Original Article

Efficacy of Bevacizumab for Uveitis

Efficacy of Bevacizumab for Uveitis Induced Cystoid Macular Oedema in Southern Punjab

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ABSTRACT

Objective: To determine the presenting with cystoid macular oedema from non-infectious uveitis.
Study Design: Observational / descriptive study.
Place and Duration of Study: This study was conducted at the OPD of Multan Medical and Dental, College Multan. Time of recruitment was from January 2015 till Feb 2016.
Materials and Methods: Seven eyes of seven patients were included in the study. They were followed over a period of twelve months with a loading dose of bevacizumab on the day of recruitment. Patients had an OCT of macula at four weekly intervals. Injections were repeated only if they had no reduction in cystoid changes, new cyst formation or increase in macular thickness. Primary outcome was measured in the form of improvement in visual acuity. Secondary outcome was reduction in central macular thickness on OCT.
Results: A total of twenty four injections were administered in seven eyes of seven patients over a period of twelve months. Main outcome was increase in visual acuity which was 9.9 ETDRS letters at the end of twelve months period. Improvement in visual acuity was found to be statistically significant (P=0.003). the mean central macular thickness decreased by 39.1% over a period of twelve months(P=0.002). Two patients had recurrence of uveitis while one developed glaucoma afterwards.
Conclusion: There was significant improvement in visual acuity as well as reduction in central macular thickness.

Key Words: Bevacizumab, Uveitis, Cystoid Macular Oedema, Central Macular Thickness

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INTRODUCTION

Cystoid macular oedema has always been considered as the main limiting factor in reduction of visual acuity post intraocular inflammation.[1,2] Common management involves use of topical and systemic steroids. Local application of triamcinolone has gained popularity in the form of subtenon, orbital floor and intravitreal injections.[1,3] Nevertheless which ever form of steroids is used, it carries a serious spectrum of side effects. Intravitreal triamcinolone carries a very high incidence of cataract and glaucoma.[3,4] Similarly use of oral glucocorticoids brig with them a list of adverse effects.
Use of glucocorticoid with steroid sparing agents as methotrexate, azathioprine etc can provide an effective management option to control uveitis; however it apparently carries a limited role in resolution of cystoid macular oedema. Similar finding is observed with the use of other immunosuppressant as cyclophosphamide and mycophenolate.[4,6]
In recent years anti vascular endothelial growth factor (anti-VEGF) has gained a vital role in the world of ophthalmology.[1,5] It is to do with its significant anti angiogenic and anti-inflammatory characteristics while bearing relatively lesser side effects. Vascular endothelial growth factor is known to induce IL-1B and IL-6.[7] This leads to compromised vascular integrity which is of pivotal role in formation of cystoid macular oedema. These interleukins were found to be in higher concentration in aqueous of uveitic patients. Since bevacizumab (anti-VEGF) holds the capacity to antagonize the effects of mentioned interleukins, hence can prove useful in resolution of cystoid macular oedema. This has been shown by several studies so far though the limitations are sample size and relatively short duration of follow up.[6,8]
This is a prospective, non-comparative, interventional study to determine the efficacy of bevacizumab for regression of cystoid macular oedema. Sample was of well controlled, non-infectious uveitis with controlled inflammation.

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MATERIALS AND METHODS

A total of seven patients were recruited from the OPD of Multan Medical and Dental, College Multan. Time of recruitment was from January 2015 till Feb 2016. A detailed informed consent was obtained from the patients. Inclusion criteria were as described below: (1) Eye with noninfectious uveitis as confirmed following detailed serology and chest x-ray. (2)Vision of 6/9 or worse in the recruited eye. (3) Proven cystoid macular

oedema on OCT with central macular thickness greater than 250 microns.

