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PRACA ORYGINALNA
ORIGINAL PAPER

Bevacizumab in age-related macular degeneration – comparison of subjective estimation of vision with objective test results

Bevacizumab w zwyrodnieniu plamki związanym z wiekiem – – porównanie subiektywnej oceny widzenia z obiektywnymi wynikami badań

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ABSTRACT

PURPOSE: Anti-VEGF therapy plays a great role in medicine, especially in opthalmology. The aim of the therapy is to inhibit the VEGF-A factors that are responsible for the angiogenesis in diseases such as the wet form of age-related macular degeneration (AMD). One of the monoclonal anti-VEGF antibodies is bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA).

The aim of the study was to compare the subjective estimation of visual acuity with objective test results in patients undergoing anti-VEGF therapy using Avastin.

MATERIALS AND METHODS: The authors report a study of 57 patients (37 females and 20 males) with exudative AMD whose near and distance visual acuity was examined before the first dose of Avastin and 1 month after the third injection. Additionally, an original questionnaire evaluating the subjective state of vision during the activities of daily routine was performed.

RESULTS: When examining distance visual acuity, 29 patients made an improvement, deterioration was reported in 5 cases and in 23 cases the results remained unaltered. The results were correlated with the subjective estimation.

CONCLUSIONS

1. Avastin stabilizes the degeneration process of AMD in most patients and sometimes improves visual acuity.
2. There is a positive correlation between the objective test results and subjective opinion in patients undergoing anti-VEGF therapy using Avastin.

KEY WORDS
age-related macular degeneration, bevacizumab, retina, vascular endothelial growth factor

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STRESZCZENIE

WSTĘP: Terapia anti-VEGF odgrywa niezwykle istotną rolę w medycynie, zwłaszcza w okulistyce. Polega na hamowaniu czynnika VEGF-A, który jest odpowiedzialny za angiogenezę w takich chorobach, jak wysiękowa postać zwyrodnienia plamki związanego z wiekiem (*age-related macular degeneration* – AMD). Jednym z przeciwciał monoklonalnych skierowanych przeciwko VEGF jest bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA). Celem badania jest porównanie subiektywnej oceny widzenia z obiektywnymi wynikami badań u pacjentów poddanych terapii anty-VEGF z zastosowaniem Avastinu.

MATERIAŁ I METODY: Badaniem objęto 57 pacjentów (37 kobiet 20 mężczyzn) z wysiękową postacią AMD, u których dokonano oceny ostrości wzorku do bliży i dali przed pierwszą dawką i miesiąc po trzeciej iniekcji doszklistkowej Avastinu. Dodatkowo przeprowadzono autorską ankietą oceniającą widzenie podczas wykonywania czynności życia codziennego.

WYNIKI: Analizując wyniki ostrości wzroku dla dali 29 pacjentów wykazało poprawę, 5 pogorszenie widzenia, a w 23 przypadkach ostrość wzroku nie uległa zmianie. Wykazano dodatnią korelację powyższych danych z wynikami subiektywnej oceny.

WNIOSKI:

1. Avastin stabilizuje proces chorobowy w wysiękowej postaci AMD, a u niektórych pacjentów obserwowana jest poprawa ostrości widzenia.
2. Istnieje dodatnia korelacja między obiektywnymi wynikami ostrości wzroku a subiektywną oceną widzenia u pacjentów poddanych terapii anty-VEGF z zastosowaniem Avastinu.

SŁOWA KLUCZOWE

zwyrodnienie plamki związane z wiekiem, beviacizumab, naczyniowy czynnik wzrostu

INTRODUCTION

Angiogenesis is the process of the formation of preserved blood capillaries. It accompanies some physiological phenomena and many pathological conditions. It was first described by Folkman in 1971 [1]**.** Excessive angiogenesis as well as its diminution have a negative impact on the homeostasis of the organism. There are several pro- and antiangiogenic factors participating in angiogenesis (Tab. I). Among the ones which stimulate the growth of blood vessels, it is crucial to mention the following endogenous factors: VEGF (vascular endothelial growth factor), TNF alfa (tumor necrosis factor-alpha), PDGF (platelet-derived endothelial cell growth factor), NO (nitric oxide), aFGF (acidic fibroblast growth factor), bFGF (basic fibroblast growth factor), angiopoietin 1 and 2, TGF-beta (transforming growth factor beta) and MMP (metalloproteinases) – 1,2,3,9,13. There are also several exogenous proangiogenic triggers, such as the prolonged hypoxia of cells, e.g. in a tumor, in which intensively proliferating cells constrict the vessels [2]. The antiangiogenic agents are presented in Table I.

