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The right choice of treatment regimen as the key to successful therapy of wet AMD

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HIGHLIGHTS

Both inflexible and *pro re nata* scheme, that is the ways how medical treatment is realized in Polish public health care system, not only causes difficulties for the patient, the doctor and the system efficiency, but also does not give satisfying therapeutic results.

ABSTRACT

Age-related macular degeneration remains the main cause of central vision impairment in the elderly population in developed countries. Currently, the most effective method that significantly inhibits the progression of wet AMD consists of intravitreal anti-VEGF injections. Not only the selection of the right active substance, but also the protocol of their administration plays an important role in proper therapy. The AMD Drug Programme[1] significantly increased the availability of modern treatment for Polish patients. However, the available therapeutic plans still do not include the so-called treat-and-extend regimen. In our work, we show the significant advantages of the above-mentioned regimen over the ones currently available in the Polish Drug Programme.

Key words: age-related macular degeneration, anti-VEGF drugs, national therapeutic programme for AMD

[1] A Drug Programme is a direct ministerial drug financing programme for particularly expensive therapies in Poland.

INTRODUCTION

Age-related macular degeneration (AMD) is the main cause of significant central vision impairment in the elderly population [1, 2]. The introduction of substances downregulating the vascular endothelial growth factor (anti-VEGF) as a treatment option for wet AMD (exudative AMD) has significantly reduced the risk of permanent and irreversible vision loss both in near and distance vision [3]. Numerous studies, both multicentric, randomized trials, as well as everyday clinical practice (real-life evidence) confirm the efficiency of this treatment method [4–6]. The drugs from this group that are currently registered are: aflibercept, ranibizumab, brolucizumab and conbercept (registered for the treatment of wAMD in China).

The choice of the correct regimen of anti-VEGF administration is a crucial factor in therapeutic success [7, 8]. The rigid protocol, especially once per month, entails high therapy costs and requires the patient to visit the clinic frequently and regularly. The reactive protocol abbreviated as PRN (*pro re nata*) consists in administering injections if choroidal neovascularization activity is identified in the patient [8]. PRN also requires consistent, regular follow-up visits and – similarly to the rigid protocol – becomes burdensome both for the patient and for the attending physician in the long term. The treat-and-extend strategy (T&E) consists in gradually increasing the interval between subsequent visits and injections. Currently, it is a protocol that, first of all, allows for an individualized approach to therapy; and secondly, reduces the number of required follow-up visits between injections, which improves cooperation with the treated patient [9, 10].

In 2015, Poland has started a therapeutic programme for wAMD, which is reimbursed from public funds: the *Treatment for neovascular (exudative) form of age-related macular degeneration (AMD)*. Patients qualified for this programme must meet specific eligibility criteria, including a specified visual acuity and morphological condition of the macula (tested by means of OCT or fluorescein angiography – AF). The drug programme for the treatment of wAMD includes two substances – aflibercept and ranibizumab. Depending on the drug that is being used, there are the following treatment protocols: for aflibercept, a rigid protocol in the first year of treatment, and the PRN in subsequent years. For ranibizumab, PRN is used as the protocol for the entire therapy. As of today, the treat-and-extend protocol is not registered as part of the Polish refunded drug programme [11].

The hereby article intends to demonstrate the advantages of treating wAMD with the treat-and-extend protocol, as compared to other existing protocols, on the basis of the analysis of our own results from our daily clinical practice (real-life evidence) carried out in the last 2 years and compared with data gathered by other researchers.

OBJECTIVES

The objectives of our study consisted in assessing the efficiency of a 2-year-long wAMD therapy in patients treated with aflibercept for MNV activity within the framework of the national wAMD drug programme, comparing anatomical and functional results, as well as analysing the number of visits in comparison with the number of administered injections depending on the kind of therapeutic protocol. Therefore, indirect results also include the assessment of potential economic advantages of including the treat-and-extend protocol in the national drug programme for wAMD.