In case of similar status in both eyes only one eye was recruited for the study. Exclusion criteria included previous intravitreal triamcinolone injection in the same eye, previous history for glaucoma, vitreomacular traction and active inflammation with associated vitreous haemorrhage. Patients who had any anti-VEGF injections in the same eye for past three months prior to enrollment were also excluded from the study. In systemic evaluation, exclusion was applied to patients with uncontrolled systemic hypertension.

A detailed informed consent was taken from the patients. Patients had their first injection on day one and were given subsequent four weekly appointments for next twelve months. Patient had an OCT done on every visit. Bevacizumab was repeated only if they were unresponsive to first injection. Other indication for reinjection were persistent or recurrence of macular oedema on OCT or an increase in central macular thickness of at least 50 microns from previous injection. Patients had a clinic visit on day 1 and day 7 post injections. On each clinic visit they had there visual acuity tested, intraocular pressure measurement using Goldmann applanation tonometry. A detailed anterior and posterior segment slit lamp examination was performed to evaluate the extent of inflammation.

Injections were administered under sterile conditions in operating theatre. Surgeon used mask, sterile gloves, theatre gowns and had surgical scrub prior to the procedure. Patients had topical anaesthetic drops preoperatively for local anaesthesia. Injections were administered using standard prefilled insulin syringes with 30 gauge needles on them. All patients had a thorough cleaning of periocular tissue and lids using 5-10% povidone iodine. Same drops were instilled in the eyes to be operated for two to three minutes in order to achieve the maximum possible sterility. Patients had a self-adhesive surgical drape covering periocular tissue, nose and part of face prior to the procedure. Patients had a sterile speculum inserted followed by the intravitreal injection. Injections were performed in the infero temporal quadrant . Needle was inserted 3.5mm from the limbus for phakic and 3.5mm for pseudophakic and aphakic patients. Following the procedure, speculum was removed and patients had a single drop of ofloxacin eye drops combined with a single drop of povidone iodine solution. All patients had a sterile eye pad and were instructed to remove it 2-3 hours post procedure. No topical antibiotics were used preoperatively. All patients were prescribed with topical ofloxacin eye drops. Clear written instructions in native language were provided to them for the use of topical antibiotic drops to be used four times a day for five days.

OCT scans were obtained on each monthly visit. Scans had a careful examination by the investigators. Central macular thickness maps were obtained along with detail cross sectional images to look for changes in retinal architecture in the form of retinal cysts. Scans were obtained on Avanti, Optovue OCT machine.

Paired t-test was used to evaluate the difference in visual acuity at base line and end of study that is 12 months. $P<0.05$ was considered to be statistically significant. Changes in central macular thickness again were analyzed in a similar way.

RESULTS

A total of nine patients were enrolled for the study but two lost to follow up, hence results were based on the remaining seven patients who completed twelve months of follow up as per study protocol. All patients had no active inflammation at the time of recruitment. The diagnosis was of sarcoidosis in one, VKH in two while remaining four had idiopathic autoimmune uveitis. Mean change in visual acuity was found to be 9.9 ETDRS letters from the base line. None of the patient had loss of visual acuity from base line. Central macular thickness was measured at baseline, month 3, 6, 9 and 12. A significant decrease, as expected was seen post first injection. A mean decrease of 49.7% was noticed following first injection. However there was a gradual increase in retinal thickness with a final mean reduction of 39.1% at the end of study $p=0.002$, which was statistically significant.

Adverse effects included development of glaucoma in one patient, while two had recurrence of inflammation by the end of study. These patients were required to be commenced on oral prednisolone. A single patient had flare up of uveitis in contralateral eye which was treated with topical prednisolone acetate eye drops.

