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РАНДОМИЗИРОВАННОЕ ИССЛЕДОВАНИЕ, СРАВНИВАЮЩЕЕ ИНТРАВИТРЕАЛЬНЫЙ БЕВАЦИЗУМАБ И ФОКУСНУЮ ЛАЗЕРНУЮ ФОТОКОАГУЛЯЦИЮ ПРИ ДИАБЕТИЧЕСКОЙ МАКУЛОПАТИИ

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Резюме. Цель: оценить эффективность и безопасность монотерапии бевацизумабом или бевацизумабом в сочетании с фокальным/сеточным лазером по сравнению с терапией только фокальным/сеточным лазером для лечения диабетической макулопатии (ДМ).

Материалы и методы. 112 подходящих для исследования пациентов в возрасте ≥18 лет с сахарным диабетом 1 или 2 типа и максимально корригированной остротой зрения (МКОЗ) в исследуемом глазу от 35 до 69 букв на расстоянии 4 м согласно Исследования раннего лечения диабетической ретинопатии (ETDRS) (эквивалент Снеллена: ≥6/60 или ≤6/12), с нарушениями зрения из-за диабетической макулопатии с вовлечением центра макулы (ДМ). Пациенты были произвольно разделены на три группы лечения: (I) интравитреальная монотерапия бевацизумабом (n= 42), (II) интравитреальная терапия бевацизумабом в сочетании с лазером (n=35), (III) лазерная монотерапия (n=35). Инъекций бевацизумаба назначено по 3 начальных ежемесячных дозы, а затем по мере необходимости на основании стабильности МКОЗ и прогрессирования ДМ. Конечными показателями первичной эффективности были среднее изменение МКОЗ и толщина центральной области сетчатки (CRST) от исходного этапа до 12-го месяца.

Результаты. Монотерапия бевацизумабом или бевацизумаб + лазер превзошли лазерную монотерапию в повышении показателей среднего изменения по количеству букв при МКОЗ с исходного уровня до 12 месяца (+8,3 и +11,3 против +1,1 букв; оба p<0,0001). На 12-м месяце большая часть пациентов добилась показателя ≥10 и ≥15 букв и показателя при МКОЗ >73 (эквивалент Снеллена: >6/12) с монотерапией бевацизумабом (23,8%, 7,1% и 4,8% соответственно), с терапией бевацизумаб + лазер (57,1%, 28,6% и 14,3% соответственно) по сравнению с лазерной монотерапией (0% и 0% и 0%). Средняя толщина центральной области сетчатки была значительно уменьшена от исходного уровня до 12 месяца на терапии бевацизумабом (-124,4 мкм) и терапии бевацизумаб + лазер (-129,0 мкм) по сравнению с монотерапией лазером (-62,0 мкм; оба p = 0,002). Конъюнктивальное кровоизлияние было наиболее распространенным явлением. Случаев эндофтальмита не было.

Заключение. Результаты монотерапии бевацизумабом или бевацизумаб+лазер превзошли лазерную монотерапию в улучшении МКОЗ у монгольских пациентов с нарушениями зрения из-за диабетической макулопатии.

Ключевые слова: диабетическая макулопатия; диабетическая ретинопатия; фактор роста сосудистого эндотелия; бевацизумаб.

A RANDOMIZED TRIAL COMPARING INTRAVITREAL BEVACIZUMAB AND FOCAL LASER PHOTOCOAGULATION FOR DIABETIC MACULAR EDEMA

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Summary. Aim: To evaluate the efficacy and safety of bevacizumab monotherapy or bevacizumab combined with focal/grid laser compared with focal/grid laser alone for treatment of diabetic macular edema (DME).

Methods. One hundred twelve eligible patients, aged ≥18 years, with type 1 or 2 diabetes mellitus and best corrected visual acuity (BCVA) in the study eye of 35 to 69 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 4 m (Snellen equivalent: ≥6/60 or ≤6/12), with visual impairment due to center-involved diabetic macular edema (DME). Patients were randomized into three treatment groups: (I) intravitreal bevacizumab monotherapy (n=42), (II) intravitreal bevacizumab combined with laser (n=35), (III) laser monotherapy (n=35). Bevacizumab injections were given for 3 initial monthly doses and then pro re nata (PRN) thereafter based on BCVA stability and DME progression. The primary efficacy endpoints were the meanchange in BCVA and central retinal subfield thickness (CRST) from baseline to month 12.

