Comparison of Intravitreal Injection of Bevacizumab and Triamcinolone Acetonide in the Treatment of Uveitic Macular Edema

Article Type: RESEARCH ARTICLE

Mansour Rahimi, Seyed Sahabaldin Shahrzad, Mohammad Banifatemi

The Iranian Journal of Immunology is a quarterly Peer-Reviewed Journal Published by Shiraz Institute for Cancer Research and the Iranian Society of Immunology & Allergy, Indexed by Several World Indexing Systems Including: ISI, Index Medicus, Medline and Pubmed

For information on author guidelines and submission visit: www.iji.ir

For assistance or queries, email: jji@sums.ac.ir
Comparison of Intravitreal Injection of Bevacizumab and Triamcinolone Acetonide in the Treatment of Uveitic Macular Edema

Mansour Rahimi*, Seyed Sahabaldin Shahrzad, Mohammad Banifatemi

Department of Ophthalmology and Poostchi Eye Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background: Cystoid Macular Edema (CME) is one of the most common and sight threatening complications of uveitis. Intravitreal injection of corticosteroids and anti-VEGF antibody are two routine options for treatment. Objective: To compare the effects of intravitreal injections of Bevacizumab and Triamcinolone Acetonide for the treatment of persistent macular edema in non-infectious uveitis. Methods: In a randomized clinical trial, sixty eyes of 55 patients were enrolled in the study. Patients were divided into two groups with randomized digits table. 29 eyes received 4 mg of intravitreal triamcinolone acetonide, and 31 eyes received 1.25 mg of intravitreal bevacizumab. Two main outcome measures were changes in visual acuity, measured with logarithm of minimal angle of resolution, and central macular thickness, measured with optical coherence tomography. Results: The mean follow-up was 25.3 weeks. The best visual acuities were achieved 6 months after injection in both groups. Improvement in visual acuity at 6 months was achieved in 28/29 (96%) of eyes in Triamcinolone group and in 26/31 (83%) eyes in Bevacizumab group (p=0.196). None of the eyes showed worsening of visual acuity after 6 months. Mean of central macular thickness in the pre-injection time for intravitreal triamcinolone acetonide (IVTA) group was 295.62 μ, and 309.87 μ in intravitreal bevacizumab (IVB) group, which were decreased after six months to 199.27 μ and 221.06 μ, respectively (p<0.001). Conclusion: This study shows that IVT and IVB are both effective in improving vision in uveitic CME. Although effects of triamcinolone on Central Macular Thickness (CMT) are more apparent, this superiority is not seen on Best Corrected Visual Acuity (BCVA).

Keywords: Bevacizumab, Cystoid Macular Edema, Triamcinolone Acetonide, Uveitis
INTRODUCTION

Uveitis is generally defined as inflammation of the uveal tract of the eye. The etiology of uveitis is categorized into infectious and non-infectious etiologies (1). The diagnosis is based on the history and physical examination and may require laboratory and medical evaluation (2).

CME is one of the most common complications of uveitis and the leading problem threatening vision. The pathogenesis of CME is not yet completely known. The impaired inner or outer blood-retinal barriers lead to fluid accumulation in CME by increased vascular permeability. This may be mediated by inflammatory cytokines, such as interferon-gamma, interleukin-2, interleukin-10, and tumor necrosis factor-alpha, as well as prostaglandins (3).

Eyes with uveitis and CME have higher concentrations of vascular endothelial growth factor (VEGF) in the aqueous humor as compared with those without CME (4). The mainstay of treatment of uveitic CME is anti-inflammatory therapy, although other treatments such as grid laser photocoagulation, Acetazolamide, and pars plana vitrectomy have also been suggested (4-7). Their mechanism of action has proposed to be stabilization of blood-retinal barrier; however the main effect is yet to be found (3). In uveitis patients, the concentration of anti-inflammatory drug should be higher in the macula in comparison to other type of CME. Sub-tenon injection of corticosteroids is the traditional approach for the drug delivery, but when there is no response to this method, intraocular injection of the drug should be considered (8).

Intravitreal injection of corticosteroids can bypass blood-retinal barrier and provide a more concentrated drug for a more prolonged time (9). This can be done with biodegradable implants or pars plana injection of synthetic corticosteroids which is the most popular rout (3,10). The effect of intravitreal application of steroids in reducing CME as monitored with OCT has improved vision as reported in several studies (10-13).

