INTRAVITREAL BEVACIZUMAB AND/OR MACULAR PHOTOCOAGULATION AS A PRIMARY TREATMENT FOR DIFFUSE DIABETIC MACULAR EDEMA

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Purpose: To evaluate the efficacy of intravitreal injection of bevacizumab (IVB) followed by modified grid laser photocoagulation (MGP) versus each alone as a primary treatment of diffuse diabetic macular edema.

Patients and Methods: A randomized 3-arm clinical trial in which 62 eyes of 48 patients with diffuse diabetic macular edema were enrolled. Eyes were randomly distributed to 1 of 3 study groups: 19 eyes underwent MGP (MGP group), 21 eyes received 1.25 mg of IVB (IVB group), and 22 eyes received IVB followed by MGP (combined group). All eyes underwent a complete ophthalmic examination including fluorescein angiography and optical coherence tomography at baseline and at 1, 3, and 6 months, after treatment. Fluorescein angiography was performed at the 3 and 6 months follow up visits. The outcome measures were the change compared with baseline in central macular thickness (CMT), changes in best-corrected visual acuity (BCVA), changes in fluorescein angiography leakage, and any reported complication. A P value less than 0.05 was considered statistically significant.

Results: One month after treatment, the reduction in the mean CMT versus baseline was 49.88 μm (10.45%) in MGP group, 150.92 μm (31.30%) in IVB group, and 110.30 μm (23.77%) in the combined group, with a corresponding improvement in the mean BCVA. At 1 month, the improvement in CMT was better than baseline in all groups, yet only significant in the IVB group ($P < 0.05$) and the combined group ($P < 0.05$). The improvement in mean BCVA was significant in the IVB ($P < 0.05$) and the combined groups at 1 month ($P < 0.05$). At 3 months, the mean CMT was still better than baseline in all groups but this improvement was significant only in the combined group ($P < 0.05$). The improvement in the mean BCVA was significant only in the IVB and the combined groups ($P < 0.05$). Six months after treatment, the reduction in the mean CMT was significant in the combined group only ($P < 0.05$) and there was no significant improvement in the mean BCVA in all groups ($P > 0.05$). The BCVA did not deteriorate below baseline in all eyes included in the study, except three eyes in the MGP group. No complication related to the intravitreal injection was reported in the injected eyes.

Conclusion: Combined therapy with IVB and sequential MGP 3 weeks later appeared to be superior to MGP or IVB alone in reducing macular thickening and improving visual acuity. However, no significant improvement in BCVA occurs 6 months after treatment. A combination of IVB and sequential MGP could be used as an initial treatment of diffuse diabetic macular edema.

RETINA 30:1638–1645, 2010

Macular edema is the main cause of vision loss in 13.9% and 25.4% of patients with diabetic retinopathy.[1,2] Since its use in the Early Treatment Diabetic Retinopathy Study, modified grid laser photocoagulation (MGP) has become the primary U.S. Food and Drug Administration–approved treatment for diffuse diabetic macular edema (DDME).[3] Its beneficial effect is believed to be due to induction of proliferation of both the endothelial cells in retinal capillaries and the retinal pigment epithelial cells, thus improving the efficacy of both the inner and outer blood–retinal barriers.[4] However, in

DDME, there is extensive breakdown of the inner and outer blood–retinal barriers and its treatment is more challenging than that of focal edema and non-center–involved diabetic macular edema, which is usually responsive to focal/grid laser photocoagulation.[5–7] Lee and Olk[7] have demonstrated that visual acuity was stabilized in 60.9%, deteriorated in 24.6%, and improved in only 14.5% of eyes with DDME after MGP. Also, the treated eyes showed a high rate of recurrence or persistence of macular edema despite appropriate macular laser therapy.[7,8] Recently, newer treatment modalities, such as intravitreal injection of biological response modifiers that block vascular endothelial growth factor (VEGF), have been developed to increase the efficacy of controlling diabetic macular edema and achieving better visual prognosis.[9,10] In diabetic eyes, the upregulation of VEGF is associated with the breakdown of the blood–retinal barrier and an increase in retinal vessel permeability resulting in macular edema.[10–12] Bevacizumab is a full length humanized monocolonal antibody that blocks all forms of VEGF. Intravitreal bevacizumab (IVB) injection has been reported to be effective in reducing DDME and improving the best-corrected visual acuity (BCVA).[10,12,13] However, the limitations of IVB include regression of visual acuity and an increase in the central macular thickness (CMT) within a few weeks after treatment.[13,14]