Results. Bevacizumab monotherapy or bevacizumab + laser were superior to laser monotherapy in improving the mean change in BCVA letter score from baseline to month 12 (+8.3 and +11.3 vs +1.1 letters; both p<0.0001). At month 12, a greater proportion of patients gained ≥10 and ≥15 letters and with BCVA letter score >73 (Snellen equivalent: >6/12) with bevacizumab monotherapy (23.8% and 7.1% and 4.8%, respectively) and bevacizumab + laser (57.1% and 28.6% and 14.3%, respectively) versus laser monotherapy (0% and 0% and 0%). The mean central retinal subfield thickness was significantly reduced from baseline to month 12 with bevacizumab (−124.4 μm) and bevacizumab + laser (−129.0 μm) versus laser (−62.0 μm; both p=0.002). Conjunctival hemorrhage was the most common ocular events. No endophthalmitis cases occurred.

Conclusion. Bevacizumab monotherapy or bevacizumab + laser showed superior BCVA improvements over macular laser treatment alone in Mongolian patients with visual impairment due to diabetic macular edema.

Key words: diabetic macular edema; diabetic retinopathy; vascular endothelial growth factor; bevacizumab.

Diabetic retinopathy is the most common microvascular complication of diabetes mellitus and the leading cause of blindness in working-age adults in the United States, Europe, and increasingly worldwide [1]. Diabetic macular edema is a major cause of the vision loss (DME visual impairment) associated with diabetic retinopathy [2]. In 2010, of an estimated 92.6 million adults with diabetic retinopathy worldwide, 20.6 million were estimated to have DME [3]. The increasing prevalence of diabetes worldwide highlights the importance of diabetic macular edema as a global health issue [4].

The Early Treatment Diabetic Retinopathy Study (ETDRS) established the role of laser in preventing up to 15 letters (ETDRS scale) loss of best-corrected visual acuity (BCVA) with prompt therapy [5]. Although laser photocoagulation has been the standard treatment for DME for nearly 3 decades, there is increasing evidence that superior outcomes can be achieved with anti-vascular endothelial growth factor (anti-VEGF) therapy [6-12]. Vascular endothelial growth factor (VEGF) plays a pivotal role in the development of DME [13]. A decade of clinical trials demonstrated anti-VEGF drugs that bind soluble VEGF restore the integrity of the blood-retinal barrier, resolve macular edema, and improve vision in most patients with DME [14-19]. In 2007, the DRCR.net reported results from a phase two randomized clinical trial that suggested intravitreal bevacizumab treatment had an effect on the reduction of DME in some eyes (Protocol H) [20]. The Pan-American Collaborative Retina Group (PACORES) also reported an apparent benefit of bevacizumab treatment for DME [21]. A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT) study randomized 80 participants to intravitreal bevacizumab or macular laser treatment and found that whereas the bevacizumab group gained a median of eight letters in visual acuity over 12 months, the laser group lost a median of 0.5 letters over the same time period [22, 23]. Three commonly used intravitreous VEGF inhibitors: Ranibizumab (Lucentis, Genentech), Bevacizumab (Avastin, Genentech), and Aflibercept (Eylea, Regeneron Pharmaceuticals) have been shown to be beneficial and relatively safe for the treatment of diabetic macular edema. Bevacizumab is a full-length recombinant humanized monoclonal antibody that, in contrast to pegaptanib's isoform-specific actions, blocks all isoforms of VEGF-A. It shares a similar molecular structure with ranibizumab, which was designed as a monoclonal antibody fragment from the same parent murine antibody [24]. In 2015, the Diabetic Retinopathy Clinical Research Network published the results of Protocol T study [25]. In this comparative-effectiveness, randomized clinical trial of center-involved DME causing decreased visual acuity, treatment with intravitreous aflibercept, bevacizumab, or ranibizumab was associated with a substantial improvement in mean visual acuity by 1 month, with the improvement sustained through 1 year.

Diabetes is becoming major public health concern in Mongolia. Most recent report from the Mongolian STEPS Survey on the Prevalence of Noncommunicable Disease and Injury Risk Factors 2009 estimated the prevalence of diabetes was 6.5% (95% CI 4.5-8.4) in the study population [26]. It has been reported that in 2010in Mongolia, the prevalence of any grade DR was 30.2%, DME 17.7% and sight threatening retinopathy was 6.4% and 96.3% of patients who needed laser or surgical treatment had not been treated [27]. This low treatment rate is explained by the lack of trained personnel, especially vitreo-retinal specialists, diagnostics and therapeutic instruments at that time. Nowadays, thanks to the introduction of the latest technology and equipment in our practice, we are able to diagnose and treat patients with diabetic retinopathy at a qualitatively new level. The purpose of this study was to treat and evaluate the clinical efficacy and safety of bevacizumab monotherapy and bevacizumab therapy combined with laser therapy versus laser monotherapy in Mongolian patients with visual impairment resulting from DME.

