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# Aflibercept therapy in diabetic macular oedema – own experience

## *Terapia afliberceptem cukrzycowego obrzęku plamki – doświadczenia własne*

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**Abstract:** Purpose: The aim of our study was to evaluate the outcomes of intravitreal aflibercept injections in patients with diabetic macular edema.
Material and methods: Twenty-five patients (15 men, 10 women) aged 45–65 (mean 57) with diabetes mellitus type 2 (28 eyes with diabetic macular edema) were analysed retrospectively. The mean duration of diabetes was 13.5 years. All patients were treated with insulin, oral antidiabetic drugs were additionally used in 8 cases. All patients (28 eyes) received 5 intravitreal injections of aflibercept (2.0 mg) at one month interval. The best corrected visual acuity and mean central retinal thickness (3D OCT 2000 Topcon) were evaluated at baseline and at the end of treatment. The follow up was 6 months.
Results: There was a significant improvement of best corrected visual acuity and central retinal thickness in the study group of 25 patients.
Conclusion: Intravitreal injections of aflibercept offer an improvement in visual acuity and central retinal anatomy in patients with diabetic macular edema.

**Key words:** diabetic macular edema (DME), intravitreal injection of aflibercept, anti-vascular endothelial growth factor (anti-VEGF), central retinal thickness (CRT), optical coherence tomography (OCT).

**Abstrakt:** Cel: ocena ostrości wzroku do dali i bliży w najlepszej możliwej korekcji oraz średniej grubości siatkówki w plamce u pacjentów z cukrzycowym obrzękiem plamki przed leczeniem iniekcjami doszklistkowymi afliberceptu i po leczeniu.
Materiał i metody: badaniu poddano 25 pacjentów (28 oczu z cukrzycowym obrzękiem plamki) w wieku 45–65 lat (średnio 57 lat). U 25 pacjentów stosowano insulinoterapię, 8 pacjentów dodatkowo leczono doustnymi lekami przeciwcukrzycowymi. Wszystkim badanym podano 5-krotnie iniekcje doszklistkowe afliberceptu w dawce 2,0 mg w czterotygodniowym odstępie czasu. Oceniano ostrość wzroku do dali i bliży oraz średnią grubość siatkówki w plamce. Badania wykonywano przed podaniem iniekcji doszklistkowej oraz po każdej iniekcji. Centralną grubość siatkówki oceniano za pomocą optycznej koherentnej tomografii (3D OCT 2000 Topcon).
Wyniki: analiza statystyczna wykazała znamienną poprawę ostrości wzroku do dali i bliży oraz zmniejszenie grubości centralnej siatkówki u pacjentów z badanej grupy.
Wnioski: terapia iniekcjami doszklistkowymi afliberceptu pozwala uzyskać poprawę ostrości wzroku u pacjentów z cukrzycowym obrzękiem plamki oraz w znaczny sposób redukuje grubość siatkówki w plamce.

**Słowa kluczowe:** cukrzycowy obrzęk plamki (DME), iniekcje doszklistkowe afliberceptu, czynniki hamujące wzrost śródbłonka naczyń (anty-VEGF), grubość centralnej siatkówki (CRT), optyczna koherentna tomografia (OCT).

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### Introduction

Diabetic retinopathy (DR) is a frequent microvascular complication of diabetes mellitus (DM) (1). It is present in almost 100% of type 1 DM sufferers and about 80% of type 2 DM sufferers after 20 years following the onset of DM. Diabetic macular edema (DME) is the main cause of visual loss in those patients (1–2). The incidence of DME in patients with type 2 DM ranges from 2% during the first 5 years of the disease to 30% after 30 years. Poor control of serum glucose (high level of HbA1c) and blood pressure, hyperlipidemia and obesity also contribute to this complication (3–4). Well-controlled DM may effectively prevent the development and progression of diabetic retinopathy and DME.

Diabetic macular edema is characterized by thickening the central retina, caused by microvascular damage (Fig. 1) (5, 6).


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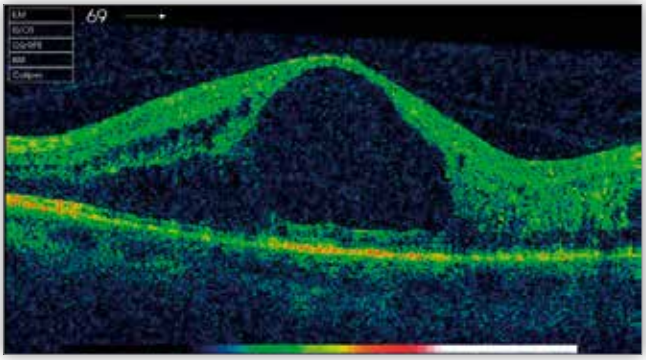


**Fig. 1.** Diabetic macular edema in OCT (at baseline).
**Ryc. 1.** Cukrzycowy obrzęk plamki w badaniu OCT (przed leczeniem).

