The functional benefit of macular laser photocoagulation after intravitreal bevacizumab for diabetic macular edema

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Abstract

Aim: To assess the efficacy of a combination therapy of bevacizumab injections followed by laser photocoagulation in order to stabilize the visual acuity in clinically significant diabetic macular edema.
Methods: This prospective single-arm study included 146 consecutive patients diagnosed with clinically significant diabetic macular edema. The patients were treated and followed-up at the American Eye Centre of the American Hospital of Tirana from January 2012 to December 2014. Each patient, before treatment and in every follow-up visit, underwent a detailed eye examination which consisted of determination of the BCVA (Best Corrected Visual Acuity) using standard Snellen charts, anterior segment assessment using a slit lamp biomicroscopy, dilated fundus examination (90D lens) and tonometry for intraocular pressure evaluation. The patients were treated with one intravitreal injection of bevacizumab followed by one session of macular laser photocoagulation, approximately three weeks later.
Results: After the first month, the mean BCVA improved from 0.32 to 0.41 Snellen decimals, a difference that was statistically significant ($P<0.001$). This significant improvement in BCVA was maintained throughout the third and the sixth months of the follow-up period. Six-month BCVA analysis by subgroups demonstrated that 52 (35.6%) eyes remained stable, 73 (50.0%) eyes improved 0.1 or more of BCVA, and 21 (14.4%) eyes decreased 0.1 or more of BCVA.
Conclusions: In this study, the combined treatment (bevacizumab + laser) for diabetic macular edema resulted effective in preserving the mean BCVA in one third of the patients and improving it in 50% of the treated group. No serious (sight threatening) adverse events were recorded.

Keywords: diabetic macular edema (DME), intravitreal bevacizumab, macular laser, visual acuity.

Introduction

The worldwide prevalence of diabetic retinopathy (DR) is estimated to be 34.6% (95% CI 34.5-34.8) (1). Approximately one-fourth of them will experience vision loss from diabetic macular edema according to different studies (2,3). Since ETDRS (Early Treatment Diabetic Retinopathy Study) revealed macular laser photocoagulation's benefit in treating macular edema and preserving vision in diabetic patients, its role has become crucial (4). Many studies tried to explain the mechanism of action of macular laser on diabetic macular edema. Although not fully understood, these mechanisms look to include the improving of the efficacy of both the inner and outer blood–retinal barriers by promoting the proliferation of both the endothelial cells in retinal capillaries and the retinal pigment epithelial cells (5). However, many cases do not respond to macular laser treatment for diabetic macular edema, and a part of them suffers from further decrease in visual acuity (6,7). In one study the authors showed the efficacy of macular laser treatment for DME in improving the visual acuity in only 14.5% of the treated eyes, and the rate of persistence of macular edema after treatment was really high (7,8). During the past decade, many researchers and authors focused their efforts in demonstrating the efficacy of using recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF), in treating DME (9,10). One of these antibodies, Bevacizumab, is giving good results in reducing the increased retinal vessel permeability (resulting in diabetic macular edema) by inhibiting the VEGF action and decreasing the breakdown of the blood–retinal barrier (10-12). Many studies demonstrated the efficacy of intravitreal bevacizumab (IVB) in reducing the DME and improving the best-corrected visual acuity (BCVA) (10-12). However, the duration of bevacizumab effect is in many cases temporary, as its action is demonstrated to last few weeks, and repeated injections maybe needed (10,13). In this study, we assessed the efficacy of a combination therapy (bevacizumab + laser) for diabetic macular edema, as each separate treatment achieves its effect by different mechanisms of action.

Methods

Study design

This prospective 6-months study was conducted at the American Eye Centre of the American Hospital of Tirana from January 2012 to December 2014. All the 146 patients (eyes) were treated for clinically significant diabetic macular edema with one intravitreal injection of bevacizumab and one session of macular laser photocoagulation after approximately three weeks. Then the patients were followed-up for at least six months, coming at regular visits after 1, 3 and 6 months after the treatment.