Materials and Methods

Study Design. The study was a prospective, randomized, laser-controlled, 12 month, single-center, clinical trial, and was undertaken at Infinity Eye Clinic, Ulaanbaatar, Mongolia. Patients were randomized into three treatment groups: (I) intravitreal bevacizumab monotherapy, (II) intravitreal bevacizumab combined with laser,(III) laser monotherapy. One eye was selected and treated as the study eye. If both eyes were eligible, the eye with the worse visual acuity (VA; assessed at visit 1) was selected for treatment, unless, based on medical reasons, the investigator deemed the other eye more appropriate to receive study treatment. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethical Committee of the School of Medicine, Mongolian National University of Medical Sciences. All study participants provided written informed consent before entering the study.

Patients. The study population consisted of 112 male and female patients ≥18 years of age with either type 1 or 2 diabetes mellitus, and visual impairment due to DME.

The key inclusion criteria were: (1) patients of either gender aged ≥18 years; (2) diabetes mellitus (type 1 or 2); (3) best-corrected visual acuity (BCVA) in the study eye between 35 and 69 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 4 m (Snellen equivalent ≥6/60 or ≤6/12); (4) center-involving diabetic macular edema (DME) with central macular thickness (CMT) on optical coherence tomography (OCT) of ≥270 μm; (5) media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus imaging; (6) intraocular pressure (IOP) <30 mmHg; (7) ability to return for regular study visits. The key exclusion criteria were: (1) macular ischemia (foveal avascular zone [FAZ] ≥1000 μm greatest linear dimension (GLD) or severe perifoveal intercapillary loss on FFA; (2) macular edema due to a cause other than DME; (3) coexistent ocular disease; (4) history of an anti-VEGF treatment for DME in the past 12 months in the study eye; (5) any other treatment for DME in the past four months (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids); (6) hemoglobin A1c (HbA1c) >12.0%; (7) BP > 160/100; (8) any stage of PDR; (9) medical history of chronic renal failure; (10) pregnancy (11) uncontrolled glaucoma.

Baseline Evaluation. After informed consent, medical and ophthalmic history was recorded and ophthalmologic examination was performed, including BCVA, applanation tonometry, and anterior segment and dilated slit-lamp biomicroscopic examination. All subjects had standard ETDRS 7 field fundus photographs, FFA and OCT imaging.

Efficacy and Safety Assessments

Best Corrected Visual Acuity. At baseline and each follow-up visit, investigators assessed the BCVA using the ETDRS-like VA testing chart at a starting distance of 4 m. The primary efficacy end point was the mean change in BCVA letter score from baseline to month 12. Secondary efficacy end points included the proportion of patients with a BCVA letter score >73 (Snellen equivalent: >6/12), the proportion of patients who gained ≥10 and ≥15 ETDRS letters (improvement), the proportion of patients who lost <15 ETDRS letters (stabilization) at month 12.

Optical Coherence Tomography. Optical coherence tomography was performed at every study visit using spectral-domain OCT (Cirrus™, Carl Zeiss Meditec, Germany). Trials for diabetic retinopathy have defined CMT values >250 μm as significant for macular edema to qualify for various trials [6,7,22].In order to control for any ceiling or floor effect, the 270 μm in CMT was considered as a eligible criteria. Retinal thickness was determined using individual A-scans along with each of 6 B-scans. Baseline and 1 year OCT scans were graded at the Infinity Eye Clinic by the investigators. The end points included the mean change in CRST and the proportion of patients with <250 μm ("dry macula") from baseline over time.

Stereoscopic Color Fundus Photography and Fluorescein Angiography Stereoscopic color fundus

photography and fluorescein angiography (VX-10, Kowa Company, Ltd, Nagoya, Japan) were performed at baseline, month 4, month 8 and month 12. After pupil dilation and before fluorescein dye injection, red-free and ETDRS 7-field color photographic images of the retina of the study eye were taken.

Safety Assessments. Safety was assessed by analysis of the incidence of adverse events (AEs) and serious adverse events (SAEs), by ophthalmic examinations, intraocular pressure measurements, and by changes in vital signs over the 12-month assessment period. All ocular and nonocular AEs and SAEs were recorded.

