Intravitreal Monotherapy With Bevacizumab (IVB) and Triamcinolone Acetonide (IVTA) Versus Combination Therapy (IVB and IVTA) for Recalcitrant Diabetic Macular Edema

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Abstract

Purpose: To ascertain whether addition of Triamcinolone acetonide to intravitreal Bevacizumab injection increased the efficacy in management of Diabetic Macular Edema (DME) and assess the pattern of DME that correlated with a favorable response.

Method: In a prospective randomized interventional study, 60 eyes received one of the three interventions. Group B (IVB): 20 eyes; Group T (IVTA): 20 eyes and Group BT (combined IVB and IVTA): 20 eyes.

Results: Visual improvement was similar in all three groups. Reduction in central retinal thickness (64 % BT Vs 59 % B Vs 45 % T); recurrence of clinically significant macular edema (15 % B and BT Vs 70 % T); elevated intraocular pressure ( 17 % T Vs 22 % BT Vs 5 % B) were observed. Greater edema and sub retinal fluid predicted a favorable response to both IVB and IVTA.

Conclusion: TA did not add to therapeutic efficacy of IVB, but increased the incidence of elevated intraocular pressure.

Introduction

Recalcitrant diabetic macular edema is characterized by the accumulation of plaques of hard exudates in a grossly edematous retina, not amenable to the standard modalities of therapy and showing a very poor visual potential. These patients usually have a poorly controlled glycaemic status of long duration with associated co-morbid condition such as systemic hypertension, dyslipidemia and chronic renal failure. Majority of these eyes would have had several sittings of laser photocoagulation and hence it is necessary to employ alternative treatment modalities.

Initial reports on uncontrolled interventional case series reported an unprecedented efficacy of intravitreal steroids in reducing diabetic macular edema often accompanied by significant improvement in visual acuity. These uncontrolled series were followed by randomized placebo-controlled trials demonstrating the efficacy of IVTA compared with standard of care, both short term and long term. The beneficial effect of intravitreal injection of triamcinolone acetonide in most
cases lasted for 6-9 months. In the Intravitreal Triamcinolone acetonide for clinically significant Diabetic Macular Edema that persists after laser treatment study (TDMO), the mean number of injections was only 2.4 over 2 years with a total potential for five injections. It has also been reported that repeated intravitreal injection may not be as effective as the initial treatment. The high incidence of adverse effects which include cataract (54 %), glaucoma (20-40 %) and need for trabeculectomy (6 %) demands caution in its use.

The introduction of IVTA has been a major advance in the treatment of refractory diabetic macular edema. The high risk of steroid related adverse effects however leaves room for improvement and innovation in treatment strategies. Focal/Grid laser photocoagulation after IVTA has been shown to maintain improved vision and may reduce recurrent macular edema.

Patients with diabetic macular edema have been found to have increased levels of VEGF in the vitreous. Hence intravitreal injection of anti VEGF may have a role in reducing diabetic macular edema. Their efficacy is similar to IVTA, but they do not cause adverse events associated with corticosteroids. On the other hand, frequent injection (every 4-6 weeks) for an extended period may be required, making injection related complications such as infectious endophthalmitis a major draw back.

There are very few studies on the efficacy of combining triamcinolone acetonide and bevacizumab (an anti VEGF antibody). We undertook a pilot study to compare the efficacy of intravitreal monotherapy with Triamcinolone and Bevacizumab versus combination of Bevacizumab and triamcinolone in the management of recalcitrant DME not amenable to laser treatment. We also assessed the OCT patterns in recalcitrant DME which showed a favorable response to intravitreal injection of Triamcinolone and Bevacizumab.

**Methods**

The study was designed as a prospective randomized interventional study which recruited 60 patients who fulfilled all the inclusion criteria from March 2006 – March 2008. The inclusion criteria for enrolment into the study were:

1. Diabetic age ≥ 10 years
2. Good Glycaemic Control (Hb A1C ≤ 7 gm %)
3. Stable Renal Status
4. Controlled serum lipid level
5. H/o prior Focal/ Grid laser PHC (≥ 3 sittings) ≥ 6 months to time of enrolment into the study.
6. Presence of DME clinically and angiographically
7. OCT showing CRT ≥ 300 µm
8. Absence of significant lens opacity
9. Absence of macular ischemia
10. Absence of VMT or a taut posterior hyaloid phase in OCT.