Because IVB and MGP achieve their effect via different pathways, a combination therapy may yield more favorable results than either therapy alone. In this study, we evaluate the efficacy of using IVB followed by MGP as a primary treatment of DDME in comparison to MGP or IVB alone.

Patients and Methods

This study was conducted at the Ophthalmic Departments of Maghraby Eye Hospital and Saudi German Hospital in Aseer region, KSA, from July 2007 to November 2008. Written consent was obtained from all patients before enrollment in the study. In this prospective study, 62 eyes of 48 subjects with DDME were randomly distributed into 3 groups: those who underwent MGP once at baseline (MGP group; n = 19 eyes), those who received 1.25 mg IVB once at baseline (IVB group; n = 21 eyes), and those who received a single injection of 1.25 mg IVB at baseline followed by MGP once after 3 weeks (combined group; n = 22 eyes). Subjects were selected to maintain minimum differences in the baseline characteristics between groups.

One surgeon (K.A.M.S.) performed MGP for all eyes in the MGP group and combined group. Intravitreal bevacizumab was delivered by one surgeon (M.M.D.) for all eyes in the IVB and combined groups. Reading and interpretation of all fluorescein angiographies and optical coherence tomographies (OCT) before treatment and during the follow-up period was performed by one author (M.A.E.).

To be included in the study, subjects had to have DDME with fluorescein angiographic evidence and CMT of at least 350 μm measured by OCT (Stratus Model 3000; Carl Zeiss Inc., Jena, Germany), with no history of intravitreal injection, surgical intervention, or retinal laser therapy for diabetic retinopathy. All subjects should be willing and able to attend follow-up visits for at least 6 months after treatment. The exclusion criteria included eyes with cystoid macular edema, vitreoretinal traction involving the macular region, macular ischemia, vitreous incarceration in a previous wound or incision, and opacity of the optical media as cataract or vitreous hemorrhage. Subjects with a history of intraocular surgery during the previous year, chronic uveitis, and retinal vein occlusion involving the macular region were excluded.

All subjects underwent a complete ophthalmic examination, including measurement of BCVA (logarithm of minimal angle of resolution notation), intraocular pressure, and fundus biomicroscopy. Fundus fluorescein angiography and OCT were performed for all eyes at baseline. In the OCT examination, six radial scans intersecting at the fovea were performed in rapid sequence. The OCT provides the average thickness as mean $\pm$ SD in the central macular region, 1000 μm in diameter centered on the patient's foveola, where the six scans intersect. The extent of macular edema was determined solely by author M.A.E. based on the fluorescein angiography and OCT studies.

Intravitreal bevacizumab was delivered in the surgical theater under complete aseptic conditions, using topical anesthesia. After disinfection and draping, 1.25 mg of bevacizumab (Avastin; Hoffman Roche Ltd., Basel, Switzerland) was injected into the vitreous cavity using a 27-gauge needle inserted through the inferotemporal pars plana 3.5 mm from the limbus. After withdrawal of the needle, sterile cotton tipped applicator was used to apply pressure over the injection

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The authors have no conflicts of interest to disclose.

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site for 1 minute. The optic nerve head was then assessed by the indirect ophthalmoscope, and the intraocular pressure was measured. Paracentesis was performed if the intraocular pressure was elevated. Postoperatively, the patient was instructed to instill topical moxifloxacin ophthalmic solution 0.5% (Alcon Laboratories, Inc., Fort Worth, TX), which was applied 4 times daily for 1 week.

