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Three-year outcomes of treatment of wet age-related macular degeneration in the Polish therapeutic program

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ABSTRACT

Aim of study: Three-year evaluation of outcomes of wet age-related macular degeneration treatment with intravitreal injections of aflibercept and ranibizumab in routine clinical practice within the framework of the Polish National Health Fund therapeutic program.

Material and methods: A total of 135 patients (135 eyes), with a median age of 82.0 [74.0, 86.5] years were enrolled in a non-randomized, retrospective, observational, single-center study. A total of 78 (57.8%) eyes were treatment-naive. Treatment was provided in accordance with the guidelines set out in the therapeutic program, based on a fixed or *pro re nata* regimen.

Results: After the first year of treatment, there was a mean gain of 4.86 [12.50], after the second year 4.72 [12.67] ($p > 0.05$), and after the third year a significantly lower gain of 3.26 [12.21] ETDRS letters. A significant reduction in central retinal thickness was observed. In the first year, 8.00 [6.00, 8.00] injections were performed. In the following years, the number was significantly smaller (5.00 [4.00, 6.00]).

In the treatment-naive subgroup, the best corrected visual acuity improved significantly during the first and second years of treatment, and was significantly higher compared to the pretreated subgroup.

Conclusions: Regular treatment of wet age-related macular degeneration in line with the guidelines set out in the therapeutic program leads to functional stabilization and significant morphological improvement over a long-term follow-up (3 years), with significantly fewer injections administered after the first year of treatment. During the initial two years of the therapeutic program, treatment-naive eyes exhibited significantly higher functional parameters compared to pretreated eyes.

KEY WORDS: wet age-related macular degeneration, intravitreal injections, aflibercept, ranibizumab, electronic database.

INTRODUCTION

Patients with wet age-related macular degeneration (wAMD) in Poland have been treated under the Polish National Health Fund therapeutic program (TP) since autumn 2015. More than 27,000 patients are currently undergoing therapy, and over 57,000 applications are registered in the electronic System for Monitoring Therapeutic Programs (SMPT) [1-3].

wAMD is a chronic progressive disease of the central retina that develops in individuals over 45 years of age. Patients with wAMD require systematic monitoring and treatment spanning many years. Nowadays, the widely accepted therapy for wAMD worldwide is based on repeated intravitreal injections of drugs blocking the vascular endothelial growth factor (VEGF) [4]. Within the framework of the TP, patients receive therapy with a non-selective VEGF inhibitor: ranibizumab (Lucentis, Genentech/Novartis) and aflibercept (Eylea, Regeneron Pharmaceuticals/Bayer), which additionally blocks placental growth factor (PlGF) [5-9].

AIM OF THE STUDY

The aim of the study was to evaluate the efficacy of wAMD treatment with intravitreal injections of anti-VEGF drugs carried out in routine clinical practice over a period of three years within the framework of the Polish therapeutic program.

MATERIAL AND METHODS

It was a non-randomized, retrospective, observational, single-center study of eligible eyes selected for wAMD treatment under the TP in the Military Institute of Medicine (WIM) between January 2016 and June 2017. The study was based on analyzing anonymized data derived from the SMPT supervised by the National Health Fund (NFZ) and the Minister of Health. The anonymized analysis of the SMPT system database was approved by the President of the National

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Health Fund and the Ethics Committee at the Military Institute of Medicine (Decision No. 68/WIM/2017).

Similarly to the TP, the study involved the following inclusion criteria: 1) presence of active (primary or secondary) classic, occult or mixed choroidal neovascularization occupying over 50% of the lesion, confirmed by OCT (optical coherence tomography) and fluorescein angiography or optical coherence tomography angiography (OCTA); 2) age over 45 years; 3) lesion size less than 12 DA (=disc area); 4) best corrected visual acuity (BCVA) in the treated eye 0.1-0.8, determined based on the Snellen chart (or the equivalent in letters according to the ETDRS (Early Treatment Diabetic Retinopathy Study)) chart; since January 2017, the lower limit of BCVA for eligibility has been 0.2; 5) patient consent to intravitreal injections; 6) no dominant geographic atrophy; 7) no dominant hemorrhage; 8) since January 2017, no significant permanent structural foveal damage (defined as fibrosis, atrophy, discoid scar). For the purpose of the study, BCVA values determined with the Snellen chart were converted to ETDRS letters [10].

The study exclusion criteria were as follows: 1) hypersensitivity to drug or excipient; 2) active infection in or around the eye; 3) active severe endophthalmitis; 4) pregnancy or breastfeeding; 5) drug-related adverse reactions precluding further treatment; 6) rhegmatogenous retinal detachment, or stage 3 or 4 macular hole; 7) disease progression defined as: a) deterioration in BCVA ≥ 30 ETDRS letters (or the Snellen equivalent) persisting for longer than 2 months; b) deterioration of BCVA to ≤ 0.05 by the Snellen chart (or the ETDRS equivalent), persisting for longer than 2 months; c) since January 2017 – deterioration of BCVA to <0.2 by the Snellen chart (or the ETDRS equivalent) persisting for more than 2 months; 8) since January 2017 – permanent structural foveal damage (fibrosis, atrophy, discoid scar).