Avastin (Bevacizumab) is a humanized monoclonal IgG_1 antibody that inhibits VEGF [3,4]. In Poland it is licensed for the treatment of metastatic colon cancer, diffused breast cancer, advanced and diffused renal cancer, ovarian cancer, non-small cell lung cancer and glioblastoma multiforme. In the above cases it is usually combined with various chemotherapeutics [4,5,6,7].

In opthalmology the positive role of Avastin has been shown in diseases such as the wet form of age-related macular degeneration (AMD), diabetic retinopathy and central serous retinopathy (CSR) [9,10,11].

Table I. Antiangiogenic agents
Tabela I. Czynniki antyangiogenne

Group	Antiangiogenic agent
I	VEGF inhibitors (eg. Avastin)
II	inhibitors of mitogenic signal transduction by VEGF receptors
III	tubulin and microtubule inhibitors of vascular endothelial cell
IV	inhibitors of metalloproteinases and integrins
V	inhibitors of various mechanisms

Age-related macular degeneration is a disease of the central retina and is a major cause of deterioration of visual acuity or vision loss in patients in their elderly (> 50) years [12]. The etiology of the disease remains unknown, however, several factors such as age, race, gender, positive family history, addiction and diet can be defined as risk factors of AMD [13,14,15]. The most common early sign is blurred vision, loss of central vision and metamorphopsy. Gradually, visual acuity deteriorates resulting in visual loss.

The diagnosis of AMD is based on opthalmological examination including visual acuity – the distance and near vision Snellen acuity test, contrast sensitivity, corneal reaction to light and colour vision test. Amsler's test, fluorescein angiography (Fig.1) and indocyanine angioghraphy also play a great role in diagnosing AMD, however, it is optical coherence tomography (OCT) that is the most common and reliable diagnostic method [16,17,18,19] (Fig. 2a-b).

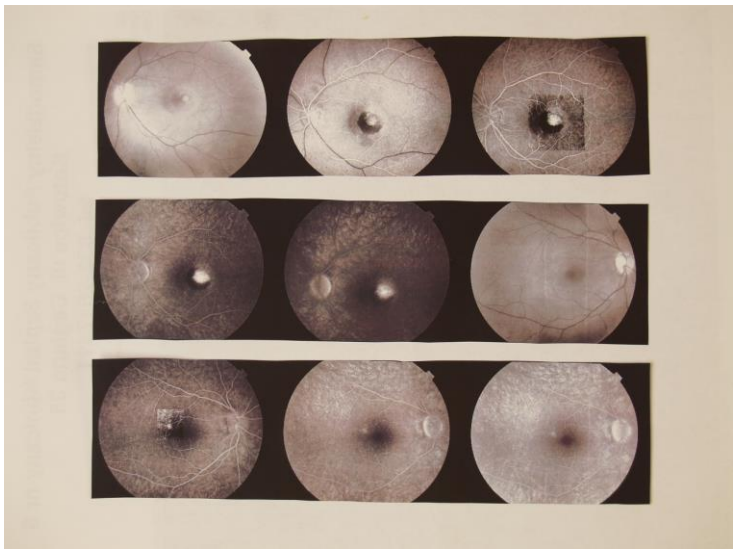

Fig. 1. Fluorescein angiography. Age-related macular degeneration. Classical neovascular type. There is area of hypofluorescence in projection of blood and diffused hyperfluorescence is apparent during recirculation, which increases during early phase in macular fovea and its region. This indicates presence of active neovascular membrane – CNV.
Ryc. 1. Angiografia fluoresceinowa. Zwyrodnienie plamki związane z wiekiem. Klasyczna postać neowaskularna. Rozlana fluorescencja w fazie recyrkulacji narastająca we wczesnych fazach w obszarze plamki. Zmiana odpowiada aktywnej błonie neowaskularnej.

