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(31)

One Year Outcomes of Wet Age-related Macular Degeneration Treatment with Aflibercept in Therapeutic Program

Ocena rocznych efektów terapii aflibercept wysiękowego zwyrodnienia plamki związanego z wiekiem w ramach programu lekowego

Małgorzata Figurska

Department of Ophthalmology, Military Institute of Medicine, The Central Clinical Hospital of the Ministry of National Defense, Warsaw, Poland
Head: Professor Marek Rękas, MD, PhD

Abstract:

Background: The article discusses the effectiveness of aflibercept treatment for wet age-related macular degeneration, carried out in routine clinical practice for at least 12 months as part of the treatment program.

Material and Methods: Ninety-four patients (95 eyes) with a median age of 79.0 years participated in the non-randomized, retrospective, observational, single-center study. Women accounted for 59.6% of the study group. Forty-four (46.3%) eyes were treatment-naïve, and 51 (53.7%) eyes continued previous treatment. The naïve eyes were treated according to the VIEW protocol, and eyes continuing therapy were treated using a *pro re nata* regimen. The median duration of participation in the study was 13.4 months (IQR=13.1–13.6 months).

Results: The mean change in best corrected visual acuity was 8.41 ETDRS letters (standard deviation [SD]=13.76 letters) when considering all study participants, 9.36 letters (SD=10.88 letters) for treatment-naïve eyes, and 7.59 letters (SD=15.90 letters) for those continuing treatment. There was no significant difference between treatment-naïve eyes and those continuing treatment (p=0.523). The median central retinal thickness was significantly reduced from 302.0 μm to 238.0 μm (IQR=203.5–268.0 μm; p<0.001). The median number of aflibercept injections was 8.0 (IQR=7.0–9.0).

Conclusion: The regular treatment of patients with aflibercept in daily practice and according to the VIEW protocol produces results that are comparable to those of randomized clinical trials. Regular aflibercept therapy allows for a significant improvement in functional and morphological parameters regardless of the stage of the disease, both in treatment-naïve eyes and in eyes continuing treatment.

Key words: Wet Age-related Macular Degeneration, Intravitreal Injections, Aflibercept, Electronic Health Records.

Abstrakt:

Cel pracy: Celem pracy była ocena efektywności terapii wysiękowego zwyrodnienia plamki związanego z wiekiem afliberceptem w codziennej praktyce klinicznej. Leczenie prowadzone było w ramach programu lekowego, w okresie co najmniej 12 pełnych miesięcy.

Materiał i metody: W nierandomizowanym, retrospektywnym, obserwacyjnym, jednoośrodkowym badaniu wzięło udział 94 chorych (95 oczu). Mediana wieku wynosiła 79,0 (71,0–84,0) lat. Kobiety stanowiły 59,6% grupy badanej. 44 (46,3%) oczu było nowych, a 51 (53,7%) oczu kontynuowało leczenie wcześniej rozpoczęte. Oczy nowe leczone były wg protokołu VIEW, a kontynuujące terapię w oparciu o schemat *pro re nata*. Mediana czasu udziału w badaniu wyniosła 13,4 (13,1–13,6) miesiąca.

Wyniki: Średnia zmiana najlepszej skorygowanej ostrości wzroku wyniosła 8,41 (13,76) liter ETDRS: 9,36 (10,88) litery w grupie oczu nowych i 7,59 (15,90) litery w grupie kontynuującej leczenie, bez istotnej różnicy między nimi (p=0,523). Mediana grubości centralnej siatkówki uległa istotnej redukcji z 302,0 do 238,0 (203,5–268,0) μm (p <0.001). Mediana liczby iniekcji wyniosła 8,0 (7,0–9,0).

Wnioski: Lecząc chorych afliberceptem regularnie, zgodnie z protokołem VIEW, można uzyskać w codziennej praktyce wyniki porównywalne z randomizowanymi badaniami klinicznymi. Systematyczna terapia afliberceptem pozwala uzyskać istotną poprawę parametrów czynnościowych i morfologicznych niezależnie od etapu choroby, zarówno w oczach nowych, jak i kontynuujących leczenie.

Słowa kluczowe: wysiękowe zwyrodnienie plamki związane z wiekiem, iniekcje doszklistkowe, aflibercept, elektroniczna baza danych.

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Background

Age-related macular degeneration (AMD) is a chronic, progressive disease of the central part of the retina, which affects people after the age of 45 (1, 2). The wet form of the disease (wAMD) is associated with the development of neovascularization in the macula. It progresses rapidly and can lead to serious vision loss (3). A longer life expectancy and the aging of the population, observed especially in highly developed countries,

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has led to an increase in the number of AMD patients. Intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors are the treatment of choice for wAMD (4). In 2007, the Food and Drug Administration (FDA) registered ranibizumab (Lucentis, Genentech / Novartis), a non-selective VEGF inhibitor (5). Then, in 2011 it registered aflibercept (Eylea, Regeneron Pharmaceuticals / Bayer), which additionally binds to placental growth factor (PlGF) (6, 7). Bevacizumab (Avastin, Genentech Inc. / Roche) has not been registered for ophthalmological treatment and is administered "off-label" (8).

