(03)

Bevacizumab intravitreal injections in the treatment of diabetic macular oedema

Doszklistkowe iniekcje bewacyzumabu w leczeniu cukrzycowego obrzęku plamki

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Streszczenie: Cel: ocena skuteczności leczenia cukrzycowego obrzęku plamki za pomocą doszklistkowych iniekcji bewacizumabu.
Materiał i metody: badaniem prospektywnym objęto 21 oczu u 21 pacjentów z klinicznie znamiennym cukrzycowym obrzękiem plamki, potwierdzonym badaniem angiografii fluoresceinowej oraz badaniem optycznej koherentnej tomografii. Średni wiek pacjentów wynosił 60,6 ± 12,4 roku, a średni czas trwania cukrzycy 16,0 ± 9,3 roku. Pacjentów badano kilkakrotnie: przed leczeniem, 3 tygodnie po każdej iniekcji oraz 3 miesiące po zakończeniu terapii. Oceniano: ostrość wzroku za pomocą tablic EDTRS (którą wyrażano w skali logMAR), przedni i tylny odcinek oczu oraz centralną grubość siatkówki, mierzoną za pomocą optycznej koherentnej tomografii (Topcon 3D OCT-1000). Bewacyzumab podawano doszklistkowo w dawce 1,25 mg/0,05 ml, w odstępach 1-miesięcznych. Trzy iniekcje otrzymało 10 pacjentów, dwie iniekcje – 5 pacjentów, jedną iniekcję 7 pacjentów. Od kolejnych podaży odstępowano, kiedy zaobserwowano powrót pełnej ostrości wzroku lub redukcję centralnej grubości siatkówki do wartości $<250\ \mu$m. Do analizy statystycznej wyników zastosowano sparowany test T przy założonym poziomie istotności $p<0,05$.
Wyniki: u pacjentów z badanej grupy średnia ostrość wzroku przed rozpoczęciem terapii wynosiła 0,50 (0,15–1,50) logMAR i po pierwszej iniekcji uległa istotnej poprawie do 0,40 (0,00–1,30) logMAR ($p = 0,044$). Dalsza stopniowa poprawa następowała po kolejnych iniekcjach. U 10 pacjentów, którzy otrzymali wszystkie 3 iniekcje, po kolejnych podażach średnia ostrość wzroku poprawiała się z 0,50 logMAR (0,15–1,50) przed leczeniem na: 0,45 logMAR (0,1–1,3) ($p = 0,078$), 0,35 logMAR (0,00–1,30) ($p = 0,011$), 0,25 logMAR (0,05–1,20) ($p = 0,007$), po 3 miesiącach wynosiła ostatecznie 0,30 logMAR (0,10–0,70) ($p = 0,018$).
U wszystkich pacjentów z badanej grupy pierwsza iniekcja nie powodowała redukcji grubości siatkówki – 368 μm (234–708) *vs* 389 μm (236–642) ($p = 0,602$). Po kolejnych podażach leku obserwowano wprawdzie jej zmniejszanie się w porównaniu do wartości wyjściowych, różnice nie były jednak znamienne. Po zakończeniu leczenia średnia centralna grubość siatkówki wynosiła 373 μm ($p = 0,235$). Natomiast u 10 osób, którym zaaplikowano 3 iniekcje, przed rozpoczęciem leczenia odnotowano średnią grubość siatkówki na poziomie 407 μm (312–701), miesiąc po pierwszej podaży wartość ta wzrosła do 441 μm (323–634) ($p = 0,959$), po drugiej zmniejszyła się do 340 μm (281–679) ($p = 0,126$), po trzeciej zmniejszyła się do 331 μm (244–568) ($p = 0,086$), po trzech miesiącach wynosiła 348 μm (147–627) ($p = 0,176$).
Wnioski: doszklistkowe iniekcje bewacyzumabu u pacjentów z cukrzycowym obrzękiem plamki powodują istotną poprawę ostrości wzroku oraz wyraźne, chociaż nieznamienne, zmniejszenie centralnej grubości siatkówki.