In order to evaluate three-year outcomes of wAMD treatment in the Department of Ophthalmology, Military Institute of Medicine in Warsaw, a group of 135 eyes (135 patients) was selected. Two subgroups of patients (eyes) were distinguished by adopting the criterion of time of initiating wAMD treatment. There were 78 (57.8%) treatment-naive (i.e. previously untreated) eyes, and 57 (42.2%) pretreated eyes (i.e. continuing treatment initiated outside the TP). The baseline demographic data (enrolment visit, V0) of the study group are presented in Table 1. The median time of previous treatment (from diagnosis to inclusion in the TP) in the pretreated subgroup was 488.0 [112.0, 1092.0] days, and the number of anti-VEGF injections (aflibercept, ranibizumab, bevacizumab) in this period was 3.0 [2.0, 5.0]. The median age of the patients was 82.0 [74.0, 86.5] years. Women made up 59.2% of the study group. The median baseline BCVA was 65.10 [50.05, 69.95] ETDRS letters (0.4 [0.2, 0.5] based on the Snellen chart). There was no significant difference in the baseline BCVA values and their percentage distribution between the subgroups, as determined with the ETDRS and Snellen charts. There was no significant difference in the percentage of active leakage in the degenerative lesion, and central retinal thickness and its percentage distribution between the subgroups. Occult neovascularization was the most common type occurring in wAMD. Aflibercept therapy was used in a total of 108 (80%) eyes. The remaining 20% of patients were treated with ranibizumab.

The recommended dose of aflibercept was 2 mg per intravitreal injection. During the first year, treatment-naive eyes received therapy according to the established treatment regimen consistent with the VIEW protocol. The treatment consisted of the loading phase (one injection per month for three consecutive months), followed by drug administration every two months. In the subgroup of pretreated eyes, aflibercept was administered on a pro re nata (PRN) basis. According to the TP, follow-up evaluations had to be performed at least every two months.

The recommended dose of ranibizumab was 0.5 mg per intravitreal injection. The drug was administered at monthly intervals until the attenuation of disease activity and BCVA stabilization. The recurrence of disease activity and/or deterioration of BCVA were indications for a repeated injection of ranibizumab. Follow-up evaluations had to be performed at least every two months.

Two parameters were analyzed statistically: the functional parameter BCVA and the morphological parameter CRT. The final outcomes were compared with the baseline values to determine statistically significant differences. A similar analysis was performed in the subgroups of treatment-naive and pretreated eyes and compared against the number of follow-up visits and anti-VEGF injections.

STATISTICAL ANALYSIS

Statistical analysis was based on the standard measures of location and dispersion. The normality of the distribution of individual variables was verified with the Shapiro-Wilk test. Where normal distribution was confirmed, the mean value and standard deviation (SD) were used. For non-parametric distribution of variables, the median and interquartile range (IQR) were used (i.e., the 25^{th} and 75^{th} percentiles or Q1 and Q3). Categorical variables were compared using Fisher's exact or Ch^2 test. With normal distribution of variables, Student's *t*-test or ANOVA (for more than two values) was used for comparison. The comparison of medians was carried out using the Mann-Whitney U test or Kruskal Wallis test. The graphs with the results were generated on the basis of data contained within the 95% confidence interval for the medians.

Values below 0.05 were regarded as statistically significant. Two independent tests were performed to confirm the result. The analysis was performed using StatSoft statistical software (version 3.4.0).

RESULTS

The first year of treatment was completed by all eligible patients, the second year by 116 (86% of the baseline group) and the third by 101 patients (75% of the baseline group). The reduction in the number of patients from year to year was due to various reasons including death, patient non-compliance, or the occurrence of an exclusion criterion (permanent irreversible foveal lesions: scarring or atrophy). The *p* values were

always calculated within groups of the same size, i.e. for the first year of treatment, groups of 135 were compared, and for the second year, the outcomes of 116 subjects were compared with their data at V0. Similarly, after the third year, the results of 101 patients were compared against their baseline data.

The functional results are listed in Table II, and morphological results in Table III. The median BCVA expressed as the number of ETDRS letters did not change significantly in clinical terms, but there was a statistically significant difference of $p < 0.05$. Likewise, BCVA determined according to the Snellen chart did not change in a clinically relevant manner over the subsequent years of follow-up, with a statistically significant difference of $p < 0.05$. A significant ($p < 0.05$) change in BCVA distribution based on the Snellen chart was observed, with