The main etiological factor in DME is hyperglycemia, which stimulates an inflammatory response negatively affecting retinal blood vessels (1, 2, 4). The earliest histological changes seen within the retinal microvasculature are leukocyte adhesion and accumulation of glycation end products within the capillaries, which triggers the activation of inflammatory mediators, endothelial cell death, leading in turn to hypoxia (6). Hypoxia causes upregulation of vascular endothelial growth factor (VEGF) and other growth factors (4, 7). The VEGF plays a significant role in the pathogenesis of DME. It disrupts the blood-retina barrier, leading to the accumulation of extracellular fluid, which causes central retinal (i.e. macular) oedema (8, 9).

Over the last 25 years, since the publication of the ETDRS study, retinal laser photocoagulation has been the gold standard in the management of DME (6, 10). The aim of laser photocoagulation is to reduce DME by occluding leakage spots, thus increasing retinal oxygenation. However, laser photocoagulation leaves the spots permanently burnt. The resulting scars might affect retinal function causing visual field scotomas, color vision impairment and onset of choroidal neovascularization (CNV) (1, 11). Furthermore, laser photocoagulation maintains stable visual acuity only in 50% of patients (1, 2). In the absence of options to improve visual acuity using available treatments, new therapies for DME have been researched. Clinical trials demonstrated significantly elevated VEGF levels in the vitreous and aqueous humour of DME patients, as compared to healthy controls. This finding gave rise to anti-VEGF treatments (12).

In Poland, two VEGF inhibitors have been approved for the treatment of DME – ranibizumab (Lucentis) and aflibercept (Eylea). Aflibercept is a new recombinant fusion protein composed of binding extracellular domains of VEGF receptors type 1 and 2 connected with Fc human immunoglobulin. It has strong potential of binding VEGF-A, VEGF-B and placental growth factor (plGF) contrary to other available inhibitors of VEGF (ranibizumab and bevacizumab) which only binds to VEGF-A. It also has longer duration of action than the other ones. Aflibercept is produced by hamster ovary cells (13). Efficiency of aflibercept therapy in patients with DME was confirmed by numerous clinical researchers: Da Vinci, VISTA, VIVID and DRCR.net (8, 14, 15).

Currently it is recommended to apply 5 injections of aflibercept in a dose of 2.0 mg in a month time interval, which is so called a loading dose. Then it is recommended to extend the period between injections and apply them depending on the clinical state of a patient (8, 14, 15).

## The aim

The aim of our study was to evaluate the outcomes of intravitreal aflibercept injections in patients with DME.

## Material and methods

The retrospective analysis of 25 patients (15 men and 10 women, 28 eyes) with diabetes type 2, aged 45–65 (mean 57), diagnosed and treated due to diabetic retinopathy with DME at the Ophthalmology Department in District Hospital No 2 Jastrzębie Zdrój, Poland in 2015–2016. All patients were treated with intravitreal injections of aflibercept into the affected eye.

The inclusion criteria were duration of diabetes of over 10 years, non-proliferative and pre-proliferative diabetic retinopathy (DR), DME, distance best corrected visual acuity (BCVA) over 0.1 (Snellen chart), and age range of 45–65 years. The exclusion criteria included distance BCVA below 0.1, DME with vitreomacular traction syndrome, ischemic DME, acute ocular inflammation, concomitant retinal disease other than DR, proliferative DR, history of vitreous hemorrhage, glaucoma, opaque optic media, and lack of patient's informed consent to participate in the study.

All patients were given a thorough ocular exam at baseline and before each injection in months 1., 2., 3., 4., and 5. The following were assessed: distance and near BCVA using Snellen chart, intraocular pressure (IOP) using applanation tonometry, anterior segment and ocular fundus using a slit lamp, macular morphology and central retinal thickness (CRT) using optical coherence tomography (OCT) (3D OCT 2000 Topcon). Fluorescein angiography (FA) was additionally performed in all cases to confirm the type of retinopathy. Patients with poorly controlled diabetes mellitus (HbA1c $>8.5$) and hypertension (systolic and diastolic blood pressure of over 160 and 100, respectively, on 2 consecutive measurements, whilst on optimum medical antihypertensive treatment regimen) were excluded from the study.