Treatment

Bevacizumab monotherapy. Bevacizumab injections were given for 3 initial monthly (every 4 weeks) doses and then pro re nata (PRN) thereafter based on BCVA stability and DME progression. Subjects were subsequently reviewed every 4 weeks. At each visit, a full history was taken, ETDRS BCVA was recorded by an investigator, and a complete ocular examination (including anterior chamber reaction, IOP and dilated fundoscopy) and OCT were performed.

Retreatment Criteria. As of month 3, one injection per month was continued if stable VA was not reached. The stable vision was defined as a change of fewer than 15 letters in an ETDRS chart. Patients were treated at monthly intervals until stable vision was achieved, that is, no further BCVA improvement attributable to treatment was observed compared with the 2 previous consecutive visits according to the investigator. After suspension, injections were resumed PRN, if there was a decrease in BCVA due to DME progression and CSMT was greater than 270 μm on OCT.

Intravitreal Bevacizumab Injection Technique. Intravitreal bevacizumab (Avastin, Genentech) injections (1.25 mg in 0.05 ml) were performed in the operating theatre of the Infinity Eye Clinic by the investigators. Bevacizumab injections were done under sterile conditions, using topical anesthesia and povidone-iodine 5% into the conjunctival sac and onto the lid margins, and following application of a drape and insertion of a lid speculum. The injections were undertaken with a 30-gauge needle through the supra- or infratemporal quadrant, with a drop of gatifloxacin placed in the fornix at the end of the procedure. Patency of the central retinal artery was determined by indirect ophthalmoscopy and VA of hand movements. The IOP was checked 30 minutes after the injection. After the injection, topical gatifloxacin was instilled 4 times per day for 5 days.

Laser Treatment. All patients in the intravitreal bevacizumab combined with laser and laser monotherapy groups underwent modified ETDRS macular laser therapy(MLT) at their baseline visit or within 7 days of randomization. ETDRS MLT was performed using the VISULAS® 532s (Carl Zeiss, Germany). Subjects were subsequently reviewed every 4 months. Re-treatments were performed if clinically indicated by ETDRS guidelines [28]. In the ETDRS, initial treatment for macular edema was usually done in one sitting. Four months after the initial treatment and at 4-month intervals thereafter, if clinically significant macular edema and treatable lesions were present, additional treatment was given to these lesions. Repeat fluorescein angiography was usually necessary to assess whether treatable lesions were present. [29]Modified ETDRS MLT used a 50 μm argon laser spot size and the laser was applied only more than 500 μm from the edge of the foveal avascular zone (FAZ), with focal treatment aiming to cause mild blanching of the retinal pigment epithelium and not darkening/whitening of microaneurysms. Areas of diffuse leakage or non-perfusion were similarly treated in a grid pattern. At each visit, a full history was taken and a complete ocular examination was performed (including IOP and dilated fundoscopy); ETDRS BCVA was recorded by the investigators; and 7-field color fundus photography, FFA, and OCT were undertaken.

Statistical Analysis. All statistical analyses were carried out using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA) software for Windows. P-values of less than 0.05 were taken as significant. One-way ANOVA was used to compare baseline BCVA. The mean change BCVA and CRST at 12 month were compared using multiple comparisons Tukey HSD test.

Results and discussion

A total of 112 participants were randomized to receive bevacizumab (n=42), bevacizumab combined with laser (n=35), or laser (n=35). The mean age of the participants was 54.5±10 years and 55.4% were women. A total of 94.6% of the participants had type 2 diabetes, and the mean duration of diabetes was 8.5±4.6 years. The mean visual acuity letter score at baseline was 55.7±8.9, and the mean central retinal subfield thickness was 399.4±114.36 μm. The baseline characteristics of each treatment group are summarized in Table 1. Overall, baseline demographics and diabetes or ocular characteristics were comparable across the 3 treatment groups. The patients received an average of 8 bevacizumab intravitreal injections in the bevacizumab group, 7.5 in the bevacizumab + laser group.

