Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema

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PURPOSE. *To evaluate the additive effect of triamcinolone to bevacizumab in comparison to standard macular laser photocoagulation versus bevacizumab in the management of diabetic macular edema (DME).*

METHODS. *In a prospective, randomized clinical trial, 130 eyes of 110 patients with type 2 diabetes with DME were included. Eligible eyes were randomly assigned to 1.25 mg intravitreal bevacizumab (42 eyes) (IVB group) or combination of 1.25 mg bevacizumab and 2 mg triamcinolone acetonide (41 eyes) (IVB+IVT group) or macular laser photocoagulation (47 eyes) (MPC). Central macular thickness (CMT) and visual acuity changes at week 6 and 16 were assessed.*

RESULTS. *The mean age of the patients was 57 ±7 years. Patients were followed 16 weeks. At week 6, all the three groups showed significant reduction in CMT but the reductions for IVB and IVB+IVT were significantly more than MPC ($p<0.001$). At week 16, the response was not stable for IVB ($p<0.001$), but IVB+IVT maintained its superior status to MPC ($p<0.001$). At week 16, visual acuities were essentially unchanged for the two groups of MPC and IVB and improvement for IVB+IVT was marginal and at most was 0.1 log MAR. No patient developed uveitis, endophthalmitis, or thromboembolic event.*

CONCLUSIONS. *Single intravitreal bevacizumab or triamcinolone plus bevacizumab injection brought about significantly greater macular thickness reduction in diabetic patients in comparison to standard laser treatment. However, the response for bevacizumab alone was short-lived. Reduction in macular thickness was only marginally associated with visual acuity improvement in the triamcinolone plus bevacizumab injection group. (Eur J Ophthalmol 2008; 18: 941-8)*

KEY WORDS. *Diabetic macular edema, Macular laser photocoagulation, Intravitreal bevacizumab, Combination of intravitreal bevacizumab and triamcinolone acetonide*

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INTRODUCTION

Diabetic retinopathy (DR) is an important cause of acquired visual loss and impairment in working ages worldwide (1-4). The Salisbury Eye Evaluation Study showed that diabetic retinopathy was the third most important cause for visual impairment (1). Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision (2).

In the Early Treatment Diabetic Retinopathy Study (ETDRS), focal photocoagulation of eyes with clinically significant macular edema (CSME) reduced the risk of moderate visual loss by approximately 50% (5). In spite of treatment, 12% of treated eyes developed moderate visual loss. Furthermore,

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central retinal thickening remained in approximately 40% and 25% of treated eyes after 12 months and 36 months, respectively (5-7).

Macular laser photocoagulation (MPC) is considered the standard treatment for focal and diffuse DME (8). However, this treatment can be destructive and its adverse effects in addition to the suboptimal efficacy have led to the advent of potential new therapies in the management of DME (7). Pharmacotherapy has been investigated in the treatment of DME (9).

Development of DR is multifactorial but vascular endothelial growth factor (VEGF) has an important role in pathogenesis of diabetic retinopathy (9-11); VEGF is upregulated in diabetic retinopathy (12, 13) so administration of some kind of anti VEGF agent seems a logical option.

Several studies are currently evaluating the role of anti-VEGF agents for the treatment of ocular disease associated with choroidal and/or retinal neovascularization and exudative processes, especially age-related macular degeneration (14-16) and diabetic retinopathy (17-22).

Corticosteroids also may work through multiple mechanisms of action. They are known to reduce vascular permeability, reduce blood–retinal barrier breakdown, downregulate VEGF production, and inhibit some matrix metalloproteinase (9, 10, 23, 24). Some studies have evaluated this drug effect in DME (25-27).

There are many factors that are involved in pathogenesis of DME, so many alternatives may be suggested for these patients (pharmacologic or surgical) (28-33).

The increase in retinal capillary permeability and subsequent retinal edema may be the result of a breakdown of the blood–retinal barrier mediated in part by VEGF (11). It seems adding intravitreal steroid to intravitreal anti-VEGF agent may intensify and/or consolidate either effect of both agents. The purpose of this trial is to evaluate the additive/combined effect of triamcinolone acetonide and bevacizumab in comparison to standard macular laser photocoagulation versus bevacizumab in the management of DME.

