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The efficacy of bevacizumab in diabetic macular oedema in a 12-month follow-up

Skuteczność bewacyzumabu w leczeniu cukrzycowego obrzęku plamki w 12-miesięcznej obserwacji

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Abstract:

Purpose: To evaluate visual acuity and anatomic response of the macula following intravitreal bevacizumab injections in diabetic macular oedema.

Material and methods: In the retrospective, non-randomised study 35 eyes of 28 subjects (whose mean age was 59.6 years) with focal or diffuse diabetic macular oedema were included. Patients underwent best corrected visual acuity testing with Snellen charts converted to a number of letters, intraocular pressure measurement, slit lamp examination, macular biomicroscopy, central macular thickness measurement by optical coherence tomography as well as fluorescein angiography at baseline and all follow-up visits. Patients were treated with one or two intravitreal injections of 1.25 mg of bevacizumab.

Results: A total of 49 intravitreal injections were performed. All patients had a 6–12-month follow-up after the first injection. The mean baseline best-corrected visual acuity was 5.0 $\pm$ 4.3 letters and the mean central macular thickness in the baseline optical coherence tomography was 482.0 $\pm$ 109.7 μm. An improvement in the mean best-corrected visual acuity (6.2 $\pm$ 6.3, $p = 0.020$) and central macular thickness (426.8 $\pm$ 131.7 μm, $p = 0.010$) was statistically significant during the follow-up after first injection. There was no statistically significant difference in the best-corrected visual acuity (6.2 $\pm$ 6.5, $p = 0.055$) and central macular thickness (461.2 $\pm$ 148.3 μm, $p = 0.200$) after the second injection. There was no correlation between the best corrected visual acuity and central macular thickness. No serious adverse events were observed.

Conclusions: Intravitreal bevacizumab injections significantly improve visual acuity and decrease central macular thickness in patients with diabetic macular edema. This treatment is safe for patients but the therapeutic effect is temporary.

Key words: diabetic macular oedema, bevacizumab, intravitreal injection, optical coherence tomography.

Abstrakt:

Cel pracy: ocena ostrości wzroku i zmian morfologicznych plamki po iniekcjach doszklistkowych bewacyzumabu w przebiegu cukrzycowego obrzęku plamki.

Materiał i metody: do retrospektywnego, nierandomizowanego badania zakwalifikowano 35 oczu (28 pacjentów, średni wiek – 59,6 roku) z ogniskowym lub rozlanym cukrzycowym obrzękiem plamki. U każdego pacjenta przeprowadzono badanie ostrości wzroku za pomocą tablic Snellena w przeliczeniu na litery, pomiar ciśnienia wewnątrzgałkowego, ocenę dna oka, pomiar centralnej grubości siatkówki za pomocą badania optycznej koherentnej tomografii oraz badania angiografii fluoresceinowej – przeprowadzano je podczas pierwszej wizyty i podczas wizyt kontrolnych. Do wszystkich gałek ocznych podano 1 lub 2 iniekcje 1,25 mg bewacyzumabu.

Wyniki: w sumie wykonano 49 iniekcji. Pacjenci byli obserwowani przez okres od 6 do 12 miesięcy po zastrzyku. Początkowo średnia ostrość wzroku wynosiła 5,0 $\pm$ 4,3 litery, a centralna grubość siatkówki zbadana za pomocą optycznej koherentnej tomografii – 482,0 $\pm$ 109,7 μm. W okresie obserwacji po 6 tygodniach od pierwszego zastrzyku wystąpiła statystycznie istotna poprawa zarówno ostrości wzroku (6,2 $\pm$ 6,27, $p = 0,020$), jak i centralnej grubości siatkówki (426,8 $\pm$ 131,7 μm, $p = 0,010$). Po drugim zastrzyku nie zauważono statystycznie istotnej zmiany ani w ostrości wzroku (6,2 $\pm$ 6,5, $p = 0,055$), ani w centralnej grubości siatkówki (461,2 $\pm$ 148,3 μm, $p = 0,200$). Nie stwierdzono korelacji między zmianą ostrości wzroku a zmianą centralnej grubości siatkówki. U żadnego pacjenta nie zaobserwowano szkodliwych działań ubocznych.

Wnioski: iniekcje doszklistkowe bewacyzumabu powodują znaczącą poprawę ostrości wzroku oraz zmniejszenie centralnej grubości siatkówki w przebiegu cukrzycowego obrzęku plamki. Jest to leczenie bezpieczne dla pacjentów, jednak efekt leczniczy jest tymczasowy.

