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Comparing the effectiveness of brolucizumab therapy alone versus that combined with subthreshold micropulse laser exposure in the treatment of diabetic macular edema

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Background: *Diabetic retinopathy (DR) is a major cause of blindness in working-age individuals in the developed countries. Studies have found that diabetic macular edema (DME) is a major cause of visual impairment in patients with diabetes mellitus (DM). Vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of DME.*

Material and Methods: *Eighty-two patients (153 eyes) with DME were divided into two treatment groups. Group 1 (37 patients, 68 eyes) was treated with injections of the anti-VEGF agent brolucizumab according to the one plus pro re nata (PRN) regimen (once plus as needed) only, whereas group 2 (45 patients, 85 eyes) received a combination of "one plus PRN" brolucizumab therapy with subthreshold micropulse laser exposure (SMPLE). Before and after treatment, a comprehensive ophthalmological examination was performed, including the best-corrected visual acuity (BCVA) and the height of retinal edema in the central fovea as assessed by optical coherence tomography. The parameters were assessed at 1, 3, 6 and 12 months after treatment.*

Results: *The percentage of patients with no need for additional anti-VEGF injections was substantially higher in the combined therapy group than in the monotherapy group (68.5% versus 12%, respectively, p <0.001).*

Conclusion: *The combination treatment (intravitreal brolucizumab combined with SMPLE) for DME was effective in 68.5% of cases within 12 months. In this way, a steady resorption of DME is accomplished through antivasoproliferative and prolonged effects of brolucizumab and the SMPLE session.*

Keywords:

diabetic macular edema, anti-VEGF therapy, subthreshold micropulse laser exposure

Introduction

The complications of diabetic retinopathy (DR) are still a major cause of visual loss in working-age individuals in the developed countries. Diabetic macular edema (DME) is a major cause of visual impairment in eyes with DR [1-5]. There has been an increase in the prevalence of diabetes mellitus (DM) (a cause of DR and, consequently, of DME) worldwide, with the disease becoming a pandemic not only in the developed, but also in the developing countries [6].

Individuals with type 1 DM tend to develop DR after three to five years from the onset of diabetes. DME affects 14-25% of patients who have had diabetes for 10 years or more [7].

Anti-vascular endothelial growth factor (VEGF) therapy is the most commonly used treatment approach in the management of DME [8, 9]. The advantage of intravitreal administration of an anti-VEGF drug in patients with DME has been identified and effectively applied in large, multicenter, randomized clinical trials [8, 10, 11]. However, Brown and colleagues [12] estimated that between 31.6% and 65.6% of patients with DME respond suboptimally to anti-VEGFs. In addition, the results of a 2-year randomized clinical trial of anti-VEGF treatments for 660 DME patients by Wells et al showed that 84% of the eyes had received at least 1 injection in the second year, and 98% of the protocol-required injections, based on visual acuity and optical coherence tomography OCT (optical coherence tomography), were given over the 2 year study period. The recurrence rate was high even after edema resorption [9]. Thus, frequent anti-VEGF injections (7-12 injections in the first year and somewhat less in subsequent years) were required to maintain the resolution of the DME [13]. Focal or grid laser photocoagulation of the retina was a major treatment for DME before the introduction of the anti-VEGF drugs into clinical practice. The Early Treatment Diabetic Retinopathy Study (ETDRS) has shown that focal laser photocoagulation treatment is beneficial in reducing the risk of visual loss from clinically significant DME [14]. The method of laser treatment employed in the ETDRS has become the technical standard of macular photocoagulation in DME. Conventional laser photocoagulation is effective in eyes with DME, but can result in complications like laser scars, choroidal neovascularization, subretinal fibrosis, retinal pigment epithe-

lial atrophy, visual field narrowing, loss of color vision, metamorphopsia and enlargement of laser scars [1,15,16]. Laser-induced damage to the retina limits the density and repeatability of laser treatment. Today, the predominant method of laser treatment for DME is the "modified ETDRS photocoagulation" (mETDRS). This technology has offered us new laser media and wavelengths [13].

