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Original Article

A clinical study to evaluate the efficacy of intravitreal Anti-VEGF therapy in treating macular edema due to retinal venous occlusions

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ABSTRACT

Background: A non-randomized, interventional study was carried out various types of retinal venous occlusions with significant macular edema who required an Anti-VEGF injection.

Method: One hundred and one consecutive patients diagnosed as a case of CRVO/HCRVO/BRVO were enrolled in the study provided they had significant macular edema. At least three intra-vitreous injections of Anti-VEGFs were given and both the pre and post injections BCVA and CMT on OCT were observed and analyzed.

Results: 87 patients (86.14%) showed a significant improvement of vision of at least two lines on the Snellen's and mean BCVA improved from log MAR +1.084 to log MAR +0.455. CMT on OCT showed reduction in thickness after Anti-VEGF therapy in 99 patients out of 101 and mean CMT decreased from 586.30 μ at baseline to 329.50 μ . Both of these findings were statistically very significant.

Conclusions: Anti-VEGF therapy had a marked improvement in BCVA along with a dramatic reduction in CMT in the vast majority of RVOs patients with no serious ocular or systemic side effects.

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Introduction

Retinal vein occlusions generally affect people more than 50 years of age and can be either central retinal vein occlusions

(CRVO), hemi central retinal vein occlusions (HCRVO) or branch retinal vein occlusions (BRVO).

Despite many years of investigation, much of the pathophysiology of this disease remains unclear. It is second only to

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diabetic retinopathy as a retinal vascular cause of visual loss and has significant effect on visual acuity and vision-related quality of life.¹ Based on retinal capillary perfusion retinal venous occlusion can be broadly classified as ischemic or non-ischemic. Although the pathogenesis is still not fully understood, some of the common factors associated with retinal vein occlusions (RVOs) are age, hypertension, atherosclerotic retinal vessel changes, diabetes, hyper homocystinemia and open angle glaucoma. CRVO/HCRVO/BRVO seem to have a comparable risk profile.²

No known effective medical/surgical treatment is available for either the prevention or the treatment of retinal vein occlusion (RVO). Grid laser photocoagulation has shown to marginally improve the visual outcome when compared with controls.³ Use of intravitreal steroids helps in resolving macular edema but has high rate of side effects like glaucoma and cataract.⁴ The most common complication of RVOs is the development of cystoid macular edema with consequent deterioration in vision.³

The major stimulus for the formation of macular edema and neovascularization in such patients is proposed to be the hypoxia induced production of vascular endothelial growth factor (VEGF) which causes neovascularisation with increased permeability.⁵ In patients with macular edema caused by retinal venous occlusions, intra-vitreous injection of Anti-VEGF has shown to be effective in resolving the macular edema with corresponding improvement in vision.⁶

There is also paucity of data in Indian literature on use of intravitreal Anti-VEGFs in RVOs, hence a study on patients with CRVO/HCRVO/BRVO was done.

Materials and methods

A non-randomized, interventional study was carried out among patients attending Eye OPD of a tertiary care eye center of the armed forces of various types of retinal venous occlusions with significant macular edema who required an Anti-VEGF injection. The study duration was from 01 Oct 2009 to 31 May 2012.

One hundred and one consecutive patients attending the Eye OPD diagnosed as CRVO/HCRVO/BRVO on the basis of visual acuity and the fundus findings were enrolled in the study provided they had significant macular edema which in the opinion of the investigators, required treatment. A complete medical history for any systemic or ocular disease was taken and the patients underwent systemic evaluation in the form of blood pressure recording, urine analysis, blood sugar, lipid profile, plasma homocysteine and ECG. The screened patients were subjected to a detailed ocular examination including best corrected visual acuity (BCVA), SLE evaluation including with 90 D, direct and indirect ophthalmoscopy, applanation tonometry/non-contact tonometry, optical coherence tomography (OCT) and fundus fluorescein angiography (FFA).

Inclusion criteria

Patients of RVOs with reduced vision and significant macular edema willing to be part of study after written informed consent. 88 patients received Bevacizumab (Avastin) and 13 Ranibizumab (Lucentis) and this distribution was at random.