All 28 affected eyes were administered five intravitreal injections of aflibercept (2.0 mg) at one month intervals under sterile conditions of an operational theatre.

## Statistical analysis

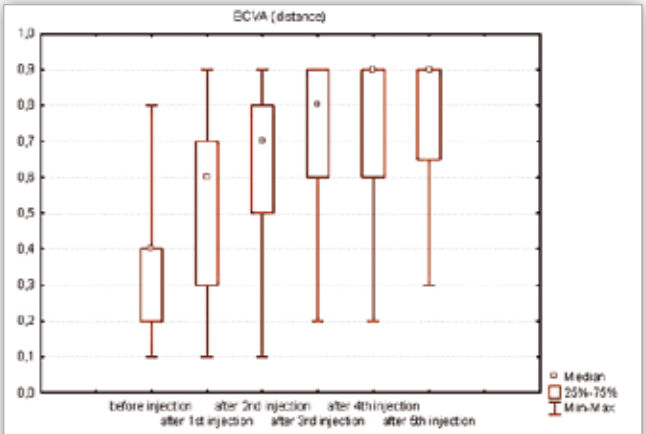
The obtained results were entered into the MS Excel 2007 (Microsoft) spreadsheet. Statistica v.7 (Statsoft, Poland) software bundle was used for all statistical analyses.

We calculated the mean, standard deviation and median for all continuous variables (BCVA, CRT, IOP). Normality of distribution was verified using the Shapiro-Wilk's test. Within-group comparisons were made using the paired-samples t-test and Wilcoxon non-parametric test. A significance level $p<.05$ was assumed for all comparisons.

## Results

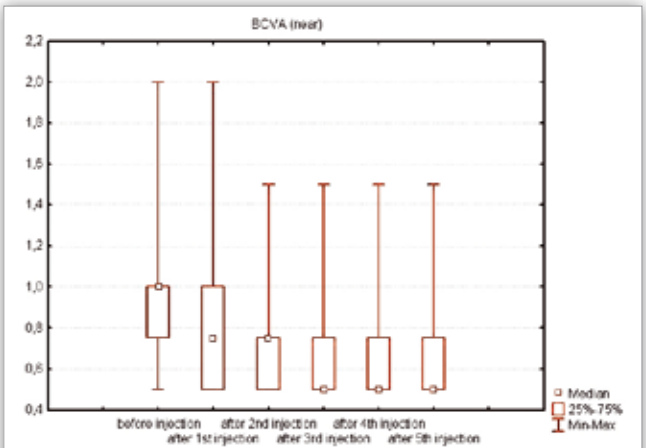
The statistical analysis of BCVA presented in Fig. 2 and 3 demonstrated vision improvement from month 1. till the end of follow up (Wilcoxon test Z, $p$).

There was a significant decrease of CRT between baseline value, month 1., and the end of follow up (Wilcoxon test Z, $p$) (Fig. 4).




| BCVA distance | Before injection | After 1st injection | After 2nd injection | After 3rd injection | After 4th injection | After 5th injection |
|---|---|---|---|---|---|---|
| Median | 0.40 | 0.60 | 0.70 | 0.80 | 0.90 | 0.90 |
| SD | 0.19 | 0.24 | 0.27 | 0.25 | 0.25 | 0.24 |
| Min | 0.10 | 0.10 | 0.10 | 0.20 | 0.20 | 0.30 |
| Max | 0.80 | 0.90 | 0.90 | 0.90 | 0.90 | 0.90 |
| *p* Wilcoxon signed-rank test vs. Before 1st injection | | p<0.05 (0.00004) | p<0.05 (0.00004) | p<0.05 (0.00001) | p<0.05 (0.00001) | p<0.05 (0.00002) |

**Fig. 2.** Distance BCVA in patients with DME before and after anti-VEGF treatment.
**Ryc. 2.** BCVA do dali u pacjentów z DME przed rozpoczęciem leczenia anty-VEGF i po leczeniu.