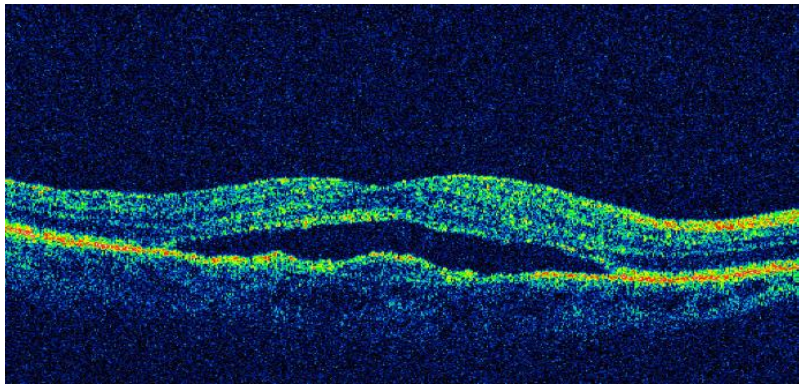

Fig. 2a. Optical coherence tomography before anti-VEGF therapy. Subretinal fluid accumulation.
Ryc. 2a. Optyczna koherentna tomografia komputerowa (OCT) przed terapią anty-VEGF. Nagromadzenie płynu pod siatkówką.

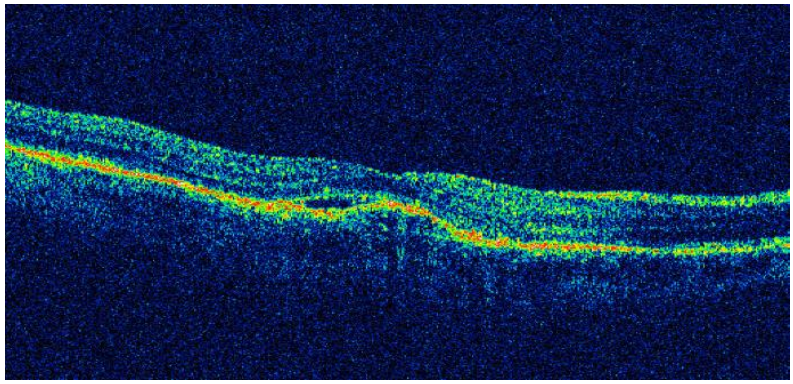

Fig. 2b. Optical coherence tomography after therapy.
Ryc. 2b. Optyczna koherentna tomografia komputerowa po terapii.

There are two types of AMD – the dry form (atrophic), which is more common and the wet one (exudative). The dry form can be characterized by druses, while in the wet form subretinal (choroidal) neovascularization (CNV) is observed. Intravitreal bevacizumab is dedicated for the second – exudative AMD.

The aim of the study is to compare the subjective estimation of visual acuity with objective test results in patients undergoing anti-VEGF therapy using Avastin.

Materials and methods

The study was performed in a private Silesian ophthalmological surgery on a group of 57 patients (57 eyes), including 37 females and 20 males between October 2010 and March 2011. In the case of both eyes affected, the visual acuity of only one and the same eye was taken into consideration. Exclusion criteria included inflammation within the eye ball and adnexae, reccurent iridocyclitis, disregulated glaucoma or advanced glaucoma optic neuropathy. The patients were examined twice in a period of 4 months – – before the first dose of Avastin and 1 month after the third injection. All the patients received intravitreal Bevacizumab (IVB) (1.25 mg) every four weeks under standard sterile protocol performed by a single clinician. The injections were repeated until the resolution of fluid observed in OCT or the absence of active leakage in fluorescein angiography was confirmed. Ofloxacin antibiotic eye drops were used 4 times daily 5 days before and after each injection. For the purpose of the study, the patients' near and distance visual acuity was examined using Snellen's chart (Fig. 3,4) and an original questionnaire evaluating the subjective state of vision during the activities of daily routine, such as watching TV, preparing meals, reading, driving and combing/shaving in front of a mirror, was completed before and after one month from the third dose of Avastin. The patients were asked to evaluate their state of vision with the application of a 5-level scale. Their subjective feeling about vision during each activity was described as very bad, bad, satisfactory, good or very good. The results from both visits were compared. Moreover, the patients assessed the presence of general changes in their visual state (Yes/No question) and in the case of positive answers, they specified the type of alteration (improvement/deterioration).

