A study Comparing Ranibizumab Monotherapy Versus Ranibizumab Plus Subtenon Injection of Triamcinolone Acetonide Combination Therapy for Treatment of Diffuse Diabetic Macular Edema

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ABSTRACT

Purpose: The aim of the study was to evaluate the hypothesis that combination therapy of intravitreal ranibizumab and subtenon injection of triamcinolone acetonide if would be more effective than ranibizumab monotherapy in patients with diffuse diabetic macular edema (DME).

Patients and methods: The study was done at Giza Memorial institute included 40 eyes of 26 patients with center-involved DME. The study included eyes with central foveal thickness greater than 300 μm on crosshair protocol, diffuse macular thickening of greater than two disc-areas on slit-lamp biomicroscopy. Eligible study participants in this prospective, nonrandomized, comparative, interventional case series were divided into two groups. The first group was chosen to receive 0.5 mg/0.05 ml ranibizumab intravitreal whereas the other group was chosen to receive 0.4 mg/1 ml subtenon injection of triamcinolone acetonide (TA) and intravitreal 0.5 mg/0.05 ml ranibizumab. Exclusion criteria included: (a) eyes with previous treatments (such as focal laser therapy, vitrectomy with silicon oil injection, (b) evidence of proliferative diabetic retinopathy on fundus fluorescein angiography or clinical examination; (c) any evidence of macular ischemia on fundus fluorescein angiography; (d) presence of a taut posterior hyaloid, vitreomacular traction or epiretinal membrane on optical coherence tomography (OCT); and (e) presence of subfoveal hard exudates. All patients were followed up for 6 weeks postinjection; changes of retinal thickness, visual acuity, and intraocular pressure were evaluated.

Results: Twenty eyes of 12 patients were treated with intravitreal ranibizumab (group 1), and Twenty eyes of another 14 patients were treated with subtenon injection of triamcinolone acetonide and intravitreal ranibizumab (group 2). In group 1, the postinjection central macular thickness showed a statistically significant improvement from a baseline of 500.1 ± 40.1 to 456.7 ± 28.4 μm (reduction of 43.4 μm, \( P < 0.001 \)) at 6 weeks. Similarly, the postinjection best-corrected visual acuity (BCVA) showed a trend toward improvement from a baseline of 0.17 to 0.22 at 6 weeks. In group 2, the postinjection central macular thickness showed a statistically significant improvement from a baseline of 508.4 ± 36.4 to 468.1 ± 33.1 μm (reduction of 40.3 μm, \( P < 0.001 \)) at 6 weeks. Similarly, the postinjection BCVA showed a trend toward improvement from a baseline of 0.17 to 0.21 at 6 weeks. The difference in postinjection intraocular pressure, BCVA, and central macular thickness between the two groups at 6 weeks was not statistically significant. Conclusion: A single injection of intravitreal ranibizumab (IVR) demonstrated similar efficacy compared with subtenon injection of triamcinolone acetonide + intravitreal ranibizumab in terms of OCT macular thickness reduction in selected cases of diffuse DME after 6-week follow-up.

Key words: Central macular thickness, diabetic macular edema, subtenon injection of triamcinolone acetonide, intravitreal ranibizumab, spectral domain optical coherence tomography

Introduction

Diabetic macular edema (DME) is a leading cause of visual impairment in diabetic patients (Klein et al., 1984), and its prevalence has been reported to be 10% (Hardy and Crawford 1999). Although focal laser treatment is effective, 12% of treated eyes nevertheless have moderate vision loss 3 years following treatment. Furthermore, eyes with diffuse DME with cystic changes had a poorer response to grid laser photocoagulation (Lee and Olk, 1991). Hence, there remains a great need for additional effective therapies for these eyes.
Intravitreal triamcinolone (IVT) shows to have a beneficial effect on DME (Sutter et al., 2004; Aurden et al., 2006), with a probable mechanism of increase in tight junction proteins, which diminish vessel leakage by a local vasoconstrictive effect (Chun et al., 2006). The side effect profile of IVTA, which includes increased intraocular pressure (IOP) and cataract progression, made retina specialists search for an alternative agent as initial therapy that would achieve efficacy similar to IVTA without incurring these potential side effects (Jonas and Sofker, 2001; Audren et al., 2006; Hirooka et al., 2006).

Subtenon injection of triamcinolone acetonide has been shown to inhibit vascular leakage induced by vascular endothelial growth factor (VEGF) in animal models of inflammation and diabetes (Edelman et al., 2005) without the complications of intravitreal injections. Subtenon injection of triamcinolone acetonide have less effect on IOP rise and cataract progression.