Słowa kluczowe: cukrzycowy obrzęk plamki, optyczna koherentna tomografia – OCT, bewacyzumab, centralna grubość siatkówki – CRT.

Summary: Purpose: To estimate effectiveness of bevacizumab intravitreal injections in the treatment of diabetic macular oedema.
Material and methods: The perspective study included 22 eyes in 22 patients with clinically significant diabetic macular oedema confirmed by fluorescein angiography and optical coherence tomography. Mean age of the patients was 60.6 ± 12.4 years, while mean diabetes duration was 16.0 ± 9.3 years. Vision acuity (expressed in logMAR scale), as well as anterior and posterior part of the eye were evaluated. Central retinal thickness was measured with the use of optical coherence tomography Topcon 3D OCT 1000 apparatus before and 3 weeks following each injection. Bevacizumab was administered intravitrealy in the dose of 1.25 mg/0.05 ml at monthly intervals. 10 patients were administered 3 injections, 5 patients – 2, while 7 – only 1 injection. The injection therapy was discontinued when the patients gained full vision acuity or when central retinal thickness was reduced to $<250\ \mu$m. Statistical analysis of the results was performed with the use of Wilcoxon test, with significance $p<0.05$.
Results: Mean vision acuity prior to the therapy amounted to 0.50 (0.15–1.50) logMAR and after the first injection improved to 0.40 (0.00–1.30) logMAR ($p = 0.044$). Further improvement was observed after subsequent injections. As regards patients who were administered 3 injections, mean vision acuity observed after further injections improved significantly from 0.50 (0.15–1.50) logMAR prior to the treatment to: 0.45 (0.1–1.3) ($p = 0.078$), 0.35 (0.00–1.30) ($p = 0.011$), 0.25 (0.05–1.20) ($p = 0.007$) and 0.30 (0.10–0.70) logMAR ($p = 0.018$). The first injection caused no reduction of retinal thickness – 368 μm (234–708) vs. 389 (236–642) μm ($p=0.602$). However, following further injections decreased retinal thickness compared to the initial values; yet the differences were not significant. Retinal thickness following three injections amounted to: 407 (312–701) μm prior to the treatment, 441 (323–634) μm one month after the first injection ($p = 0.959$), 340 (281–679) one month after the second injection ($p = 0.126$), 331 (244–568) one month after the third injection ($p = 0.086$) and 348 (147–627) three months after the third injection ($p = 0.176$).
Conclusions: Intravitreal bevacizumab injections in patients with diabetic macular oedema caused a significant improvement of vision acuity and a significant reduction of central retinal thickness.

Key words: diabetic macular oedema, optical coherence tomography – OCT, bevacizumab, central retinal thickness – CRT.

The term diabetes refers to a group of metabolic diseases which involve disorders of carbohydrate metabolism in form of hyperglycemia resulting from insulin deficiency or insulin-resistance. The number of diabetic patients, type 2 in particular, is rapidly increasing, hence an increasing number of complications affecting also the sight. The most common are diabetic retinopathy, refraction changes caused by hyperglycemia and increased lenticular opacity. The most dangerous is retinopathy, especially maculopathy followed by macular oedema, in which the pathomechanism is based on ischemic processes and blood-retina barrier disorders. Ischemic maculopathy involves formation of areas in which is lack of capillary circulation. As regards the collapse of blood-retina barrier, it is responsible for macular oedema and results from function disorders of cell-connecting proteins, including e.g. occludin. The latter is a component of endothelial intercellular connections and influences endothelial permeability.

Chronic hyperglycemia and secondary ischemia lead to increased production of vascular endothelial growth factor (VEGF) which stimulates pathological changes in the retina. Macular oedema, defined as intraretinal fluid accumulation or hard exudates located one diameter of optic nerve disc away from central fovea, is caused by a reduction of occludin expression due to VEGF, which increases vascular permeability. This factor is responsible for subretinal neovascularization which may be accompanied by a leakage and retinal elevation.