Additional vitamin supplementation as well as previous treatment history was examined.

The results were analysed using Statistica 7 PL for MS Windows XP/Vista. The statistically relevant significance level was set at < 0.05. Differences in the non-parametric variables without normal distribution were evaluated by the Wilcoxon signed-rank test. Correlations for all the variables were identified and Spearman's rank correlation was evaluated.

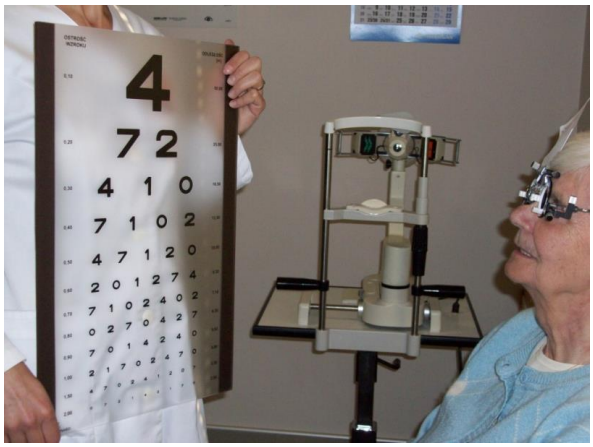

Fig. 3. Examination of distance visual acuity.
Ryc. 3. Badanie ostrości wzroku do dali.

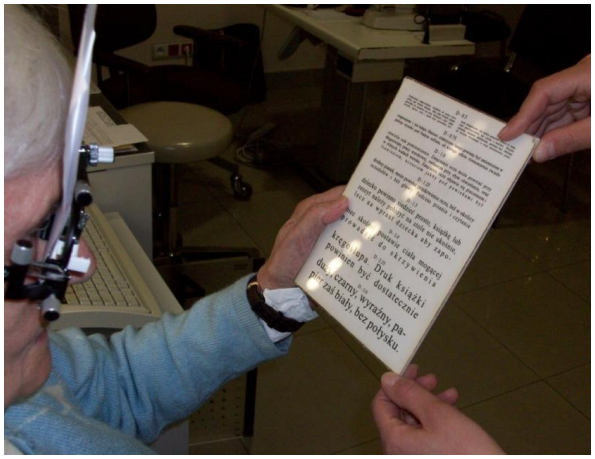

Fig. 4. Examination of near visual acuity.
Ryc. 4. Badanie ostrości wzroku do bliży.

Results

The study showed that the wet type of age-related macular degeneration was the most common disease in patients referred to the ophthalmological surgery. The patients' characteristics are presented in Table II.

The mean age was 67 years and the majority of patients were between 60 and 74 years of age. An objective analysis of visual acuity for distance vision revealed that 29 (51%) patients made an improvement, 5 (9%) there was deterioration and in 23 (40%) cases the results remained unaltered (Fig. 5).

The results were statistically relevant in the Wilcoxon signed-rank test ($p < 0.05$) (Fig. 6). In the case of improvement, the majority of eyes gained at least one line.

Table II. Patients' characteristics data
Tabela II. Charakterystyka grupy badanej