Fig. 1 – Anti-VEGF (Bevacizumab) intra-vitreous injection procedure.

Fig. 2 – Age distribution of the patients.

Exclusion criteria

These included systemic exclusion criteria like uncontrolled hypertension, history of any other thromboembolic events or anticoagulant therapy. Ocular exclusion criteria included retinal diseases like diabetic retinopathy, age related macular degeneration, conditions where fundus could not be visualized and patients who had undergone retinal laser/intravitreal Anti-VEGF/steroid injections.

Institutional ethical clearance was obtained and informed written consent was taken from all patients.

During the period of study, if a patient required either grid or panretinal laser photocoagulation he was removed from the study, though on retrospective analysis, these patients too did well with a lesser number of Anti-VEGF injections.

The intra-vitreous injections were given under topical anesthesia under sterile conditions in the operation theater. A topical broad spectrum antibiotic was given one day prior to the Anti-VEGF injection and continued for about 7 days. Individual tuberculin syringes were prepared taking 1.25 mg Bevacizumab in 0.05 cc. (Fig. 1) or 0.5 mg of Ranibizumab and given through pars plana route at 3–4 mm from limbus depending on phakic status of patients with a 30-gauge needle.

Fig. 3 – Distribution of baseline best corrected visual acuity (BCVA).

Fig. 4 – Baseline CMT (microns) on OCT of patients of RVO's.

Regular follow up of all patients was done on day 1, 1st week, 4th–6th week after each injection and 4 weekly if no re-injection were required. All patients received a minimum of three intra-vitreous injection of Anti-VEGFs to be included in the study except seven patients, who had complete recovery of vision as well as resolution of macular edema before the standard three injections. The need for further injection was based on combination of visual acuity and macular assessment on clinical evaluation, OCT and FFA.

The results of these 101 patients were collected, tabulated and analyzed.

Results

The mean age of the patients was 63.45 years with a range of 23–86 years (Fig. 2). 58 patients were males (57.43%) and 43 were females (42.57%).

Thirty-three patients had CRVO, five patients had HCRVO and rest sixty three patients had BRVO when considering only

Fig. 5 – BCVA of patients after Anti-VEGF treatment.

Fig. 6 – CMT (microns) of patients of RVO after Anti-VEGF therapy.

the affected eye under treatment. On further analysis of the BRVO patients, 39 patients had supero temporal BRVO while 24 had infero temporal BRVO. 46 patients (45.55%) showed right eye involvement whereas left eye was involved in 55 patients (54.46%). Though there were 6 patients with bilateral venous occlusions, we have included only the treated eye or the eye treated first.

Hypertension was present in 68 patients which was well controlled with drugs. 22 patients had IHD, 21 had diabetes while deranged lipid profile was seen in 34 patients. Surprisingly 53 patients (52.48%) had hyper homocysteinemia out of a total of 82 who got the test done. Primary open angle glaucoma was seen in 5 patients of BRVO (7.9%) and 2 patients of CRVO (6.1%).

The duration of onset of retinal venous occlusion to Anti-VEGF therapy varied from 4 days to 8 months.

All patients had a BCVA of 6/18 or worse. The best corrected visual acuity at baseline was as in Fig. 3. Snellens visual acuity was converted to log MAR visual acuity for statistical analysis and at presentation mean log MAR was +1.084.

The central retinal thickness on OCT at baseline ranged between 296 μ and 1482 μ with a mean of 586.30 μ (Fig. 4). All patients had baseline CMT of more than 320 μ who were taken

for Anti-VEGF therapy except two with CMT of 296 μ , as clinically and FFA picture was suggestive of CME.

07 eyes (6.93%) demonstrated complete recovery of vision and resolution of macular edema earlier and therefore did not receive the requisite three injections. The average no of injections given to patients was 4.59 with a maximum of thirteen injections given to a single eye. The patients were evaluated for best corrected visual acuity and OCT at each visit while FFA was done after the third injection and earlier, whenever clinically indicated.