The structure of the aflibercept molecule comprises domain 2 of vascular endothelial growth factor receptor (VEGFR)-1 and domain 3 of VEGFR-2, combined with the Fc fragment of human immunoglobulin G1 (6, 7). The result is a trap receptor (VEGF Trap) that can bind to many VEGFR ligands (9, 10). The molecular structure of aflibercept results in prolonged inhibition of the growth factors under its influence (11, 12). The results of the registered, randomized clinical trial VIEW showed an average visual acuity (VA) improvement of 8.4 letters as a result of treatment with 2.0 mg of aflibercept every 8 weeks. No significant functional difference was observed compared to treatment with 0.5 mg of ranibizumab administered every month. However, there was a difference in the number of injections used. For aflibercept, 7.5 injections were administered a year, and for ranibizumab 11.8. In addition, in the second year of the VIEW study, 48–54% of patients treated with aflibercept required ≤3 intravitreal injections to maintain the functional effects obtained in the first year of treatment (13, 14).

In Poland, AMD is a significant epidemiological problem. It is estimated that AMD affects about 1.9 million people, with more than 30% of patients in the advanced stage of the disease. About 200 thousand people are diagnosed with dry AMD and about 20 thousand with wAMD annually in Poland (15).

The aim of this study was to evaluate the outcomes of treatment with aflibercept for wAMD, carried out in routine clinical practice as part of the treatment program (TP) for at least 12 months.

Material and Methods

It was a non-randomized, retrospective, observational, single-center study of eyes treated for wAMD in a TP between November 2015 and June 2017. The study used the data contained in the electronic Therapeutic Program Monitoring System (TPMS), maintaining the anonymity of the patients. It was supervised by the National Health Fund (NHF) and the Minister of Health. Anonymous analysis of the TPMS database was approved by the President of the NHF and the Bioethical Commission of the Military Institute of Medicine in Warsaw.

In the study, as in the therapeutic program, the following eligibility criteria were applicable: 1) presence of active classic, occult or mixed choroidal neovascularization (CNV) occupying more than 50% of the lesion in the course of AMD, confirmed in optical coherence tomography (OCT) and fluorescein angiography (FA) or in optical coherence tomography angiography (OCT-A); 2) age over 45 years; 3) total size of degenerative lesion less than 12 optic disc areas (DA); 4) best corrected visual acuity (BCVA) in the treated eye of 0.1–0.8, determined on a decimal scale according to the Snellen chart (or ETDRS equivalent); 5) consent of the patient to undergo intravitreal injections; 6) no dominant geographic atrophy; and 7) no dominant hemorrhage. In this study, VA was calculated from the Snellen decimal scale to the number of ETDRS letters (16).

Exclusion criteria were: hypersensitivity to the drug or to any of the excipients, active infection of the eye or its surroundings, endophthalmitis, pregnancy or breastfeeding, adverse drug-related effects preventing its further use, and retinal detachment or macular hole. An additional criterion for exclusion from the program was progression of the disease, defined as BCVA deterioration to ≤0.05 according to Snellen's chart (or ETDRS equivalent) or by ≥30 letters on the ETDRS chart, lasting longer than 2 months.

Initial analysis of TPMS data obtained between November 2015 and June 2017 included 172 eyes classified as "in progress" and "qualified". Only observations for individuals with "in progress" status (166 eyes) were involved in further analysis. Cases with other status, i.e. "entered", "rejected", "completed" or "sent back for completion" were not analyzed. To assess the outcomes of wAMD treatment as part of the TP in the Department of Ophthalmology at the Military Institute of Medicine, a group of eyes with a minimum duration of aflibercept treatment of 12 months was selected. In other words, the time between V1 (the first drug administration in the TP) and the last visit was not less than 12 months and not more than 30 days from the end of the full 12 months. The group thus defined included 95 eyes in 94 patients. The median duration of participation in the study was 13,4 months (IQR=13.1–13.6 months). Forty-four (46.3%) eyes were naïve, and 51 (53.7%) eyes continued treatment started earlier outside the program. The baseline demographic data of the study group was measured during the qualifying visit (V0) and is presented in Table I. The median time of previous treatment in the group continuing therapy, considered from the diagnosis of the disease to inclusion in the TP, was 21.0 months (IQR=6.2–39.0 months). The median number of anti-VEGF injections during this period was 5.0 (IQR=3.0–9.0). Previous treatment was carried out in B02 group within homogeneous groups of NFZ patients or private centers. If the treatment was conducted according to B02, patients received three saturation doses of drug and subsequent injections were administered based on visual and anatomical parameters (attending physician's decision). Treatment was not regular due to the system restrictions. Three anti-VEGF drugs were used: ranibizumab, bevacizumab and aflibercept. Patients received various medications, there was no harmonization in terms of previous anti-VEGF treatment. Similarly, in private centers the treatment was not systematic.