Exclusion criteria were poorly controlled diabetes with associated nephropathy and dyslipidemia, significant cataract precluding fundus evaluation or presence of macular ischemia. The patients were randomized to receive one of the three modes of interventions tested in this study.

- **Group B:** Received 0.05 ml / 1.25 mg Intravitreal injection of Bevacizumab.
- **Group T:** Received 4 mg / 0.1 ml Triamcinolone acetonide injection intravitreally.
- **Group BT:** Received both Bevacizumab and Triamcinolone acetonide injections administered intravitreally.

All patients underwent a thorough preoperative evaluation. The best corrected visual acuity was determined after dilated refraction. Slit lamp biomicroscopy of the macula, applanation tonometry and indirect ophthalmoscopic evaluation of the fundus were performed and the findings noted. The degree of cataract was assessed prior to intervention. All patients underwent a fluorescein angiographic evaluation and OCT assessment of central retinal thickness and pattern of edema as part of the baseline evaluation. An informed consent was obtained in all the patients. The intervention was performed under strict aseptic precautions in the operation theatre under topical anesthesia in all the patients. Paracentesis was performed to bring the IOP under control and the eye was kept patched for an hour after the procedure. Postoperatively 3 hours after the procedure applanation tonometry was performed in all patients using the Keeler Pulsair non contact tonometer. The patients were
instructed to use topical antibiotic drops qid, topical
non steroidal anti inflammatory drops qid and topical
dorzolamide drops once at bed time for a period of
7 days postoperatively. Counseling on the appearance
of floaters and slight visual blurring were discussed with
the patients.

The patients were followed up on day 7, 30 days and
90 days after the procedure. At each visit an assessment
of the glycaemic status, control of BP, renal status and
serum lipid profile was assessed. FFA and OCT were
performed at 30 days and 90 days after the procedure.
Refraction, tonometry, slit lamp evaluation for cataract
and biomicroscopic macular evaluation for degree of
macular edema was performed at all visits. Response
to therapy was assessed by 1) Improvement in the best
corrected visual acuity 2) Slit lamp biomicroscopy and
OCT showing reduction in retinal thickness 3) FFA
showing decrease in fluorescein leakage 4) Progression
of lenticular changes 5) Presence or absence of post
tratment IOP spike and 6) Recurrence

Follow up data in the IVTA group (Fig 1), IVB group
(Fig 2) and combined group (Fig 3) showing regression
of macular edema.

Fig. 1. Pre treatment and post treatment fundus photography,
Fluorescein angiographic and OCT appearance
showing minimal regression in a patient who received
intravitreal triamcinolone acetonide injection

Fig. 3. Pre and post treatment FFA & OCT showing regression
of CSME

Results

This study was designed as a prospective randomized
comparative interventional case series which recruited
60 patients enrolling 20 patients for each mode of
intervention. The patients were of the age group
ranging from 45-70 years (Mean age 58 years). There
were 46 males and 14 females in our study giving a
M: F ratio of 2:1. The mean duration of diabetes was
13.5 years (Range 7 years -20 years) and the mean value
of glycosylated hemoglobin at baseline was 6.7 (Range
5.9 - 7.5). Associated co-morbid conditions were:

1. Hypertension   :  25 (41.67 %)
2. Hyperlipidemias :  40 (66.67 %)
3. Chronic Renal failure  :  3 (5 %)
4. Both HT and HL  :  30 (50 %)
5. No associated disease :  15 (25 %)

50 % of the patients had proliferative diabetic
retinopathy associated with maculopathy and 50 % had
background diabetic retinopathy with clinically
significant macular edema. In group T (IVTA Group)
an improvement in visual acuity was observed in 9/20
eyes (45 %) who showed a mean reduction of central
retinal thickness in the OCT scans from a baseline mean
CRT value of 550 μm ± 26 μm to 285 μm ± 20 μm.
This 45 % reduction in central retinal thickness
persisted up to 6-9 months after which the
recurrence of CSME was observed in 15 of the 20 eyes
(75 %). These eyes underwent focal/grid laser
photocoagulation / or repeat IVTA in 4 eyes (20 %).
In the remaining 11 patients the mean reduction in central retinal thickness was by 20 % of baseline value (from a mean CRT at baseline of 550 μm ± 26 μm to 350 μm ± 20 μm) at 6 months follow up. Although there was no improvement in visual acuity, the vision stabilized at the baseline level. Recurrence of edema was noticed in 9/11 patients (81.81 %).