A similar process can be observed in the exudative form of macular degeneration related to age (AMD) which also involves increased production of VEGF as well as subsequent neovascularization and macular oedema. Currently, intravitreal preparations from VEGF inhibitor group, such as bevacizumab or ranibizumab, are a standard element in AMD treatment. They bind vascular endothelial growth factor and block its reaction with the receptors. These preparations impede neovascularization and thus stop the progression of the disease. Due to the fact that both macular changes in the course of AMD and diabetic maculopathy are similar, VEGF inhibitors used in AMD may be expected to be equally effective in the treatment of maculopathy.

Material and methods

The clinical study was a prospective, not randomized description of a series of case reports. 21 patients with type 1 or 2 diabetes were qualified. Based on clinical examination and fluorescein angiography they were diagnosed with clinically significant diabetic macular oedema in the course of diabetic retinopathy which impaired vision acuity in all the individuals. The patients were included in the study regardless of age, vision acuity, type and duration and the diabetes control, as well as leakage size in fluorescein angiography and retinal thickness measured with the use of optical coherence tomography. Some of the patients had been administered focal or grid retinal photocoagulation with no satisfactory results. The period of time between laser therapy and qualification for intravitreal bevacizumab administration was at least 6 months. Exclusion criteria were contraindications to fluorescein angiography or past history of stroke or myocardial infarction. All the patients were informed about local condition, prognosis, therapeutic possibilities, the risk of bevacizumab intravitreal injections and potential benefits as well as about the fact that the test is a clinical study. All the patients gave their written informed consent. The approval of the Bioethics Commission of the Medical University of Bialystok was obtained.

All the individuals underwent ophthalmological examination which included distant vision acuity test, intraocular pressure measurement and the examination of the anterior and posterior part of the eye ball in the slit lamp following mydriasis. The fundus of the eye was examined by means of direct and indirect ophthalmoscopy, vision acuity was measured with Snellen's charts and the score was expressed in the logMAR scale.

Macular area was examined by means of fluorescein angiography (FG), Kowa 10x apparatus and optical coherence tomography (OCT), Topcon Mark II apparatus. Fluorescein angiography allowed to set the diagnosis and determine the type and severity of the oedema. The OCT was used to confirm the diagnosis and measure mean central retinal thickness in the macula, i.e. within the circle of a 500 μm radius from the fovea. Moreover, OCT was used to evaluate retinal morphology and to monitor the oedema in the course of treatment.

The study included 3 injections for each patient administered at monthly intervals. The qualification and control tests were performed 1–7 days prior to the injection and 3 weeks after it. The last examination was performed 3 months following the third injection and the last bevacizumab administration. 10 patients were administered 3 injections, 5 patients – 2 and 7patients – only 1 injection. The injection therapy was discontinued when patients gained full vision acuity, when central retinal thickness was reduced to <250 μm or in the lack of consent.

Bevacizumab preparation (Avastin; Roche Ltd, Basel, Switzerland) was administered following local intravitreal anesthesia, 1.2 μg /0.05 ml, in the superior or inferior temporal quadrant, 3.5 mm from the limbus in the pseudophakic eyes and 4.0 mm from the limbus in the phakic eyes. Suitable asepsis principles were applied.

Visual acuity and mean central retinal thickness were presented as arithmetical average and standard deviation. Statistical analysis was performed with the use of the paired t-test. Statistical significance was considered $p<0.05$. Statistical analysis was performed with SPSS 15.0 (SPSS, Chicago, USA).

Results

The study involved 21 eyes in 21 patients (11 women and 10 men) with mean age of 60.6 $\pm$ 12.4 years with the mean history of type 1 or 2 diabetes of 16 $\pm$ 9.3 years. 10 patients were administered 3 injections, 4 patients – 2 while 7 patients received only 1 injection.