The median age of the patients was 79.0 years (IQR=71.0–84.0 years). Women accounted for 58.9% of the study group. The median baseline BCVA was 58.86 ETDRS letters (IQR=50.05–67.3 ETDRS letters), equivalent to 0.30 (IQR=0.20–0.45) according to the Snellen chart. There was no significant difference in the baseline BCVA between the eyes continuing the therapy (median 58.86 ETDRS letters, IQR=35.00–65.10 ETDRS letters) and the naïve eyes (median 58.86 ETDRS letters, IQR=50.05–69.95 ETDRS letters; p=0.25). There was no significant difference in the percentage distribution of BCVA according to ETDRS and Snellen charts be-

Variable	Category	Total	Therapy: continuation	Therapy: naive	p-value
n		95	51	44	
Age (years); (median [IQR])		79.0 [71.0, 84.0]	78.0 [70.0, 83.0]	80.0 [72.8, 85.0]	0.255
Sex (%)	women	56 (58.9)	33 (64.7)	23 (52.3)	0.308
	men	39 (41.1)	18 (35.3)	21 (47.7)	
Baseline BCVA (ETDRS letters); (median [IQR])		58.9 [50.1, 67.5]	58.9 [35.0, 65.1]	58.9 [50.1, 69.9]	0.250
Baseline BCVA (%); ETDRS letters	<=35	21 (22.1)	14 (27.5)	7 (15.9)	0.397
	(35, 70]	65 (68.4)	33 (64.7)	32 (72.7)	
	>70	9 (9.5)	4 (7.8)	5 (11.4)	
Baseline BCVA (Snellen chart); (median [IQR])		0.30 [0.20, 0.45]	0.30 [0.10, 0.40]	0.30 [0.20, 0.50]	0.250
Baseline BCVA (%); Snellen chart	0.1	21 (22.1)	14 (27.5)	7 (15.9)	0.627
	0.2	22 (23.2)	10 (19.6)	12 (27.3)	
	0.3	15 (15.8)	9 (17.6)	6 (13.6)	
	0.4	13 (13.7)	8 (15.7)	5 (11.4)	
	0.5	15 (15.8)	6 (11.8)	9 (20.5)	
	0.6	5 (5.3)	2 (3.9)	3 (6.8)	
	0.7	3 (3.2)	2 (3.9)	1 (2.3)	
	0.8	1 (1.1)	0 (0.0)	1 (2.3)	
Baseline lesion size (DA;) (median [IQR])		2.0 [2.0, 3.0]	3.0 [2.0, 4.0]	2.0 [1.8, 3.0]	<0.001
Baseline lesion area (%); (median [IQR])		80.0 [70.0, 80.0]	80.0 [69.0, 80.0]	80.0 [80.0, 80.0]	0.062
Baseline central retinal thickness (μm); (median [IQR])		302.0 [254.5, 345.5]	292.0 [249.0, 344.5]	302.0 [265.5, 348.0]	0.326
Baseline central retinal thickness (%); μm	(0-200)	3 (3.2)	2 (3.9)	1 (2.3)	0.429
	(200-400)	85 (89.5)	47 (92.2)	38 (86.4)	
	(400+)	7 (7.4)	2 (3.9)	5 (11.4)	
Form of neovascularization	classic	11 (11.6)	4 (7.8)	7 (15.9)	0.110
	mixed	36 (37.9)	24 (47.1)	12 (27.3)	
	occult	48 (50.5)	23 (45.1)	25 (56.8)	

Tab. I. Baseline characteristic of the study groups.
Tab. I. Wyjściowe dane grup badanych.

tween the groups. The median initial size of the degenerative lesion was 2.0 DA (IQR=2.0–3.0 DA). It was significantly higher in the eyes continuing treatment (3.0 DA, IQR=2.0–4.0 DA) than in naïve eyes (2.0 DA, IQR=1.8–3.0; $p<0.001$). There was no significant difference in the percentage of active leaks in the degenerative lesion between the group of eyes continuing therapy (median 80.0%, IQR=69.0–80.0%) and the treatment-naïve eyes (median 80.0%, IQR=80.0–80.0%; $p>0.05$). The difference in central retinal thickness (CRT) between eyes continuing therapy (median 292.0 μm, IQR=249.0–344.5 μm) and naïve eyes (median 302.0 μm, IQR=265.5–348.0 μm) was also not statistically significant ($p>0.05$). There was no significant difference in the percentage distribution of CRT and type of exudative degenerative lesion between groups. The mixed form of wet AMD was the most common in both groups.

The recommended dose of aflibercept was 2 mg per intravitreal injection. In the case of naïve eyes, treatment in the first year was carried out according to the regimen established in the VIEW protocol. The saturation phase consisted of one injection per month for three consecutive months. After this period, the drug was administered every 2 months. For eyes continuing therapy within the TP, a *pro re nata* regimen of aflibercept was used (according to the therapeutic program, subsequent doses of the drug were administered in case of deterioration in visual or anatomical parameters, which in practice means the appearance or increase in the amount of subretinal fluid, the occurrence of intraretinal edema or progression of pigment epithelial detachment parameters), but control tests had to be performed at least every 2 months.