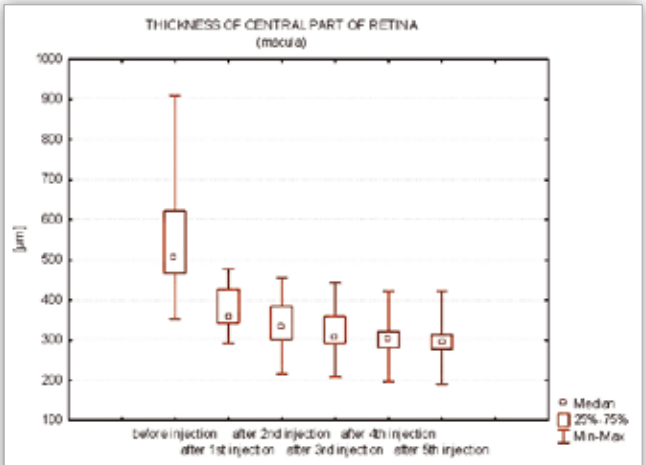



| VISUAL ACUITY | Before injection | After 1st injection | After 2nd injection | After 3rd injection | After 4th injection | After 5th injection |
|---|---|---|---|---|---|---|
| Median | 1.00 | 0.75 | 0.75 | 0.50 | 0.50 | 0.50 |
| SD | 0.32 | 0.34 | 0.29 | 0.28 | 0.23 | 0.23 |
| Min | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 |
| Max | 2.00 | 2.00 | 1.50 | 1.50 | 1.50 | 1.50 |
| *p* Wilcoxon signed-rank test vs. Before 1st injection | | p<0.05 (0.00029) | p<0.05 (0.00008) | p<0.05 (0.00004) | p<0.05 (0.00004) | p<0.05 (0.00012) |

**Fig. 3.** Near BCVA in patients with DME before and after anti-VEGF treatment.
**Ryc. 3.** BCVA do bliży u pacjentów z DME przed rozpoczęciem leczenia anty-VEGF i po leczeniu.

The OCT confirmed CRT reduction after intravitreal injections (Fig. 5, 6.)

No systemic complications were observed during aflibercept treatment. Local complications included conjunctival irritation (6 patients) and subconjunctival hemorrhage (5 patients). We did not observe any clinically significant elevation of intraocular pressure after injections.




| CRT | Before injection | After 1st injection | After 2nd injection | After 3rd injection | After 4th injection | After 5th Injection |
|---|---|---|---|---|---|---|
| Median | 508.50 | 355.50 | 314.00 | 305.50 | 300.00 | 294.00 |
| SD | 129.89 | 56.52 | 58.69 | 54.69 | 49.16 | 51.12 |
| Min | 353.00 | 292.00 | 216.00 | 207.00 | 196.00 | 191.00 |
| Max | 910.00 | 478.00 | 456.00 | 443.00 | 422.00 | 422.00 |
| *p* Wilcoxon signed-rank test vs. Before 1st injection | | p<0.05 (0.00001) | p<0.05 (0.00001) | p<0.05 (0.00001) | p<0.05 (0.00001) | p<0.05 (0.00001) |

**Fig. 4.** CRT in patients with DME before and after anti-VEGF treatment.
**Ryc. 4.** CRT u pacjentów z DME przed rozpoczęciem leczenia anty-VEGF i po leczeniu.

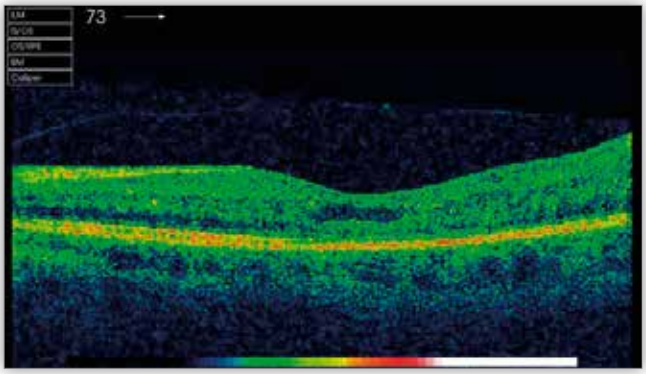



**Fig. 5.** OCT of the macula in a patient imaged in Fig. 1 – after the first injection of aflibercept.
**Ryc. 5.** Plamka w badaniu OCT po pierwszym wstrzyknięciu aflibercептu u pacjenta przedstawionego na ryc. 1.

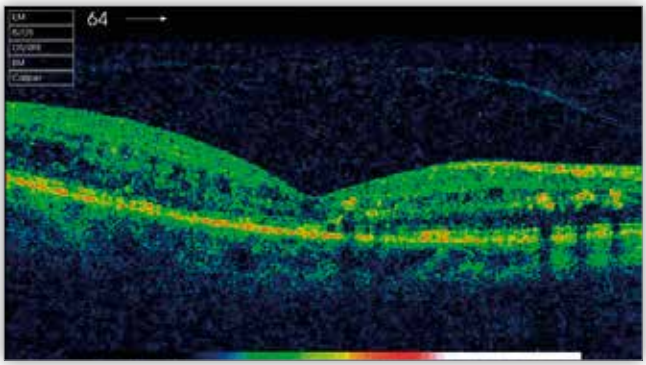



**Fig. 6.** OCT of the macula after five injections of aflibercept.
**Ryc. 6.** Plamka w badaniu OCT po pięciu wstrzyknięciach aflibercептu.