A novel laser delivery modality was invented by Pankratov in 1990 wherein the laser energy was delivered in short pulses or "micro pulses" instead of a continuous wave [17]. Advances in the field of laser systems have led to a new approach called subthreshold micropulse laser exposure (SMPLE) [18,19]. It is now possible to deliver a subthreshold laser that is above the threshold of biochemical effect but below the threshold of a visible, destructive lesion, thereby preventing potentially limiting progressive enlargement of laser scars, which can lead to scotoma and loss of color vision [2,15]. Many investigators believe that this may be the safest form of laser treatment for DME [2,18]. There are, however, several treatment protocols regarding surgical or delayed micropulse laser treatment. Some of them can be combined with anti-VEGF therapy [20].

The purpose of this study was to compare the effectiveness of a combination of anti-VEGF therapy with SMPLE versus anti-VEGF therapy alone in the treatment of DME.

Material and Methods

A prospective study was conducted at the eye clinic "SIHAT KO`Z" and Tashkent State Dental Institute and was a 12-month follow-up. Eighty-two patients (150 eyes) with DME were involved in the study and their eyes were compared for the morphofunctional parameters of the central retina. All patients had a verified diagnosis of type 2 DM. The age of the patients ranged from 48 to 69 years. There were 48 women and 34 men. Intraocular pressure (IOP) readings by pneumotonometry ranged from 11.0 to 20.0 mm Hg. Patients with a vision reducing cataract were excluded from the study.

Patients were divided into two treatment groups. Group 1 (37 patients, 68 eyes) was treated with anti-VEGF injections according to the one plus pro re nata (PRN) regimen (once plus as needed) only whereas group 2 (45 patients, 85 eyes) received a combination of "one plus PRN" anti-VEGF therapy with SMPLE.

Before and after treatment, a comprehensive ophthalmological examination was performed, including the best-corrected visual acuity (BCVA) and the height of retinal edema in the central fovea as assessed by OCT. Parameters were assessed before treatment and at 1, 3, 6 and 12 months after treatment.

Brolucizumab, a monoclonal antibody that binds to VEGF-A, was administered as an anti-VEGF intraocular injection at a dose of 0.2 ml (2.0 mg). Intravitreal injections were performed in a standard fashion using surgical instruments. Palpebral skin and the area around the eye were treated with a 10% iodopyrone solution. Epibulbar anesthesia was locally administered. After an epibulbar anesthetic was instilled, a sterile speculum was inserted to separate the lids, and the conjunctival sac was flushed with betadine diluted with saline in a ratio of 1:2. Calipers were used to mark the injection site 3.5 mm laterally from the limbus at 10 o'clock. The syringe was extracted and the conjunctiva was pulled over the injection site with forceps to reduce the release of vitreous beneath the conjunctiva. An antibacterial medication was instilled.

A general ophthalmological examination was carried out the next day after injection to timely identify any post-injection complications such as retinal detachment, vitreous hemorrhage, intraocular inflammation, toxic damage to the lens, etc. In the postoperative period, topical antibacterial and anti-inflammatory eye drops were instilled for 14 days.

SMPLE was performed on a 577-nm Easyret laser system (Quantel medical, France) in a micropulse mode with a power of 200–400 mW. The spot size is 100 μm, the pulse burst duration is 200 ms with a duty cycle of 5%. The micropulse laser power used in SMPLE was derived for each eye from a test burn. The test burn was performed using a 100 μm spot diameter and a 200 pulse burst duration outside the vascular arcade with the power titrated from 50 mW upward until a burn became barely visible. SMPLE was then performed continuously on the macular region using the same spot size, reducing the laser power to half the power of the test burn. The number of spots applied varied depending on the extension of the edema.

With combined treatment, the SMPLE session was performed 3 days after a single loading of the anti-VEGF drug.

Descriptive statistics was calculated using Microsoft Office Excel (v.2016, Microsoft Corporation, Redmond, WA). Quantitative characteristics are presented as means and standard errors of means. Qualitative characteristics are presented as numbers and percentages. A Student t-test was applied to determine whether there were any significant differences between groups and between pre- and post-treatment periods. The level of significance $p \leq 0.05$ was assumed.