Słowa kluczowe: cukrzycowy obrzęk plamki, bewacyzumab, iniekcje doszklistkowe, optyczna koherentna tomografia.

Background

In Western countries, diabetes is a paramount cause of blindness in the professionally active population (1). In the year 2000, 171 million individuals in the world were ill with diabetes and, according to estimates, their number will rise to 366 million in 2030 (2). According to data published by the Polish Diabetes Association, there are about 2 million diabetics in Poland (3). In 2002 alone, loss of eyesight affected 160,000 patients from developed countries (4). Diabetic maculopathy is the leading cause of vision deterioration among diabetics, especially

in type 2 diabetes (5). Maculopathy can be caused by the increased permeability or the absence of flow in small retinal vessels. Studies have shown that the breakdown of the blood-retina barrier and the proliferation of pathological vessels found in diabetic retinopathy are the effects of several factors including angiopoietin 2, IL-6, VEGF (vascular endothelial growth factor) and ICAM-1 (inter-cellular adhesion molecule 1) (6–9). In response to such findings, the industry searches for therapeutic agents, which could inhibit the effects of any of these substances. One of the products of such research is bevacizumab (Avastin; Genetech, Inc.), a recombinant full-length humanised monoclonal antibody, which blocks all VEGF isoforms and is used in the treatment of metastatic colorectal cancer (10). Recently, it has also been used as intravitreal injections for the treatment of a variety of ocular vascular diseases, including diabetic macular oedema (11–13).

The aim of the study was to assess the best corrected visual acuity (BCVA) and morphological macular changes following intravitreal bevacizumab injections (IVB) in diabetic macular oedema.

Material and methods

The study was was approved by the local Institutional Review Board. Written informed consent to the treatment was obtained from all participants.

The study design was retrospective and non-randomised. The patients with focal or diffuse diabetic macular oedema, who had earlier undergone laser therapy of the retina, were enrolled. The examination of each patient included best corrected near and distance visual acuity with Snellen charts, fundoscopy, intraocular pressure measurement and fluorescein angiography (CF-1, Canon). The BCVA for distance was measured using Snellen charts, with conversion to letters. In 26 eyes, the central retinal thickness (CRT) measurement was performed (3D OCT-1000 Mark II, Topcon). The patients with ischaemic maculopathy identified during the baseline fluorescein angiography and patients with epiretinal membranes found in the baseline optical coherence tomography (OCT) were excluded from the study. Other exclusion criteria included: bacterial infection in the treated eye, advanced glaucoma in the treated eye, thrombo-embolic disease, the history of myocardial infarction or stroke within the last 12 months and the uncontrolled arterial hypertension.

All patients had their first follow-up examination on day 3 following the injection. Further follow-up visits were scheduled at 6 weeks, 3, 6 and 12 months after the injection. If an improvement in visual acuity was confirmed, the patient was elligible for the second injection, whose aim was to maintain the achieved response. The second injection was administered at 6 to 8 weeks after the first one. Intravitreal bevacizumab (Avastin) injections were performed off-label.

Injection technique

All injections were done in an operating theatre. The procedure involved the periorbital skin rub with 10.0% iodine solution; lid speculum insertion; anaesthetic drop instillation; irrigation of the conjunctival sac with 5.0% iodine solution; intravitreal administration of 1.25 mg (0.05 ml) of Avastin through the pars plana, 3.5 to 4.0 mm posteriorly to the limbus; injection site tamponade with a cotton bud steeped in iodine solution, to prevent reflux from the vitreous chamber; another irrigation with iodine solution; instillation of topical antibiotic solution (levofloxacin); and placement of a sterile dressing. Intra-ocular pressure was measured in the treated eye directly after the procedure. All patients received antibiotic drops (ofloxacin or levofloxacin) q.i.d. for 5 days following the injection.

Statistical analysis

All results were processed statistically with Statistica Pl 9.0 software (by StatSoft). Normal distribution was confirmed by Shapiro-Wilk's W test. Differences between analysed groups were verified with the Student's *t* test and Wilcoxon's matched-pairs signed rank test. Quantitative correlations between analysed parameters were checked by Spearman's correlation test. The whole statistical analysis was performed using a confidence level of $\alpha = 0.05$. Statistical significance was attributed to results with a $p < 0.05$.