Patient	Eye injected	Age	Sex	Baseline VA		Post-treatment VA		Other supplements
				Baseline VA-OD	Baseline VA-OS	Post-treatment VA-OD	Post-treatment VA-OS	
1	2	3	4	5	6	7	8	9
1	OS	57	F	0.6	0.4	0.9	0.9	Y
2	OD	76	F	HM	HM	CF	CF	N
3	OS	72	F	0.8	0.4	0.9	0.4	N
4	OD	51	F	0.2	1	0.5	1	Y
5	OS	63	M	0.3	0.04	1	0.1	Y
6	OD	67	M	0.5	0.2	0.2	0.6	Y
7	OS	85	M	HM	0.01	CF	0.012	N
8	OD	75	M	0.5	1	0.3	1	Y
9	OS	62	M	0.2	0.04	0.3	0.1	N
10	OS	66	F	0.8	0.04	0.8	0.04	N
11	OD	85	F	0.1	0.2	0.1	0.2	N
12	OS	76	F	0.2	0.1	0.5	0.1	N
13	OS	54	F	1	0.4	1	0.7	N
14	OS	61	F	1	0.7	1	0.8	N
15	OS	72	F	1	0.4	1	0.4	Y
16	OS	64	M	1	0.2	1	0.3	Y
17	OD	68	M	0.2	0.01	0.2	0.01	Y
18	OD	19	F	0.7	1	0.7	1	N
19	OD	57	F	1	1	1	1	N
20	OD	76	M	CF	0.04	0.01	0.02	Y
21	OS	68	F	1	0.4	1	0.4	N
22	OD	52	F	0.5	1	0,6	1	Y
23	OD	47	M	0.9	1	1	1	N
24	OS	29	F	1	0.2	1	1	N
25	OD	59	M	HM	no eye ball	HM	no eye ball	N
26	OD	69	F	0.1	0.8	0.1	1	N
27	OS	56	M	1	0.1	1	0.1	N
28	OS	73	F	0.7	0.4	1	0.5	N
29	OD	76	F	0.04	0.1	0.06	0.7	N
30	OS	74	F	0.2	0.1	0.2	0.3	Y
31	OD	73	F	0.02	HM	0.02	HM	Y
32	OD	74	F	0.2	0.8	0.2	0.8	Y
33	OS	73	M	0.3	0.2	0.5	0.5	Y
34	OD	68	M	0.5	1	0.4	1	N
35	OS	66	F	0.1	0.625	0.1	0.3125	Y
36	OS	82	F	0.08	0.04	0.02	0.1	N
37	OS	79	M	0.42	0.125	0.2	0.2	Y
38	OS	60	M	0.02	HM	0.7	0.1	Y
39	OD	72	F	0.42	0.02	0.9	0.1	Y
40	OD	72	F	0.5	CF	0.5	CF	Y
41	OD	78	M	HM	HM	0.02	CF	Y
42	OD	70	M	0.02	0.2	0.02	0.2	Y
43	OD	37	M	0.5	0.5	1	0.5	N
44	OS	77	M	1	0.7	1	0.7	Y

cd. tab. II

1	2	3	4	5	6	7	8	9
45	OS	62	F	0.2	0.3	0.3	0.9	Y
46	OS	66	F	0.6	0.2	0.9	0.8	Y
47	OD	75	F	0.3	0.9	0.6	0.8	Y
48	OD	67	F	0.9	0.01	0.9	0.01	Y
49	OS	84	F	CF	CF	CF	0.5	N
50	OD	75	M	0.1	0.3	0.2	0.3	Y
51	OD	83	M	0.3	0.7	0.3	0.7	Y
52	OS	54	F	0.4	0.6	0.5	0.6	Y
53	OS	78	F	0.5	0.02	0.1	0.1	Y
54	OS	79	F	0.6	0.2	0.6	0.1	Y
55	OD	75	F	0.1	CF	0.1	CF	N
56	OD	71	F	0.1	0.1	0.1	0.2	N
57	OS	73	F	0.04	0.7	0.04	0.7	N

OD – right eye, OS – left eye, F – female, M – male, VA – visual acuity, HM – hand motion, CF – counting fingers, Y – yes, N – no, VA – 5/5 = 1.

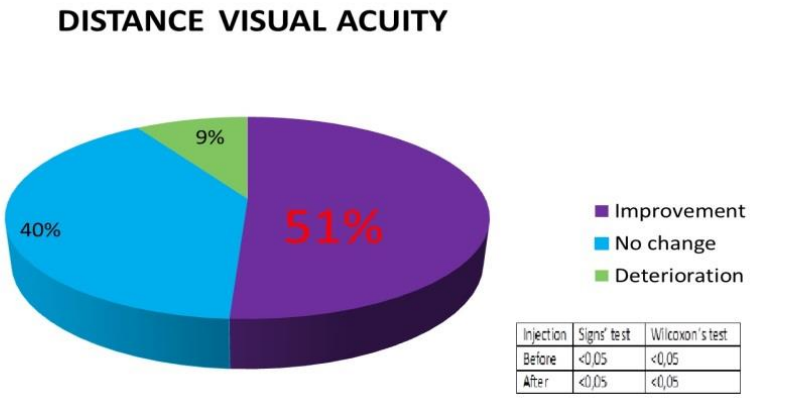

Fig. 5. Alterations in distance visual acuity.
Ryc. 5. Zmiany w ostrości wzroku do dali.