Visual acuity

Mean values of vision acuity expressed in logMAR scale are presented in Table I. The values prior to treatment commencement were compared to the values following subsequent injections. Compared to the initial values a gradual improvement of visual acuity was observed after the first ($p = 0.052$), the second ($p = 0.008$) and the third injection ($p = 0.000$). The effect lasted 3 months after the last bevacizumab administration ($p = 0.006$). Statistically significant improvement of visual acuity

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was observed also between the first and the second injection. The third injection caused no further improvement compared to the second injection. Figure 1 presents visual acuity in all the patients before and after the first injection. Figure 2 refers to the patients who were administered 3 injections.

	n	logMAR mean vision acuity/ Średnia ostrość wzroku logMAR	p
Before vs. after 1 month/ Przed badaniem *vs* 1 miesiąc po badaniu	21	0.60±0.35	0.54±0.38
Before vs. after 2 months/ Przed badaniem *vs* 2 miesiące po badaniu	15	0.58±0.38	0.44±0.40
Before vs. after 3 months/ Przed badaniem *vs* 3 miesiące po badaniu	10	0.70±0.41	0.46±0.41
Before vs. after 6 months/ Przed badaniem *vs* 6 miesięcy po badaniu	7	0.50±0.26	0.29±0.21
After 1 month vs. after 2 months/ 1 miesiąc po badaniu *vs* 2 miesiące po badaniu	15	0.54±0.40	0.44±0.40
After 2 months vs. after 3 months/ 2 miesiące po badaniu *vs* 3 miesiące po badaniu	10	0.49±0.42	0.46±0.41

Tab. I. Comparison of mean vision acuity before and after subsequent bevacizumab intravitreal injections administered at monthly intervals and 3 months after the last injection, i.e. 6 months following inclusion into the study.

Tab. I. Średnia ostrość wzroku przed badaniem i po kolejnych iniekcjach bewacyzumabu.

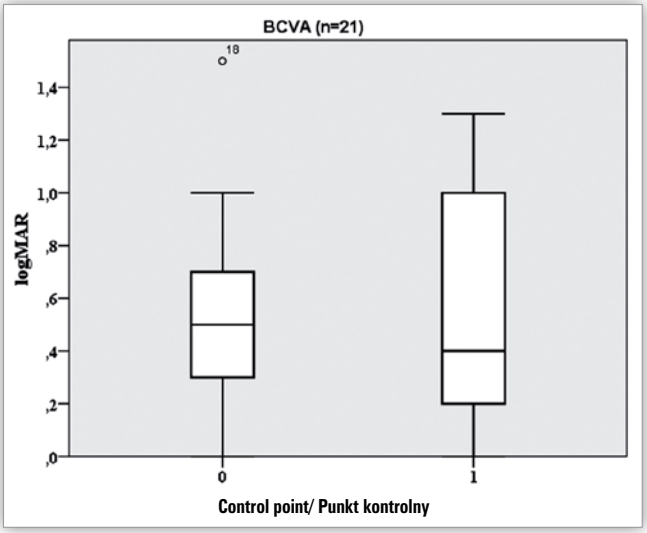

Fig. 1. Visual acuity before (0) and 1 month after the first bevacizumab intravitreal injection (1) in 21 patients.

Ryc. 1. Ostrość wzroku wyjściowa (0) i po miesiącu od pierwszej iniekcji bewacyzumabu (1).