Table I. Baseline data of the study group

Variable/Category	Value	Subgroup: treatment-naive eyes	Subgroup: pretreated eyes	*p*-value
Number of patients (eyes)	135	78	57	
Age (median [IQR])	82.0 [74.0, 86.5]	82.0 [74.25, 87.0]	81.0 [74.0, 85.0]	0.355
Sex				
Men	55 [0.41]	32 [0.41]	23 [0.40]	1.000
Women	80 [0.59]	46 [0.59]	34 [0.60]	
Drug				
Ranibizumab	26 [0.19]	15 [0.19]	11 [0.19]	1.000
Aflibercept	108 [0.80]	62 [0.79]	46 [0.81]	
BCVA based on ETDRS; (median [IQR])	65.10 [50.05, 69.95]	65.10 [50.05, 69.95]	65.10 [50.05, 69.95]	0.295
BCVA based on ETDRS				
≤ 35	12 [0.09]	6 [0.08]	6 [0.11]	0.337
(35, 70]	99 [0.73]	55 [0.71]	44 [0.77]	
> 70	24 [0.18]	17 [0.22]	7 [0.12]	
BCVA by Snellen chart; (median [IQR])	0.4 [0.2, 0.5]	0.4 [0.2, 0.5]	0.4 [0.2, 0.5]	0.160
BCVA by Snellen chart				
0.1	12 [0.09]	6 [0.08]	6 [0.11]	0.645
0.2	29 [0.21]	18 [0.23]	11 [0.19]	
0.3	49 [0.36]	27 [0.35]	22 [0.39]	
0.4	29 [0.21]	15 [0.19]	14 [0.25]	
0.5	21 [0.16]	13 [0.17]	8 [0.14]	
0.6	11 [0.08]	6 [0.08]	5 [0.09]	
0.7	7 [0.05]	6 [0.08]	1 [0.02]	
0.8	6 [0.04]	5 [0.06]	1 [0.02]	
% leakage in the degenerative lesion; (median [IQR])	80.0 [77.5, 80.0]	80.0 [80.0, 80.0]	80.0 [70.0, 80.0]	0.278
CRT (μm); (median [IQR])	320.0 [271.5, 355.0]	320.0 [273.25, 355.0]	315.0 [269.0, 350.0]	0.856
CRT (μm)				
(0–200]	6 [0.04]	1 [0.01]	5 [0.09]	0.106
(200, 400]	115 [0.85]	68 [0.87]	47 [0.82]	
(400+)	14 [0.10]	9 [0.12]	5 [0.09]	
wAMD type				
classic	12 [0.09]	7 [0.58]	5 [0.42]	0.108
mixed	55 [0.41]	26 [0.47]	29 [0.53]	
occult	68 [0.50]	45 [0.66]	23 [0.34]	

BCVA – best corrected visual acuity; wAMD – wet age related macular degeneration; CRT – central retinal thickness

Table II. Functional outcomes in consecutive time intervals

Variable	Year	Value	Subgroup: treatment-naive eyes	Subgroup: pretreated eyes	*p*-valaue
Number of eyes	V0	135	78	57	
	1.	135	78	57	
	2.	116	66	50	
	3.	101	59	42	
BCVA based on ETDRS; (median [IQR])	V0	65.10 [50.05, 69.95]	65.10 [50.05, 69.95]	65.10 [50.05, 69.95]	0.295
	1.	65.10 [58.86, 74.79]	69.95 [60.26, 78.81]	65.10 [50.05, 73.91]	**< 0.05**
p		< 0.001	< 0.001	0.057	
BCVA based on ETDRS; (median [IQR])	2.	65.10 [60.26, 74.79]	69.95 [60.26, 74.79]	65.10 [50.05, 69.95]	**< 0.005**
p		< 0.001	< 0.001	0.084	
BCVA based on ETDRS; (median [IQR])	3.	65.10 [54.90, 74.79]	69.95 [60.26, 74.79]	65.10 [54.90, 69.95]	0.413
p		< 0.01	0.108	< 0.05	
Δ BCVA based on ETDRS (mean (sd))	1.	4.86 [12.50]	5.88 [11.77]	3.46 [13.30]	0.270
	2.	4.72 [12.67]	5.65 [11.65]	3.49 [13.81]	0.366
p		0.622	0.833	0.580	
	3.	3.26 [12.21]	2.71 [12.65]	4.05 [11.52]	0.592
p		< 0.05	< 0.05	0.633	
BCVA by Snellen chart; (median [IQR])	V0	0.4 [0.2, 0.5]	0.4 [0.2, 0.50]	0.4 [0.2, 0.5]	0.160
	1.	0.4 [0.3, 0.625]	0.4 [0.32, 0.76]	0.4 [0.2, 0.6]	**< 0.01**
p		< 0.001	< 0.001	< 0.05	
	2.	0.4 [0.32, 0.625]	0.5 [0.32, 0.63]	0.4 [0.2, 0.5]	**< 0.005**
p		< 0.001	< 0.001	0.149	
	3.	0.4 [0.25, 0.625]	0.5 [0.32, 0.63]	0.4 [0.25, 0.5]	0.305
p		< 0.05	0.234	0.060	
Δ BCVA by Snellen chart; (median [IQR])	1.	0.10 [0.00, 0.20]	0.10 [0.00, 0.22]	0.00 [–0.10, 0.10]	0.185
	2.	0.10 [–0.07, 0.20]	0.10 [–0.06, 0.22]	0.02 [–0.08, 0.20]	0.252
p		0.356	0.628	0.326	
	3.	0.10 [–0.10, 0.20]	0.10 [–0.10, 0.20]	0.07 [0.00, 0.13]	0.640
p		< 0.05	< 0.05	0.358	