Results

Mean baseline BCVA was 0.51±0.08 and 0.48±0.05 in group 1 and group 2, respectively. At baseline, mean retinal edema height at the central fovea was 388.4±19.1 μm and 350.6±15.8 μm in group 1 and group 2, respectively (Tables 1-3).

At one month after the loading injection, BCVA improved to 0.71±0.04 in the monotherapy group and to 0.78±0.03 in the combined therapy group. These improvements were comparable in both groups and significant (P = 0.001). Mean central retinal thickness decreased to 257.4±14.5 μm in the monotherapy group and 252.4±24.8 μm in the combined therapy group (P = 0.77). In addition, three patients in the monotherapy group needed an additional injection.

At six months, BCVA was still better than baseline, 0.66±0.02 in the monotherapy group and 0.75±0.02 in the

Table 1. Demographic characteristics of patients and baseline characteristics of eyes in groups

Parameter	Groups	
	Group 1	Group 2
Number of patients/eyes under study	37/68	45/85
Mean age	56.3±3.7	54.6±3.4
Number of men/women	18/22	15/26
Best-corrected visual acuity	0.51±0.08	0.48±0.05
Retinal edema height at the central fovea as assessed by OCT	388.4±19.1	350.6±15.8

combined therapy group. These differences were statistically significant (P = 0.001).

By month 12, BCVA improved to 0.65±0.03 in the monotherapy group and to 0.79±0.03 in the combined therapy group, but the improvement in the latter group was not statistically significant (P = 0.62).

The trends for improvements in the central retinal thickness were similar to improvements in BCVA. By month 6, mean central retinal thickness decreased to 275.3±22.7 μm in the monotherapy group and 258.5±14.6 μm in the combined therapy group (P = 0.4). By month 12, mean central retinal thickness was 276.5±15.9 μm in the monotherapy group and 255.4±18.7 μm in the combined therapy group, with no significant difference between groups (P = 0.16).

Over the 12 month follow-up, 31/37 patients (88%) in the monotherapy group needed additional anti-VEGF injections. Particularly, 6 cases (24%) needed 2 additional injections; 5 cases (20.0%), 3 additional injections; 6 cases (24.0%), 4 additional injections; 3 cases (12.0%), 5 additional injections; 2 cases (8.0%), 2 additional injections; and only 3 cases (12.0%), no additional injections.

In addition, over the 12 month follow-up, in the combined therapy group, 5 cases (23.4%) needed 2 additional injections, 4 cases (8.1%), needed 3 additional injections, and the rest (68.5%) needed no additional injections.

By the end of the study, the combined therapy group needed substantially less anti-VEGF injections than the monotherapy group. Particularly, 68.5% of the former group needed no additional injections, whereas 88% of the latter group needed additional injections.

Mean number of injections received over 12 months was 4.33±1.02 for the total study cohort, 3.18±0.48 for the combined therapy group and 5.49±1.56 for the monotherapy group ($p < 0.001$). By the end of the study, the percentage of patients with no need for additional anti-VEGF injections was substantially higher in the combined therapy group than in the monotherapy group (68.5% versus 12%, respectively, $p < 0.001$).

Discussion

DME is one of the most unfavorable and difficult to treat manifestations of DR [12]. About 32-50% of eyes with clinically significant DME if untreated will have significant irreversible vision loss and reduced vision-related quality of life, leading to visual disability and increased social and economic costs [14]. Intravitreal injections of VEGF inhibitors have become the first line of treatment for this condition instead of laser retinal photocoagulation. However, clinical reports on the application of anti-VEGF drugs in patients with DME have demonstrated that about 30% of patients may be insufficiently responsive to this intravitreal therapy [21]. The disadvantages of intravitreal injection include development of certain complications,

Table 2. Best-corrected visual acuity (mean plus/minus standard error of means) at baseline and at time points in groups