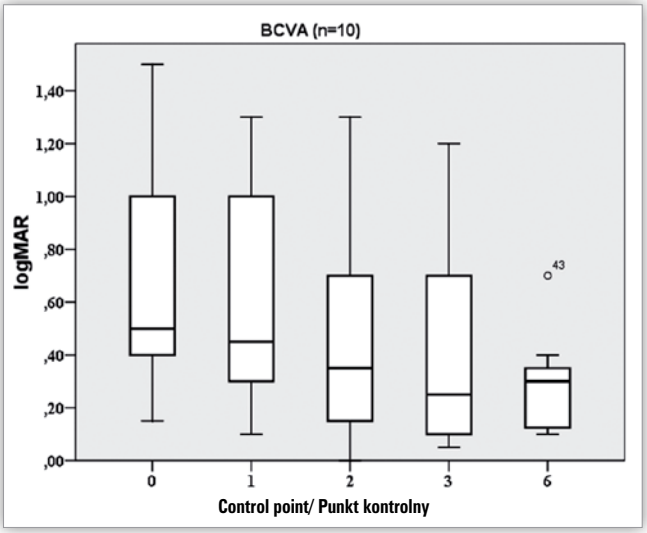

Fig. 2. Visual acuity before (0) and in further months following bevacizumab intravitreal injection in 10 patients who were administered 3 injections at monthly intervals. Mean values at particular controls and the comparison with the initial visual acuity: before (0) 0.70 ± 0.41; 1 month after the first injection (1) 0.62 ± 042, p = 0.076; 1 month after the second injection (2) 0.49 ± 0.42, p = 0.001; 1 month after the third injection (3) 0.46 ± 0.41, p = 000; 3 months after the third injection (6) 0.30 ± 0.21 p = 0.006.

Ryc. 2. Ostrość wzroku wyjściowa (0) i jej wartości w kolejnych badaniach u 10 pacjentów, którym podano 3 iniekcje bewacyzumabu.

Mean central retinal thickness in the macula

Table II presents mean central retinal thickness. Its reduction was observed following administration of the injections compared to the initial values. However, these differences were not statistically significant except for the comparison of retinal thickness after the second and the third injection. Figure 3 presents mean central retinal thickness in all the patients before and after the first injection. Figure 4 refers to patients who were administered 3 injections.

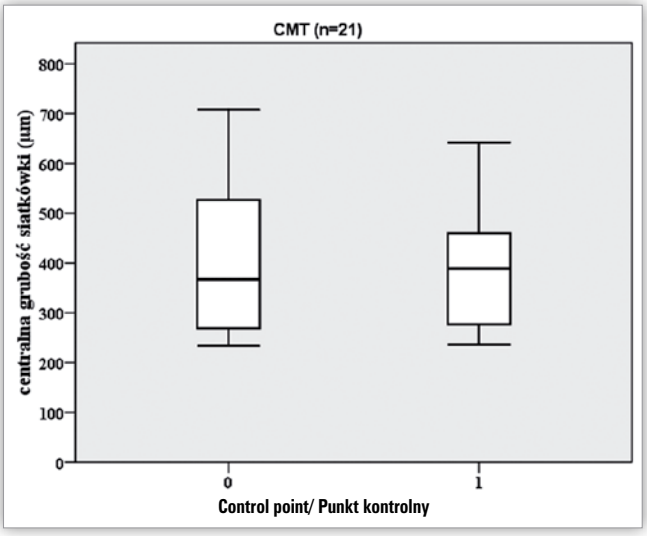

Fig. 3. Central retinal thickness before (0) and 1 month after the first bevacizumab intravitreal injection (1) in 21 patients.

Ryc. 3. Centralna grubość siatkówki przed leczeniem (0) i 1 miesiąc po pierwszej iniekcji bewacyzumabu (1).