Table 1

Key Baseline Demographics, Diabetes, and Ocular Characteristics

Variable	Total		Treatment groups						P value
			Bevacizumab		Bevacizumab + laser		Laser		
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	
Number of patients	112		42		35		35		
Age	54.54	10.14	54.36	9.76	54.03	12.24	55.26	8.38	0.872[a]
Gender									0.139[b]
Male	50	44.6%	20	47.6%	11	31.4%	19	54.3%	
Female	62	55.4%	22	52.4%	24	68.6%	16	45.7%	
Diabetes type									0.703[b]
Type 1	6	5.4%	3	7.1%	2	5.7%	1	2.9%	
Type 2	106	94.6%	39	92.9%	33	94.3%	34	97.1%	
HbA1c (%)	10.17	3.14	9.85	3.08	10.8	3.26	9.92	3.07	0.357[a]
Duration of DM	8.47	4.19	8.12	3.61	8.6	4.73	8.77	5.52	0.812[a]
Baseline BCVA	55.72	8.95	56.59	8.87	54.94	8.59	55.46	9.54	0.710[a]
Baseline CRST (μm)	399.41	114.36	397.33	114.76	410.14	116.9	391.2	113.8	0.781[a]

BCVA = best-corrected visual acuity; CRST = central retinal subfield thickness; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin A1c; SD = standart deviation; [a]ANOVA; [b] χ^2 test.

Efficacy

Best-Corrected Visual Acuity. The mean change ± SD in the BCVA letter score from baseline to month 12 improved significantly with bevacizumab and bevacizumab + laser treatment versus laser monotherapy (8.3 ± 3.2 letters and 11.3 ± 4.5 letters vs 1.1 ± 3.7 letters), hence the primary end point was achieved (Table 2) (Figure 1). There was a significant difference between the mean ETDRS BCVA at 12 months in the bevacizumab and laser monotherapy group (mean difference 7.2; p<0.0001); bevacizumab + laser and laser monotherapy group (mean difference 10.2; p<0.0001) (Table 2). In the laser group, mean BCVA stabilized around baseline level at month 12. At month 12, 4.8% of patients in the bevacizumab group and 14.3% of patients in the bevacizumab + laser group had a BCVA letter score >73 (Snellen equivalent: >6/12).

The mean number of bevacizumab injections administered was 8.07 in the bevacizumab group, 7.51 in the bevacizumab + laser treatment group. The percentages of eyes with a change in the letter score of 10 or more and 15 or more are provided in Table 3.

Table 2

Efficacy Outcome Measures in the Three Treatment groups

Efficacy Outcome Measure	Total	Treatment groups			P value
		Bevacizumab (n=42)	Bevacizumab+ laser (n=35)	Laser (n=35)	
Baseline BCVA					0.710
Mean (SD)	55.72 (8.95)	56.59 (8.87)	54.94 (8.59)	55.46 (9.54)	
BCVA at 12 month					<0.0001
Mean (SD)	62.40 (9.72)	64.9 (8.6)	66.3 (6.6)	56.0 (10.1)	
Change in BCVA[a]					<0.0001
Mean (SD)	7.17 (5.58)	+8.3 (3.2)	+11.3 (4.5)	+1.1 (3.7)	
Baseline CRST (μm)					0.781
Mean (SD)	399.41 (114.36)	397.33 (114.76)	410.14 (116.9)	391.2 (113.8)	
CRST at 12 month (μm)					0.003
Mean (SD)	293.07 (77.07)	272.9 (51.6)	281.1 (52.9)	329.2 (106.7)	
Change in CRST (μm)[b]					0.002
Mean (SD)	-106.35 (84.39)	-124.4 (82.4)	-129.0 (74.6)	-62.0 (80.8)	

BCVA = best-corrected visual acuity; CRST = central retinal subfield thickness; SD=standart deviation; [a]Difference between Bevacizumab and Laser (Multiple Comparisons, Tukey HSD); Difference between Bevacizumab combined with laser and Laser (Multiple Comparisons, Tukey HSD); [b] Difference between Bevacizumab and Laser (Multiple Comparisons, Tukey HSD); Difference between Bevacizumab combined with laser and Laser (Multiple Comparisons, Tukey HSD)

Central Retinal Subfield Thickness. The mean change in CRST from baseline to month 12 decreased significantly for bevacizumab (124.4 μm; p<0.002) and bevacizumab + laser (129.0 μm; p<0.002) compared with laser (62.0 μm). There was no difference detected between the two bevacizumab treatment groups.At month 12, the proportion of patients with CRST < 250 μm was greater in the bevacizumab monotherapy group (40.5%) and the bevacizumab + laser group (28.6%) compared with the laser group (14.3%).

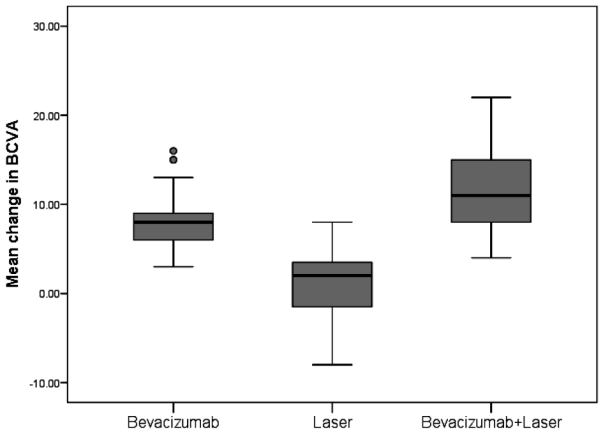

Figure 1. Mean change in BCVA from baseline to month 12 (ETDRS letter score).