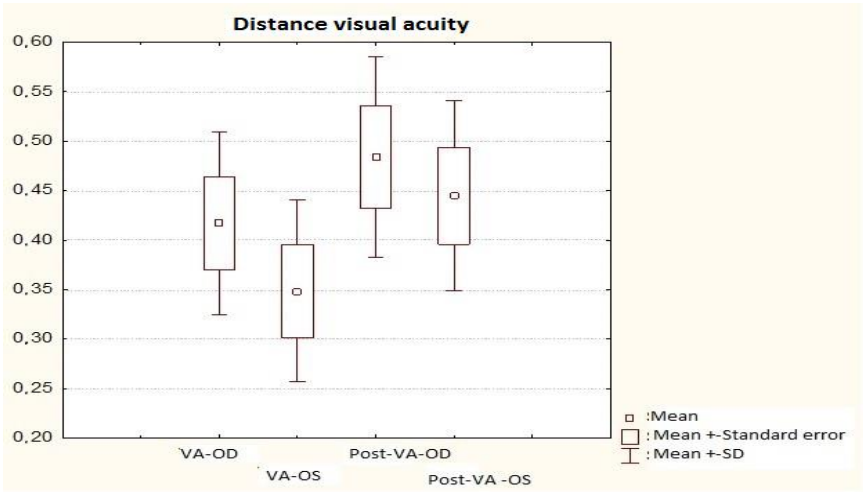

Fig. 6. Distance visual acuity . VA – visual acuity before the first dose of Avastin, OD – right eye, OS – left eye, Post-VA – visual acuity one month from the third IVB.
Ryc. 6. Ostrość wzroku do dali. VA – ostrość wzroku przed pierwszą dawką Avastinu; OD – oko prawe; OS – – oko lewe; Post-VA – ostrość wzroku miesiąc po trzeciej iniekcji doszklistowej bevacizumabu.

Table III. Subjective assessment of state of vision during daily routine activities
Tabela III. Subiektywna ocena widzenia podczas wykonywania czynności życia codziennego

	Reading	Watching TV	Driving	Prepearing meals	Combing/shaving
Improvement	23 (40%)	21 (37%)*	9 (45%)	9 (16%)	9 (16%)
No changes	29 (51%)	35 (61%)	10 (50%)	47 (82%)	48 (84%)
Deterioration	5 (9%)	1 (2%)*	1(5%)	1 (2%)	0 (0%)

* Statistically relevant significance – P < 0.05 except for

Similarily, the OCT results were analysed. The mean central retinal thickness (CRT) decreased from about 329 um at the first visit to 275 um after the treatment and the changes were statistically significant (Wilcoxon test – p = 0.0003). An improvement was observed in about 30 (53%) subjects. Additionally, the londitudinal diameter of subretinal fluid decreased (p = 0.027).

As far as the correlations are concerned, it has been found that the alterations in visual acuity positively correlated with the changes in OCT (p < 0.05). Namely, the improvement in visual acuity corresponded with better results in OCT (smaller CRT and subretinal fluid). Moreover, the above findings corresponded positively with the subjective estimation. According to the questionnaire, 49% of patients assessed their general visual state after 1 month from the third dose of Avastin as 'satisfactory', 42% as bad, 7% as good and 2% as very bad. No patient declared his state of vision as very good. The majority of patients declared no alterations in their state of vision before and after the treatment doingdaily routine activities and it was most evident in the case of preparing meals and combing/shaving in front of a mirror (Tab. III).

Half of the drivers (n = 10) did not notice any changes in their state of vision.

Among all the patients, 31 (52%) used an additional vitamin supplementation, eg. Lutein, vitamin A and vitamin E (see Tab. II). Two patients underwent another form of treatment other than Avastin, namely photodynamic therapy. Two patients were previously treated with an alternative medicine, i.e. Lucentis.

No serious ocular or nonocular adverse events were noted.

DISCUSSION

Anti-VEGF therapy with the application of Avastin is an off-label therapy which causes many controversies in the ophtalmological environment. However, the authors are in favour of this treatment method. So far, no similar studies with the application of Avastin and comparison of subjective and objective results has been conducted or published. It is also difficult to correlate the authors' findings with other studies on ranibizumab (Lucentis), as the inclusion criteria in this type of anti-VEGF therapy differ from IVB to a high extent. According to the Polish Opthalmological Association, Lucentis can be injected when BCVA ranges from 0.05 to 0.9, while in our experiment the visual acuity was much lower.