PATIENTS AND METHODS

We performed a retrospective analysis of medical documentation of 107 eyes of 99 patients who had been treated within the framework of the wAMD drug programme and had completed one year of therapy; as well as 45 eyes of 42 patients who completed 2 years of therapy and continued to meet the eligibility criteria. The patients were treated in the Ophthalmology Clinic of the Poznan University of Medical Sciences from November 2015 to September 2018. All these patients were treated with aflibercept, in the dose of 2 mg in 0.05 ml of solution per single injection. In all of them, we analysed the functional improvement by assessing the changes in the best corrected visual acuity (BCVA) and also anatomical improvement consisting in the changes of central macular thickness (CMT) with the use of OCT technology. Additionally, we took into account the number of visits of each patient and compared them to the number of injections that were administered depending on the therapeutic protocol that was used in each case. Moreover, the adverse effects that appeared during therapy were also taken into account.

The entire group was divided into two subgroups depending on the year of therapy and, as a result, the treatment protocol. In the first year, the patients were treated following a rigid protocol (subgroup I, 107 eyes). Each of them received a total number of 7 injections: the first 3, once per month; and the remaining 4, every two months. In the second year of therapy, the patients were treated according to the PRN protocol (subgroup II, 45 eyes), which means that injections were given on the basis of the MNV activity. The best corrected visual acuity was assessed with the use of Snellen charts, and later the result was converted into the number of letters on ETDRS charts. The central macular thickness (CMT) was measured with a swept source DRI OCT device.

The activity of neovascular membrane was assessed on the basis of OCT images of the macula, which were analysed taking into account the presence of retinal edema and/or subretinal fluid. The above-mentioned subgroups were also

evaluated in view of the impact of former anti-VEGF treatment on the current therapy performed as part of the drug programme.

The eligibility criteria included: presence of active MNV in the course of AMD, MNV less than 12 DD; lack of permanent damage to the fovea centralis, lack of dominant haemorrhage and geographic atrophy; age > 45 years, BCVA 0.2–0.8; informed consent given by the patient. The exclusion criteria were the following: hypersensitivity to the active substance; active infection in the eye or the surrounding area; pregnancy and breastfeeding; rhegmatogenous retinal detachment or macular hole; reduction of BCVA < 0.2; permanent damage to the structure of fovea centralis.

STATISTICAL EVALUATION

Descriptive statistics were calculated for all the quantitative variables. The normal distribution was checked with the use of the Shapiro-Wilk test. Due to the lack of confirmation of the hypothesis concerning normal distribution and homogeneity of variance in the subgroups, the changes between individual measurements (I–VII in the 1st year and I, III, IV, VIII and the last measurement in the 2nd year) were analysed with the Friedman's ANOVA test and the *post hoc* Dunn test with Bonferroni adjustment. The magnitude of the effect was assessed with the use of Kendall's W statistics, expressed by the formula:

$$W = \frac{(X^2 w)}{N(k\text{-}1)}$$

where:
$\chi^2 w$ – value of Friedman's ANOVA statistics
N – sample size
k – number of measurements.

In order to evaluate the degree of changes throughout the entire study, we calculated the differences between the initial and final values for the CMT variable, as well as the differences between the final and initial values for the ETDRS variable, in a way that positive results signify improvement and negative results indicate a worsening of the parameter. The analysis of these variables was carried out with the use of the two-way ANOVA model (non-normal distribution, but with asymmetry <|1.0| and fulfilled hypothesis concerning homogeneous variance in the subgroups) for patients in the 1st year, as well as one-way ANOVA model for patients in the 2nd year of treatment. Moreover, the Pearson's linear correlation coefficient and Spearman's rank correlation coefficient were calculated for selected variables in the group of patients in the 2nd year of therapy.

The level of significance assumed for statistical inference was $\alpha = 0.05$. The analyses were carried out using the Statistica software (StatSoft, Inc., 2011).