Statistical analysis

Statistical analysis was used to compare the final values of the functional parameter BCVA and the morphological parameter CRT with baseline values. The analysis was carried out within each group of eyes, as well as between groups. Both groups were also assessed and compared in terms of the number of follow-up visits and aflibercept injections.

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For categorical variables, the number and percentage of occurrences were reported. The distribution of continuous variables was first evaluated with the Shapiro-Wilk test. Descriptive statistics for normally distributed variables were reported as the mean and SD; otherwise, the median and IQR (i.e. the 25th and 75th percentile or Q1 and Q3) were provided. Categorical variables were compared using Fisher's test or chi-squared test, depending on the size of the categories. The normally distributed continuous variables were compared by means of Student's t-test or, if more than two variables were compared, an ANOVA. Otherwise the Mann-Whitney test or Kruskal-Wallis test were used, respectively. Box plots, plots of the means with 95% confidence intervals (CI), locally weighted scatterplot smoothing (LOESS) curves, and bar plots were used to present and analyze the results.

The significance level was set at a p value of 0.05. Two-sided tests were used. The statistical analysis was performed with R statistical software, version 3.4.0 (17).

Results

The visual and morphological outcomes observed in the whole group are summarized in Table II. The median final BCVA was significantly improved to 65.10 ETDRS letters (IQR=58.86–73.91 ETDRS letters) and 0.4 according to Snellen chart ($p<0.001$). A significant change in the distribution of BCVA according to the Snellen chart was shown ($p<0.001$).

The percentage of eyes with a BCVA of 0.1 was significantly reduced from the initial 21.1% to 4.2% at the end of the study. The percentage of eyes with a BCVA of 0.8 increased significantly from the initial 1.1% to 14.7% at the end of the study. The median CRT was significantly reduced to 238.0 μm (IQR=203.5–268.0 μm; ($p<0.001$). A significant change in the CRT distribution was also found ($p=0.001$). The percentage of eyes with CRT below 200 μm significantly increased from an initial 3.2% to 20%, and the percentage of eyes with CRT above 400 μm was significantly reduced from 7.4% to 3.2%.

In the group of naïve eyes, the median final BCVA significantly improved to 67.53 ETDRS letters (IQR=58.86–77.98 ETDRS letters) and 0.45 (IQR=0.30–0.72) according to the Snellen chart ($p<0.001$). In the group continuing treatment, it improved to 65.10 ETDRS letters (IQR=50.05–69.95 ETDRS letters) and 0.40 (IQR=0.20–0.50) according to Snellen chart ($p<0.05$). There was a statistically significant difference between final median BCVA in the naïve subgroup and in the group continuing therapy ($p=0.047$; Table III). The mean change in BCVA was 8.41 ETDRS letters (SD=13.76 letters). For treatment-naïve eyes it was 9.36 letters (SD=10.88 letters), and for those continuing treatment it was 7.59 letters (SD=15.90 letters). There was no significant difference between groups ($p=0.523$). There were no significant differences between the groups in terms of the number of eyes with significant improvement in BCVA by ≥10 ETDRS letters. At the end of the study, there was a significant difference in BCVA distribution between groups ($p=0.043$). The percentage of eyes with BCVA >70 ETDRS letters was significantly higher in the group of treatment-naïve eyes (40.9% vs. 23.5%), and the percentage of eyes with BCVA ≤35 ETDRS letters was significantly lower (0.00% vs. 7.5%). The BCVA values and the changes in BCVA in successive time intervals are illustrated in Figures 1 and 2. Figure 3 shows BCVA values in consecutive time periods divided into ranges defined by the baseline parameter value.

For treatment-naïve eyes, the final CRT decreased to 237.0 μm (IQR=200.2–257.8 μm; $p<0.001$), and for those continuing therapy it decreased to 240.0 μm (IQR=217.0––291.5 μm; $p<0.001$). The difference in the final values between the groups was not statistically significant ($p=0.145$). The me-

Variable	Category	Visit: V0	Last Visit	p-value
n		95	95	
BCVA (Snellen chart); (median [IQR])		0.30 [0.20, 0.45]	0.40 [0.30, 0.60]	<0.001
BCVA (Snellen chart); (%)	0.1	21 (22.1)	4 (4.2)	<0.001
	0.2	22 (23.2)	19 (20.0)	
	0.3	15 (15.8)	16 (16.8)	
	0.4	13 (13.7)	14 (14.7)	
	0.5	15 (15.8)	12 (12.6)	
	0.6	5 (5.3)	14 (14.7)	
	0.7	3 (3.2)	2 (2.1)	
	0.8	1 (1.1)	14 (14.7)	
BCVA (ETDRS chart); (median [iqr])		58.86 [50.05, 67.53]	65.10 [58.86, 73.91]	<0.001
Central retinal thickness (μm); (median [IQR])		302.0 [254.5, 345.5]	238.0 [203.5, 268.0]	<0.001
Central retinal thickness (μm); (%)	(0-200)	3 (3.2)	19 (20.0)	0.001
	[200-400)	85 (89.5)	73 (76.8)	
	[400 +)	7 (7.4)	3 (3.2)	

Tab. II. The visual and morphological outcomes observed in the whole group.
Tab. II. Wyniki czynnościowe ostrości wzroku i morfologiczne w całej grupie badanej.