BCVA – best corrected visula acuity; Δ BCVA – change in BCVA; wAMD – wet age related macular degeneration; CRT – central retinal thickness

a decrease in the number of eyes with low BCVA values in the range of 0.1 to 0.3. After the first and second years of treatment, the mean gain of ETDRS letters was 4.86 [SD 12.50] and 4.72 [SD 12.67], respectively. After the third year, the mean gain of ETDRS letters was significantly lower, reaching the value of 3.26 [SD 12.21]. With regard to BCVA, a clinical improvement of one line in the Snellen chart was achieved, with a significant difference noted at the end of the follow-up. The functional results are shown in Figure 1. Another observation was a significant reduction in CRT, persisting over consecutive years, in relation to baseline values (Table III). It was accompanied by a significant (< 0.01) change in the distribution of parameter values, with an increase in the number of eyes with CRT < 200 µm. In the first year, 8.00 [6.00, 8.00] injections were performed. In the following years, the number was significantly smaller, reaching 5.00 [4.00, 6.00] (Table III, Figure 2). During the first year, 9.00 [8.50, 9.00] visits were completed, but in the following years, the number was significantly smaller (7.00 [7.00, 7.00]).

In the subgroup of treatment-naive eyes, the median BCVA after the first year improved significantly to 69.95 [60.26, 78.81], and after the second year to 69.95 [60.26, 74.79] ETDRS letters. After the third year, it was 69.95 [60.26, 74.79], and was not significantly different from the baseline. After the first and second years, the mean gain in treatment-naive eyes was 5.88 [SD 11.77] and 5.65 [SD 11.65] ETDRS letters, respectively, without a significant difference. After the third year, the mean gain was significantly lower, reaching the value of 2.71 [SD 12.65] ETDRS letters. Based on the Snellen chart, a clinical improvement in BCVA of one line was

Table III. Morphological results in consecutive time intervals

Variable	Year	Value	Subgroup: treatment-naive eyes	Subgroup: pretreated eyes	*p*-value
Number of eyes	V0	135	78	57	
	1.	135	78	57	
	2.	116	66	50	
	3.	101	59	42	
CRT (µm); (median [IQR])	V0	320.00 [271.50, 355.00]	320.00 [273.25, 355.00]	315.00 [269.00, 350.00]	0.856
	1.	241.00 [208.50, 279.50]	238.00 [208.25, 260.75]	254.00 [215.00, 316.00]	**< 0.05**
p		< 0.001	< 0.001	< 0.001	
	2.	246.50 [212.00, 275.00]	245.50 [212.00, 275.00]	247.50 [216.25, 273.75]	0.997
p		< 0.001	< 0.001	< 0.001	
	3.	243.00 [210.00, 286.00]	245.00 [211.00, 293.50]	240.00 [210.25, 278.75]	0.691
p		< 0.001	< 0.001	< 0.005	
Δ CRT (µm); (median [IQR])	1.	–59.00 [–103.00, –13.50]	–77.00 [–111.00, –23.25]	–45.00 [–98.00, 0.00]	0.127
	2.	–54.50 [–110.75, –2.75]	–48.00 [–111.00, –0.50]	–74.50 [–109.00, –11.50]	0.822
p		< 0.001	< 0.001	< 0.001	
	3.	–68.00 [–126.00, –15.00]	–70.00 [–133.50, –10.00]	–66.00 [–112.50, –24.75]	0.827
p		< 0.001	< 0.001	< 0.005	
Injections (median [IQR])	1	8.00 [6.00, 8.00]	8.00 [7.00, 8.00]	6.00 [5.00, 7.00]	**< 0.001**
	2	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	4.00 [3.00, 5.00]	0.082
p		< 0.001	< 0.001	< 0.001	
	3	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	4.00 [3.00, 5.00]	0.082
p		< 0.001	< 0.001	< 0.001	

CRT – central retinal thickness; Δ CRT – change in CRT

achieved, with a significant difference noted at the end of the follow-up. Also, a significant reduction in CRT from the baseline was detected. After the first year, CRT in the subgroup of treatment-naive eyes was significantly smaller compared to pretreated eyes. In the first year, 8.00 [7.00, 8.00] injections were performed. In the following years, the number was significantly smaller (5.00 [4.00, 6.00]). During the first year, 9.00 [9.00, 9.00] visits were completed, but in the following years the number was significantly smaller (7.00 [7.00, 7.00]).