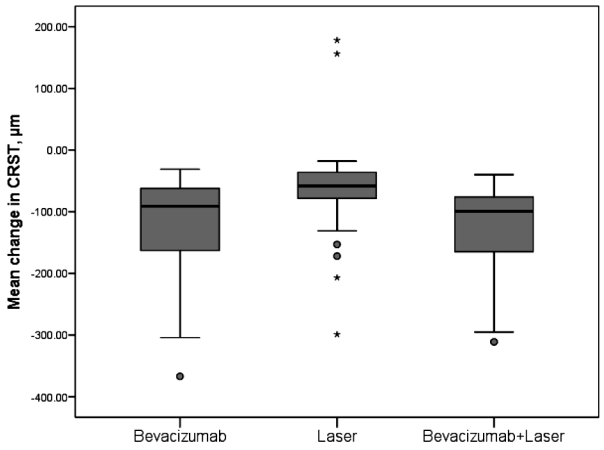

Figure 2. Mean change in CRST from baseline to month 12.

Table 3

Categorized BCVA letter score and CRST outcomes at month 12

Efficacy Outcome Measure	Bevacizumab (n=42)		Bevacizumab + Laser (n=35)		Laser (n=35)		P value
	n	%	n	%	n	%	
Proportion with final VA>73	2	4.8	5	14.3	0	0.0	0.044[a]
Proportion with <10 letter gain	32	76.2	15	42.9	23	100.0	0.0001[b]
Proportion with ≥10 letter gain	10	23.8	20	57.1	0	0.0	
Proportion with <15 letter gain	39	92.9	25	71.4	23	100.0	0.002[a]
Proportion with ≥15 letter gain	3	7.1	10	28.6	0	0.0	
Proportion with <30 letter gain	42	100.0	35	100.0	23	100.0	
Proportion with ≥30 letter gain	0	0.0	0	0.0	0	0.0	
Proportion with <10 letter loss	0	0.0	0	0.0	10	83.3	
Proportion with ≥10 letter loss	0	0.0	0	0.0	2	16.7	
Proportion with <15 letter loss	0	0.0	0	0.0	12	100.0	
Proportion with ≥15 letter loss	0	0.0	0	0.0	0	0.0	
Proportion with <30 letter loss	0	0.0	0	0.0	12	100.0	
Proportion with ≥30 letter loss	0	0.0	0	0.0	0	0.0	
Proportion with final CRST <250	17	40.5	10	28.6	5	14.3	0.040[b]

BCVA = best-corrected visual acuity; CRST = central retinal subfield thickness; VA= visual acuity; BOLD = significant p<0.05; [a]Fisher's Exact test; [b]χ^2 test.

Safety

Serious Adverse Events. There were no ocular and nonocular SAEs reported in any of the treatment arms. No endophthalmitis cases occurred.

Adverse Events. Conjunctival hemorrhage was themostcommonocularevents. Bevacizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study.

This prospective, randomized clinical trial has demonstrated that treatment with bevacizumab as monotherapy or combined with laser treatment is superior to laser treatment alone in improving and sustaining visual acuity in Mongolian patients with DME visual impairment. A greater proportion of patients treated with bevacizumab gained ≥10, ≥15 BCVA letter scores and with BCVA letter score >73 from baseline compared with the laser-treated patients. Bevacizumab treatment consistently improved BCVA across all subgroups regardless of baseline characteristics as compared with the laser treatment alone.

The functional improvement in BCVA was accompanied by a significant improvement in anatomic end points, CRST on OCT, and resolution of leakage on fluorescein angiography. The mean change CRST from baseline to month 12 decreased significantly for bevacizumab and bevacizumab + laser (both; p=0.002) compared with laser (Figure 2). At month 12, 40.5% (bevacizumab), 28.6% (bevacizumab + laser), and 14.3% (laser) patients had CRST <250 μm. This study showed that the bevacizumab monotherapy or bevacizumab therapy combined with the laser therapy were safe and well tolerated in DME visual impairment patients.