METHODS

Study population

We conducted a prospective, randomized clinical trial from March 2006 through May 2007 on 130 eyes (110 type 2 diabetic patients) with DME. Inclusion criteria were best-corrected visual acuity equal to or less than 20/40 (ETDRS chart) (≤0.3 logMAR) and central macular thickness (CMT) ≥250 μm. The exclusion criteria were macular edema related to recent intraocular surgery or other procedures, vitreous traction (based on OCT), history of any treatment for diabetic retinopathy at any time or anticipating the need for panretinal laser photocoagulation (PRP) in the 6 months following randomization, uncontrolled glaucoma, a recent history of arterial thromboembolic event, and poorly controlled hypertension.

Assignment and interventions

The patients were fully informed on the risks and the benefits of treatments; written informed consents were obtained next. Eyes were randomly assigned via balanced blocked randomization to receive either MPC (MPC group) or 1.25 mg intravitreal bevacizumab (IVB group), or a combination of 1.25 mg bevacizumab and 2 mg intravitreal triamcinolone acetonide (IVB+IVT group). An ophthalmologist who was masked about treatment arms performed final assessment. The institutional review board approved the study protocol.

MPCs were carried out according to ETDRS protocol by one of the authors (H.F.). All intravitreal injections were performed using a standard protocol under topical anesthesia and considering sterile conditions. Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA) (0.05 mL; 1.25 mg) was injected through the superotemporal pars plana. Triamcinolone acetonide (Triamhexal, Hexal AG, Holzkirchen, Germany) (0.05 mL; 2 mg) was injected in a separate syringe inferotemporally for the IVB+IVT group in addition to bevacizumab. Central retinal artery was assessed after injection.

Patients were followed at 24 hours postoperatively and weekly thereafter for the assessment of anterior chamber reaction and/or intraocular pressure (IOP). Best-corrected visual acuity determination, funduscopy, fluorescein angiography, and posterior segment OCT version 3.0 (Carl Zeiss, Meditec Inc., Dublin, CA) were conducted at baseline and weeks 6 and 16 postoperatively. Central subfield (1 mm) thicknesses were measured. Complications like cataract formation, vitreous hemorrhage, and endophthalmitis were looked for.

In case of persistent macular edema (thickening at the center of the fovea more than 250 μm [leakage from the perifoveal capillary vessels on fluorescein angiography] beyond 16 weeks following any of the procedures), retreatment was performed.

Statistical analysis

The primary efficacy outcome was BCVA improvement and CMT reduction at weeks 6 and 16 (in comparison to their baseline status). Baseline and follow-up logMAR BCVA and CMT data of the three study groups were compared within each group through general linear model (repeated measure test; and if p values were significant, paired comparisons were made through paired sample *t* test). One-way analysis of variance was done to compare logMAR BCVA and CMT between groups (post-hoc Student-Newman-Keuls). LogMAR BCVA and CMT correlation was evaluated by Pearson correlation.

RESULTS

A total of 130 eyes of 110 patients were included in the study; 47, 42, and 41 eyes were randomly assigned to MPC, IVB, or IVB+IVT groups, respectively. The age of the patients varied from 40 to 74 years with mean age of 57±7 years. Forty-nine percent of the participants were male. The distribution of baseline characteristics in terms of age, gender, macular thickness, and visual acuity among the three study groups was comparable (Tab. I).

Mean BCVA and CMT±SD in all treatment groups at baseline and week 6 and 16 are showed in Tables II and III.

After 6 weeks of follow-up, significant reduction of CMT was demonstrated in all study arms (mean reductions: –27±43, –90±94, and –102 ±74 µm, respectively, for MPC, IVB, and IVB+IVT) but comparison between groups revealed that reductions for IVB and IVB+IVT were more than MPC group (p<0.001) (Tab. II, Fig. 1).

After 16 weeks of follow-up, CMT reductions in IVB+IVT group was more than other groups (p<0.001) (Tab. III).

The analysis of functional outcome, i.e., BCVA, did not show a corresponding improvement. BCVA changes were not significant among study groups at week 6 (p=0.109); although it was significant at week 16 (p=0.04), the week 16 visual acuities were essentially unchanged in comparison to the baseline figures for the two groups of MPC and IVB and the improvement for IVB+IVT was marginal and at most was 0.1 logMAR (Tab. III).