Results

35 eyes of 28 subjects (10 female and 18 male) with non-proliferative (n = 18, 51.4%) and proliferative (n = 17, 48.6%) diabetic retinopathy were enrolled in the study. The subject mean age was 59.6 years (SD – 12.6, age range: 23–78). The group included 20 subjects with type 2 diabetes (71.0%) and 8 with type 1 diabetes (29.0%). 24 patients (30 eyes) had 12-month follow-up and four patients withdrew from the study after 6 month's participation. Prior to injections, all patients had undergone retinal laser therapy, with the panretinal photocoagulation performed in 22 eyes, and macular focal or grid laser photocoagulation performed in 20 eyes. The interval between laser therapy and study enrollment was at least 4 months. Statistically significant demographic data is presented in Table I.

	Number/ Liczba	%
Patients/ Grupa badanych	28	100
– women/ kobiety	10	36
– men/ mężczyźni	18	64
Eyes/ Liczba oczu	35	100
– right/ prawe	20	57%
– left/ lewe	15	43%
Diabetes/ Cukrzyca		
– type 1/ typu 1.	8	29%
– type 2/ typu 2.	20	71%
Diabetic retinopathy/ Retinopatia cukrzycowa		
– Non-proliferative/ nieproliferacyjna	18	51%
– proliferative/ proliferacyjna	17	49%

Tab. I. Demographic data of patients enrolled in the study.
Tab. I. Dane demograficzne pacjentów zakwalifikowanych do badania.

We performed a total of 49 intravitreal injections, with 35 eyes receiving 1 injection and 14 eyes receiving 2 injections.

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Post-injection follow-up revealed no serious adverse events, neither local (e.g. endophthalmitis, retinal detachment) nor systemic.

Visual acuity

The mean baseline BCVA was 5.0 ± 4.3 letters (range: 0.1––18.0). Six weeks after the first injection, the mean BCVA improved to 6.2 ± 6.3 letters (p = 0.020). The distance BCVA improvemed in 14 eyes (40.0%), remained stable in 16 eyes (46.0%), and deteriorated in 5 eyes (14.0%). Six weeks after the second injection, the mean BCVA was 6.2 ± 6.5 letters (p = 0.055). Among subjects who received the second injection, distance BCVA improved in 3 eyes (21.0%), remained stable in 8 eyes (57.0%), and deteriorated in 3 eyes (21.0%). Compared to baseline, mean BCVA for all patients at 6 months was 5.8 ± 6.5 letters (p = 0.790), and it was 5.0 ± 6.3 (p=0.530) at 12 months. Changes in the best-corrected visual activity during 12-month follow-up are presented in Figure 1.

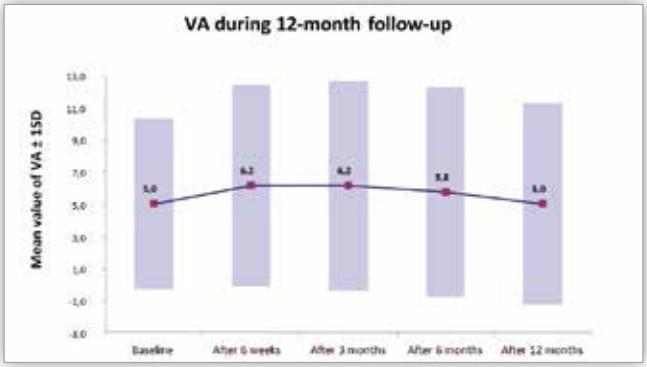

Fig. 1. Visual activity changes during the 12-month follow-up.
Ryc. 1. Zmiany w ostrości wzroku w czasie 12-miesięcznego okresu obserwacji.

Central retinal thickness

OCT studies were performed to assess central retinal thickness in 26 eyes. The mean CRT in the baseline OCT was 482.0 ± 109.7 μm. Six weeks after the first injection, CRT was 426.8 ± 131.7 μm (p = 0.010). A reduction of CRT after the first injection was found in 18 eyes (69.0%). The mean CRT for all eyes at 12-week follow-up was 461.2 ± 148.3 μm (p = 0.200). In the subset of subjects who received the second injection, CRT reduction was found in 6 eyes (50.0% of 12 eyes, which were examined by OCT). At 6 months, the mean CRT of all eyes was 470.0 ± 141.1 μm (p = 0.390); after 12 months, it was 476.8 ± 123.1 μm (p = 0.830). Changes in central retinal thickness during 12-month follow-up are presented in Figure 2.