DISCUSSION

Results of this study shows that Bevacizumab appears to have significant results on improvement in visual acuity as well as reduction in central mean macula thickness. Macular oedema is considered as to be the main limiting factor in reducing visual acuity.[9] The pathogenesis of cystoid macular oedema in uveitic patients is poorly understood. The main mechanism is considered to be disruption of blood aqueous barrier as well as increased vascular permeability.[11,12] Several interleukins especially IL-1B and IL-6 have considered as the main culprit in this mechanism. It has already been demonstrated that VEG-F concentration is higher in the aqueous of uveitic patients with CMO as compared to patients without CMO. [10,11] Corticosteroids have been long use for the treatment of cystoid macular oedema but we all are aware of the significant spectrum of side effects, to name a few glaucoma and cataract formation. [12] The patients who are refractory to steroids can be considered for steroid sparing immune suppression but that carries a further increase in the extent of side effects.

It has been nearly a decade since VEGF is used for the treatment of uveitis related cystoid macular oedema. [13]It has shown to reduce foveal thickness and improve visual acuity in short term. There have been variable results quoted in different studies since than, with some showing improvement while in other visual acuity has remain unchanged or has slightly declined following Bevacizumab injections. [14]Majority of studies are based on a single loading dose of anti-VEGF with three to six months of follow up. Acharya et al have published a study looking at the effect of Ranizumab on uveitic macular oedema. In their study, they have reported a significant increase in visual acuity (an average increase of 13 ETDRS letters) and a significant decrease in central macular thickness, very similar to what we have noted with Bevacizumab in our study.[10]

Reddy et al published a similar study using Ranibizumab as their choice of anti-VEGF but with extended follow up i.e. twelve months.[15] In their study again they have found similar results in terms of improvement in visual acuity as well as reduction in central macular thickness. Reddy et al have also published a very interested finding, i.e. need for injections gradually reduces with time as patients required an average of 4.6 injections in first six and 1.8 in the next six months.[15] We do agree with their findings as we have noticed a comparable frequency of injections but interestingly with Bevacizumab.

Improvement in visual acuity during our trial was found to be statistically significant i.e. p=0.003. We found that visual acuity continues to improve steadily, though maximum improvement is seen in the first month post injection. Since recurrence of uveitis was not noticed in our patient group, hence that can be excluded as a confounding factor, which otherwise potentially can mask the useful effect of Bevacizumab.

If we follow the MUST study guidelines, decrease in central macular thickness was very much noticeable with our patients. According to MUST study a 20% decrease in retinal thickness is considered to be significant.[1,16] In our study a decrease of 39.1%, almost twice was noticed, hence making it to be a very significant value.

In our study we used Bevacizumab as anti-VEGF of choice. Authors consider this intervention as to be of vital importance. Due to financial restrains and Pakistan being a developing country Ranibizumab is used at a very limited level. Hence it is important to publish our national data incorporating available treatment modalities i.e. Bevacizumab in this case. Moreover this study provides an insight on the demographics of uveitic macular oedema in Southern Punjab. More than 50% of our patients were found to carry idiopathic noninfectious uveitis. Intervention was well tolerated by all patients enrolled in the study. No serious side effects as retinal detachment or endophthalmitis was found in any patient post injection.[17,18] However some patients noticed minor problems as floaters and occasional discomfort. One of our patient developed glaucoma by the end of study. It was not clear whether this was secondary to uveitis as apparently this patient was not found to have recurrence of inflammation during the study time. His intraocular pressures were controlled with topical IOP lowering medication. Authors believe gain in visual acuity was a direct translation of improvement in retinal architecture. [19]

Sample size was considered to be the main limitation of this study. Authors believe that the time for follow up was appropriate and at par with similar international studies done on the same subject. It is important to conduct a similar study with larger sample size and a comparative arm. It will be extremely useful to have similar study comparing effect of Bevacizumab, Ranibizumab and intravitreal steroids. Anterior uveitis itself has been described as one of the side effects of Bevacizumab, though this finding was not observed in our study.[20]

CONCLUSION

Authors believe this study helps us to understand our local Southern Punjab cohort, clinical practice patterns, patient demographics and effect of Bevacizumab on uveitic cystoid macular oedema.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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