Modified grid laser photocoagulation was performed with an argon laser delivering 2 to 3 rows of 100 μm spots, 100 μm apart in the parafoveal region, and can include the edge of the foveal avascular zone if it showed leakage in fluorescein angiography. Then, 150 to 200 μm spots were applied 200 μm apart to the remaining areas of retinal thickening and capillary nonperfusion. Focal leaks outside or within the zones of diffuse leakage were treated with 100 to 150 μm spots to achieve a mild whitening of the microaneurysms. Panretinal photocoagulation was not performed on any subject before treatment. However, panretinal photocoagulation of the peripheral retina was performed in 6 eyes with proliferative diabetic retinopathy (PDR) with retinal neovascularization in the MGP group, 1 session each, 4 to 6 weeks after the MGP.

After treatment, patients were examined at 24 hours, 1 month, 3 months, and 6 months. At each visit, the patients underwent a complete ophthalmic examination using the same procedures performed at baseline except fluorescein angiography that was performed at the 3-month and 6-month follow-up visits.

The outcome measures are the changes in CMT, changes in BCVA, changes in leakage based on fluorescein angiography, and any reported complications. Statistical analysis was performed using SPSS software version 15 (SPSS Inc., Chicago, IL). A P value less than 0.05 was considered statistically significant. The paired samples t-test was performed to compare the CMT and the BCVA to baseline values within each treatment group.

Results

Of the 62 subjects enrolled in this study, 35 (56%) were men, and 27 (43%) were women. The mean age of subjects was 57 years. Baseline characteristics of patients in each treatment group are presented in Table 1. There were no significant differences between the 3 treatment groups with regard to sex ($P > 0.05$), age ($P > 0.05$), or baseline characteristics ($P > 0.05$). However, the combined group had a more equal distribution of patients between nonproliferative diabetic retinopathy (12 eyes) and PDR (10 eyes) compared with the MGP group (13 nonproliferative diabetic retinopathy versus 6 PDR eyes) and IVB group (16 nonproliferative diabetic retinopathy eyes versus 5 PDR eyes) who have less patients in the PDR category. Patients with PDR in all groups had variable degrees of retinal neovascularization with no vitreoretinal traction. The mean extent of macular edema did not significantly differ between groups ($P > 0.05$).

There was no significant difference between the baseline mean CMT ($P > 0.05$) and mean BCVA of all groups ($P > 0.05$). One month after treatment, there was a significant reduction in the mean CMT of the IVB ($P < 0.05$) and the combined ($P < 0.05$) groups but not in the MGP group ($P > 0.05$). The reduction in the mean CMT versus baseline was 49.88 μm (10.45%) in the MGP group ($P > 0.05$), 150.92 μm (31.30%) in the IVB group ($P < 0.05$), and 110.30 μm (23.77%) in the combined group ($P < 0.05$) (Figure 1, Table 2). One month after treatment,

Table 1. Baseline Data of Patients of the MGP Group, IVB Group, and the Combined Group

	MGP Group	IVB Group	Combined Group
Number of eyes (patients)	19 (13)	21 (18)	22 (17)
Sex			
Male	11	11	13
Female	8	10	9
Age (years)			
Range	49–69	43–72	47–68
Mean ± SD	57	56	59
Duration of diabetes (years)			
Range	12–23	13–27	13–23
Mean ± SD	17.62 ± 2.73	19.34 ± 3.06	17.91 ± 2.33
Stage of retinopathy			
NPDR	13	16	12
PDR	6	5	10

NPDR, nonproliferative diabetic retinopathy.