Variable	Category	Total	Therapy: continuation	Therapy: naive	Missing data	p-value
n		95	51	44		
Baseline BCVA (ETDRS letters); (median [IQR])		58.9 [50.1, 67.5]	58.9 [35.0, 65.1]	58.9 [50.1, 69.9]	0 (0.0%)	0.250
Final BCVA (ETDRS letters); (median [IQR])		65.1 [58.9, 73.9]	65.1 [50.1, 69.9]	67.5 [58.9, 78.0]	0 (0.0%)	0.047
Δ BCVA (ETDRS letters) (mean (sd))		8.4 (13.8)	7.6 (15.9)	9.4 (10.9)	0 (0.0%)	0.523
Gain≥10 ETDRS letters		42 (44.2)	21 (41.2)	21 (47.7)		0.664
Final BCVA (%); ETDRS letters	<=35	4 (4.2)	4 (7.8)	0 (0.0)	0 (0.0%)	0.043
	(35, 70]	61 (64.2)	35 (68.6)	26 (59.1)		
	>70	30 (31.6)	12 (23.5)	18 (40.9)		
Baseline BCVA (Snellen chart); (median [IQR])		0.30 [0.20, 0.45]	0.30 [0.10, 0.40]	0.30 [0.20, 0.50]		0.250
Final BCVA (Snellen chart); (median [IQR])		0.40 [0.30, 0.60]	0.40 [0.20, 0.50]	0.45 [0.30, 0.72]		0.047
Δ BCVA (Snellen chart); (median [IQR])		0.10 [0.00, 0.20]	0.10 [0.00, 0.20]	0.20 [0.07, 0.30]		0.125
Baseline central retinal thickness (um); (median [IQR])		302.0 [254.5, 345.5]	292.0 [249.0, 344.5]	302.0 [265.5, 348.0]	0 (0.0%)	0.326
Final central retinal thickness (um); (median [IQR])		238.0 [203.5, 268.0]	240.0 [217.0, 291.5]	237.0 [200.2, 257.8]	0 (0.0%)	0.145
Δ Central retinal thickness (um); (median [IQR])		-51.0 [-95.0, -5.0]	-30.0 [-71.0, 0.0]	-58.5 [-113.8, -27.0]	0 (0.0%)	0.010
Injections; (median [IQR])		8.0 [7.0, 9.0]	7.0 [6.0, 8.0]	9.0 [8.0, 9.0]	0 (0.0%)	<0.001
Visits; (median [IQR])		9.0 [8.0, 9.0]	8.0 [8.0, 8.0]	9.0 [9.0, 9.0]	0 (0.0%)	<0.001

Tab. III. Visual and morphological outcomes for all eyes, naïve and continuing therapy.
Tab. III. Wyniki czynnościowe ostrości wzroku i morfologiczne w grupie oczu nowych i kontynuujących terapię.

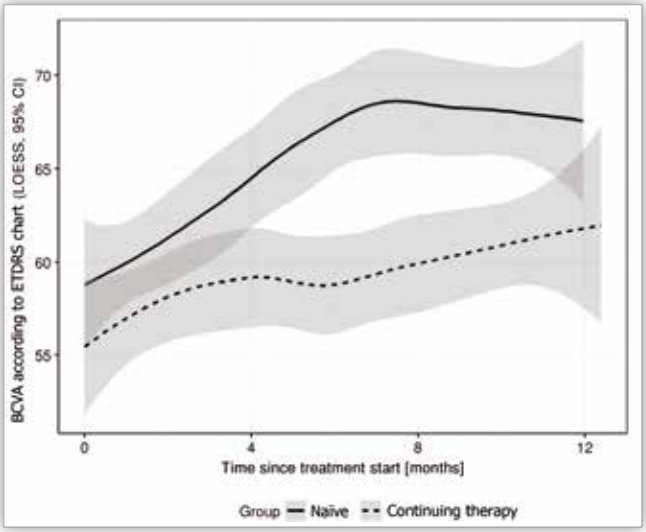

Fig. 1. LOESS curves (95% CI) for the dependence of BCVA from the time, in the group of naïve eyes and in those continuing therapy.
Ryc. 1. Krzywa LOESS (95% CI) obrazująca BCVA w czasie obserwacji, w grupie oczu nowych i kontynuujących terapię.