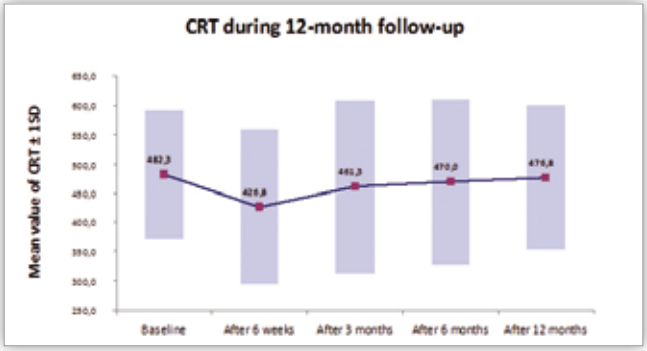

Fig. 2. Changes in central retinal thickness during the 12-month follow-up.
Ryc. 2. Zmiany w centralnej grubości siatkówki w czasie 12-miesięcznego okresu obserwacji.

The correlation coefficient for the change in BCVA and the change in CRT was statistically insignificant, both after the first and second injection (p=0.058 and p = 0.065, respectively). Graphs presenting the relationship between the change in BCVA and the change in CRT following injections 1 and 2, are presented in Figure 3 and Figure 4.

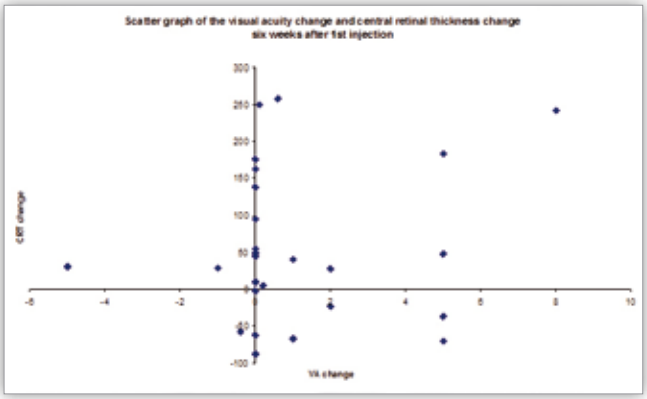

Fig. 3. Scatter graph of the visual acuity change and central retinal thickness change at six weeks after the first injection.
Ryc. 3. Wykres rozrzutu między zmianą ostrości wzroku a zmianą centralnej grubości siatkówki po 6. tygodniach od pierwszego zastrzyku.

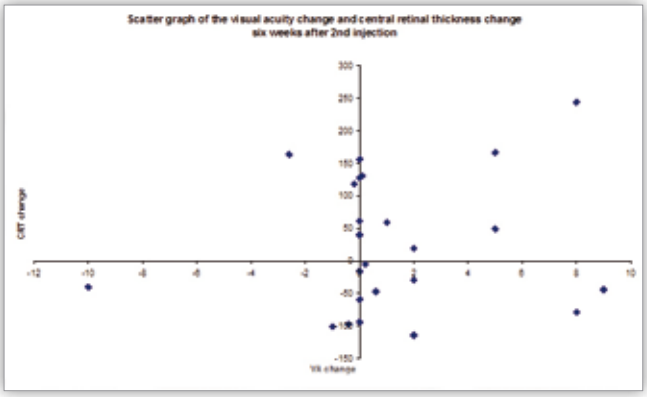

Fig. 4. Scatter graph of the visual acuity change and central retinal thickness change at six weeks after the second injection.
Ryc. 4. Wykres rozrzutu między zmianą ostrości wzroku a zmianą centralnej grubości siatkówki po 6. tygodniach od drugiego zastrzyku.

Discussion

We set out to assess the efficacy of intravitreal injections of 1.25 mg bevacizumab in diffuse or focal diabetic macular oedema.

We enrolled subjects with either diffuse or focal macular oedema. Subjects with focal oedema had leaks in the foveal region and could not receive laser therapy. Our group included both laser-naive patients and those who had undergone macular laser therapy. In earlier published series, similar IVB therapy was applied in eyes, which previously had laser therapy (14–20), vitrectomy (14, 15, 20, 21), intravitreal triamcinolone acetate injections (14, 15, 18, 20) or no previous treatment (18–20, 22, 23).