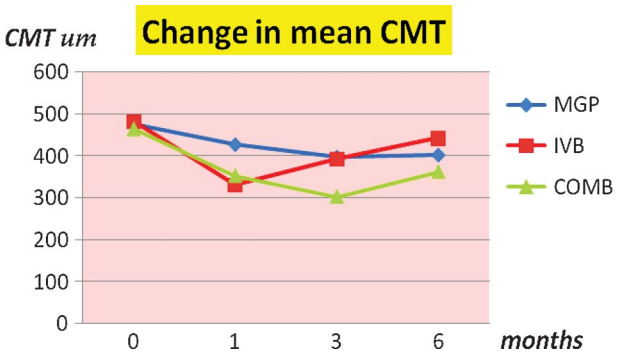

Fig. 1. Changes in the mean CMT 1 month, 3 months, and 6 months after treatment in the MGP group, IVB, group and combined group (COMB).

there was a significant improvement in mean BCVA in the IVB (38.09%) ($P < 0.05$) and the combined (21.69%) ($P < 0.05$) groups. In the MGP group, the mean BCVA was not significantly different 1 month after treatment ($P > 0.05$) (Figure 2, Table 3).

Three months after treatment, the mean CMT was still better than baseline in all groups, but this improvement was significant only in the combined group ($P < 0.05$). The reduction in the mean CMT versus baseline was 79.72 μm (16.71%) in the MGP group ($P > 0.05$), 88.83 μm (18.43%) in the IVB group ($P > 0.05$), and 160.29 μm (34.54%) in the combined group ($P < 0.05$) (Figures 1, 3A, 3B, Table 2). The mean BCVA was improved by 10.71% in the MGP group ($P > 0.05$), 15.48% in the IVB group ($P > 0.05$), and 22.89% in the combined group ($P < 0.05$) (Figure 2, Table 3). Fluorescein angiography revealed decreases of macular leakage in 10 (52.63%) eyes in the MGP group, 13 (61.90%) eyes in the IVB group, and 16 (77.27%) eyes in the combined groups with corresponding decreases in the mean extent of macular edema in the 3 groups.

Six months after treatment, the mean CMT was higher than the 3-month values in all groups but remained below the baseline and the difference was significant only in the combined group ($P < 0.05$) (Figure 1, Table 2). The mean BCVA in the MGP and the IVB groups regressed to approximately baseline values, whereas in the combined group, the improvement (10.84%) was not statistically significant ($P > 0.05$) (Figure 2, Table 3). The BCVA did not deteriorate below baseline in all eyes included in the study, except three eyes in the MGP group: one of them lost one line and two eyes lost two lines. No complications related to the intravitreal injection were reported in the IVB or combined groups. At 6 months, the mean extent of macular edema as was demonstrated by fluorescein angiography was more than that detected at 3 months but still less than the baseline.

Discussion

Diffuse diabetic macular edema remains a challenging problem that causes severe vision loss in patients with diabetes.[1,2] Historically, MGP has been considered the mainstay of treatment, yet the visual outcomes have been unsatisfactory.[3,4,7,8] Recently, promising results have been reported after the use of IVB for the treatment of DDME; however, the effect lasts for a few months only.[10–14] To enhance the therapeutic effects, this study was conducted to evaluate the results obtained by using a combination of IVB and sequential MGP as a primary treatment of DDME and to compare these results with those obtained by using each treatment modality alone.

In this study, we found that eyes treated with IVB injection followed by MGP 3 weeks later had statistically significant reductions in CMT at 1, 3, and 6 months ($P < 0.05$). However, eyes that had IVB only had a statistically significant reduction in CMT at 1 month ($P < 0.05$), whereas the reduction in CMT in eyes that had MGP alone was not significant at any time point ($P < 0.05$). This additive synergistic effect of MGP if performed after IVB injection could be because the laser photocoagulation might be more effective in a less thickened macula (previously treated with IVB) and thus produces more marked and more prolonged reduction in macular edema. At 1 month, the IVB group showed a greater reduction in CMT than the combined group (31.30% versus 23.77%) and this is likely due to the transient increase in macular edema after laser photocoagulation, which was used in the combined group. This transient increase in

Table 2. Change Over Time in Mean CMT (in Micrometers) in the MGP Group, IVB Group, and the Combined Group

Duration	MGP Group	IVB Group	Combined Group
Baseline	477.14 ± 39.11	482.11 ± 40.15	464.02 ± 42.47
1 month	427.26 ± 33.41	331.19 ± 39.04*	353.72 ± 23.19*
3 months	397.42 ± 28.56	393.28 ± 35.58	303.73 ± 26.08*
6 months	402.48 ± 31.84	442.94 ± 37.66	362.64 ± 25.53*

*Statistically significant change from the baseline value; $P < 0.05$.