Patients

The study population consisted of 146 patients (78 females and 68 males; mean age of 61 years), suffering from diabetes mellitus (both Type 1 or 2). The main inclusion criterion was the presence of clinically significant macular edema (CSME), diagnosed at the first visit, and the exclusion criteria included: age <18 years old at the time of enrollment; diagnosed glaucoma; history of previous intraocular surgeries; pregnancy or breast feeding; previous laser photocoagulation of the macula; high risk proliferative diabetic retinopathy; uncontrolled diabetes; BCVA <0.05 or >0.5 of Snellen decimals; any other eye disease that can cause vision loss or prevent vision improvement. Socio-demographic and disease data at baseline are shown in Table 1.

Each patient, before treatment and in every follow up visit, underwent a detailed eye examination which consisted of determination of the BCVA (Best Corrected Visual Acuity) using standard Snellen charts, anterior segment assessment using a slit lamp biomicroscopy, dilated fundus examina-

tion (90D lens) and tonometry for intraocular pressure evaluation. Fundus fluoresceine angiography was performed at the first visit and after 6 months. The patients were treated with one intravitreal injection of bevacizumab followed by one session of macular laser photocoagulation, after approximately 3 weeks (mean 20.7 days). All the patients completed a follow up period of 6 months.

Study endpoints

The primary endpoint of this study was to demonstrate the efficacy of combined therapy (bevacizumab + laser) for diabetic macular edema to preserve the functional level (visual acuity) of the treated eye. The secondary endpoint was to assess the treatment effect on macular edema grade and the safety profile of this combined therapy.

Table 1. Socio-demographic data and disease status at baseline

Variable	Bevacizumab 1.25 mg + Laser (n = 146)
Mean age ± SD (years)	61.07 ± 9.18
Gender, n (%)	
Men	68 (46.6)
Women	78 (53.4)
Diabetes type, n (%)	
Type I	12 (8.2)
Type II	134 (91.8)
Mean time since first diagnosis of diabetes ± SD (years)	10.29 ± 5.48
DME* type, n (%)	
Focal	60 (41.1)
Diffuse	86 (58.9)
Mean BCVA† ± SD (Snellen decimal)	0.322 ± 0.152

* DME = diabetic macular edema

† BCVA = best corrected visual acuity

Best-Corrected Visual Acuity: The visual function (BCVA) was assessed using standard Snellen charts at 6 m of distance. The result was documented in decimal values, e.g. the Snellen visual acuity of 20/40 was documented as 0.5, and so on. All the results were collected and analyzed in order to evaluate the mean average change in visual acuity (primary study endpoint) at 6 months. The linear trend of the mean BCVA during this period was also evaluated.

Diabetic Macular Edema: The macular edema was diagnosed on slit lamp stereoscopic biomicroscopy of the macula (using 90D lenses) and confirmed with fluorescein angiography (FFA). We performed FFA in every patient before enrollment and on the last follow-up visit (at 6 months). FFA helped also grading the DME as focal or diffuse.