RESULTS

The demographic data of subgroup I are shown in table 1. All the patients from subgroup I (107 eyes) experienced an improvement in BCVA as a result of the treatment (Me = 2.5 letters). In the group under research, in case of patients who had been previously treated with anti-VEGF preparations (30 eyes), the visual acuity improvement (Vis) was not statistically significant and amounted to 2.5 letters in ETDRS charts; while in case of patients who had not been previously treated with anti-VEGF (the remaining 77 eyes) the improvement amounted to 5 letters and was statistically significant ($p < 0.01$). The patients who could continue the therapy after one year (64 eyes), i.e. who met the criteria required to remain in the programme, also experienced a statistically significant Vis improvement amounting to Me = 5 letters ($p < 0.01$), while patients who were excluded from the drug programme after one year (43 eyes) did not experience improvement of visual acuity.

All the patient subgroups described above achieved an anatomical improvement at the end of the 12th month of treatment (in the 1st year, when rigid protocol was followed), expressed as a significant reduction of retinal thickness in the macula ($p < 0.01$). The average change in retinal thickness in 43 eyes of patients who were excluded from the drug programme amounted to 218.6 μm, while in the 64 eyes of the patients who remained in the programme, the average change was of 116.96 μm. The differences between groups were statistically significant. The average retinal thickness reduction was also significantly higher in the group of patients who had not been treated previously, and amounted to 218.3 μm, while in the group of previously treated patients the thickness decreased by 117.26 μm on average (fig. 1). At the end of the first year, active neovascular membrane was present in 48.9% of the patients.

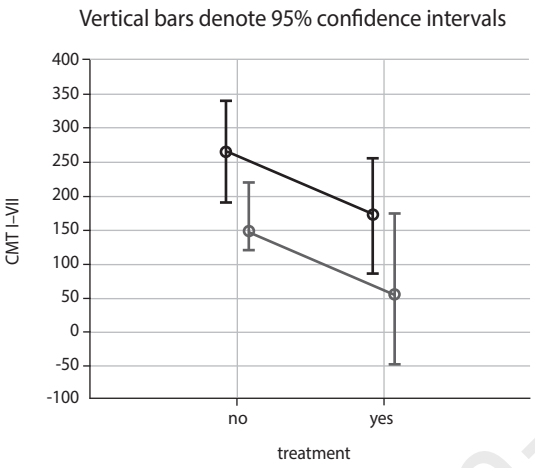
TABLE 1

Demographic data of patients from subgroup I.

Average age	Gender	Eye	Therapy	Injections
76.9 y.o.a.	F – 70 (65%)	OD – 54 (50.5%)	new – 77 (72%)	**6.8**
	M – 37 (35%)	OS – 53 (49.5%)	continued – 30 (28%)	

FIGURE 1

Average CMT changes in subgroups (μm).



The demographic data of subgroup II have been presented in table 2. In the 2nd year of PRN therapy in patients who had not been previously treated (31 eyes) the number of correct letter readings increased by almost 4 letters after the treatment, while in the group of pre-treated patients (14 eyes) the number of letters read was reduced, on average, by more than 2. The differences were not statistically significant. The average reduction of central macular thickness (CMT) in the 2nd year of therapy in previously treated patients was not statistically significant and amounted to 79 μm, while in patients who had not been treated previously, the difference was statistically significant and amounted to 129 μm ($p < 0.001$) (fig. 2). At the end of the second year, active neovascular membrane was present in 66% of the patients.

FIGURE 2

Average CMT changes in subgroups (μm).

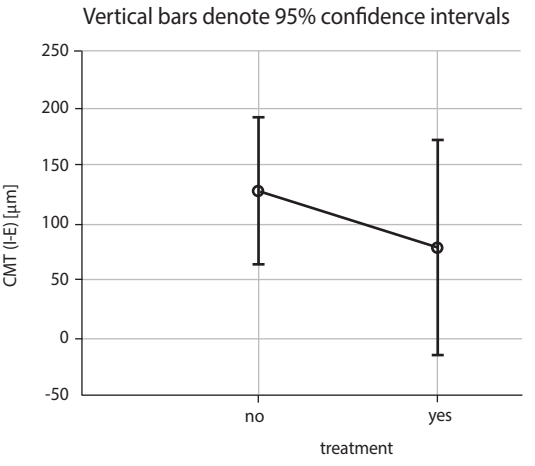


TABLE 2

Demographic data of patients from subgroup II.