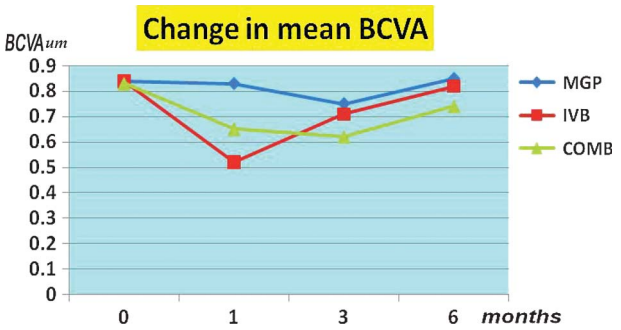

Fig. 2. Change in the mean logarithm of minimal angle of resolution BCVA 1 month, 3 months, and 6 months after treatment in the MGP group, IVB group, and combined group (COMB).

macular edema may also explain the nonsignificant reduction in CMT in the MGP group 1 month after treatment. The reduction in CMT remained significant up to 6 months in the combined group ($P < 0.05$). This duration indicated a more pronounced and prolonged effect of using a combination therapy. The possibility exists that the reduction in CMT observed in the MGP group ($P > 0.05$) and in the combined group at 3 and 6 months ($P < 0.05$) may partially be due to loss of neural tissue caused by laser treatment. However, the response to treatment and outcome might be affected by the randomization process that did not differentiate patients with attenuated neural tissue and increased interstitial fluid from those with retained retinal neural mass but less edema. The response to any treatment and the outcome might be different in these two scenarios even though they may present with similar retinal thickness. It is also possible that eyes with PDR have macular edema that is more VEGF dependent and therefore more responsive to IVB than eyes with nonproliferative diabetic retinopathy. This could explain better results in the combined group that had more eyes with PDR (10 of 22 eyes had PDR) compared with MGP group (6 of 19 eyes had PDR) and IVB group (5 of 21 eyes had PDR). An advantage in the eyes that require repeated IVB is that the repeat injection will be performed at longer intervals if the eye was initially treated with MGP. The reductions in CMT were parallel to the decrease of macular leakage as detected in fluorescein angiography in all groups after treatment for the duration of the study.

The combined group had statistically significant better BCVA at 1 and 3 months ($P < 0.05$), whereas eyes in the IVB group were found to have statistically significant better mean BCVA at 1 month ($P < 0.05$). Mean BCVA was not significantly different from baseline during follow-up in the MGP group. Soheilian et al[14] reported that the improvement in visual acuity associated with IVB may be explained by increased macular perfusion rather than leakage reduction and/or fluid resorption. Reliability of the correspondence between vision and the CMT as measured by OCT depends on many factors such as duration, extent and severity of macular edema, presence of foveal hard exudates, age of the patient, status of the macula before the onset of edema, and intensity of macular laser treatment in eyes treated with MGP. These factors could explain why visual acuity changes are not always parallel to CMT changes in eyes with DDME. Other studies also have demonstrated the unreliable correspondence between the OCT-measured CMT and the visual acuity in patients with diabetic macular edema, but the reasons for this lack of association were not provided.[15,16]

Panretinal photocoagulation to the peripheral retina was done in the 6 eyes with PDR and neovascularization in the MGP group, 1 session each, 4 to 6 weeks after the MGP. This was effective in controlling the activity of PDR for the duration of the study. Patients with PDR in the IVB group and combined group responded well to the IVB that has previously been shown to induce regression of retinal neovascularization.[17,18] None of the subjects who received IVB required panretinal photocoagulation during the study period.