The treatment efficacy reported in the bevacizumab studies to date is comparable to that described in this report (Table 5). The DRCR.net Protocol H study was uncontrolled with only two intravitreal injection protocol. [20]The Pan-American Collaborative Retina Study (PACORES) was a nonrandomized, uncontrolled with only a 3 injection

protocol for 6 months. [21]The BOLT study was based on 6-week injection intervals, and was a 2-arm, randomized, controlled, masked clinical trial. The results of this study on bevacizumab replicate the observations made with ranibizumab in DME in larger randomized controlled trials, suggesting that pan-VEGF-A inhibitors appear to have similar effects on DME.[22]

A recent prospective randomized 3-arm trial (1.25 mg intravitreal bevacizumab alone, intravitreal bevacizumab in combination with intravitreal triamcinolone acetonide, and MLT) in patients with clinically significant macular edema (CSME) reported positive visual outcomes similar to those of our trial. [30]However, the findings were at the 36-week time point, ETDRS VA charts were not used, retreatments were performed at 12-week intervals, and a significant reduction of CRST from baseline was only observed at 6 weeks. Additionally, all of those studies use Stratus OCT, a time domain OCT which is subject to frequent artifacts and lower repeatability compared to spectral-domain Cirrus OCT which was used in our study. This study is different from other studies in that, all enrolled participants in this study were first time diagnosed with the DME and, importantly, they have never been received the MLT. The other studies, all enrolled patients with persistent DME who have received at least 1 prior MLT. Other differences were observed in the baseline characteristics of the participants in our study in comparison with other studies are that, they were comparatively young, more shorter duration of diabetes after the initial diagnosis and poor control of DM.

Our study used initiation of treatment with 3 initial monthly (every 4 weeks) doses and then pro re nata (PRN) dosing regimen addressing individual patient needs with reduced treatment burden. Currently, monthly injections (RISE and RIDE [10,11]), pro re nata (PRN) approach (RESOLVE[9]), and treat-and-extend (RETAIN [31]) are the main strategies of treating DME with anti-VEGF agents. The PRN and treat-and-extend strategies are considered more favorable compared with the monthly approach because of the reduced cost burden.

The limitations of our clinical trial were small number of patients and relatively short follow-uptime course. Further large multicenter studies are required with longer follow-up (at least 3 years). Because of the chronic nature of the underlying disease process and the mechanism of action of anti-VEGF agents, monotherapy with anti-VEGF drugs is likely to be impractical, although the development of slow delivery systems may yet address this issue. Nevertheless, one would anticipate that treating patients with the clinically significant macular edema with the repeated intravitreal bevacizumab at an earlier time point, before irreversible structural damage has been sustained, will result in even better visual outcomes. Furthermore, more rapid reduction in macular edema compared with MLT may lead to a superior longer-term visual acuity. In conclusion, this study demonstrated the superiority of bevacizumab therapy with or without laser therapy over laser monotherapy in improving BCVA and reducing CRST in Mongolian patients with DME visual impairment.

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ЛИТЕРАТУРА – REFERENCES

1. *Bourne R.R., Jonas J.B., FlaxmanS.R., et al.* Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe: 1990-2010 // Br J Ophthalmol. 2014. Vol. 98. P.629-638.

2. *Boyer D.S., Hopkins J.J., Sorof J., Ehrlich J.S.* Anti-vascular endothelial growth factor therapy for diabetic macular edema // Ther Adv Endocrinol Metab. 2013. Vol.4. P.151-169.

3. International Diabetes Foundation. IDF Diabetes Atlas. Seventh Edition. 2015.

4. *Yau J.W., Rogers S.L., Kawasaki R., et al.* Global prevalence and major risk factors of diabetic retinopathy // Diabetes Care. 2012. Vol. 35. P.556-564.

5. *Early Treatment Diabetic Retinopathy Study Research Group.* Early photocoagulation for diabetic retinopathy: ETDRS report number 9 // Ophthalmology. 1991. Vol. 98. P. 766-785.

6. *Diabetic Retinopathy Clinical Research Network.* Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema // Ophthalmology. 2010. Vol. 117. P. 1064-1077.

7. *Bressler S.B., Qin H., Beck R.W., Chalam K.V., Kim J.E., et al.* Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab // Arch Ophthalmol.2012. Vol. 130. P.1153-1161. DOI: 10.1001/archophthalmol.2012.1107

8. *Nguyen Q.D., Shah S.M., Khwaja A.A., et al.* Two-year outcomes of the Ranibizumab for Edema of the Macula in Diabetes (READ-2) study // Ophthalmology. 2010. Vol. 117. P.2146-2151.