Recently anti-VEGF therapy has been introduced for many ocular diseases such as choroidal neovascularization, retinal neovascularization, neovascular glaucoma, radiation-induced retinopathy, Coat’s disease and CME (14). In one study Cordero et al. reported improvements in visual acuity and the fluorescein angiography pattern as well as OCT in uveitic patients with macular edema after injection of Bevacizumab (15). Bevacizumab is a recombinant humanized Anti-VEGF monoclonal antibody, which is approved by FDA for curing metastasis of colorectal cancer (15). In another study, Acharya and colleagues used Ranibizumab for treatment of CME in uveitic patients. They concluded that this therapy is useful in decreasing CME and improving vision in uveitic patients with refractory macular edema intolerant to corticosteroids (16).

Intravitreal injections have not been associated with severe systemic complications. Rare cases of elevated blood pressure, stroke, MI and death has been reported. Ocular side effects include vitreous hemorrhage, endophthalmitis, rhegmatogenous retinal detachment, tractional retinal detachment and uveitis (17).

In this study we compared the long-term effect of IVTA and IVB in a randomized clinical trial. Our main outcome measures for comparison are Central Macular Thickness (CMT) and log MAR of Best Corrected Visual Acuity (BCVA). We have also compared some
other characteristics of ocular inflammation such as anterior chamber and vitreous reactions as disease activity signs.

MATERIALS AND METHODS

This study was designed as a randomized clinical trial and was approved by the review board/ethics committee of the Poostchi Ophthalmic Research Center (Shiraz, Iran). Sixty eyes of 55 patients were enrolled in the study. None of the patients had a systemic or an ocular disease other than the one causing uveitis. Patients with history of other diseases causing macular edema (such as diabetes mellitus and retinal vein occlusions) were excluded from the study. All of the patients had decreased vision due to Cystoid Macular Edema (CME), diagnosed by Stratus Optical Coherence Tomography (OCT) Carl Zeiss Meditec, Inc, Dublin, Calif. and were non-responding to conventional topical medication such as corticosteroids. Patients were divided into two groups with a randomized digits table. Twenty nine eyes were included in group one and 31 in group two. All systemic medications for the control of uveitis were continued by the patients. No significant difference was found between the two groups with regard to the number of topical medications for the control of uveitis. Before doing the injections, pre-operation OCT and complete ocular examination including slit lamp examination, funduscopy and Intra-Ocular Pressure (IOP) measurement were done for the patients. For all of the patients, injection of intravitreal drug was done in the operating room. After prepping with 5% Povidone Iodine solution and draping the eyes, injection into the vitreous cavity was done from pars plana (3.5 to 4 mm posterior to limbus) with a 27-gauge needle. For patients in group 1, 4 mg of Triamcinolone Acetonide (Triamhexal; Hexal AG, Holzkirchen, Germany) in a total volume of 0.1 ml and for those in group 2, 1.25 mg of Bevacizumab (Avastin; Genetech, Inc, South San Francisco, CA) in a total volume of 0.1ml was injected. Following the injections, ciprofloxacin eye drop was instilled and the eyes were patched for 4 hours. One tablet of acetazolamide (250 mg) was also administered for each patient to decrease the chance of IOP rise. The patients were instructed to open their eye patch after 4 hours and use ciprofloxacin eye drop every 6 hours for 3 days. All patients were visited on days 1, 3, 7 and months 1, 2, 3and 6 after injections. Complete ocular examination including measuring BCVA, slit lamp examination, funduscopy, and IOP were done for each patient 1 week, 1 month, 2 months, 3 months and 6 months after the injections. In each session of follow up grading of the inflammation of the anterior chamber and the vitreous cavity were defined according to the Standardization of Uveitis Nomenclature (SUN) working group (18). Macular OCT was done on months 1, 3 and 6 of the follow ups for measuring CMT. Second and third injections were done for the patients in each group 4 and 12 weeks after the first injection if no improvement was seen (defined as persistent cystic spaces in macular OCT).