TABLE I - BASELINE CHARACTERISTICS IN TREATMENT GROUPS

	MPC	IVB	IVB+IVT	p values
No. of eyes	47	42	41	
% Male	46.8	54.8	46.3	0.68
Mean age (y) ± SD	56±7	59±6	56±7	0.204
Mean CMT (µm) ± SD	336±71	356±116	387±154	0.128
Mean BCVA (log MAR) ± SD	0.77 ±0.27	0.70±0.31	0.77±0.33	0.399
Mean IOP (mm Hg) ± SD	14±3	15±2	14±1	0.180

MPC = Macular photocoagulation; IVB = Intravitreal bevacizumab; IVT = Iintravitreal triamcinolone; CMT = Central macular thickness; BCVA = Best-corrected visual acuity; IOP = Intraocular pressure

TABLE II - MEAN CENTRAL MACULAR THICKNESS (in µm ± SD) FOR TREATMENT GROUPS AT BASELINE, WEEK 6, AND WEEK 16 FOLLOW-UPS AND ITS CHANGE FROM BASELINE TO WEEK 6 AND WEEK 16 FOLLOW-UPS

	MPC group	IVB group	IVB/IVT group	p Among groups
Baseline	336±71	356±116	387±154	
Week 6	308±90	265±70	285±111	
Change from baseline	–27±43	–90±94	–102±74	<0.001
p Within group	<0.001	<0.001	<0.001	
Week 16	300±82	328±91	288±110	
Change from baseline	–36±59	–27±87	–98±79	<0.001
p Within group	<0.001	0.050	<0.001	

MPC = Macular photocoagulation; IVB = Intravitreal bevacizumab; IVT = Intravitreal triamcinolone

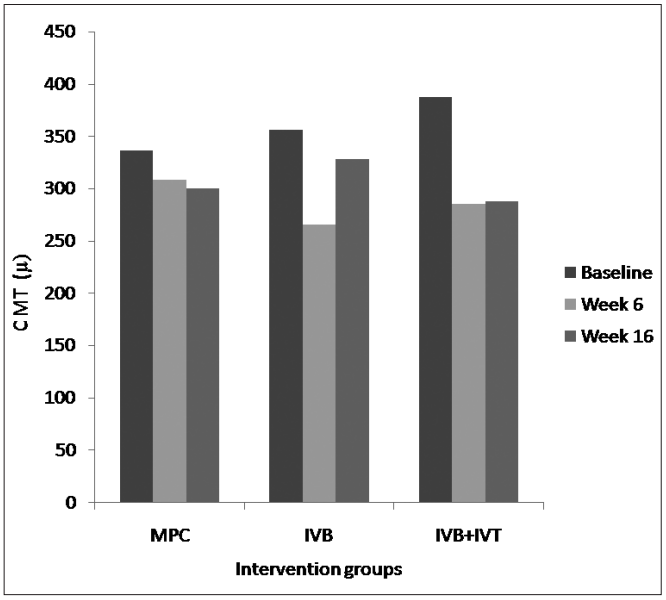

Fig. 1 - *Macular thickness status in three different types of interventions at baseline and weeks 6 and 16 of follow-up. CMT = central macular thickness; IVB = intravitreal bevacizumab; IVB+IVT = intravitreal bevacizumab + intravitreal triamcinolone.*

BCVA and CMT changes correlated weakly and were only significant at week 16 in IVB+IVT group (r=0.559 and p=0.01). We did not observe correlations between foveal subretinal exudates and visual acuity improvement in any groups (p values were 0.80 and 0.55 at weeks 6 and 16).

Only two eyes in IVB+IVT group had a rise in IOP, which were controlled medically. There were no complications related to intravitreal injections, such as endophthalmitis and vitreous hemorrhage. No thromboembolic event was noted during the follow-ups.

DISCUSSION

Because of some unsatisfactory outcomes with respect to inadequate vision improvement following laser photocoagulation in DME (7), some alternative approaches have been investigated. Pharmacotherapy is a treatment modality that has generated considerable interest in vitreoretinal diseases such as choroidal neovascularization in age-related macular degeneration or DME (14-22).

In this study we evaluated the additive/combined effect of triamcinolone acetonide to/and bevacizumab in comparison to standard macular laser photocoagulation versus bevacizumab in the management of DME.