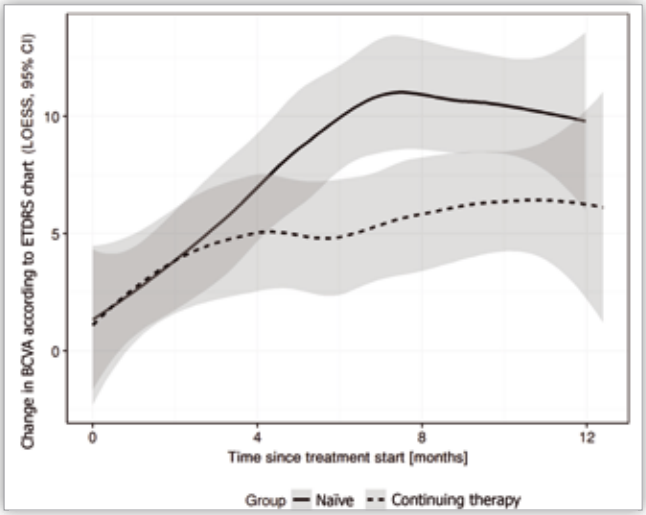

Fig. 2. LOESS curves (95% CI) showing the change in BCVA from the beginning of treatment, in the group of naïve eyes and in eyes continuing the therapy.
Ryc. 2. Krzywa LOESS (95% CI) obrazująca zmianę BCVA od rozpoczęcia terapii, w grupie oczu nowych i kontynuujących terapię.

dian CRT change was significantly higher in the treatment-naïve subgroup compared to the group continuing therapy (p=0.010). In the group of treatment-naïve eyes, a significant change in the CRT distribution was observed compared to baseline (p<0.001). The percentage of eyes with a CRT below 200 μm significantly increased at the end of the study from 2.3% to 25%, and the percentage of eyes with CRT above 400 μm significantly decreased from 11.4% to 0.00%. There was no significant change in the distribution of CRT values in the group continuing treatment (p=0.117).

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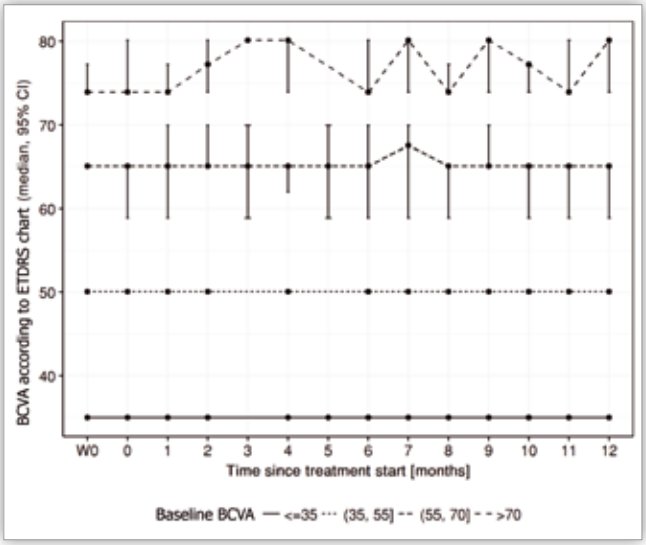

Fig. 3. Median BCVA during treatment, grouped in ranges according to the number of ETDRS letters determined at the beginning of the study.

Ryc. 3. Mediana BCVA podczas leczenia, w przedziałach określonych wyjściową liczbą liter ETDRS.

The median number of visits was 9.0 (IQR=8.0–9.0) when considering both groups together, 9.0 (IQR=9.0–9.0) for treatment-naïve eyes, and 8.0 (IQR=8.0–8.0) for those continuing treatment ($p<0.001$). The median number of injections was 8.0 (IQR=7.0–9.0) when considering both groups together, 9.0 (IQR=8.0–9.0) for treatment-naïve eyes, and 7.0 (IQR=6.0–8.0) for those continuing treatment ($p<0.001$). The median percentage of visits on which an injection was given was 88.9% (IQR=87.5–100.0%) for both groups together, 100.0% (IQR=88.9–100.0%) for treatment-naïve eyes, and 87.5% (IQR=75.0–100.0%) for those continuing treatment ($p=0.001$).

No serious adverse events associated with drug administration within the TP were reported. During the time period of analysis, none of the patients in the study group met exclusion criteria described in the therapeutic program attachment (aforementioned in the exclusion criteria for participation in the study – the Material and Methods section). It was practically impossible for the new patients to switch the drug to another one (according to the record of program drug can be changed to another one after 7 doses of the same medication, which in the case of aflibercept closes the first year of treatment). Since the exclusion criteria of the therapeutic program (or withholding treatment) were not met in the group of eyes continuing therapy, a drug switching before a full year of systematic aflibercept treatment was not considered.

Discussion

A treatment regimen with aflibercept for wet AMD, established according to the VIEW protocol, was implemented in everyday practice. Following the VIEW guidelines, the protocol included a saturation phase and further dosing of the drug every two months. In subsequent years of treatment, aflibercept was administered intravitreally in case of recurrence of disease activity. The protocol also followed the guidelines outlined in the extended VIEW trial, which recommend quarterly injections in the second year, even in the absence of active degenerative process (13, 18). Currently, information on the effectiveness of wet AMD treatment in daily clinical practice comes from analyses of anonymous data contained in electronic databases. Own observations were also based on the analysis of data contained in the electronic system used during patient monitoring. In Poland, it is possible to obtain systematic, electronic data of patients treated for wet AMD since November 2015, which was date of the introduction of the TP. According to the database from the Military Institute of Medicine, from the period between November 2015 and June 2017, individual eyes participating in the TP received treatment for varying lengths of time. This resulted in heterogeneity and influenced the number of visits, injections, and functional parameters. Therefore, a group of 95 eyes treated for at least 12 months was selected for the detailed analysis of effectiveness.