The study results reveal that distance visual acuity improves in ca. 50% of cases and no alteration can be observed in a slightly smaller group (40%). According to other publications, anti-VEGF therapy stabilizes the disease [20], but to date, there is no satisfactory explanation as to why some patients with neovascular AMD respond poorly to treatment. Increasingly more researchers suggest reducing the injection frequencies. It is presumed that the more injections, the decreased efficacy of treatment and poorer best corrected visual acuity [21]. Furthermore, no standard protocol of intervals between each dose of Avastin has been so far established. Algvere et al. [22] suggest 6-week intervals, while others state that 4 weeks are appropriate [23]. We performed a study on patients who were administered Avastin every four weeks.

The analysis of subjective visual state during activities of daily routine showed that the patients did not feel much difference after one month from the third IVB. This might be explained by the fact that the primary state of vision on the day of diagnosis is already so poor that the patients do not qualify for Lucentis therapy. Therefore, it is difficult to observe any improvement in a 4-month period. What is more, it is possible that three doses of Avastin are insufficient for the presented study group. As far as preparing meals and combing/shaving in front of a mirror are concerned, the authors state that these activities might be relatively easily and automatically undertaken, so that meaningful differences in visual state were not noticeable for the patients. Yet, surprisingly the results in reading are not similar. We presume that the situation is caused by the fact that preparing meals and combing/shaving are activities that do not demand sight participation to the same extent as reading and they depend more on routine and good co-ordination of movements rather than visual perception.

There are several limitations of the study that should be mentioned. Firstly, in the case of exudative AMD of both eyes, the outcomes could be interfered by low visual acuity of the contralateral eye. Another limiting

factor might be the relatively few patients included in the study. A larger study group and further analysis of long-term results is needed.
It is worth considering that anti-VEGF therapy is possibly associated with serious adverse events, such as endopthalmitis and arteriothrombotic ones [24]. However, the authors have not observed the complications mentioned.
Recent studies show that Avastin can be used in the treatment of central serous retinopathy, although its role in inhibition of the pathogenesis is uncertain [9,10]. However, the majority of authors report spectacular improvement in visual acuity after anti-VEGF treatment. From our own 6-year experience, we can prove similar findings to those of other scientists. Moreover, additional adjunctive treatments such as topical non-steroidal anti-inflammatory drugs, e.g. Bromfenac are nowadays being taken under consideration by many scientists [25,26,27]. The authors have recently presented the results of the above combination therapy in a pilot-study published in another journal [28].

CONCLUSIONS

Avastin seems to stabilize the degeneration process in most patients and it sometimes improves visual acuity. The study has revealed that there is a positive correlation between the objective test results and the subjective opinion in patients undergoing anti-VEGF therapy.
Nevertheless, the long-term results of anti-VEGF therapy using Avastin still remain unknown.

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We hereby certify that none of the authors has a direct financial relation with the commercial identity, i.e. Avastin®; Genentech, Inc. mentioned in our paper that might lead to a conflict of interest for any of the authors.
No financial support was received for this submission.
The results of the study were presented and awarded with 2nd place in the Session of Other Operative Specialties as an oral presentation entitled " Comparison of subjective estimation of visual acuity with subjective test results in patients undergoing anti-VEGF therapy using Avastin' at the 6th International Scientific Conference of Medical Students and Young Doctors, Katowice 5th-6th May 2011.

Author's contribution

Study designe – A. Piotrowska-Gwóźdź, A. Piotrowska-Seweryn, G. Mazur-Piotrowska
Data collection – A. Piotrowska-Gwóźdź, A. Piotrowska-Seweryn, G. Mazur-Piotrowska
Data interpretation – A. Piotrowska-Gwóźdź, A. Piotrowska-Seweryn, G. Mazur-Piotrowska
Statistical analysis – A. Piotrowska-Seweryn
Manuscript preparation – A. Piotrowska-Gwóźdź, A. Piotrowska-Seweryn
Literature research – A. Piotrowska-Gwóźdź, A. Piotrowska-Seweryn, G. Mazur-Piotrowska

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