After 6 weeks of follow-up, all study arms showed significant reduction in macular thickness (mean reductions: 27, 90, and 102 µm, respectively, for MPC, IVB, and the IVB+IVT) and among groups the reductions for IVB and IVB+IVT were significantly more than MPC ($p< 0.001$).

The response was stable for MPC and IVB+IVT but not for IVB as this group showed significant relapse ($p<0.001$). IVB+IVT maintained its superior status to MPC at week 16 ($p<0.001$) (Tab. II and Fig. 1).

The analysis of functional outcome, i.e., visual acuity, did not show a corresponding improvement; the week 16 visual acuities were essentially unchanged in comparison to the baseline figures for the two groups of MPC and IVB and the improvement for IVB+IVT was marginal and at most was 0.1 logMAR (Tab. III).

BCVA may not improve following resolution of macular edema (34) because of foveal atrophy, pigmentary changes, subfoveal hard exudates, macular ischemia, and nonretinal conditions. Although we did not find any relationship between the presence of subfoveal exudates and visual acuity improvement, these factors should be inves-

TABLE III - MEAN BCVA (logMAR ± SD) FOR TREATMENT GROUPS AT BASELINE, WEEK 6, AND WEEK 16 FOLLOW-UPS AND ITS CHANGE FROM BASELINE TO WEEK 6 AND WEEK 16 FOLLOW-UPS

	MPC Group	IVB Group	IVB+IVT Group	p Among groups
Baseline	0.77±0.27	0.70±0.31	0.77±0.33	
Week 6	0.73±0.30	0.57±0.27	0.67±0.34	
Change from baseline	–0.04±0.14	–0.12±0.18	–0.10±0.20	0.109
p Within group	0.029	<0.001	0.002	
Week 16	0.71±0.30	0.70±0.31	0.67±0.32	
Change from baseline	–0.05±0.15	+0.0048±0.18	–0.097±0.20	0.040
p Within group	0.013	0.87	0.005	

BCVA = Best-corrected visual acuity; MPC = Macular photocoagulation; IVB = Intravitreal bevacizumab; IVT = Intravitreal triamcinolone

tigated in a larger number of patients.

Diabetic retinopathy leads to breakdown of the blood–retina barrier at the level of the retinal capillaries and the retinal pigment epithelium. This might be due to changes in tight junction proteins such as occludin and zonula occludens 1 (35) which seem to be mediated in part by VEGF (10). These will lead to increase in retinal capillary permeability and retinal edema.

Anti-VEGF therapy, therefore, may represent a useful therapeutic modality that targets the underlying pathogenesis of DME. Bevacizumab neutralizes all VEGF-A isoforms (36, 37). Corticosteroids are also known to reduce vascular permeability, reduce blood–retinal barrier breakdown, downregulate VEGF production, and inhibit certain matrix metalloproteinases (9, 10, 23, 24).

The major complications of intravitreal triamcinolone include elevated IOP in approximately 30% to 50% of patients, cataract progression, severe inflammatory response, and less commonly endophthalmitis (9). In our study, only two eyes in IVB+IVT group had a rise in IOP, which were controlled medically. There were no complications related to intravitreal injections, such as endophthalmitis and vitreous hemorrhage.

A CMT reduction of –90±94 µm has been observed with single IVB injection in short term (6 weeks). The short-lived nature of the response to IVB has been reported previously even in case of proliferative diabetic retinopathy (38) and multiple injections have been proposed. Anti-VEGF drugs have been shown to be effective in reducing CMT and edema secondary to retinal vascular diseases, including diabetic retinopathy in short term (17, 39, 40). Haritoglou et al reported a CMT reduction of 15–25% with multiple Avastin intravitreal injections (39).

The half-life of IVB in vitreous cavity is 4.3 to5.6 days (41, 42); considering the ongoing nature of the pathologic process further response and/or stability could only be anticipated by better systemic control (38) or additional interventions like MPC or IVT.

The half-life for 4 mg IVT in the vitreous cavity is 18.6 days (26, 27) and it has been demonstrated that DME recurred after a median period of 20 weeks vs 16 weeks in the 4- and 2-mg groups (26). Intravitreal triamcinolone has already been shown to effectively increase VA and reduce CMT in diffuse DME (26, 43-45). Paccola et al compared intravitreal triamcinolone with bevacizumab for the treatment of patients with refractory DME; they concluded that a single intravitreal injection of triamcinolone may offer certain advantages over bevacizumab in the short-term management of refractory DME, specifically with regard to changes in central macular thickness which persisted up to week 24 (45).

