As much as 30% of non-ischemic CRVO will progress to ischemic CRVO and result in further deterioration, such as neovascular glaucoma.[1]

Ischemia in RVO triggers the production of VEGF which acts as survival factor for endothelial cells in vivo and in vitro. VEGF prevents endothelial apoptosis induced by serum starvation mediated by PI3k/Akt pathway and triggers expression of antiapoptotic proteins BCL-2, A1, XIAP and survivin in endothelilal cells.[9] VEGF also promotes hydraulic conductivity of isolated microvessels, an effect that is mediated by increased calcium influx.[9] VEGF also induces endothelial fenestration in vascular beds. These events would disrupt blood-retinal barrier, stimulate neovascularization and increase vascular permeability.[9] These pathological processes lead to edema and becomes the main reason of visual deterioration in RVO.

Current therapeutic options include laser, glucocorticoids and anti-VEGF agents. Anti-VEGF provides to be an excellent option with satisfying visual outcomes by reducing macular edema and ischemic complications. Anti-VEGF agents such as ranibizumab, bevacizumab, peptaganib and aflibercept work by direct inhibition of extracellular VEGF dimer, similar to how antibodies block antigens.[7] There has been many studies proving the efficacy and effectiveness of these agents. Ranibizumab (Lucentis, Genentech, San Fransisco CA, USA/Novartis Ophthalmics, Basel, Switzerland) is a fragment of a humanised monoclonal anti VEGF-A antibody, which works against VEGF-A, one of the most potent VEGF isoforms. Ranibizumab has 10 times higher affinity than bevacizumab.[7] It also has smaller molecular size which facilitates quick penetration to retina and choroid. Ranibizumab has been approved for ophthalmic use and has been used widely for age-related macular degeneration (AMD), diabetic retinopathy (DR) and RVO.[7]

Many trials, such as Branch Retinal Vein Occlusion (BRAVO) and Central Retinal Vein Occlusion (CRUISE) studies, have studied the effect of ranibizumab in cases of macular edema due to RVO.[10,11] In these two studies, subjects were given different doses once a month of ranibizumab over the course of 6 months. After the course of 6 months, injection of ranibizumab was given pro-renata (PRN). These studies showed that there were significant improvement in visual acuity during the study and was sustainable to 12 months. In addition, there was reduction in central foveal thickness (CFT). The treatment regiment was generally well-tolerated, small number of cases reported adverse events such as cataract, haemorrhagic stroke, acute myocardial infarction, hypertension, unstable angina, non-ocular haemorrhage and intestinal perforation. The CRUISE study involved 392 subjects with improvement of 12.7 and 14.9 BCVA letters in 0.3 and 0.5 mg ranibizumab in comparison to 0.8 in sham group ($p<0.0001$).[11] As much as 46.2% subjects who received 0.3 mg ranibizumab and 47.7% who received 0.5 mg ranibizumab obtained ≥15 letters compared to 16.9% in sham group ($p<0.0001$).[11] These, along with other results such as reduction in center point thickness (CPT) showed that 6 monthly injections of 0.3 or 0.5 mg ranibizumab are beneficial for patients with CRVO.

Gerding, et al.[12] recommended that monthly injections of ranibizumab should be administered monthly until no changes in BCVA is observed for three consecutive months. Afterwards, ranibizumab injections could be halted and monthly follow up should continue. Ranibizumab injection should be continued if there is deterioration in BCVA and should be halted once BCVA has been stabilised for three consecutive months. The injection is deemed ineffective if there is no improvement of BCVA for three consecutive months; ophthalmologists are revised to seek other options of therapy.

Study by Papadia, *et al.*[13] showed that resolution occurs after 1-4 injections. Another study by Adijevska, *et al.*[8] found improvement of BCVA after mean of 1.98 injections.[8] However, large part of this study had panretinal photogoaculation (PRP) administered prior to injections. The authors argued that PRP was delivered to prevent further complications but not to improve BCVA and reduce CMT. One trial (MARVEL) used pro renata (PRN) dosing of anti-VEGF. This trial aimed at comparing the effectiveness of ranibizumab and bevacizumab in the events of macular edema after BRVO. Both groups achieved significant improvement of BCVA after six months with average of 3.2 ± 1.5 injections in the ranibizumab group and 3.0 ± 1.4 injections in the bevacizumab group ($p=0.55$).[14]

These previous findings and the cases presented above suggest that less than six injection of anti-VEGF may provide comparable benefit for patients and prevent complications of anti-VEGF injections. However, PRN dosing and monthly follow up of patient with RVO are still required. Both our patients suffered from non-ischemic RVO. The course of the patients in our study suggests that less than six loading injections may work and the result may be sustainable over the follow up period. We do not recommend less than two loading dose injections. We also strongly urge constant monthly monitoring as the first case showed visual and anatomical deterioration after loss of follow up for two months.

Patient in the second case suffered from less severe CRVO and benefited from two injections of anti-VEGF. Patient also came for routine follow up and condition was still maintained after six months. Thus, showing a less severe case of CRVO could benefit from less injections compared to those with worse conditions. Additional injection can be and should be given at ophthalmologists' discretion. According to Gerding, *et al.*[6] reinitiation of injections should be carried out when there is evidence of VA loss due to macular oedema secondary to RVO or there is evidence of worsening condition in OCT result.

We recommend that each patient should be treated accordingly as there are many factors predicting treatment outcomes. Study by Brogan, *et al.*[15] in Glasgow found that older age, VA at presentation, presence of cotton wool spots were associated to worse outcomes. Our first case presented with older age, worse degree of macular edema, and worse retinal hemorrhage compared to second patient. However, our second patient had presence of cotton wool spots and worse baseline VA. We suggest that further study is required to draw conclusion on anti-VEGF treatment outcome predicting factors.

As the benefits of anti-VEGF in cases of RVO have been widely proven, guideline directed anti-VEGF regime in RVO cases is necessary. However, individualized treatment of anti-VEGF injection regiment may provide similar benefits with better and a more cost-effective option. Furthermore, it allows lesser requirement for constant compliance. Randomised controlled trials are required to establish the benefit of PRN injections in RVO treatment.

CONCLUSION

According to our case studies, minimum of two initial loading doses of monthly anti-VEGF injection along with monthly monitoring is required for RVO cases in order to maintain VA and anatomic improvement. Further high quality randomised controlled trials and guidelines for this loading dose and subsequent PRN dosing are required.

Conflict of Interest

Author declare no conflict of interest.

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