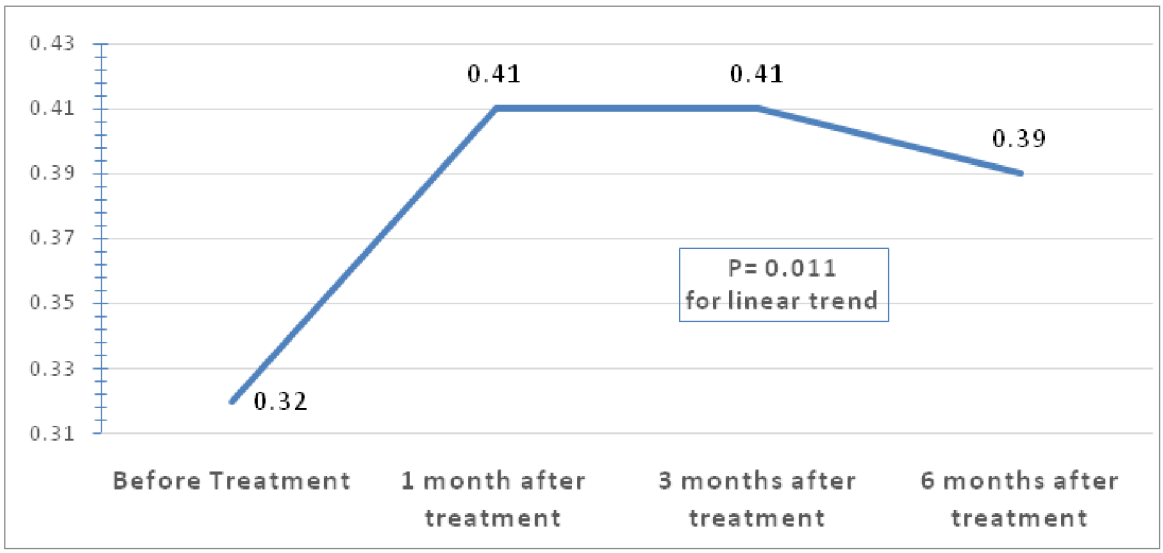
Safety Assessments: We assessed the safety profile of this combination therapy in every follow-up visit by taking a detailed history for any systemic adverse event, complete eye examination, intraocular pressure measurement and dilated fundoscopy. The incidence of any adverse event or complication was registered.

Results

The clinical records of 146 consecutive patients (146 eyes) with clinically significant DME were collected and analyzed. All the participants completed a follow up period of 6 months. All patients (100%) were of Caucasian ethnicity. They had a mean age of 61.07 ± 9.18 years, and 46.6% of them were males (68 men, 78 women). In the current study, 12 (8.2%) patients had Type 1 Diabetes Mellitus whereas 134 (91.8%) patients had Type 2 Diabetes Mellitus. Regarding the

severity of diabetic retinopathy (DR), 12 (8.2%) eyes had mild non-proliferative (NP) DR, 66 (45.2%) eyes had moderate NPDR, 60 (41.1%) eyes had severe NPDR, and 8 (5.5%) eyes had Proliferative DR. All eyes had clinically significant DME diagnosed by stereoscopic biomicroscopy of the macula and confirmed with fluorescein angiography (FFA) at baseline. Within 1 month after the combined treatment, improvements in BCVA were observed, and these significant changes continued throughout the 6 month follow-up. At 1 month, mean BCVA improved from 0.32 to 0.41 Snellen decimals, a difference that was statistically significant (P<0.001). This improvement in BCVA was maintained throughout the 3- and 6-month follow-up period. In addition, the mean BCVA at 6 months was 0.39 (P<0.001), a statistically significant difference from baseline BCVA. The linear trend of mean BCVA during the follow-up period is shown in Figure 1.

Figure 1. Linear trend of mean BCVA during the follow-up period



Six–month BCVA analysis by subgroups demonstrated that 52 (35.6%) eyes remained stable, 73 (50.0%) eyes improved 0.1 or more Snellen decimals of BCVA, and 21 (14.4%) eyes decreased 0.1 or more Snellen decimals of BCVA (Table 2).

All the eyes had diabetic macular edema in the first visit (main inclusion criterion); 60 (41.1%) of the eyes had focal DME and 86 (58.9%) diffuse DME. Six months after treatment, the number of eyes with no edema, focal and diffuse DME was 16 (11.0%), 64 (43.8%), and 66 (45.2%) respectively. The effect of the actual combination therapy on the macular edema grade (focal vs. diffuse) during the entire follow up period is shown in Table 3.

The response to combination therapy between patients with proliferative DR was compared with that of patients with non-proliferative diabetic retinopathy and DME to see if there was any statistically significant difference. However, when the multivariate analysis of measurements was carried out to compare mean values to statistically analyze the mean BCVA adjusting for the grade of diabetic retinopathy as a covariate, no statistical significance (P = 0.511) was found.