87 patients (86.14%) showed a significant improvement of atleast two lines on the Snellen's visual acuity chart after the Anti-VEGF injections (Fig. 5). Mean visual acuity (VA) improved from log MAR +1.084 to log MAR +0.455. This was statistically significant ($P < 0.0001$). Moreover it was observed that the initial improvement was marked within 1st week in most patients and to be more specific within the first 48 h with a tendency to deteriorate after 4–6 weeks. Fourteen patients either had no significant improvement, or vision deteriorated after Anti-VEGF therapy. Over the follow up period, one patient had diminution of vision after initial visual improvement, due to retinal/vitreous hemorrhage along with vitreomacular traction/fibrosis in the macular region who later on underwent pars plana vitrectomy. There was no significant visual improvement despite the surgical procedure.

Similarly, CMT on OCT showed marked and dramatic reduction in thickness after Anti-VEGF therapy in 99 (98.02%) patients out of 101 (Fig. 6) and subsequently around 4–06 weeks showed a tendency to increase. Only 2 patients with long standing RVO with VMT did not respond to Anti-VEGF treatment. However, it was noticed that reduction in CMT did not always result in improvement of BCVA. Mean CMT decreased from 586.30 μ at baseline to 329.50 μ ($P < 0.001$) which was statistically significant.

Commonly seen side effects included subconjunctival hemorrhage seen in 19 patients after intra-vitreous injections which usually resolved within 2–3 weeks. Small conjunctival laceration and superficial corneal abrasions were seen in two patients each. Mild inflammatory reaction was observed in three patients. Others included one case of subretinal hemorrhage/vitreous hemorrhage, and in addition one patient developed glaucoma after the third Anti-VEGF injection. None

Fig. 7 – Comparison of CMT & BCVA before and after Anti-VEGF therapy.

Fig. 8 – Serial OCTs showing the waxing and waning course of CME in a case of ischemic CRVO.

Fig. 8 – (continued)

of the patients developed any serious ocular complications like retinal tear, retinal detachment, hyphaema, hypotony, anaphylactic reaction or endophthalmitis.

Discussion

Use of Anti-VEGF's in the treatment of macular edema secondary to retinal vein occlusions is increasingly being reported following first publication by Rosenfeld and associates⁷ regarding the efficacy in improving vision and OCT changes following intra-vitreous injection of Bevacizumab for recurrent macular edema secondary to CRVO in an eye previously treated by intra-vitreous triamcinolone acetonide injection.

The following observations were made at end of the study. The prevalence of vascular occlusions is strongly age related as the mean age of patients was 63.45 years with a range of 23–86 years and was in accordance with the CVO study³ which found a mean age of 60 years. Surprisingly 13 patients with RVOs had age of less than 45 years. There is mild variance with other studies which have not found a significant difference in the sex distribution of venous occlusions¹ This could either be because of the peculiar clientele at this center comprising of more number of male patients or the inability of female patients to come unaccompanied especially from distant places.

BRVO was found to be the most common type of vascular occlusion 63 (62.38%) and most frequently involved the supero temporal branch. CRVO was seen in 33 (32.67%) of patients and least common was HCRVO in 5 patients (4.95%). These findings are consistent with other studies.

Hypertension was the strongest risk factor present in 68 (67.33) patients along with diabetes in 21 (20.79%), hyperlipidemia in 34 (33.66%), IHD in 22 (21.78%) and elevated plasma homocysteine in 53 (52.48%) in all types of venous occlusions. There is a strong evidence to support the fact that these patients should undergo systemic evaluation for holistic management.

All patients included in this study had vision of less than 6/18. The central macular thickness was more than 296 μ in all patients based on Spectral domain OCT. Kreutzer et al have reported a mean decline in retinal thickness from 474 μ at baseline to 316 μ at 6 months.⁸ Kreichbaum et al have reported a decrease of central macular thickness from 558 μ at baseline to 382 μ at 6 months with 3, one monthly injection.⁹ In our study we found a decrease in central macular thickness from a mean of 586.30 μ at baseline to a mean of 329.10 μ at approximately 12–16 weeks, i.e. after the third Anti-VEGF injection, which was again statistically significant ($p < 0.0001$).