Progression of cataract was noticed in 6 eyes (30 %) and 2 patients with significant cataract underwent phacoemulsification with foldable IOL implantation under topical anesthesia.

Intraocular pressures increased to mid twenties in 3 eyes (15 %) but could be controlled medically with single antiglaucoma medication (Dorzolamide).

There were no cases of endophthalmitis, vitreous hemorrhage or retinal detachment in this group.

Group B (Intravitreal Bevacizumab injection): An improvement in visual acuity was observed in 11/20 eyes (55 %) in this group. All 20 eyes showed some reduction in central retinal thickness, however a 25 % reduction from baseline value was obtained in 59 % of our patients in this group. Maximum beneficial effect was observed within 30 days of the injection and with additional laser therapy the effect persisted up to 9 months. Repeat injection was not necessary up to 12 months. However some increase in CRT was noticed in 15 % of patients after 9 months for which additional laser was given. Further follow up alone will give an idea of the course of disease and the necessity for reinjections. Elevation in intraocular pressure was noticed in one patient (5 %) which was amenable to medical therapy.

Group BT (Combined IVTA & IVB) : An improvement in visual acuity was observed in 60 % (12/20) eyes. The reduction in the central retinal thickness was maximum in this group and was observed in 64 % of eyes. The reduction in retinal thickness peaked at one month post injection and persisted up to 9 months. Recurrences in 15 % of eyes were similar to group B showing than an additional injection of TA did not have any effect in preventing recurrences. A higher incidence of elevated intraocular pressure in 22 % of cases questioned the efficacy of adding TA, when IVB alone would have sufficed.

<table>
<thead>
<tr>
<th>Table 1. Effectiveness of treatment on Vision</th>
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<tbody>
<tr>
<td><strong>MEAN</strong></td>
</tr>
<tr>
<td>IVTA</td>
</tr>
<tr>
<td>BT</td>
</tr>
<tr>
<td>AT</td>
</tr>
<tr>
<td>IVB</td>
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<tr>
<td>BT</td>
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<tr>
<td>AT</td>
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<tr>
<td>IVB + IVTA</td>
</tr>
<tr>
<td>BT</td>
</tr>
<tr>
<td>AT</td>
</tr>
</tbody>
</table>

Fig. 4. Efficacy of intervention with respect to vision gain
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There was no statistically significant difference between the increase in visual scores in the 3 groups by ANOVA test and hence all three modalities are equally effective with respect to visual gain.

Effectiveness of Treatment on Central Retinal Thickness

- There was a mean decrease in CRT of 167 μm, 201 μm and 208 μm in the IVTA, IVB and the combined group which was statistically significant by the paired “t” test (p=0.000) (Table 2).
- There was no statistically significant difference in the decrease of central retinal thickness in the 3 groups by the ANOVA test (p=0.110) & hence all 3 interventions were equally effective.

Analysis of the complications showed that the incidence of cataract formation was highest in the IVTA & Combined Groups (30%). Elevated intraocular pressures were observed in 15% of patients in the IVTA Group and in 25% in the combination group while only one patient (5%) had elevated intraocular pressure in the IVB group. The correlation was not statistically significant by the chi squared test (Chi^2 = 3.17; p = 0.208).
- The highest rate of recurrence of CSME was observed in the IVTA group (70%) and occurred within 6 months of the intravitreal pharmacotherapy. Clinically significant macular edema recurred in 15% of the patients randomised to receive IVB & combined pharmacotherapy. This correlation was statistically significant by chi squared test p=0.000 (Table 3).
- There was no added benefit in adding IVTA to IVB

### Table 2. Effectiveness of treatment on OCT

<table>
<thead>
<tr>
<th></th>
<th>MEAN</th>
<th>SD</th>
<th>N</th>
<th>MEAN DIFFERENCE</th>
<th>PAIRED 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT</td>
<td>511.9</td>
<td>113.5</td>
<td>20</td>
<td>167 μm</td>
<td>8.21**</td>
<td>0.000</td>
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<tr>
<td>AT</td>
<td>345.2</td>
<td>87.1</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/IVB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT</td>
<td>538.1</td>
<td>73.8</td>
<td>20</td>
<td>208 μm</td>
<td>17.02**</td>
<td>0.000</td>
</tr>
<tr>
<td>AT</td>
<td>330.3</td>
<td>66.1</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 + IVB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT</td>
<td>539.5</td>
<td>65.6</td>
<td>20</td>
<td>20 μm</td>
<td>17.06**</td>
<td>0.000</td>
</tr>
<tr>
<td>AT</td>
<td>338.8</td>
<td>67.2</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Comparison of Complications