In the group of pretreated eyes with wAMD, the median BCVA in terms of the number of ETDRS letters did not change significantly after the first and second years of treatment. After the third year, BCVA was 65.10 [54.90, 69.95] ETDRS letters, with no clinical difference from the baseline, but at $p < 0.05$. After the first two years of the TP, BCVA in the pretreated subgroup was significantly lower compared to treatment-naive eyes, regardless of the type of chart used for visual evaluation (Figure 3). After the first, second and third years, the mean gain in pretreated eyes was 3.46 [SD 13.30], 3.49 [SD 13.81], and 4.05 [SD 11.52] ETDRS letters, respectively, without significant differences. In the subgroup of pretreated eyes, there was no clinically significant difference in BCVA change according to the Snellen chart. In subsequent time intervals, there were no significant differences between the treatment-naive and

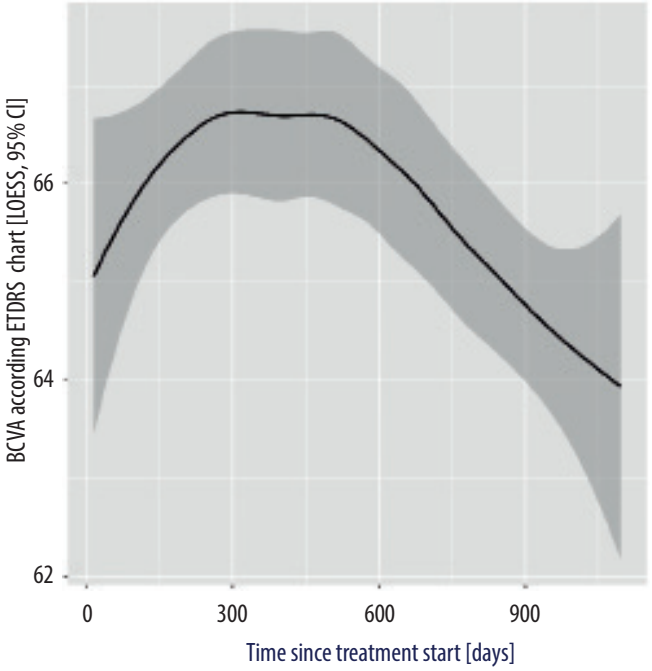

Figure 1. LOESS curve (95% CI) for the dependence of BCVA from the time, in the whole group

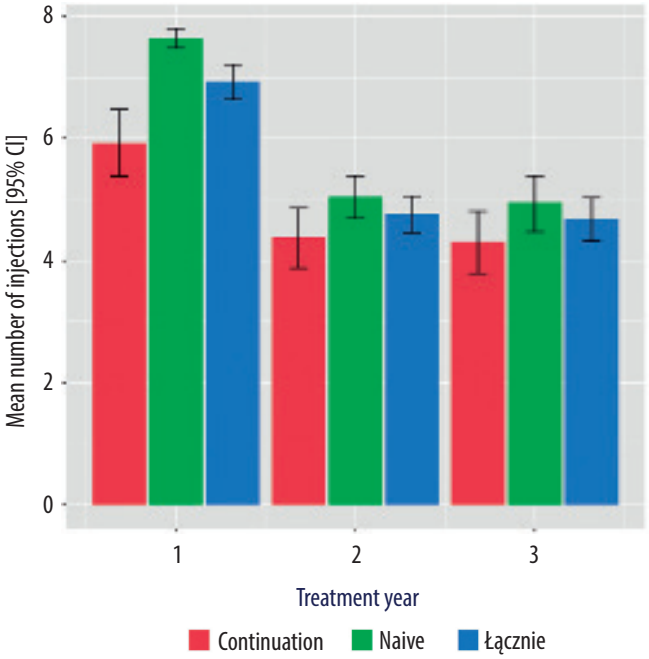

Figure 2. Number of injestions in the following years

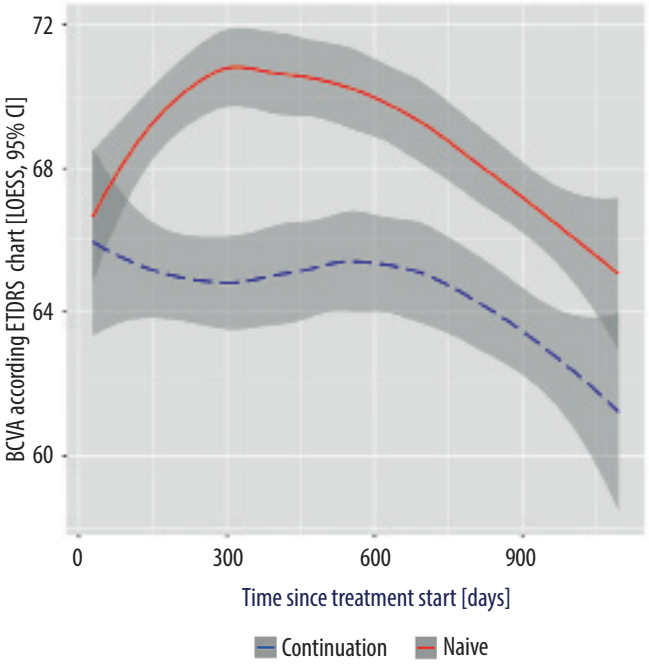

Figure 3. LOESS curves (95% CI) for the dependence of BCVA from the time, in the treatment-naive and pretreated subgroup