## Discussion

The increasing number of patients with diabetes worldwide is the reason why DR and DME are still the main causes of visual loss (16, 17). Intravitreal injections of anti-VEGF agents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are relatively new methods of treatment for this complication. Numerous clinical studies (8, 14, 15) demonstrated that anti-VEGF treatments significantly improve visual acuity in patients with DME.

In the current study, we demonstrated a significant improvement in BCVA after aflibercept treatment over the 6-month follow up in a group of DME patients. Our findings are consistent with other authors (8, 14, 15). Do and co (8) presented the results of the second stage in DAVINCI trials. They determined the BCVA in patients with DME before and after aflibercept injections and compared the findings to those of the control group treated with traditional laser photocoagulation. Aflibercept was administered at two doses (0.5 mg and 2.0 mg) and according to two dosing regimens (every 4 weeks, every 8 weeks) as assessed clinically after the first 3 loading-dose injections. The authors reported a significant improvement of visual acuity in all study groups, regardless of the dose and dosing regimen, as compared to the control group in month 6. and 12. Although all differences were significant, greater gain was achieved in groups receiving 2.0 mg rather than 0.5 mg of aflibercept.

DCR.net study (14) evaluated the effect of VEGF inhibitors (aflibercept, bevacizumab, and ranibizumab) on visual acuity in patients with DME. The authors reported significant BCVA improvement in one-year follow up, regardless of anti-VEGF agent used. The differences in vision improvement between aflibercept, bevacizumab and ranibizumab were non-significant. However, in cases with very low visual acuity at baseline, aflibercept offered the best outcomes.

In the third stage VISTA and VIVID study (15), aflibercept was administered in two treatment regimens (every 4 or 8 weeks, after 5 loading-dose injections administered at 1-month intervals). There was a significant improvement of visual acuity in both study groups as compared to the control group treated with laser photocoagulation as per EDTRS protocol. Interestingly, there were no significant differences in treatment outcomes between the two study groups.

In our study, we demonstrated a significant CRT reduction from baseline to the end of the 6-month follow-up. The mean CRT at baseline was 508.5 $\mu$m and the ultimate CRT at the end of follow up was 294.0 $\mu$m. Similarly, the authors of DA VINCI study (8) demonstrated a significant CRT reduction in months 6. and 12. in groups receiving 0.5 mg and 2.0 mg of aflibercept. The 2.0 mg dose was associated with greater CRT reduction.

In DCR.net study, Wells and co. (14) evaluated CRT after different anti-VEGF treatments in one-year follow up. The CRT was reduced to 169.0 $\pm$ 138.0 $\mu$m, 147.0 $\pm$ 134.0 $\mu$m and 101.0 $\pm$ 121.0 $\mu$m after aflibercept, ranibizumab and bevacizumab injections, respectively, suggesting superior performance of aflibercept to the two comparators in resolving macular oedema ($p<.001$). Additionally, ranibizumab offered better outcomes than bevacizumab ($p<.001$), which remained true regardless of the initial visual acuity. Similarly, VISTA and VIVID studies (15) demonstrated a significant reduction in mean CRT across all DME study groups treated with aflibercept as compared to the laser control group (VISTA: 191.4 $\pm$ 180.0 $\mu$m and 191.1 $\pm$ 160.7 $\mu$m vs. 83.9 $\pm$ 179.3 $\mu$m; VIVID: 211.8 $\pm$ 150.9 $\mu$m and 195.8 $\pm$ 141.7 $\mu$m vs. 85.7 $\pm$ 145.8 $\mu$m).

In the current study, we additionally evaluated near BCVA using Snellen chart, and compared the baseline and ultimate values yielding a significant improvement. To our knowledge, there has been no similar research to evaluate this parameter. What seems vital is the demonstrated improvement in near BCVA, which translates directly into the better quality of life in patients with DME.

## Conclusion

Based on the available literature and our findings, we can conclude that intravitreal injections of VEGF inhibitors, such as aflibercept, are a very effective treatment for visual acuity impairment secondary to DME.

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