- **CATARACT**: 30% in IVTA group alone developed cataract
- **GLAUCOMA**: Increase in IOP in 15% IVTA GP, 5% IVB GP, & 25% Combined GP was not statistically significant by chi squared test (Chi^2 = 3.17; p=0.208)
- **RECURRENT**: In 70% IVTA, 15% IVB, 15% Combined group was statistically significant by chi squared test (Chi^2 = 18.15, p=0.000)

- All 3 groups are similar with respect to age, sex, diabetic age, HbA1C, pre treatment vision, and baseline central retinal thickness on OCT and hence they are comparable.
- There was a mean increase of 1.6, 1.6 & 1.7 in the pre treatment and post treatment visual scores in the IVTA, IVB and the combined group which was statistically significant by the paired “t” test (p = 0.005 in IVTA group, p = 0.001 in the IVB group, & p = 0.000 in the combined group) (Table 1, Fig. 4).

### Table 4. OCT GRADING

<table>
<thead>
<tr>
<th>OCT GRADING</th>
<th>Pre injection CRT (Mean)</th>
<th>Post-injection CRT (Mean)</th>
<th>Pre-injection vision (Mean)</th>
<th>Post-injection vision (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse edema</td>
<td>500 μm</td>
<td>309 μm</td>
<td>5/60</td>
<td>6/18</td>
</tr>
<tr>
<td>Cystoid edema</td>
<td>422 μm</td>
<td>315 μm</td>
<td>3/60</td>
<td>5/60</td>
</tr>
<tr>
<td>Subfoveal serous RD</td>
<td>418 μm</td>
<td>256 μm</td>
<td>CF 2m</td>
<td>6/36</td>
</tr>
<tr>
<td>Plaques of H/E</td>
<td>325 μm</td>
<td>250 μm</td>
<td>CF1m</td>
<td>CF1m</td>
</tr>
<tr>
<td>Combination</td>
<td>550 μm</td>
<td>350 μm</td>
<td>CF 2m</td>
<td>4/60</td>
</tr>
</tbody>
</table>
We divided the patients into 4 groups based on the preinjection OCT findings: 1) Diffuse edema 2) Cystoid edema 3) Subfoveal serous retinal detachment 4) Plaques of hard exudates under fovea. 5) Combination and tried to correlate with the response to therapy as measured by CRT and improvement in vision.

Our results showed that maximum reduction of central retinal thickness and maximum visual gain were observed in eyes with greater degree of diffuse macular edema and presence of subfoveal serous RD (Table 4).

**Discussion**

The role of steroids is mediated through 1) Suppression of VEGF 2) Stabilizing the leakage from retinal vessels 3) Suppression of the release of endothelial cell activators and 4) Possibly its anti-inflammatory action.

Initially uncontrolled interventional case series reported an unprecedented efficacy of intravitreal steroids (usually triamcinolone acetonide) in reducing diabetic macular edema accompanied by significant improvement in visual acuity. These uncontrolled series were followed by randomized placebo controlled trials demonstrating the efficacy of IVTA compared with standards care both short and long term.

Several studies in eyes with persistent DME despite focal and/or grid laser photocoagulation have demonstrated the efficacy of IVTA over laser. However, the NEI (National Eye Institute) sponsored trial have conclusively shown that a focal / grid laser photocoagulation gave longer lasting beneficial effects when compared to the transient effect of intravitreal triamcinolone acetonide injection.

Although most studies have shown a beneficial effect the optional dosage of IVTA is still somewhat confusing. Audren F et al conducted a randomized prospective trial comparing the efficacy of 2 mg Vs 4 mg of Triamcinolone acetonide in the management of diffuse diabetic macular edema. This results showed that there was no dose dependent difference in the response to intervention. However Lam DS et al and Spandau UH et al demonstrated close dependency in the response to intravitreal injection of triamcinolone acetonide.

The beneficial effect of an intravitreal injection of triamcinolone acetonide in most cases lasts for 6 months – 9 months and repeated injection may not be as efficacious as the initial treatment.

The high incidence of steroid related adverse effects such as (1) necessity for cataract extraction in 54 % of phakic treated eyes (2) steroid related evaluation of IOP in 44 % of treated eyes necessitates the use of caution.