In this study, there was a significant improvement in VA in the whole group by 8.41 ETDRS letters (SD=13.76ETDRS letters). With the improvement in BCVA, there was a significant shift in its distribution towards higher values. There was a significant number of control visits (9.0 [IQR=8.0–9.0]), which corresponded to the number of injections (8.0 [IQR=7.0–9.0]). This means that the control tests were effective and focused on the preservation of the treatment schedule and careful assessment of disease activity. A significant reduction in CRT was achieved, with a significant shift in its distribution towards lower values. The results from own analysis, which illustrate everyday clinical practice, correspond to the results of the randomized VIEW trial in terms of the parameters analyzed. The curves illustrating BCVA and its changes (Fig. 1 and 2) rose during the first 4 months of the study, and remained stable in subsequent time intervals. Similar results were noted by researchers conducting observations in larger groups of patients, but also in groups of sizes similar to those in own study. Talks et al. published the results of a one-year, multicenter, anonymous, retrospective analysis of data from electronic documentation of naïve wet AMD patients treated with aflibercept according to the VIEW protocol in the United Kingdom (19). In the first year of treatment, 1,840 treatment-naïve eyes (1,682 patients) received an average of 7 injections. During that period, 7.3 visits were made on average. Patients gained on average 5.1 letters. The percentage of eyes with VA≥70 letters increased significantly from 16.4% initially to 33.7% at the end of the one-year follow-up period. In own study, the percentage of eyes with BCVA >70 ETDRS letters was significantly higher in the group of treatment-naïve eyes at the end of follow-up (40.9% vs. 23.5%). In addition, as was observed by Talks et al., there was a tendency for the BCVA to remain within the initial parameter values (Fig. 3). This allows for the prediction of BCVA stabilization over time with maintenance of systematic control and aflibercept treatment.

A PERSEUS multicenter study was carried out in Germany, which included a population of wet AMD patients treated with aflibercept in daily clinical practice (20). The number of patients that completed 12-month follow-up and treatment was 848. In this study, like in present, two groups of eyes were distinguished: treatment-naïve (55.7%) and previously treated for wet AMD (44.3%). The percentage of patients that received afli-

bercept regularly according to the VIEW protocol was 26.1%, and 73.9% were treated irregularly with departures from the adopted schedule. In own study, regardless of the stage of the disease, all patients were treated regularly. The baseline mean VA observed in the multicenter study was 53.2 ETDRS letters. In the group of treatment-naïve eyes treated regularly, there was a VA improvement of 8.0 ± 17.7 letters, comparable to the improvement seen in own study of 9.36 letters. In contrast, in the group of treatment-naïve eyes treated irregularly, the improvement was only of 4.0±17.1 letters. There was a significantly higher number of injections in the group with regular aflibercept dosing (7.4±0.6 vs. 5.1±2.2; $p<0.001$). In the group of patients treated previously, regular injections were associated with a significant improvement in VA (+3.1±10.7 vs. -1.1±16.8 letters) and a significantly higher number of drug administrations (7.5±0.6 vs. 5.3±2.5). Functional effects obtained in the eyes treated regularly were comparable to the VIEW study. In the PERSEUS study, significantly better functional results were obtained in the naïve eyes compared to eyes that were previously treated. In own study, at the end of the follow-up period, a significantly higher BCVA was also obtained in naïve eyes as compared to eyes continuing treatment, but without a significant difference in the number of letters gained. Also, the number of injections in the group of treatment-naïve eyes was significantly higher in own analysis than in the group continuing treatment (9 vs 7). In own study, a gain of 7.59 letters was recorded in the group continuing previous treatment. Hence, the functional effect was better than that obtained in the PERSEUS study, with a comparable number of injections. Almuhtaseb et al. presented the one-year outcomes of regular aflibercept treatment for wet AMD in a group of 255 naïve eyes (223 patients) in the United Kingdom (21). The VA improved by an average of 8 letters, which was again comparable to the results of the VIEW 1 and VIEW 2 studies, as well as with own observations. After 11 months of treatment, the mean CRT significantly decreased from 311 μm to 211 μm ($p<0.001$). In own study, a significantly higher reduction of CRT was observed in the naïve eyes. Similarly, only in the treatment-naïve eyes, a change in the CRT distribution and a shift towards lower values were observed.