To our knowledge, this is the first peer review study evaluating the efficacy of combined IVB and MGP for treatment of DDME. This lack of other studies limits comparison of our results to studies using a combination of intravitreal triamcinolone acetonide and MGP. Evaluating eyes with DDME treated with and without MGP 3 weeks after intravitreal triamcinolone acetonide,

Table 3. Change Over Time in Mean BCVA (logMAR) of the MGP Group, IVB Group, and the Combined Group

Duration	MGP Group	IVB Group	Combined Group
Baseline	0.84 ± 0.15	0.84 ± 0.74	0.83 ± 0.32
1 month	0.83 ± 0.19	0.52 ± 0.23*	0.65 ± 0.19*
3 months	0.75 ± 0.08	0.71 ± 0.54	0.62 ± 0.01*
6 months	0.85 ± 0.79	0.82 ± 0.13	0.74 ± 0.33

logMAR, logarithm of minimal angle of resolution.
*Statistically significant change from the baseline value; $P < 0.05$.

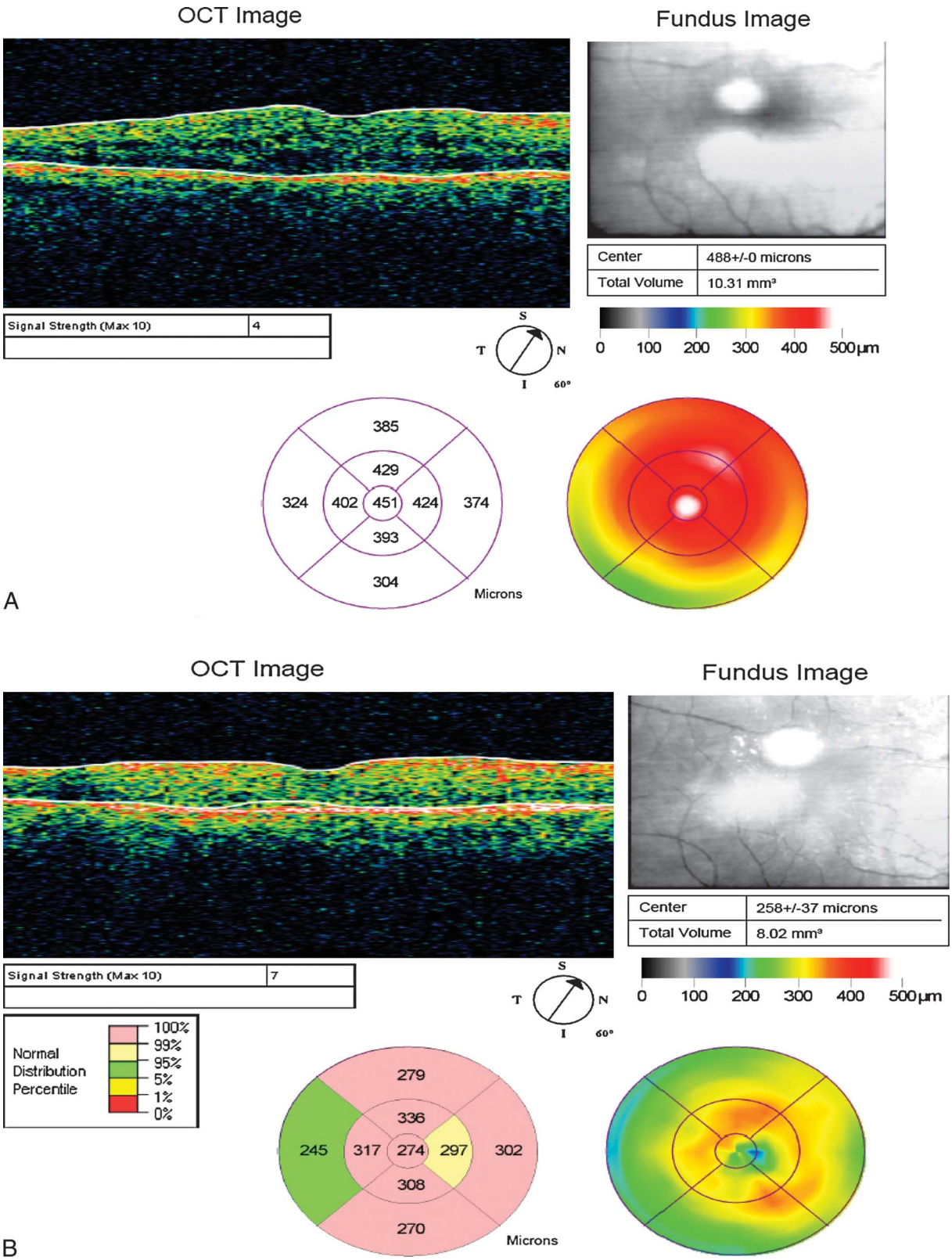

Fig. 3. A, Optical coherence tomography of DDME before combined therapy of IVB followed by modified grid laser photocoagulation 3 weeks later. **B,** Optical coherence tomography of DDME 3 months after combined therapy of IVB followed by modified grid laser photocoagulation 3 weeks later.

Kang et al[19] reported statistically significant reductions in CMT at 3 and 6 months after combination therapy, whereas eyes that received intravitreal triamcinolone acetonide experienced a statistically significant reduction at 3 months only. Additionally, eyes that received MGP after intravitreal triamcinolone acetonide had significantly better logarithm of minimal angle of resolution BCVA at 3 and 6 months, which concur with the outcomes of our study. Lam et al[20] have concluded somewhat similar results, reporting that combined therapy (intravitreal triamcinolone acetonide and MGP) appeared to be superior to laser or intravitreal triamcinolone acetonide alone in reducing macular thickening, but the difference in the BCVA between the three groups did not reach statistical significance at any time point.