Functional improvement in a patient is reflected by increase in BCVA. Kreutzer et al⁸ reported improvement in visual acuity from 0.79 (0.39) log MAR to 0.51 (0.34) log MAR at 6 months ($p = 0.009$). Kreichbaum et al⁹ reported an increase in BCVA from a mean of 20/100 at baseline to 20/50 at 6 months. In our study we observed an improvement in best corrected visual acuity from a mean of log MAR +1.084 at baseline (Snellen's equivalent = 5/60 approximately) to a mean of log MAR +0.455 (Snellen's equivalent = 6/18). This shows that intravitreal Anti-VEGF is highly efficacious in improving vision and reducing central macular thickness (Fig. 7).

The average number of injections required per patients was 4.59 which was comparable to that reported by Itturalde et al¹⁰ (4.8 injections). Most of our patients have been followed up for more than 12 months with OCT and FFA.

The maximum improvement in best corrected visual acuity and central macular thickness occurred within 1 week and the effect of the first injection was maintained till 4–6 weeks with maximum need for second injection around the same period. The waxing and waning course of CME as documented on OCT with Anti-VEGFs was seen in a large number of patients (Fig. 8). A nonrandomized, prospective, interventional study by Sivakami et al¹¹ showed marked short term improvement of vision and reduction of macular edema following intra-vitreous injection of Bevacizumab in most of the patients. Here too, Anti-VEGF therapy had a dramatic improvement in BCVA along with a reduction in CMT in the vast majority of patients. 66 patients ended up with a BCVA of 6/36 or better after Anti-VEGF therapy compared to just 31 before treatment along with reduction in CMT in 99 patients.

Recent CATT trial¹² has reported systemic adverse events (primarily hospitalizations) occurred at a rate of 24% for patients receiving Avastin and a 19% for patients receiving Lucentis. In our study we encountered only minor ocular side effects due to the injection. None of the serious side effects like endophthalmitis were encountered in the study.

Conclusion

The use of Anti-VEGFs in management of complications of RVOs specifically macular edema is extremely promising. Intra-vitreous injection of Anti-VEGFs leads to improvement of vision and resolution of macular edema based on OCT. Though it is not a permanent cure but after few injections the vision stabilizes in a large percentage of patients. A few patients may have to be given intra-vitreous injections almost 4–6 weekly for a longer period, and at times around a year. Results are better if injections/treatment is initiated earlier. No serious ocular and systemic side effects were observed during follow up of the study.

This study was undertaken to study the efficacy and safety of intravitreal Anti-VEGF's predominantly Bevacizumab in management of complications of retinal venous occlusion specifically macular edema and the following conclusions were drawn:

1. Retinal venous occlusions can occur in younger people too as 3 patients were less than 30 years of age and 13 below 45 years and can no longer be considered a disease of the elderly. This is all the more relevant for the armed forces.
2. Elevated levels of plasma homocysteine was found in nearly 53% of patients therefore it is recommended that RVOs patients should undergo systemic evaluation as this is an easily treatable entity. In addition, systemic diseases like hypertension was present in 67%, hyperlipidemia in 34% and diabetes in 22% approximately.
3. Intra-vitreous injection of Anti-VEGF showed statistically significant reduction in central macular thickness and

significant improvement in best corrected visual acuity in the vast majority of the patients.

4. The effect of one intra-vitreous injection of Bevacizumab/Ranibizumab was found to last for about four–six weeks. Repeat injections may be given in case of residual macular edema of retinal vein occlusions.
5. The drug appears to be well tolerated and no significant ocular or systemic side effects were observed in this study.
6. Though it was outside the purview of this study but combining Anti-VEGF with laser (PRP and peripheral) is likely to be equally effective as well as reduce the number of injections.
7. Anti-VEGFs should be strongly considered as an early intervention in patients of RVOs with macular edema.

Intellectual contribution of authors:

Study concept: Col Poninder Kumar, Brig Ajay Banarji, Brig Sagarika Patyal, Brig VS Gurunadh, Brig TS Ahluwalia, Sqn Ldr Avadesh Oli, Col PS Moulick, Anuradha Makkar.

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Conflicts of interest

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