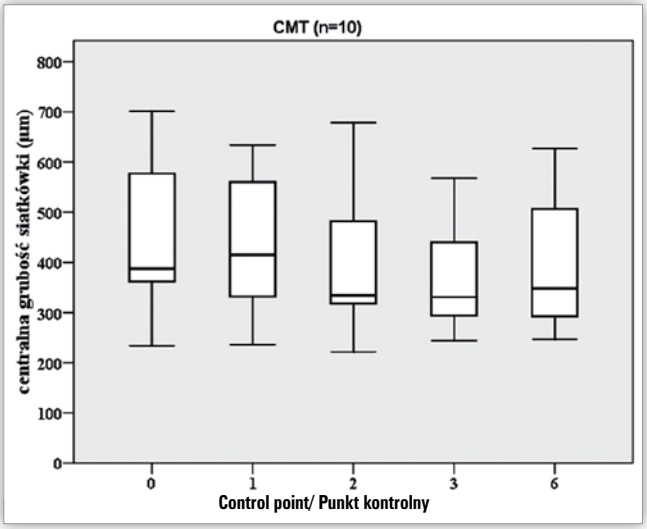

Fig. 4. Central retinal thickness before (0) and in subsequent months after bevacizumab intravitreal injection in 10 patients who were administered 3 injections at monthly intervals. Mean values at particular controls and the comparison with initial central retinal thickness: before (0) 449 ± 153; 1 month after the first injection (1) 432 ± 129, p = 0.502; 1 month after the second injection (2) 393 ± 137, p = 0.225; 1 month after the third injection (3) 373 ± 111, p = 0.90; 3 months after the third injection (6) 402 ±1 58, p = 0.235.

Ryc. 4. Zestawienie średnich wartości centralnej grubości siatkówki przed leczeniem (0) i w kolejnych badaniach kontrolnych u 10 pacjentów, którzy otrzymali 3 iniekcje bewacyzumabu.

	n	Mean central retinal thickness (µm)/ Średnie wartości centralnej grubości siatkówki (µm)	p
Before vs. after 1 month/ Przed badaniem *vs* 1 miesiąc po badaniu	21	421±158	396±133
Before vs. after 2 months/ Przed badaniem *vs* 2 miesiące po badaniu	15	404±146	361±124
Before vs. after 3 months/ Przed badaniem *vs* 3 miesiące po badaniu	9	473±141	373±111
Before vs. after 6 months/ Przed badaniem *vs* 6 miesięcy po badaniu	7	434±135	402±158
After 1 month vs. after 2 months/ 1 miesiąc po badaniu *vs* 2 miesiące po badaniu	14	393±130	364±129
After 2 months vs. after 3 months/ 2 miesiące po badaniu *vs* 3 miesiące po badaniu	9	412±130	373±111

Tab. II. Comparison of mean central retinal thickness before and after subsequent bevacizumab intravitreal injections administered at monthly intervals and 3 months after the last injection, i.e. 6 months from the inclusion into the study.

Tab. II. Średnie wartości centralnej grubości siatkówki przed badaniem i po kolejnych iniekcjach bewacyzumabu.

Adverse effects

None of the patients developed adverse effects either general or local ones connected with intravitreal injection (in form of retinal detachment, haemorrhage to the vitreous body, inflammatory reaction of the anterior part of the eye, inflammation of eye ball interior, persistent increase in the intraocular pressure). Some patients developed a mild subconjunctival haemorrhage during the injection therapy but it was absorbed within a few days. Some patients reported itching and burning.

Discussion

According to the study, bevacizumab therapy is effective in the treatment of diabetic macular oedema (DME). After a single drug administration an improvement of visual acuity (BCVA) was observed from 0.50 logMAR to 0.40 logMAR 4 weeks after the injection (p = 0.44). In 47.6% of the patients an improvement in visual acuity was observed, in 42.8% – no change in BCVA, while in 9.5% a deterioration of visual acuity was noted. Similar results were obtained by Arevalo et al. in the group of 74 patients who were administered 1.25 mg IVB. An improvement of visual acuity was observed from 0.9 to 0.76 logMAR a month after treatment commencement (p<0.001) (1). In 52.7% of the eyes an improvement ≥ 2 ETDRS lines was observed, in 39.8% BCVA did not change, while in 8.1% a deterioration ≥ 2 ETDRS lines was noted.