9. *Massin P., Bandello F., Garweg J.G.,* ***et al.*** Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study // Diabetes Care. 2010. Vol. 33. P.2399-2405.

10. *Nguyen Q.D., Brown D.M., Marcus D.M., et al.* Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE // Ophthalmology. 2012. Vol. 119. P.789-801.

11. *Brown D.M., Nguyen Q.D., Marcus D.M., et al.* Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE // Ophthalmology. 2013. Vol. 120. P.2013-2022.

12. *Do D.V., Nguyen Q.D., Khwaja A.A., et al.* Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment // JAMA Ophthalmol. 2013. Vol. 131. P.139-145.

13. *Simo R., Sundstrom J.M., Antonetti D.A.* Ocular Anti-VEGF therapy for diabetic retinopathy: the role of VEGF in the pathogenesis of diabetic retinopathy // Diabetes Care. 2014. Vol. 37. P.893-899.

14. *Mitchell P., Bandello F., Schmidt-Erfurth U., et al.* The RESTORE study: ranibizumabmonotherapy or combined with laser versus laser monotherapy for diabetic macular edema // Ophthalmology. 2011. Vol. 118. P.615-625.

15. *Do D.V., Nguyen Q.D., Boyer D., et al.* One-year outcomes of the DaVinci Study of VEGF Trap-Eye in eyes with diabetic macular edema // Ophthalmology. 2012. Vol. 119. P.1658-1665.

16. *Schmidt-Erfurth U., Lang G.E., Holz F.G., et al.* Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study // Ophthalmology. 2014. Vol. 121. P.1045-1053.

17. *Elman M.J., Ayala A., Bressler N.M., et al.* Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results // Ophthalmology. 2015.Vol. 122. P.375-381.

18. *Ishibashi T., Li X., Koh A., et al.* The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema; REVEAL Study Group // Ophthalmology. 2015. Vol. 122. №7. P.1402-1415.

19. *Korobelnik J.F., Do D.V., Schmidt-Erfurth U., et al.* Intravitreal aflibercept for diabetic macular edema // Ophthalmology. 2014. Vol. 121. P.2247-2254.

20. *Diabetic Retinopathy Clinical Research Network, Scott I.U., Edwards A., et al.* A phase II randomized clinical trial of intravitreal

bevacizumab for diabetic macular edema // Ophthalmal. 2007. Vol. 114. №10. P.1860-1867.

21. *Arevalo J.F., Jans F.J., Hugo Q.M., et al.* Primary Intravitreal Bevacizumab (Avastin) for Diabetic Macular Edema. Results from the Pan-American Collaborative Retina Study Group (PACORES) at 6-Month Follow-up // Ophthalmology. 2007. Vol. 114. P.743-750.

22. *Michaelides M., Kaines A., Hamilton R.D., et al.* A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2 // Ophthalmology. 2010. Vol. 117. P.1078-1086.

23. *Rajendram R., Fraser-Bell S., Kaines A., et al.* A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema; 24-month data: report 3 // Arch Ophthalmol. 2012. Vol. 130. P.972-979.

24. *Genentech I.* AVASTIN (bevacizumab) injection, solution. Available at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=14571. Accessed: 12 July 2010.

25. *Diabetic Retinopathy Clinical Research Network*. Comparative effectiveness study of intravitreal aflibercept, bevacizumab, and ranibizumab for DME (Protocol T). 2014. Available at https://clinicaltrials.gov/ct2/show/NCT01627249.

26. Ministry of Health Mongolia, World Health Organization Western Pacific Region. Mongolian STEPS Survey on the Prevalence of Noncommunicable Disease and Injury Risk Factors 2009. Geneva: World Health Organization; 2010.

27. *Chimgee Ch.* Evaluating diabetic retinopathy amongst registered diabetic patients in urban and rural Mongolia. 2010.

28. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. ETDRS research group // Arch Ophthalmol. 1985 Dec. Vol. 103. №12. P.1796-806.

29. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group // Ophthalmology. 1987. Vol. 94. №7. P.761-774.

30. *Soheilian M., Ramezani A., Obudi A., Bijanzadeh B., Salehipour M., Yaseri M., et al.* Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema // Ophthalmology. 2009. Vol. 116. P.1142–1150.

31. *Pruente C.; RETAIN Study Group*. Efficacy and safety of ranibizumab in two treat-and-extend versus pro-re-nata regimes in patients with visual impairment due to diabetic macular edema: 24-month results of RETAIN study // ARVO Meeting Abstracts. 2014. Vol. 55. P.1700.

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