Ranibizumab is a fully humanized monoclonal antibody fragment (Fab), which binds to multiple variant of VEGF-A (Ascale et al., 2010), and is approved for the treatment of neovascular age-related macular degeneration. The expression of VEGF is elevated in DME. Ranibizumab binds to and inhibits multiple VEGF variants. The ranibizumab for edema of the macula in diabetes (READ-2) showed that ranibizumab had a significantly better visual acuity (VA) outcome than macular laser photocoagulation (MPC) at 6, 18 months, and 2 years (Gillies et al., 2006). In a recent published study by http://DRCR.net, it was reported that intravitreal ranibizumab with prompt or deferred laser was more effective compared with MPC alone through at least 1 year (Elman et al., 2010).

In this prospective randomized trial, we tried to evaluate the hypothesis that combination therapy of intravitreal ranibizumab and Subtenon injection of triamcinolone acetonide if would be more effective than ranibizumab monotherapy in patients with diffuse DME.

**Patients and methods**

The study included twenty eyes of 12 patients (8 patients bilaterally treated and 4 patients unilaterally treated) were treated with ranibizumab (group 1), and twenty eyes of another 14 patients (6 patients bilaterally treated and 8 patients unilaterally treated) were treated with subtenon injection of triamcinolone acetonide + ranibizumab (group 2). with center-involved DME. The study was carried out at Giza Memorial institute of ophthalmology, Egypt. All patients provided written informed consent after thorough explanation of the procedure. The enrollment period extended over 9 months from 15 of January 2016 till 15 of September 2016.

Eligible participants in this prospective study, nonrandomized, comparative, cases were divided into two groups. The first group was chosen to receive 0.5 mg/0.05 ml ranibizumab, whereas the other group was chosen to receive 0.4 mg/1 ml subtenon injection of triamcinolone acetonide and intravitreal 0.5 mg/0.05 ml ranibizumab.

The study included eyes with central foveal thickness greater than 300 μm on cross-hair protocol, diffuse macular thickening of greater than two disc-areas on slit-lamp biomicroscopy. These cases were included independent of the age, metabolic control, and type of diabetes.

Exclusion criteria included: (a) Eyes with previous treatments (such as focal laser therapy, vitrectomy with silicon oil injection (b) Evidence of proliferative diabetic retinopathy on fundus fluorescein angiography or clinical examination; (c) Any evidence of macular ischemia on fundus fluorescein angiography; (d) Presence of a taut posterior hyaloid, vitreomacular traction or epiretinal membrane on OCT; (e) Presence of subfoveal hard exudates; (f) Any other ocular cause that would interfere with BCVA, such as significant cataract, glaucoma, age-related macular degeneration, branch retinal vein occlusion, etc; and (f) Personal history of previous thromboembolic events. At the initial visit, patients underwent complete eye examination, including determination of BCVA using a decimal chart, slit-lamp examination, IOP measurement, stereoscopic biomicroscopy of the macula, retinal thickness measurement by optical coherence tomography (obtained from a single spectral domain OCT machine, FA, and fundus photography). All patients were followed up for 6 weeks postinjection; changes of retinal thickness, visual acuity, and IOP were evaluated.
Statistical analysis

All data were collected on a MS-Excel 2000 spreadsheet (Microsoft Corporation, Redmond, Washington, USA) and analyzed using SPSS 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). All tests were two tailed and set at $P$-value of significance less than 0.05.

Results

Twelve eyes of 14 patients were treated with ranibizumab (group 1), and twenty eyes of another 16 patients were treated with IVD + ranibizumab (group 2). In group 1, all 12 patients were pseudophakic with a baseline IOP of 13.65 mmHg. In group 2, five patients were phakic. The seven remaining patients were pseudophakic with a mean baseline IOP of 13.3 mmHg. None of the study patients was lost to follow-up for the 6-week duration of the study. The mean age was $60 \pm 4.4$ years in group 1 and $59.1 \pm 4.6$ years in group 2. The comparisons of means between the two groups before injection and after 6 weeks of injection are shown in (Table 1).