Average age	Gender	Eye	Therapy	Injections
77.6 y.o.a.	F – 29 (69%)	OD – 22 (49%)	new – 31 (69%)	10.1
	M – 13 (31%)	OS – 23 (51%)	continued – 14 (31%)	

In subgroup I (1st year of therapy), an average number of seven injections were given to each patient and the patients participated, on average, in 7 visits. In subgroup II (2nd year of therapy) the patients received an average number of 3.1 injections and participated in 7.3 follow-up visits, on average.

A statistically significant, moderate ($|0.3| \leq r \leq |0.5|$) and positive correlation was observed between the number of letters read during the first visit and the number of visits in the 2nd year, as well as the number of injections (tab. 3).

A similar correlation was demonstrated in the group of patients who had not been previously treated (tab. 4), while patients who had been treated in the past did not show such correlation (tab. 5).

DISCUSSION

Considering the development of VEGF inhibitors and their introduction as a universal form of treatment for exudative AMD, the next crucial issue consists in determining the optimal treatment protocol to achieve the most satisfying results, especially considering the difficulties of daily clinical practice. When considering the therapeutic success, both anatomical effects measured by OCT and the improvement of visual acuity need to be considered. Another, equally important factor consists of the life quality of patients, which can improve thanks to the subjective feeling of being able to cope with daily activities on one's own, but is also affected by the necessity to travel to subsequent follow-up visits, even if there are no indications for an injection.

Eliminating unnecessary follow-up visits, while at the same time preserving the maximum level of efficiency, seems to be the biggest challenge for today's anti-VEGF therapy used in wAMD treatment. From the medical point of view, it is important to customize the treatment for each individual, among other reasons, because of the potentially highest benefit from this treatment for patients who have never received anti-VEGF treatment before. Similar results have also been achieved in our study. Moreover, it has been proven that patients with residual subretinal and intraretinal fluid achieve better therapeutic effects when injections are given to them more often [12].

The assessment of the activity of this disease consists, among others, of monitoring the central macular thickness (CMT) via the OCT test. The accumulation of subretinal fluid (SRF) and intraretinal fluid (IRF) is evidence of active AMD related to neovascularization. A leakage from inappropriate vessels in the macular area results in progressive damage to the photoreceptor layer and RPE [13]. Therefore, a prolonged presence of fluid is unfavourable, not only as a factor that worsens current visual acuity, but also due to the risk of permanent damage to the central visual field that will persist even after the regression of neovascular membrane activity. Although it seems obvious that from the point of view of the patient an improvement of BCVA is the most important factor, the appearance of SRF visible in the OCT scan can be a predictor of impending functional deterioration, and as such it constitutes an efficient prognostic indicator and an indication for administering the injection [14].

On the one hand, the results of our study confirm the efficiency of anti-VEGF therapy for wAMD both in its anatomical and functional aspects; but on the other hand, the treatment protocols available in the Polish drug programme leave a high percentage of patients with an active stage of the disease. This is particularly visible at the end of the 2nd year of therapy, when MNV activity is present even in 66% of the treated patients. We suppose that this is due to not administering enough injections to our patients during the second year of treatment, which, in turn, is caused by a high number of patients actively treated in our Centre.

TABLE 3

Correlation between the number of letters read and the number of injections and visits in the 2nd year of therapy (N = 45).

		ETDRS I	ETDRS III	ETDRS IV	ETDRS VIII	ETDRS E	ETDRS (E-I)
No. of visits	r_{xy}	0.34*	0.18	0.12	0.20	0.12	-0.27
	r_s	0.39**	0.2	0.16	0.16	0.07	-0.28
No. of injections	r_{xy}	0.32*	0.17	0.05	0.09	-0.06	-0.38**
	r_s	0.30*	0.19	0.1	0.07	-0.05	-0.35*

* p < 0.05; ** p < 0.01; *** p < 0.001.

TABLE 4

Correlation between the number of letters read and the number of injections and visits in patients who had not been treated previously (N = 31).