The literature also includes reports from studies based on everyday clinical practice, but with different durations and following different aflibercept treatment regimens. Duval et al. evaluated the efficacy of wet AMD treatment in daily practice at the University Hospital of Bordeaux (22). The follow-up period ranged between 3 months and 2 years. All patients received three monthly doses of aflibercept followed by personalized monitoring. The study included 43 patients with an average age of 77.7 years. Twenty-five eyes completed the first year of observation, and 5 eyes were followed for 2 years. The baseline BCVA was 55.7 letters. Patients received an average of 7.5 aflibercept injections during the first year and 2.6 injections in the second year. After the saturation phase, patients gained an average of 7.3 ETDRS letters and after 12 months, 6.2 letters. Functional improvement was maintained until the end of the second year of follow-up, when the mean improvement in BCVA of 6.8 letters as compared to baseline was recorded. The OCT examination showed a significant reduction in anatomical parameters in relation to their initial values. Duval et al. emphasized the functional and morphological outcomes of aflibercept therapy in daily practice, despite the prolongation of time between follow-up visits and drug administration after the saturation phase. Epstein and Amrén presented the results of a retrospective 18-month non-randomized observation of 85 wet AMD patients treated with aflibercept (23). In the first year, patients were treated according to the VIEW protocol and in the following 6 months according to the *treat and extend* (TREX) strategy. The effect of aflibercept therapy on distance and near vision was evaluated. After 12 months, the mean VA improved significantly from 60.9 letters to 68.1 letters. The average number of injections during this period was 7.7, compared to 8 in own study. After 18 months, the mean VA was maintained at 69.6 letters, with an average of 2.2 injections over 6 months according to TREX. After 12 months, a significant improvement in near-VA was also achieved ($p<0.001$), and it persisted until the end of the 18th month of follow-up. The results of the study confirmed that, in real practice, the functional effects obtained after aflibercept treatment are comparable to those achieved in clinical trials. They also confirmed that this treatment has a beneficial effect on near vision, an outcome which is very relevant for patients. In 2017, Eleftheriadou et al. published the results of a 2-year aflibercept therapy for naïve eyes with wet AMD in the Moorfields Eye Hospital in London (24). It was a retrospective, non-randomized study based on data from electronic medical records. Eighty-eight patients (94 eyes), mostly women (65.9%), completed the two-year follow-up. The mean age of patients was 77.5 ± 8 years. In the first year, the patients were treated according to the VIEW protocol, and in the second year according to the TREX regimen. During the 2-year treatment period, patients received an average of 11.4±4 aflibercept injections (7.3 injections in the first year). In the first year, VA improved by 5.4 letters on average and in the second year by 5.1±14.9 letters. A significant reduction in the CRT was observed. At the end of the second year, symptoms of disease activity were not found in 72.7% of eyes. Barthelmes et al. presented the results of aflibercept therapy on 136 naïve eyes (123 patients) with wet AMD. The eyes were treated with aflibercept for two years according to the TREX strategy in everyday clinical practice (25). The mean age of the patients was 77.2 years, and 59% were women. After two years of treatment, the mean VA improved by 6 ETDRS letters. Researchers showed that aflibercept therapy according to the TREX regimen has good results in daily practice, comparable to those obtained in randomized studies, with a significant reduction in both the number of follow-up visits and drug administrations.

Own study, which is the first analysis of the effectiveness of aflibercept treatment on wet AMD patients as part of a TP at the Military Institute of Medicine, had some limitations. The number of patients included in the study was relatively low. It was the first group of patients treated systematically as part of a TP. Before the introduction of the TP, the treatment of wet AMD in Poland was not systematic. Previously, patients received three saturation doses of the anti-VEGF drug, and subsequent treatment was based on the evaluation of disease activity. Currently, the Polish drug program requires increased, double control of disease activity. This includes the assessment of the

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VA functional parameter and morphological OCT data during each visit, as well as a specific, strict pattern of control visits (at least every 62 days). Hence the high number of visits and injections observed in own study in comparison to other countries, reflecting the current, everyday clinical practice (26, 27).

The TP for wet AMD treatment is ongoing. The number of patients being treated is constantly increasing. Currently in Poland, over 30,000 wet AMD patients are systematically treated in the program. At the Military Institute of Medicine, the number of patients treated exceeds 300. The methodical and regular treatment received by patients in the TP is of unlimited duration. It is financed by the National Health Fund, and it is a guaranteed service in Poland. Because wet AMD is a chronic disease, future work will include extending the analysis of the effectiveness of aflibercept therapy for wet AMD with data from subsequent years of treatment.

Conclusion

The regular treatment of patients with aflibercept in daily practice carried out according to VIEW protocol, produces results that are comparable to those of randomized clinical trials. Regular aflibercept therapy allows for a significant improvement in functional and morphological parameters regardless of the stage of the disease, both in treatment-naïve eyes and in eyes continuing therapy. Better baseline VA suggests that it will be maintained over time with continuing systematic control and treatment.

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Corresponding author (Autor korespondencyjny):
dr hab. n. med. Małgorzata Figurska
Department of Ophthalmology, Military Institute of Medicine, The Central Clinical Hospital of the Ministry of National Defense
Szaserów Street 128
04-141 Warsaw, Poland
mfigurska@wim.mil.pl

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