pretreated subgroups in the number of ETDRS letters gained. Similarly, there was no significant difference between the subgroups in the number of eyes gaining ≥ 10 ETDRS letters. Except for the second year of the TP, there were no significant differences in BCVA distribution (number of ETDRS letters) between the subgroups. In the subgroup of pretreated eyes, there was a significant reduction in CRT from the baseline, persisting over consecutive years. There were no significant differences in terms of change in CRT values between the subgroups in subsequent time intervals. In the first year, 6.00 [5.00, 7.00] injections were performed, but in the second and third years the number was significantly smaller (4.00 [3.00, 5.00]). During the first year, 8.00 [8.00, 9.00] visits were completed. In the following years, the number was significantly smaller (7.00 [6.25, 7.00]). During the first year, the numbers of injections and visits in the subgroup of pretreated eyes were significantly lower than in the subgroup of treatment-naive eyes.

No adverse effects associated with the intravitreal administration of drugs in the TP were noted during the study period.

DISCUSSION

Demographic information and real-world data on the efficacy of wAMD treatment in developed countries are currently recorded in electronic databases. The findings reported in this study are also based on the analysis of data collected in the SMPT. During the first year of treatment, the mean gain was 4.86 [SD 12.50] ETDRS letters with a median of 8.00 [6.00, 8.00] anti-VEGF injections. For treatment-naive eyes, the gain was 5.88 [SD 11.77], and for pretreated eyes it was 3.46 [SD 13.30] ETDRS letters, without a significant difference. Under the TP, patients receive treatment with either of two drugs: aflibercept and ranibizumab. In our study, a total of 80% subjects were treated with aflibercept. Accordingly, in the first year the majority of treatment-naive eyes received therapy according to a fixed regimen of three loading doses followed by an aflibercept injection administered every 2 months. During the period of three years, there were no cases of drug switching within the framework of the TP.

The functional outcomes in the first year are comparable to previously published reports on the basis of TP data. The study conducted by Figurska in a group of 94 wAMD patients treated with aflibercept showed a gain of 8.41 ETDRS letters after one year of systematic therapy, with the median number of injections equal to 8 [1]. In a one-year multi-center follow-up of 2,718 patients with wAMD treated under the TP, a mean gain of 2.9 ETDRS letters in treatment-naive eyes was noted, with a similar median of 7 injections [2]. In both cited studies, a significant morphological improvement was observed together with a shift of CRT towards lower values, similarly to our study material.

The outcomes obtained after a year of treatment under the TP in our study are similar to the findings reported by other authors. Talks *et al.* [11] analyzed a group of 1,840 treatment-naive eyes receiving therapy in accordance with the VIEW protocol, noting a gain of 5.1 letters after a mean of 7 injections. In the German multi-center PERSEUS study, regular treatment with aflibercept led to an improvement in BCVA from +3.1 ±10.7 (subgroup of pretreated eyes; 7.5 ±0.6 injections) to +8.0 ±17.7 (subgroup of treatment-naive eyes; 7.4 ±0.6 injections) ETDRS letters [12]. Regardless of the treatment regimen used, the mean improvement in BCVA in treatment-naive eyes was 5.3 ETDRS letters. Based on the outcomes of the PERSEUS study, Watchlin *et al.* concluded that regular treatment had a significantly greater positive effect on the functional parameters, compared to the scheme where the number of injections was

≥ 7 during the first year, but they were administered inconsistently with the VIEW protocol [13]. In our study, at the end of the first year, no significant differences were found in the number of ETDRS letters gained, with a significantly lower number of injections in the pretreated subgroup. In turn, Almuhtaseb *et al.* [14] reported one-year outcomes of regular AMD treatment with aflibercept in a group of 255 treatment-naive eyes (223 patients) in the UK. The BCVA improved by a mean of 8 letters, which was again comparable with the results of the VIEW 1 and VIEW 2 studies, as well as with our observations.

In a two-year study based on the real-world evidence of aflibercept therapy for wAMD in France (four-year observational RAINBOW trial), Weber *et al.* [15] noted an improvement in BCVA by a mean of + 3.0 ETDRS letters (in our study, the gain was 4.72 ETDRS letters; +5.65 ETDRS letters in the subgroup of treatment-naive eyes, and +3.49 in the pretreated eyes). Regular therapy was characterized by a gain of 4.9 ETDRS letters (a value comparable to our study).

The TP incorporates the principle of obligatory follow-up evaluations scheduled at fixed regular intervals. During subsequent years of treatment, injections are performed according to the PRN scheme, i.e. in cases of recurrence of disease activity with BCVA deterioration and/or morphological changes. In the RAINBOW trial, there was a mean loss of 2.5 ETDRS letters after two years in the subgroup of patients receiving irregular aflibercept treatment. In our study, no deterioration of BCVA was shown in long-term follow-up in any of the subgroups. In the RAINBOW trial, a mean of 6.0 injections were administered during the first year of treatment (median of 8.0 in our study), and 8.8 injections during two years (median of 5.0 injections over subsequent years in our study). The numbers of injections, both in the RAINBOW trial and in our study, are similar to the VIEW trial. Weber et al. highlight the importance of the loading phase and regularity of wAMD therapy for achieving significantly superior and lasting functional effects. The guideline is met by the Polish TP and our own study.