Table 2. Best-Corrected Visual Acuity (BCVA) change at six months

Bevacizumab 1.25 mg + Laser (n = 146)	
Mean average change in BCVA letter score from baseline at 6 months (primary endpoint)	
Mean	0.07
95% CI* for mean	(0.05, 0.08)
Categorized BCVA letter score outcome at month 6, n (%)	
Gain of ≥ 0.1	73 (50.0)
Loss of ≥ 0.1	21 (14.4)
Gain of ≥ 0.2	40 (27.4)
Loss of ≥ 0.2	14 (9.6)
Gain of ≥ 0.3	16 (10.9)
Loss of ≥ 0.3	4 (2.7)

* CI = confidence intervals

Safety Assessment: We assessed the safety profile of the actual combination therapy in every control visit by taking a detailed history for any systemic adverse event, complete eye examination, intraocular pressure measurement and dilated fundoscopy. The incidence of any adverse event or complication was registered. During the follow-up period, there were no serious eye or systemic adverse event (endophthalmitis, cataract, significant intraocular raised pressure, stroke, etc.) registered. 22 (15.1%) patients had sub-conjuctival hemorrhage which resolved within 10 days in all cases; 46 (31.6%) complained of mild to moderate local discomfort the first 24-48 hours after the injection and 29 (19.8%) patients after the laser session. 18 (12.3%) patients referred small flying objects (floaters) the first day after the injection, which disappeared within a few days, except for 3 (2.1%) patients in which posterior vitreous detachment (PVD) was diagnosed with no further complications throughout the follow-up period.

Table 3. Change in macular edema grade during the follow-up period

Time of the study	DME			P-value
	No DME	Focal DME	Diffuse DME	
Before treatment	0 (0.0)*	60 (41.1)	86 (58.9)	0.701†
1 month after treatment	14 (9.6)	68 (46.6)	64 (43.8)	<0.001
3 months after treatment	18 (12.3)	60 (41.1)	68 (46.6)	0.008
6 months after treatment	16 (11.0)	64 (43.8)	66 (45.2)	0.601

*Absolute number and percentages

† Statistical significance value according to the chi-square test.

Discussion

Diabetic macular edema is a manifestation of DR that produces loss of central vision. Although several treatment methods are under investigation, the only proven treatment to reduce the risk of vision loss from DME and preserve the visual acuity in a part of the treated eyes, is laser photocoagulation, as shown by the ETDRS (3). This study showed the efficacy of macular laser photocoagulation in reducing the risk of vision loss in three years, in approximately half of the patients suffering from clinically significant macular edema. According to this study, the treatment provided improved visual acuity more than three lines in only 3% of the cases (3).

Taking into account that most eyes with DDME treated with laser photocoagulation show no

improvement in VA (7), there has been an interest in other treatment methods such as pharmacologic therapy with oral protein kinase C inhibitors and the use of intravitreal corticosteroids (14-16). The use of antibodies targeted at VEGF is another treatment method that has generated considerable interest and is being investigated (10-13,17). In RESTORE study (18), Ranibizumab (a similar anti-VEGF molecule), combined with laser showed superiority versus laser therapy alone in improving mean BCVA letter score throughout the 12 month follow-up period (+5.9 vs +0.8; P<0.0001).

The results of our study suggest that intravitreal bevacizumab injection appears to be effective, as a combined treatment, in potentiating the laser effect in the primary treatment of DME. In our study, 73 (50.0 %) eyes showed an improvement in VA with a decrease in fluorescein leakage on FFA on the last follow-up visit at 6 months (Table 2 and 3), and 52 (35.6%) eyes remained stable during this period. The results of our study are in accordance with previous reports showing the beneficial effect of intravitreal bevacizumab in the treatment of DME (10-13,18). We recommend using this combined therapy, especially in the eyes with VA in our study range ($0.05 \leq VA \leq 0.5$). The limitations of this study include its non-comparative type, and the relatively short follow-up period. Further investigations should be made to precise the role of bevacizumab as a monotherapy and as a combination, the number of injections and laser sessions needed and also the role of other medicaments in the diabetic macular edema treatment.

Conflicts of interest: None declared.

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