We administered the second bevacizumab injection to patients who had an improvement in visual acuity after the first injection, in order to maintain the response. Overall, the maximum number of injections was 2. This mode of treatment differs from regimens reported by some authors (14, 17–19, 24, 25) who in the majority administered 2 to 3 IVB injections, set 6 weeks apart, while further dosing was performed in response to VA deterioration and/or the presence of intraretinal fluid seen in OCT coexisting with the re-emergence of central retinal oedema. In a minority of reports, authors administered only one injection (20, 22, 23, 26).

Hartiglou et al. studied the effect of one or two IVB injections in 126 eyes (14). They reported that VA improved significantly at post-injection week 6 to revert to near-baseline values at week 12. The study by Fang et al. with one injection, found that VA improved after 4 weeks, but by week 8, the VA was back to baseline (20). Similarly, Faghihi et al. showed improvement of VA after one IVB injection but only at week 6 of follow-up (23). The DRCRN study demonstrated that two injections groups had significant improvement in vision over the single injection group through the 12-week monitoring period (19). Kumar and Sinha administered only 2 IVB injections, and noticed significant improvement of VA sustained during 6 months (16). Ahmadieh et al. observed that in a group treated with 2 IVB injections improvement of VA lasted for 18 weeks (17). Soheilian et al. reported that after one IVB injection 74.0% of patients had an improvement of VA, which lasted for 36 months (22). Authors who administered 2 or more injections found a more sustained VA improvement (15–17, 22, 24). Yanali et al. administered 3 injections after a vitrectomy procedure but saw no improvement of VA during a 6-month follow-up (21).

There have been no randomised trials to determine the appropriate number and frequency of IVB injections. The DRCRN study results suggest that the optimum interval between injections should be less than 6 weeks (19); Fang et al. propose to inject every 4 weeks in post-vitrectomy eyes and every 8 weeks in eyes with an intact vitreous (20) whereas Soheilian et al. achieved many months of functional improvement after only 1 injection (22). In summary, it seems that injections should be repeated every 3 to 12 weeks, where an optimum time window is 3 to 6 weeks. On the other hand, every intravitreal injection is stressful for the patient. In addition, there is a risk of local and systemic side-effects of such treatment and repeated injections generate significant costs. Animal studies have shown VEGF to be an important agent of neuroprotection and neurogenesis stimulation (27, 28). It remains unclear, whether multiple IVB injections inhibit the neuroprotective effects of VEGF on the retina in long-term follow-up.

In our current study a significant reduction of central retinal thickness at 6 weeks has been shown in OCT. The majority of authors found a significant reduction of CRT at 6 weeks (15, 18, 22, 24, 25). Some investigators reported a significant CRT reduction at 6 months (15, 21), 12 months (15, 25) and 24 months (24). Soheililan et al. and DRCRN Study noticed that CRT changes were not significant at all follow-up visits except for week 6 and week 3 (18, 22). Similarly to the report by Kook et al., we found no correlation between VA and changes in CRT as seen in OCT (15). Roh and colleagues studied IVB in 56 eyes with diffuse retinal thickening or cystoid macular edema (CME) in OCT (29). They found that patients presenting with CME achieved greater VA and macular thickness improvement after IVB injection as compared to patients with diffuse macular edema.

In our study, we found a temporary and minor BCVA improvement following IVB injections. It seems that the intravitreal bevacizumab injections could be more effective in combination with other treatments, although the literature offers inconclusive data. In the DRCRN study, better VA outcomes were achieved in patients receiving bevacizumab as compared to those treated with either macular laser photocoagulation (MLP) or combined MLP and 2 IVB injections (19). In other studies, authors also reported better functional outcomes in IVB groups (22, 25). In comparative studies of groups receiving IVB or ITA (intravitreal triamcinolone acetate) as one injection only, better outcomes were found with ITA alone or with concomitant IVB/ITA (23, 26, 30).

Our study has certain limitations related to its retrospective, non-randomised design and the absence of a control group. Furthermore, we did not test patients for systemic parameters, such as glycated haemoglobin (HbA1c), lipid profile or arterial blood pressure, which may play an important role in the progression of diabetic maculopathy (31, 32). After the completion of the study, most patients underwent macular laser photocoagulation. We did not find any regression of epimacular hard exudates following the second injection. In our opinion, this suggests a need for dual therapy, i.e. MLP combined with injections.

Conclusions

In summary, intravitreal bevacizumab injections lead to a transient improvement of vision and a reduction in central retinal thickness. This treatment is safe for patients but the effect lasts only for several weeks following the injection.

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