Eter *et al.* [16] presented two-year outcomes of the German PERSEUS trial. Regularly treated treatment-naive eyes achieved a mean improvement of 6.7 ETDRS letters at two years of treatment, compared to a mean of 1.8 letters among irregularly treated eyes. Regularly treated pretreated eyes showed a mean gain of 0.8 ETDRS letters, while the irregularly treated pretreated eyes had a mean loss of 2.7 letters. The mean gain noted for the entire study group was 1.1 ETDRS letters (treatment-naive eyes: +4.3 letters, previously treated eyes: –1.0 letter). The researchers found that, unfortunately, more than 80% of patients had received irregular treatment. Over the two-year study period, irregularly treated patients received a mean of 7.8 [±4.09] aflibercept injections. In regularly treated patients, the number of aflibercept injections was significantly higher (13.1 [±1.3]). The study by Eter et al. also provides evidence that the best functional effects are achieved by regular visits and injections. In the PERSEUS trial, the best functional effects (+8.1 letters) after 2 years were observed in treatment-naive eyes receiving therapy consistent with the VIEW protocol in the first year, and ≥ 4 injections of aflibercept in the second year. In our study, we also observed significantly higher BCVA during the first two years of the TP in treatment-naive eyes receiving regular injections from the onset of therapy. In addition, a significantly lower CRT value was noted after a year in the subgroup of treatment-naive eyes.

Eleftheriadou *et al.* [17] published three-year outcomes of aflibercept treatment for wAMD, based on the data derived from the Moorfields Eye Hospital electronic database. The study included a total 157 eyes with newly diagnosed wAMD, with treatment initiated in 2013-2014. Overall, 108 eyes of 102 patients completed the three-year follow-up. Over the consecutive years, the following BCVA changes were noted: year 1: +5.9 ±13.8; year 2: +6.4 ±14.9; year 3: +6.6 ±15.4 ETDRS letters. The functional outcomes were comparable with our observations. The researchers reported a reduction in CRT by 77.9 ±101.4 μm, which was similar to our observations (-68.00 [-126.00, -15.00] μm) at the end of the third year of treatment. The mean number of injections after 3 years was 15.9 ±6.1 (and was thus similar to our study). The long-term study by Eleftheriadou *et al.* provided more evidence, consistent with our observations, that regular therapy is associated with good and stable functional and morphological effects in patients with wAMD.

Even though the vast majority of patients in our study were treated with aflibercept, it is fitting to report data on ranibizumab therapy as well. According to a UK report (a multi-center study involving a total of 92,976 ranibizumab injections administered to 11,135 patients), ranibizumab treatment used in daily practice based on the regimen consisting of a loading phase followed by PRN treatment, results in a functional effect of +2.0 ETDRS letters after the first year, +1.0 after two years, and -2.0 after three years [18]. Of note, the number of injections administered in successive years is not small: 5.4 in the first year, and 4 in subsequent years, with a considerable number of follow-up visits according to the report: 9.2 in the first year, 8.2 in the second year, and 8.2 in the third year. In our study, improved functional outcomes were achieved in all time intervals, along with a greater number of injections but comparable number of follow-up visits. The findings mean that regulated wAMD treatment provided under the TP, mainly with aflibercept, translates into good long-term functional effects.

The results of 5-10 years of wAMD treatment with anti-VEGF injections are now published. Chandra *et al*. reported the outcomes of a single center (Moorfields Eye Hospital) study evaluating long-term (5-year) wAMD therapy with aflibercept [19]. The study enrolled treatment-naive patients with wAMD diagnosed in 2013-2014. The subjects were divided into three groups based on the injection scheme: Group A – continuous regular treatment, Group B – early cessation of treatment, and Group C – interrupted irregular treatment. A total of 468 patients (512 eyes) were entered for the study, with 66% completing 5 years of treatment. The final BCVA change was –2.9 (SD 23.4) ETDRS letters, while the cumulative number of injections was 24.2. Patients in Group A (regular treatment) received a significantly higher cumulative number of injections compared to Groups B and C (31.8 vs. 14.6 vs. 18.4; $p = 0.001$). BCVA was +8.0 ETDRS letters higher in the ≥ 20 injections group than in the < 20 group ($p = 0.001$). The results show significantly better

long-term functional effects of wAMD treatment with systematic injections of aflibercept, without limitations in number.

Brynskov *et al.* reported the 10-year outcomes of wAMD therapy in a group of 3,668 patients with newly diagnosed wAMD [20]. The patients received a mean of 5.4 intravitreal anti-VEGF (aflibercept, ranibizumab) injections in the first year of treatment, and 4.0-4.3 injections during subsequent years. After 10 years, the researchers noted a mean deterioration in BVCA of 5.0 (± 2.2) ETDRS letters, which in practice corresponds to many years of functional stabilization. For comparison with our observations, after the first year the authors found a change in BCVA by +0.7 ETDRS letters. After the second and third years, the change was –1.0 and –1.8 ETDRS letters, respectively.