Group	Baseline and time points				
	Baseline	1 month	3 months	6 months	12 months
1	0.51±0.08	0.71±0.04 **	0.68±0.02 **	0.66±0.02 *	0.65±0.03 *
2	0.48±0.03	0.78±0.03 **	0.81±0.02 **	0.75±0.02 **	0.79±0.03 **

Notes: *, significant inter-group difference at time point (p≤0.05); **, significant inter-group difference at time point (p≤0.01)

Table 3. Retinal edema height at the central fovea (mean plus/minus standard error of means; μm) as assessed by OCT at baseline and at time points in groups

Group	Baseline and time points				
	Baseline	1 month	3 months	6 months	12 months
1	388.4±19.1	257.4±14.5 **	282.8±18.4 *	275.3±22.7 *	276.5±15.9 *
2	385.6±15.8	252.4±24.8 **	256.8±19.8 **	258.5±14.6 **	255.4±18.7 **

Notes: *, significant inter-group difference at time point (p≤0.05); **, significant inter-group difference at time point (p≤0.01)

such as endophthalmitis, retinal and intravitreal hemorrhages, intraocular lens dislocation, etc [12, 17].

In the current study, we compared anti-VEGF therapy alone with anti-VEGF therapy combined with SMPLE in terms of efficacy over a 12-month follow-up. Both groups achieved substantial improvements in BCVA and retinal height at the fovea. Final BCVA was better in eyes treated with anti-VEGF therapy combined with SMPLE (0.79±0.03). The percentage of patients with no need for additional anti-VEGF injections was substantially higher in the combined therapy group than in the monotherapy group (68.5% versus 12%, respectively, $p < 0.001$).

This is the first study in the literature to use the anti-VEGF drug (brolucizumab) and its combination with an SMPLE session in DME patients with relatively high baseline BCVA. Thus, adding an SMPLE session after loading an anti-VEGF drug appears to significantly reduce injection load without sacrificing improvement in vision. We found that the treatment effectiveness assessed after 12 months of follow-up differed significantly between groups 1 and 2. This combination provides a statistically significant improvement in BCVA and a decrease in the height of the retina in the fovea in DME with a central foveola thickness of less than 400 μm. SMPLT may be an option for patients who do not respond well to or cannot follow anti-VEGF therapy due to its high cost, or who experience adherence problems due to the frequent visits required for injection and ophthalmologic monitoring.

Fedchenko and colleagues [21] concluded that, unlike suprathreshold, subthreshold laser mode is a non-damaging procedure and can be used in clinical practice as a laser retinal treatment approach providing the least invasive effect on the chorioretinal complex. According to the selected duty cycle, the laser remains on only 5% of the time, thus generating less heat with consequent less retinal damage than continuous photocoagulation. Our experience shows that micropulse laser treatment for DME is more effective in patients whose central retinal thickness with edema is less than 400 μm.

Conclusion

The combination treatment (intravitreal brolucizumab combined with SMPLE) for DME was effective in 68.5% of cases within 12 months. The combination treatment (intravitreal brolucizumab combined with SMPLE) for DME was effective in 68.5% of cases within 12 months. In this way, a steady resorption of DME is accomplished through antivasoproliferative and prolonged effects of brolucizumab and the SMPLE session.