Table 1: Summary of the group means with respect to age, sex, VA before and after injection, IOP before and after injection, and CMT before and after injection

<table>
<thead>
<tr>
<th>Variables studied</th>
<th>Group 1 (R)</th>
<th>Group 2 STTA and R</th>
<th>$P$ value (two tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean±SD)</td>
<td>60±4.4</td>
<td>59.1±4.6</td>
<td>0.480</td>
</tr>
<tr>
<td>(Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (%, femal)</td>
<td>57</td>
<td>40</td>
<td>0.317</td>
</tr>
<tr>
<td>VA before (Mean±SD)</td>
<td>0.17±0.02</td>
<td>0.17±0.22</td>
<td>0.242</td>
</tr>
<tr>
<td>VA after 6 weeks (Mean±SD)</td>
<td>0.22±0.02</td>
<td>0.21±0.02</td>
<td>0.092</td>
</tr>
<tr>
<td>IOP before (mmHg)</td>
<td>13.6±0.99</td>
<td>13.3±0.7</td>
<td>0.406</td>
</tr>
<tr>
<td>(Mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP after 6 weeks (mmHg)</td>
<td>16.1±1</td>
<td>15.6±1.1</td>
<td>0.159</td>
</tr>
<tr>
<td>(Mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT Before (µm)</td>
<td>500.1±40.1</td>
<td>508.4±36.4</td>
<td></td>
</tr>
<tr>
<td>(Mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT After 6 weeks (µm)</td>
<td>456.7±28.4</td>
<td>468.1±33.1</td>
<td></td>
</tr>
<tr>
<td>(Mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CMT, Central Macular Thickness; IOP, Intraocular Pressure; R, Ranibizumab

In group 1, the postinjection central macular thickness showed a statistically significant improvement from a baseline of $500.1 \pm 40.1$ to $456.7 \pm 28.4$ µm (reduction of $43.4$ µm, $P < 0.001$) at 6 weeks. Similarly, the postinjection BCVA showed a trend toward improvement from a baseline of $0.17$ to $0.22$ at 6 weeks. In group 2, the postinjection central macular thickness showed a statistically significant improvement from a baseline of $508.4 \pm 36.4$ to $468.1 \pm 33.1$ µm (reduction of $40.3$ µm, $P < 0.001$) at 6 weeks. Similarly, the postinjection BCVA showed a trend toward improvement from a baseline of $0.17$ to $0.21$ at 6 weeks (Table 2).

Table 2: Outcomes of the two groups with respect to VA, IOP, and CMT after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1 (IVR)</th>
<th>Group 2 (TA+D)</th>
<th>Significance (two tailed)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA improvement</td>
<td>0.0497±0.040</td>
<td>0.0387±0.031</td>
<td>0.249</td>
</tr>
<tr>
<td>IOP change</td>
<td>2.5167±0.819</td>
<td>2.2867±1.269</td>
<td>0.573</td>
</tr>
<tr>
<td>CMT change</td>
<td>-43.3967±58.183</td>
<td>-40.3033±49.733</td>
<td>0.826</td>
</tr>
</tbody>
</table>

CMT, Central Macular Thickness; IOP, Intraocular Pressure; R, Ranibizumab; $^a$- test for equality of means

The difference in postinjection IOP (Figure 1) between the two groups at 6 weeks was not statistically significant. The difference in postinjection BCVA (Figure 2) between the two groups at 6 weeks was not statistically significant ($P = 0.0066$) (Table 1). The difference in postinjection macular thickness (Figure 3) between the two groups at 6 weeks was not statistically significant ($P = 0.159$).

No patients in both groups had IOP elevations greater than 21 mmHg during the study period nor did any patients require anterior chamber paracentesis for loss of retinal perfusion after injections. No instances of endophthalmitis, noninfectious intraocular inflammation, retinal tear, or retinal detachment were seen. None of the cases had cataract progression as per lens opacity classification during the follow-up period.
Fig. 1: Box plot showing the distribution of the IOP in the two groups before injection (blue) and after 6 weeks from injection (green). IOP, intraocular pressure.

Fig. 2: Box plot showing the distribution of the VA in the two groups before injection (blue) and after 6 weeks from injection (green).
Discussion

Intravitreal injection of steroids has gained a wide acceptance and is being used as an off-label treatment option for management of macular edema from various retinopathies (Jonas and Sofker 2001; Martidis et al., 2002). Despite the rapid and wide acceptance of this treatment modality, the optimal dose, case selection criteria, safety, and efficacy of intravitreal steroids are not well known, as large randomized clinical trial results are currently lacking.

This study is the first to compare directly the use of a combination of subtenon injection of triamcinolone acetonide + ranibizumab with ranibizumab as a monotherapy in patients with DME in terms of efficacy and safety. This pilot study represents a preliminary evaluation of the hypothesis that subtenon injection of triamcinolone acetonide anti-inflammatory properties could provide a useful adjunct to the treatment of diffuse DME in combination with intravitreal ranibizumab.