Chandra *et al.* also extended their analysis of the Moorfields Eye Hospital database to 10 years [21]. The study enrolled patients who started wAMD treatment with intravitreal injections in 2008-2009. The mean change in BCVA was –2.1 ETDRS letters. In 87.5% of cases, the drug was switched from ranibizumab to aflibercept during the follow-up period. Over the course of 10 years, a mean of 52.2 (SD 18.1) injections were administered (between 18 and 98). At the end of the follow-up, 67.1% of the subjects were found to have lost < 15 ETDRS letters, which was recognized as long-term functional stability attributed to regular follow-up visits and treatment. Low baseline BCVA, foveal atrophy, and the final size of the atrophic lesion had a significant negative impact on the ultimate functional outcomes. Regarding the Polish TP, during the following years, the analysis should be extended to include in-depth morphological assessment focused on atrophy and scarring, and the correlation of these changes with long-term functional outcomes.

As mentioned above, the treatment of wAMD in the Polish TP, with the exception of the first year of treatment with aflibercept, is based on the PRN regimen. However, the treat-and-extend (T&E) regimen is becoming increasingly widely used around the world, especially for patients treated with aflibercept. Eleftheriadou *et al.* followed up a total of 84 patients (94 eyes) treated with aflibercept for two years (year 1: VIEW protocol, year 2: T&E) [22]. The patients received a mean of 11.4 ±4 injections of aflibercept (7.3 injections during the first year). In the first year of therapy, VA improved by a mean of 5.4 letters and in the second – by 5.1 ±14.9 letters. Barthelmes *et al.* studied a group of 136 treatment-naive eyes (123 patients) with wAMD receiving aflibercept therapy according to the T&E regimen in daily clinical practice for two years [23]. The mean BCVA was found to have improved by 6 ETDRS letters. The researchers showed that aflibercept therapy based on the T&E regimen produced good results in daily practice, comparable to those obtained in randomized trials, with a significant reduction both in the number of follow-up visits and drug administrations over time. Traine *et al.* presented the results of 4-year aflibercept therapy of treatment-naive eyes with wAMD, according to the T&E regimen [24]. After the first year of therapy, the mean gain in ETDRS letters was 5.7, and after the fourth year +3.6 (+3.26 ETDRS letters after the third year in our study). In the first year, a mean of 7.7 (±1.2) injections were administered, and 4.4 (±1.6) visits were completed. During the consecutive years, the mean numbers of injections and visits were 4.4 (±1.9) and 4.3 (±1.3), respectively. Even though in our study the number of injections was similar, the number of visits was higher, with a median of 9 visits in the first year, and 7 in subsequent years. This is due to the obligatory follow-up visits within the TP which take place at intervals not less than 62 days. The findings reported by Traine *et al.* can be used in the future to modify the Polish TP scheme in favour of the T&E regimen which relieves the healthcare system of the burden of an excessive number of patient follow-up visits, and provides an effective therapeutic option with a number of injections comparable to our observations.

Our study, which was conducted on the basis of data from the WIM, had certain limitations. The number of patients was relatively low, but it was the first group to undergo a long-term follow-up and systematic treatment under the TP in a single center. Consequently, the results were associated with less error than a multi-center analysis of data collected by different researchers, usually with different methodologies, e.g. with regard to the evaluation of functional parameters or OCT. Since the treatment of wAMD in Poland was not systematized before the introduction of the TP, in line with the adopted methodology patients were divided into treatment-naive and pretreated groups. In this regard, the methodology of our study was similar to the PERSEUS trial. In the author's opinion, the methodology is suitable for a detailed analysis of the structure of the population treated under the TP. As shown by our findings and the experience of other researchers, the adopted methodology is able to demonstrate the importance of early and regular treatment of wAMD, which in practice may be more relevant than the number of injections per se. A limitation of our study is the rigorous provision included in the TP which restricts treatment to fixed or PRN regimens and requires that follow-up examinations are performed no later than at 62-day intervals. This results in a high number of follow-up visits, especially during the first year of treatment. However, taking into account other previous real-world studies, such as AURA or LUMINOUS, compliance with the follow-up evaluation regime and regular wAMD therapy translate into significantly better, stable functional effects.

The TP for the treatment of wet AMD is being continued. Modifications of the exclusion criterion introduced from 2020 indicate the orientation of the TP towards injections, i.e. active treatment, with limited follow-up examinations. Since wAMD is a chronic disease, the author of this manuscript is planning to extend the TP evaluation by subsequent years.

CONCLUSIONS

Regular treatment of wAMD in line with the guidelines of the therapeutic program leads to functional stabilization and significant morphological improvement over a long-term follow-up period (3 years), with significantly fewer injections administered in consecutive years. During the initial two years of the therapeutic program, treatment-naive eyes exhibit significantly higher functional parameters compared to pretreated eyes.

DISCLOSURE

The author declares no conflict of interest.

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