In order to avoid the adverse effect associated with intravitreal therapy, particularly infectious endophthalmitis, the use of periocular steroids in the management of diabetic macular edema has been studied. The results of these trials have been contradictory to each other showing either a beneficial effect or no appreciable effect of the intervention on DME.

Investigators continue to report their experience with intravitreal injections of Bevacizumab, a humanized monoclonal IgG antibody directed against all five VEGF isoforms, in the setting of primary therapy. In a study of 51 patients, Haritoglou et al. observed that at 6 weeks after a single Bevacizumab injection, patients with DME resistant to other therapies had increased visual acuity as well as decreased central retinal thickness by OCT relative to pre-injection baseline, though the effect on visual acuity was not sustained at 12 weeks. The Pan – American Collaborative Retina Study Group studied intravitreal Bevacizumab as a primary treatment for DME in 78 eyes of 64 patients and found, at six months, over 96 % of eyes had either stable or improved visual acuity or reduction in the mean central retinal thickness by OCT. A phase II DCRC.net study of 109 patients compared two does of Bevacizumab to focal laser photocoagulation and demonstrated its efficacy in decreasing DME in some eyes. To date, no phase III trials have been reported that demonstrate a clear benefit for Bevacizumab in the treatment of DME.

While Ranizumab, an affinity – matured humanized monoclonal antibody fragment directed against all VEGF isoforms, is currently in clinical trials for DME, its off label use in DME patients is limited likely as a result of its increased cost and less widespread availability world wide, as compared to Bevacizumab. Clinical trials in DME patients are limited as a result of its increased cost and less widespread availability.
worldwide, as compared to Bevacizumab. Clinical trials in DME patients are on going. Two pilot studies of 10 patients each, suggested that it was well tolerated and may have some efficacy in promoting improvement in visual acuity and reduction in central retinal thickness by OCT. The READ – 2 (Ranibizumab for edema of the macula in diabetics) studies, a phase II trial comparing the relative efficacy of Intravitreal Ranibizumab, macular laser photocoagulation, and the combination of both treatments among patients with DME, who have not received prior laser is currently ongoing. Six months outcomes suggests a greater improvement in visual acuity for patients undergoing intravitreal Ranibizumab alone as compared to laser or combination treatments.

A report on 101 consecutive eyes with DDME treated with intravitreal Bevacizumab, resulted in both anatomic and functional improvement. Interestingly, the reduction of retinal thickness and improvement of BVCA were detected within the first 4 weeks after the injection in most of the patients. In addition, both doses (1.25 mg and 2.5 mg) were associated with improvement of BVCA and a greater reduction in central macular thickness, and no difference in between were found. Ocular tolerance of the 2 different doses of IVB was demonstrated, and no serious systemic adverse events were noticed during the study.

There are several studies in the literature on the intravitreal administration of antibodies against VEGF for DDME. However, none of them deal with anti-VEGF as a primary treatment. Haritoglou et al reported that intravitreal Ranibizumab has the potential to maintain or improve BVCA and reduce retinal thickness in patients with DDME not responding to previous treatments such as photoacoagulation, intravitreal injection of triamcinolone, or vitrectomy. Their follow-up period was too short (6 weeks) to provide specific treatment recommendations. Kumar and Sinha reported results of 20 eyes with DDME treated with intravitreal Bevacizumab at baseline and at months 1, 2, 4, and 6. Results showed that at month7, one month after the final administration of Bevacizumab and the primary endpoint of the study, the median reduction of the excess foveal thickness was 97%, and there was a median improvement of 10 letters.

The results of this retrospective study demonstrated the efficacy of 1.25 mg or 2.5 mg of IVB as primary treatment of DDDME, as 49.5 % of eyes showed anatomical and functional improvement. In addition, our results suggest a reduced risk of visual acuity loss in eyes with DDME treated with IVB (82.2 % of eyes). We found that the anatomical and visual benefit of the intravitreal Bevacizumab appears and reaches its maximum value during the first month and maintains itself over 12 months. Nevertheless, we did not find statistically significant differences between the 2 doses of Bevacizumab evaluated.