At each follow up measurement of BCVA and OCT were performed with examiners who were not informed of randomization and the previous examinations. In order to compare our main outcome measures i.e. CMT and BCVA at 6 months after injection, their differences in successive times after injections were calculated in
each group using Repeated Measurement. Differences of CMT (as measured with macular OCT) between two groups on the first week, 3rd month periods and 6 months and differences of BCVA (converted to the Log MAR) between the two groups after 1 week, 1 month, 2 months, 3 months and 6 months were calculated with independent t-test. For comparison of our non-numeric data such as anterior chamber cells and vitreous cells between the two groups prior to their injection and 6 months after injection, Mann-Whitney test was used. For intra-group comparison of this measure during time Wilcoxon signed rank test was used. All of the statistical analysis was done with SPSS version 17. p<0.05 was considered statistically significant in all calculations. The confidence interval was considered as 95%.

RESULTS

Patients. Twenty nine females and 26 males with a mean age of 23 ± 11.5 years (range, 9-44 years) participated in this study. The mean follow-up period was 25.3 weeks (range, 14-38 weeks). There were 24 cases with intermediate uveitis, 15 with pars planitis, 7 with idiopathic anterior uveitis, 6 with Behcet’s disease, 4 with idiopathic posterior uveitis, 2 with VKH and 2 with idiopathic pan-uveitis and vasculitis (Table 1).

Table 1. Demographic and Clinical Characteristics of Patients in the IVB and IVTA Groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IVB</th>
<th>IVTA</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients (55)</td>
<td>26</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>No. Eyes (60)</td>
<td>31</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Age (mean), years</td>
<td>23.2 ± 11.7</td>
<td>23 ± 10.9</td>
<td>0.948</td>
</tr>
<tr>
<td>Male : female</td>
<td>12/14</td>
<td>14/15</td>
<td>0.809</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>12</td>
<td>12</td>
<td>0.833</td>
</tr>
<tr>
<td>Pars planitis</td>
<td>10</td>
<td>5</td>
<td>0.179</td>
</tr>
<tr>
<td>Idiopathic anterior uveitis</td>
<td>2</td>
<td>5</td>
<td>0.247</td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td>3</td>
<td>3</td>
<td>0.931</td>
</tr>
<tr>
<td>Idiopathic posterior uveitis</td>
<td>1</td>
<td>3</td>
<td>0.346</td>
</tr>
<tr>
<td>VKH</td>
<td>1</td>
<td>1</td>
<td>0.962</td>
</tr>
<tr>
<td>Idiopathic Panuveitis and Vasculitis</td>
<td>2</td>
<td>0</td>
<td>0.492</td>
</tr>
<tr>
<td>Mean VA (log MAR) ± SD</td>
<td>0.47 ± 0.18</td>
<td>0.48 ± 0.22</td>
<td>0.823</td>
</tr>
<tr>
<td>Mean CMT (µ) ± SD</td>
<td>309.87 ± 52.43</td>
<td>295.62 ± 33.19</td>
<td>0.211</td>
</tr>
</tbody>
</table>

IVB: Intravitreal Bevacizumab; IVTA: Intravitreal Triamcinolone Acetonide; VA: Visual acuity, log MAR: logarithm of the minimum angle of resolution; SD: standard deviation; CMT: central macular thickness; IOP: intraocular pressure
Table 2. Comparison of results of CMT (µ) and BCVA (Log MAR) in each group and between groups in successive times after injection.

<table>
<thead>
<tr>
<th>Time</th>
<th>Pre-Injection</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVTA</td>
<td>IVB</td>
<td>IVTA</td>
<td>IVB</td>
</tr>
<tr>
<td>Mean CMT(µ) ± SD</td>
<td>295.62 ± 33.19</td>
<td>309.87 ± 52.43</td>
<td>251.75 ± 30.41</td>
<td>254.54 ± 30.15</td>
</tr>
<tr>
<td>P value comparison with pre-injection</td>
<td>-</td>
<td>-</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inter-group significance</td>
<td>0.211</td>
<td>0.723</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BCVA (LogMAR) ± SD</td>
<td>0.48 ± 0.22</td>
<td>0.47 ± 0.18</td>
<td>0.15 ± 0.08</td>
<td>0.14 ± 0.08</td>
</tr>
<tr>
<td>Significance of each time vs. preinjection</td>
<td>-</td>
<td>-</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inter-group significance</td>
<td>0.823</td>
<td>0.539</td>
<td>0.772</td>
<td>0.326</td>
</tr>
</tbody>
</table>

IVB: Intravitreal Bevacizumab; IVTA: Intravitreal Triamcinolone Acetonide; CMT: Central Macular Thickness; BCVA: Best Corrected Visual Acuity; Log MAR: logarithm of the minimum angle of resolution; SD: Standard Deviation
The intraocular inflammation was considered stabilized if there were less than 1+ cell in the anterior chamber or the vitreous cavity. All patients received topical steroid in the form of Prednisolone Acetate 1% as a standard treatment protocol, with or without systemic treatment. There were no significant differences between the two study groups in the pre-injection status of BCVA, CMT and the age (p<0.05). During the follow ups, none of the patients developed complications related to injection or drugs.