In group 1 (ranibizumab), the postinjection central macular thickness showed a statistically significant improvement from a baseline of 500.1 ± 40.1 to 456.7 ± 28.4 μm (reduction of 43.4 μm, \( P < 0.001 \)) at 6 weeks. Similarly, the postinjection BCVA showed a trend toward improvement from a baseline of 0.17 to 0.22 at 6 weeks. Similarly, the postinjection central macular thickness in group 2 (subtenon injection of triamcinolone acetonide + ranibizumab) showed a statistically significant improvement from a baseline of 508.4 ± 36.4 to 468.1 ± 33.1 μm (reduction of 40.3 μm, \( P < 0.001 \)) at 6 weeks. In addition, the postinjection BCVA showed a trend toward improvement from a baseline of 0.17 to 0.21 at 6 weeks.

As expected in this small pilot study, most of these differences were not statistically significant. The difference in postinjection macular thickness between the two groups at 6 weeks was not statistically significant (\( P = 0.159 \)). The difference in postinjection BCVA between the two groups at 6 weeks was again not statistically significant (\( P = 0.0066 \)). The difference in postinjection IOP between the two groups at 6 weeks was not statistically significant (\( P = 0.09 \)).

Soheilian et al. (2009) found that combination therapy with IVTA and IVA demonstrated no additional benefit when compared with IVA alone.

Ollendorf et al. (2013) reported in their work that no statistically significant and/or consistent differences were found between anti-VEGF agents used for treatment of eyes with DME with respect to BCVA changes or the percentage of patients gaining more than 10 letters. No discernible differences in the potential harms of anti-VEGFs, including ocular events, myocardial infarction,
stroke, and other cardiovascular events, as well as death, were noted between aflibercept, pegaptanib, and ranibizumab. Data on harms for bevacizumab were under-reported (Ollendorf et al., 2013).

In a prospective, randomized clinical trial by Faghihi et al. (2008), including 130 eyes of 110 patients with type 2 diabetes suffering from DME, eligible eyes were randomly assigned to 1.25 mg intravitreal bevacizumab (42 eyes) (the IVB group) or combination of 1.25 mg bevacizumab and 2 mg triamcinolone acetonide (41 eyes) (the IVB + IVT group) or MPC (47 eyes). At week 6, all three groups showed significant reduction in CMT but the reductions for IVB and IVB + IVT were significantly more than macular photocoagulation ($P < 0.001$) (Faghihi et al., 2008). Taking into consideration the difference in the study design, we can pinpoint that IVB, an anti-VEGF agent shown to bear no difference with IVR with respect to efficacy in case of DME (Ollendorf et al., 2013) showed no statistically different results as compared with IVTA + IVB at 6 weeks.

Similarly, no significant macular volume change or improvement in BCVA was observed in the study by Sheth et al. (2011), in the IVA (intravitreal avastin) group, although supplemented with IVD. They investigated a possibility that IVD + avastin could have shown a very immediate significant reduction in macular volume (1-week or 2-week follow-up) because of the ultrashort-acting nature of dexamethasone, but this was not the case. In the latter study, the OCT measurements were taken at weekly intervals for the first 4 weeks and none showed a significant reduction in macular volume (Sheth et al., 2011).

Our study is in agreement with another study (Entezari et al., 2005) in suggesting that subtenon injection results in no severe complications such as endophthalmitis, retinal detachment, inadvertent intraocular penetration, and orbital masses and has a relatively lower risk of IOP complications and cataract progression compared with intravitreal injection (Byun and Park, 2008).

All authors claimed that the steroid-induced IOP increase may not be a major contraindication for the treatment of endovascular and edematous ocular diseases with intravitreal injection, because adverse effects need to be balanced against the potential beneficial effects of any treatment (Bakri and Kaiser, 2005).

Weaknesses of this study include small sample size. It was also limited by the available budget. The primary goal of this study, being a pilot study, was to identify signals that might warrant further work on this research point, and we believe that the current study did so. The absence of a longer follow-up remains a limitation of the current study. Moreover, some may argue in favor of administering multiple injections of subtenon injection of triamcinolone acetonide + ranibizumab to achieve a progressive reduction in macular thickening and attain an OCT appearance more suitable to treatment with focal grid laser. Keeping in mind the off-label use of subtenon injection of triamcinolone acetonide and the short duration of action of IVR, we did not consider using multiple injections of any agent.

Conclusion

A single injection of IVR demonstrated similar efficacy compared with subtenon injection of triamcinolone acetonide + ranibizumab in terms of OCT macular thickness reduction in select cases of diffuse DME after 6-week follow-up.

References