A phase 1 study (the READ-1 Study, Ranibizumab for Edema of the macula in Diabetes, sponsored by the Juvenile Diabetes Research Foundation) of 20 patients with DME treated with repeated intravitreous injections 0.5 mg of ranibizumab, showed evidence of biological activity of ranibizumab in DME as well as safety and tolerability (Nguyen, et al. 2006). In the Phase 1 study, patients were given intravitreal ranibizumab at baseline and at months 1, 2, 4, and 6. Results showed that at month7, one month after the final administration of ranibizumab and the primary endpoint of the study, the median reduction of the excess foveal thickness was 97%, and there was a median improvement of 10 letters.

There have been no adverse events that were believed to be related to the study drug; in particular, intraocular inflammation was not observed.

The READ-2 Study is a Phase 2 randomized, multicenter clinical trial sponsored by the Juvenile Diabetes Research Foundation. The study enrolled 126 patients from 14 clinical centers through out the United States.
Each study subject in the trial was randomized 1:1:1: to 1 of 3 treatment groups.

Group 1 (ranibizumab only)
Group 2 (Laser)
Group 3 (ranibizumab and laser)

The patients were followed every 12 weeks until month 24 (secondary time endpoint). At any study visit, if there is an increase of a specified amount of retinal thickness on OCT that meets re-treatment criteria, the patients will have the opportunity to receive a ranibizumab injection of ranibizumab injection plus laser 7 days later.

The re-treatment criteria for patients in all 3 randomized groups are an absolute retinal thickness in OCT central subfield of ≤ 250 mm (at time of study visit).

**Combination Therapy**

As diverse mechanism and patterns of DME are recognized, clinicians are using multi-model therapies to approach DME. In theory, targeting various pathologic mechanisms of DME with combination therapies may have a more lasting effect on reversing and maintaining a clinical benefit to patients. Commonly Focal Laser Photocoagulation is being combined primarily with Ocular Steroid therapy (either IVTA or PSTTA) or anti VEGF agents. This strategy seeks to take advantage of the more immediate effects of pharmacologic agents while employing laser therapy for long term stabilization. Anti VEGF agents have been used to salvage eyes refractory to steroid therapy, in eyes experiencing steroid related side effects, and more recently in combination with IVTA therapy with positive results. Pharmacological agents also used at the time of vitrectomy surgery help to prevent recurrent DME.

The present study also has tried to compare the efficacy of monotherapy with combined modalities of treatment.

A comparative analysis of the response to all three modalities of treatment is given in TABLE 5

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>Group T</th>
<th>Group B</th>
<th>Group BT</th>
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<tbody>
<tr>
<td>Vision</td>
<td>45 %</td>
<td>55 %</td>
<td>60 %</td>
</tr>
<tr>
<td>Resolution</td>
<td>45 %</td>
<td>59 %</td>
<td>69 %</td>
</tr>
<tr>
<td>IOP</td>
<td>17 %</td>
<td>5 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Cataract</td>
<td>30 %</td>
<td>-</td>
<td>30 %</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Recurrence</td>
<td>75 %</td>
<td>15 %</td>
<td>15 %</td>
</tr>
</tbody>
</table>

Thus the result of this study show that:

1. IVTA has an excellent transient effect of causing resolution. Recurrences in 75 %, elevated IOP in 17 % of cases point to the fact that IVTA should be advised with caution and the patients monitored regularly after intervention.

2. IVB is as efficacious or more so with respect to visual gain (45 % Vs 55 %) and resolution of CSME ( 45 % Vs 59 %). The incidence of elevated IOP in only 5 % and recurrence in 15 % point to the fact that IVB may be a better option to IVTA

3. Combining IVB with IVTA, did not have the expected effect of doubling the resolution and visual recovery. A higher incidence of glaucoma in 22 % makes this combination unsafe. The incidence of recurrence was same as in IVB group.

These results comprehensively prove that there is no added benefit of combining IVB and IVTA.

4. Greater degree of diffuse edema and presence of sub foveal serous RD are indicators of a favorable response to IVTA and IVB.
5. The prediction of poor visual prognosis included poor preoperative vision, HbA$_1C$ $>$ 7 during the study period, plaques of hard exudates under fovea and presence of large cystoid spaces under fovea. Our results compared favourably with those of Soheilian et al and Ahmadieh et al. who also demonstrated that there was no added beneficial effect of combining IVTA & antiVEGF therapy (Table 5).

Maximum reduction of central retinal thickness and maximum visual gain were obtained in eyes with greater degree of diffuse DME and in the presence of subfoveal serous RD. These eyes responded best to IVTA/ or IVB.

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