In the study that evaluated phase 2 IVB, it was demonstrated that 1.25 mg and 2.5 mg IVB caused more than 11% CMT reduction at week 3 and the difference was significant in comparison to MPC but this reduction was not stable until 12 weeks of follow-up. The reduction in retinal thickness associated with bevacizumab at 3 weeks appeared to plateau or decrease in most eyes between the 3- and 6-week visits, suggesting that 6 weeks may be too long for an optimal initial injection interval (46). This is similar to our study that explains the slippage of retinal thickness reduction at week 16.

There are limited studies that have evaluated IVB+IVT in primary DME. Soheilian et al compared these three groups; they had better visual results for IVB groups at 12 weeks and have indicated that at least a 12-week interval between intravitreal bevacizumab injections in the treatment of DME may be reasonable (47) which is different from a previous study by Diabetic Retinopathy Clinical Research Network (46). The IVB+IVT group had worse results in comparison to IVB group that they related this point to IOP, cataract, and preservatives of triamcinolone. Although this study result was similar to ours at week 6, it was different at week 16; our patients did not have uncontrollable IOP; only one patient developed mild cataract. It is noteworthy that our sample size is lager and our follow-up is longer in comparison (12 weeks vs 16 weeks). The important point is that perhaps the patients' basic criteria and systemic factors are different in these studies. Our results are comparable with Diabetic Retinopathy Clinical Research Network, i.e., CMT reduction was not sustained until 16 weeks.

We considered 2 mg IVT in addition to IVB to prevent immediate IOP rise and to reduce other complications. Audren et al have demonstrated no difference in dose in regard to CMT, visual acuity, and IOP changes (26) but some studies have shown lower rate of IOP rise for 2 mg vs 4 mg IVT (9.1%) (43, 44) which is comparable to ours in that only 2 out of 41 (4%) patients had controllable IOP rise.

Although the most important evidence-based data for treatment of diabetic retinopathy and maculopathy is laser photocoagulation (9), there have been many advances in the treatment of diabetic retinopathy and its complications over the past 25 years. There is some interest in other treatment modalities, such as pars plana vit-

rectomy, of course in a specific subtype of eyes with a component of vitreomacular traction contributing to the edema, but it may have its own disadvantages (28-33). Other treatment modalities such as pharmacologic therapy with oral protein kinase C inhibitors and use of intravitreal corticosteroids are under investigation (9).

Overall, the retrospective nature of many studies and lack of standardization regarding the number of injections and anti-VEGF drug dosage make a comparison of the 4-month results difficult. Simple comparison of different modalities seems not sufficient for future trials; durations of MPC, IVB, and IVT efficacies should be revisited considering their pharmacology and clinical observations. We have to marshal these into orchestrated combinations of modalities to be compared clinically and as our interventions do not necessarily translate into functional improvement, it is prudent to redefine our thresholds for the institution of the interventions. Alternatively, slow/constant releasing of intravitreal medications could be devised and implemented.

Macular edema encompasses a wide range of diabetic retinopathy (i.e., diffuse, focal, and/or cystoids) for which the response to the interventions is not expected to be similar. Restricted inclusion of the patients for the studies or subgroup analysis (OCT-based) in case of large sample sizes is recommended.

The role of systemic diabetic control and hypertension on diabetic retinopathy treatments, i.e., initial response and its stability, has been proven in many studies (9, 34, 48-51). In a recent study reported from our center (38) we were able to prove a statistically as well as clinically important association between HbA1c level and the stability of response to IVB in addition to laser therapy in proliferative diabetic retinopathy, so it is also recommended to conduct a study considering systemic factors and evaluating their effect on macular thickness reduction and VA. Assessment of IVT only groups in a trial in comparison to other groups is also ideal.

In conclusion, single intravitreal bevacizumab or combination of bevacizumab and triamcinolone injection brought about significantly greater reduction of macular thickness in diabetic patients in comparison to standard laser treatment, but the response to bevacizumab alone is short-lived. Improvement in macular thickness was only marginally associated with visual acuity improvement in the triamcinolone plus bevacizumab injection group.

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