References

1. **Volodin PL, Ivanova EV., Khrisanfova ES.** [Navigational technology of targeted topographically oriented laser coagulation in the treatment of focal diabetic macular edema: First clinical results]. Modern technologies in ophthalmology. 2018;1:65-68. Russian.
2. **Bobykin EV.** Modern approaches to the treatment of diabetic macular edema. Ophthalmosurgery. 2019;1:67-76.
3. **Umanets NN, Rozanova Z A, Alzein M.** [Combination of intravitreal injections of ranibizumab and selective laser coagulation of retinal pigment epithelium in the treatment of diabetic cystoid macular edema]. Oftalmol Zh. 2013;3:18-22. Russian.
4. **Lipatov DV, Lyshkanets OI**. [Intravitreal therapy of diabetic macular edema in Russia: the current state of the problem]. Bulletin of ophthalmology. 2019;135(4):128–39. Russian.
5. **Okhotsimskaya TD, Zaitseva OV. [**Aflibercept in the treatment of retinal diseases. Review of clinical studies]. Russian Ophthalmological Journal. 2017;2S:103-111.
6. Diabetic Retinopathy Clinical Research Network (DRCR.net) Beck RW, Edwards AR, Aiello LP, Bressler NM, Ferris F, Glassman AR, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol. 2009 Mar;127(3):245–51.
7. **Busch C, Fraser-Bell S, Zur D, et al.;** International Retina Group. Real-world outcomes of observation and treatment in diabetic macular edema with very good visual acuity: the OBTAIN study. Acta Diabetol. 2019;56(7):777–784.
8. **Akkaya S, Açıkalın B, Doğan YE, Çoban F.** Subthreshold micropulse laser versus intravitreal anti-VEGF for diabetic macular edema patients with relatively better visual acuity. Int J Ophthalmol. 2020; 13(10): 1606–1611.
9. **Wells JA, et al.** Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123:1351–1359.
10. **Ashraf M, Souka A, Adelman R, Forster SH.** Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option. Eye (Lond) 2017;31(2):342–345.
11. **Hodzic-Hadzibegovic D., Sander B.A., Monberg T.J. et al.** Diabetic macular oedema treated with intravitreal anti-vascular endothelial growth factor — 2–4 years follow-up of visual acuity and retinal thickness in 566 patients following Danish national guidelines. Acta Ophthalmol. 2018;96(3):267–278.
12. **Brown DM, Emanuelli A, Bandello F, et al**. KESTREL and KITE: 52-Week Results From Two Phase III Pivotal Trials of Brolucizumab for Diabetic Macular Edema. Am J Ophthalmol. 2022;238:157–172.
13. **Fursova AZh, Derbeneva AS, Tarasov MS.** Clinical efficacy of anti-angiogenic therapy for diabetic macular edema in real clinical practice (2-year results). Russian Ophthalmological Journal. 2021;14(2):42–9.
14. Early Treatment Diabetic Retinopathy Study research group. Early Treatment Diabetic Retinopathy Study (ETDRS). Photocoagulation for diabetic macular oedema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol. 1985;103:1796–806.
15. **Kim JY, Park HS, Kim SY.** Short-term efficacy of subthreshold micropulse yellow laser (577-nm) photocoagulation for chronic central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2015;253(12):2129–2135.
16. **Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al.** Guidelines for the management of diabetic macular edema by the European society of retina specialists (EURETINA). Ophthalmologica. 2017;237(4):185–222.
17. **Pankratov MM.** Pulsed delivery of laser energy in experimental thermal retinal photocoagulation. Proc Soc Photo Opt Instrum Eng. 1990;1202:205–13.

18. **Moisseiev E, Abbassi S, Thinda S, Yoon J, Yiu G, Morse LS.** Subthreshold micropulse laser reduces anti-VEGF injection burden in patients with diabetic macular edema. Eur J Ophthalmol. 2018;28(1):68–73..
19. **Su D, Hubschman JP.** A review of subthreshold micropulse laser and recent advances in retinal laser technology. Ophthalmol Ther. 2017;6(1):1–6.
20. **Wu Y, Ai P, Ai ZS, Xu GT.** Subthreshold diode micropulse laser versus conventional laser photocoagulation monotherapy or combined with anti-VEGF therapy for diabetic macular edema: a Bayesian network meta-analysis. Biomed Pharmacother. 2018;97:293–299.
21. **Fedchenko SA, Zadorozhnyy OS, Molchaniuk NI, Korol AR**. Comparing ultrastructural changes in the rabbit chorioretinal complex after 577-nm and 532-nm laser photocoagulation. J Ophthalmol (Ukraine). 2017;6:56-71.

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Abbreviations: *Anti-VEGF – anti-vascular endothelial growth factor; DME – diabetic macular edema; DR – diabetic retinopathy; BCVA – best-corrected visual acuity; OCT – optical coherence tomography; SMPLE – subthreshold micropulse laser exposure*