**Visual Acuity and Central Macular Thickness.** Table 2 shows the differences between the pre-injection time and 1 month, 3 months and 6 months after injection in each of the two groups with regard to CMT and BCVA as well as the inter-group comparisons. The mean of pre-injection BCVA (Log MAR) was 0.48 ± 0.22 and 0.47 ± 18 in IVTA and IVB groups, respectively (p=0.823). The best visual acuities were achieved 6 months after injection in both groups. The mean of BCVA (Log MAR) after 6 months improved significantly from baseline by 0.42 in IVTA group (p<0.001) and by 0.43 in IVB group (p<0.001). Improvement in visual acuity at 6 months was achieved in 28/29 (96%) of eyes in IVTA group and in 26/31 (83%) eyes in IVB group (p=0.196). One eye (4%) in IVTA group and 5 eyes (17%) in IVB group had no change in visual acuity after 6 months. None of the eyes showed worsening of visual acuity after 6 months.

Mean of CMT in group one was 295.62 μ in the pre-injection time which diminished to 251.75 μ, 218.13 μ and 199.27 μ after 1, 3 and 6 months, respectively. In group two, CMT was 309.87 μ in the pre-injection time and decreased to 254.54 μ, 233.90 μ and 221.06 μ after 1, 3 and 6 months, respectively. All the measurements decreased significantly in each group compared to the pre-injection values (p<0.001).

For comparison of our inter-group numeric and non-numeric data, independent t-test and Mann-Whitney U test were used, respectively. Results of independent t-test for comparison of the mean of CMT, 1 month, 3 months and 6 months after injection between the two groups are shown in Table 4. As seen, CMT changes were non-significant (p=0.723) between the two groups one month after injection and became significant after 3 and 6 months (p=0.010 and <0.001, respectively). However, during all the times after injection when the follow ups were done (1, 3 and 6 months), there were no significant difference in the mean value of BCVA (Log MAR) between the two groups (Table 2). It means that Triamcinolone Acetonide and Bevacizumab were the same in their clinical effects although they were different paraclinically.

**Anterior Chamber and Vitreous Reaction.** The mean grade for anterior chamber reaction in group one and two were 0.9 and 0.7, respectively in the pre-injection time which diminished to 0.1 and 0.15 six months after injection. The mean grade for vitreous reaction were 1.24 and 2.00 in groups one and two, respectively, and decreased six months after injection to value of 0.55 and 0.52, respectively. Comparison of these measures with Mann-Whitney U test showed that the p-value for the anterior chamber and the vitreous reaction grades between the two groups six months after injection were 0.445 and 0.893,respectively which means that there was no difference between Triamcinolone Acetonide and Bevacizumab in decreasing intraocular reactions.

**Intraocular Pressure.** The mean of maximum increase in IOP was 20.00 ± 1.89 mmHg in IVTA group and was significantly greater than that of IVB group (17.77 ± 2.15 mmHg) (p<0.001).
All patients were well controlled with topical anti-glaucoma medications. Systemic therapy or filtration surgery was not required in any patient, and there was no change in optic nerve head appearance.

DISCUSSION

Macular edema is thickening of retina due to accumulation of fluids (vascular extravasates) into the extracellular spaces. When this extravasation occurs in cystic spaces, it is called cystoid macular edema (CME). These cystic spaces can be seen with OCT, fluorescein angiography (FAG) and biomicroscopy. Cystic spaces can be formed in different layers of retina but usually in outer plexiform layer (14). The volume of extracellular fluid in retina is regulated with inner and outer blood-retina barriers and RPE pumping action (19). Various pathologic mechanisms are explained for CME, the three most important ones are: 1- increased vascular permeability 2- RPE dysfunction and 3-drug reactions (prostaglandin analogues, epinephrine, nicotinic acid, ...) (20,21). Increased vascular permeability is the most important cause of CME. It is modulated by molecules such as leukotrienes, prostaglandins, nitric oxide, vascular endothelial growth factor (VEGF), TNF-α and interleukins. Uveitis causes CME with this mechanism (22,23).