The authors of the study observed a further improvement in BCVA following subsequent injections. As regards the patients who were administered 3 injections, visual acuity improved from 0.5 logMAR prior to the therapy to 0.45; 0.35; 0.25 and 0.3 logMAR 1 month after the first, the second, the third injection and 3 months after the third injection respectively. As regards the study conducted by Ahmadieh et al. on a group of patients who were administered bevacizumab intravitrealy three times at 6-week intervals, the following improvement of BCVA compared to the initial values was observed: 0.076 logMAR after 6 weeks, 0.15 after 12 weeks, 0.21 after 18 weeks and 0.18 after 24 weeks, which is in accordance with our observations (2).

Surprisingly, in this study an increase in retinal thickness was observed after the first injection from 368 to 389 µm, yet the difference was not statistically significant (p = 0.602). A similar effect was observed only by Yanyali et al. as the following CRT changes were observed after 3 bevacizumab injections administered at monthly intervals: an increase from 408 µm prior to therapy commencement to 453 µm after 3 months and 454 µm after 6 months of the therapy (3). Also, no improvement of BCVA in the course of treatment was noticed. However, it is worth to note that all the patients in this study had undergone vitrectomy before.

All the other publications showed that despite the reduction of macular oedema in the course of bevacizumab therapy (4), CRT changes were not always statistically significant (5). In this study, CRT of 3 patients who were administered 3 intravitreal injections amounted to 407 µm prior to therapy commencement, 441 µm 1 month after the first injection, 340 µm 1 month after the second injection, 331 µm 1 month after the third injection and 348 µm 3 months after the third injection. Therefore, a reduction of macular oedema was observed after the second and third injection.

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According to this study, vision improvement is not correlated with a statistically significant decrease in CRT. This effect may result from the fact that BCVA improvement is more strongly connected with perfusion increase in the macula than with the leakage reduction or fluid resorption. Moreover, BCVA changes are not always related to changes in CRT in diabetic macular oedema (6).

What is more, central retinal thickness was not very high prior to the treatment and it has been proved that the larger the oedema the more intense response to intravitreal injections (7).

Most cases analyzed in this study were chronic DME. As much as 76% of the qualified patients had undergone laser therapy before. Thus, it may be assumed that intravitreal bevacizumab is effective in the treatment of photocoagulation resistant macular oedema. Similar conclusions were drawn by Kook et al. (8) in the study that included patients with the history of laser treatment, vitrectomy and triamcinolone intravitreal injection. It was observed that repeated bevacizumab injections improved BCVA from 0.82 logMAR to 0.76 and 0.74 logMAR 6 weeks and 6 months after the first injection respectively.

According to the presented results, CRT increased and BCVA deteriorated 3 months after the last injection compared to the control tests performed 1 month after the procedure, which indicates that the drug has temporary effect and further injections are required. Roh et al. also observed DME relapse and a deterioration of visual acuity 12 weeks after the injections (9).

Paccola et al. observed deterioration of visual acuity as early as 8 weeks after the last drug administration (10). According to the DRCnet study, the drug effect in form of retinal thickness reduction decreases between the third and the sixth week (11).

In this study the dose of 1.25 mg of bevacizumab was used. No statistically significant difference was observed with respect to effectiveness in terms of anatomical and functional effect between 1.25 and 2.5 mg (12).

No local or general adverse effects were observed. As regards other studies, general adverse effects in form of myocardial infarction, hypertension, deterioration of renal parameters and anaemia were observed very rarely. Occasionally, vision threatening complications can be observed in the case of intravitreal bevacizumab administration. In the DRCRnet study, 1 case of endophthalmitis out of 185 injections was observed. According to the meta-analysis presented by Goyal et al., the most common local adverse effects were: increased intraocular pressure (8–16%) and inflammatory reaction in the camera anterior (18–20%) (13).

Although this study was limited by a small group and a great variety of patients in terms of diabetes control and the severity of diabetic retinopathy, the results allow for great hopes with respect to this new therapy.

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