Although IVB has been shown to downregulate VEGF and reduce the permeability of retinal capillaries,[10,12,13] it does not affect the underlying cause of the problem that is macular hypoxia.[21] Thus, recurrence of macular edema occurs within a few weeks once bevacizumab is cleared from the vitreous. Grid laser photocoagulation causes destruction of some photoreceptors that are high oxygen consumers, thereby increasing the inner retinal oxygen levels and improving hypoxic conditions. Hence, when MGP is used in conjunction with IVB, it aids in reducing macular hypoxia prolonging the effect of IVB and decreasing the rate of recurrence of diabetic macular edema. Alternately, reduction of macular thickness and restoration of retinal transparency achieved by IVB facilitate the delivery of laser energy selectively to the photoreceptors and the retinal pigment epithelium.[19] Based on these observations, it seems that both treatment modalities are potentiating the effect of the other, due to the differing modes of action.

However, some factors that might affect macular edema and the treatment outcome such as presence or absence of the crystalline lens, degree of glycemic control, level of cholesterol, and other lipids as well as presence of hypertension and renal disease were not considered in the present study. However, we did address other confounding factors such as intersurgeon variability by selecting one surgeon for each procedure. Furthermore, differences in interpretation were mitigated by having one ophthalmologist read all fluorescein and OCT studies. A larger number of patients and a longer follow-up period are needed to verify and confirm the results of the present study, to select the correct timing for MGP after IVB, and to establish parameters for selection of patients who are most suitable for undergoing combined therapy as a primary treatment. We are planning to compare the long-term safety and efficacy of this combined therapy versus the use of repeated IVB injections in eyes with DDME.

In conclusion, this preliminary study of eyes with DDME showed that combined therapy with IVB and sequential MGP 3 weeks later appeared to be superior to MGP or IVB alone in reducing macular thickening and improving visual acuity. The improvement in BCVA was not significant at 6 months. A combination of IVB and sequential MGP could be used as an initial treatment of DDME.

Key words: intravitreal bevacizumab, macular photocoagulation, diffuse diabetic macular edema, VEGF.

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