Treatment of CME (especially uveitic CME) is mainly addressed with anti-inflammatory drugs. Triamcinolone acetonide has been used more frequently due to its more lipophilic characteristics and prolonged residence time (23). In one report after 4mg of intravitreal injection, it was measureable in non-vitrectomized human eye after 3 months (10). Potential complications can be either drug related or injection related. Drug related side effects include cataract and elevated IOP and injection related complications are retinal detachment, endophthalmitis and vitreous hemorrhage (3).

Vascular Endothelial Growth Factor (VEGF) is proved to be more concentrated in aqueous humor of uveitis patients with CME than in those without CME. The main mechanism of action of this molecule is to increase vascular permeability (24). The off-label use of anti-VEGF drug Bevacizumab (Avastin) is one of the most commonly used medication in ocular diseases. Intraocular injection of this drug causes simultaneous improvement in fluorescein angiographic and OCT pattern of CME (25).

Comparison between effects of Bevacizumab and Triamcinolone has been done in few studies. Lavase reported the superior effect of single intravitreal Triamcinolone (IVT-4mg) in comparison to intravitreal Bevacizumab (IVB-2.5mg) for refractory uveitic macular edema (26). Although the dosage of IVB in our study was 1.25mg, its affect was not less than triamcinolone at 6 months. This discrepancy between our results and other studies may be due to repeated injections by us and because of the shorter half life of Avastin.

In another study, Soheilian and his colleagues declared that triamcinolone is as effective as Bevacizumab in decreasing CME (27). They followed the patients for 36 weeks and found that improvement of the condition by BCVA compared to the baseline was significant at 12, 24 and 36 weeks for IVB group and at 24 and 36 weeks for IVT group. Surprisingly, CMT reduction was observed only in IVT group. They also concluded that irrespective of
the Triamcinolone-induced cataract, IVT may be more effective than IVB. We found that CME reduction and BCVA improvement were significant in both groups at 4, 12 and 24 weeks compared to the baselines. Comparing our two groups, we have also found that BCVA has no significant difference in two groups at 3 and 6 months after injections (p=0.772 and 0.326, respectively), despite of the significant difference in mean CME (p=0.01 and 0.00, respectively). Therefore the more OCT-apparent effect of triamcinolone may not be necessarily parallel with the visual acuity improvement.

Soheilian have also reported a transient anterior chamber reaction in both of their groups after injections (more in IVB group but not statistically significant) (27). In our study, anterior chamber and vitreous reaction decreased significantly in both groups after 6 months. In contrast to their study in which there was no anterior chamber reaction in the beginning of the trial, our groups were identical in the mean grade for anterior chamber and vitreous reactions at baseline (p>0.05).

Systemic side effects of Avastin include hypertension, nephrotic syndrome, arterial thrombi, cutaneous and gastertointestinal complications as well as menstrual irregularity (18). None of these were encountered in our study which may be due to intravitreal injection rather than intravenous route and also lower dosages and shorter follow ups.

No major injection related complications were seen in this study. These complications may include retinal break, retinal detachment, vitreous hemorrhage, endophthalmitis, uveitis, traumatic lens damage and decreased vision without any identifiable cause. Intravitreal injection of bevacizumab had little effect on IOP, so it seems that IVB can be a good treatment modality for those eyes which do not tolerate any rise in IOP. Cataract formation was not evaluated as a factor in our follow ups.

Possible pitfalls of this study include our inability to stop systemic and topical anti-uveitic medications. This study shows that IVT and IVB are both effective in improving vision in uveitic CME. Although effects of triamcinolone on CMT are more apparent, this superiority is not seen on BCVA. Despite of the appearance of advent of newer anti-VEGF drugs, the traditional treatment of CME with anti-inflammatory drugs may have similar effects.

ACKNOWLEDGMENTS

We would like to thank our colleagues at the Poustchi Ophthalmic Research Center, Mrs. Ghorbani Zadeh and Mrs. Mostafavi for helping with the research proposal and data collection. This work was financially supported by a grant from Shiraz University of Medical Sciences, grant No: 88-1394.

REFERENCES

1 Basic and clinical Science Course/Vol: 9- Intraocular Inflammation and Uveitis. 2009-2010, San Francisco: AAO,2009;101