Not pre-treated		ETDRS I	ETDRS III	ETDRS IV	ETDRS VIII	ETDRS E	ETDRS (E-I)
No. of visits	r_{xy}	0.36*	0.22	0.17	0.17	0.06	-0.39*
	r_s	0.38*	0.24	0.18	0.06	0.02	-0.41*
No. of injections	r_{xy}	0.37*	0.21	0.12	0.17	-0.06	-0.50**
	r_s	0.31	0.21	0.15	0.14	-0.05	-0.44*

* p < 0.05; ** p < 0.01; *** p < 0.001.

TABLE 5

Correlation between the number of letters read and the number of injections and visits in pre-treated patients (N = 14) – none of the tested parameters was found to be statistically significant.

Pre-treated		ETDRS I	ETDRS III	ETDRS IV	ETDRS VIII	ETDRS E	ETDRS (E-I)
No. of visits	r_{xy}	0.33	0.01	-0.01	0.32	0.26	-0.03
	r_s	0.44	0.07	0.04	0.41	0.20	0.00
No. of injections	r_{xy}	0.10	0.01	-0.15	-0.24	-0.08	-0.13
	r_s	0.28	0.02	-0.11	-0.06	0	-0.08

* p < 0.05; ** p < 0.01; *** p < 0.001.

The studies carried out up to date in daily clinical practice show that patients treated according to the treat-and-extend protocol continuously from the very beginning, have MNV activity after the second year of treatment only in 10% of the cases [9]. Other observations related to the group of patients treated according to the rigid protocol in the 1st year and treat-and-extend in the second year, have confirmed the presence of active neovascular membrane in slightly over 27% of patients at the end of the 2nd year of therapy [4]. Another study compared the functional results of patients who were treated for 2 years according to the treat-and-extend protocol with the results of patients treated with T&E in the first year and PRN in the 2nd year. The results of this study also clearly indicate that the proactive approach of T&E is better [14].

When comparing data from the quoted publications with our own observations carried out for 2 years in our Centre, it becomes obvious that the treat-and-extend protocol is well justified from the medical point of view, permits to personalise the therapy to a sufficient degree, and to maximise its effects. The PRN system forces the patients to participate in follow-up visits between subsequent drug administrations, which unfortunately prolongs the waiting time for the next injection and, as a result, exacerbates the pathological process of the disease. In spite of coming to over 7 visits during the 2nd year of treatment, patients received, on average, only slightly over 3 injections during that year. Therefore, unless a casual treatment for wAMD is developed in the future, we must focus on improving the efficacy of therapy with available means. When considering the economic aspect of wAMD treatment, it is worth noting that in a 2-year-long observation comparing patients treated with the rigid protocol to a group of patients treated according to the treat-and-extend protocol, the functional effect was slightly better in the first group, where injections were given at similar intervals, but the number of injections that were administered in total was much higher in the rigid protocol [15].

The above-mentioned study was continued in the 3rd year, and the rigid protocol was switched to PRN, which resulted in a significant worsening of the patients' functional capacities. In patients who continued their treatment according to the treat-and-extend protocol, there was only a very small reduction of the number of letters they were able to read at the end of the 3rd year of therapy. The cooperation of patients and their families in the process of a long-term therapy can also be more effective if unnecessary, burdensome visits that do not translate into clinical improvement are eliminated. This thesis seems intuitively true, but there is also scientific evidence that confirms it.

In a 4-year-long observation of daily clinical practice it was noted that patients treated only with the proactive (T&E) protocol for the entire duration of the therapy were able to read more and more letters every year, although the increase got smaller in subsequent years [10]. For the sake of comparison – within the Polish drug programme, therapeutic success is defined as lack of progression of the disease measured with functional results, even if there is no visible improvement. The studies mentioned above prove that, after 1 year of treatment, an important share of patients (80%) required injections in intervals over 2 months, and in the subsequent years almost half of the patients needed 4 or less injections per year [10].

When we combine the above results with the fact that in the treat-and-extend protocol each visit goes together with an injection, the conclusions concerning economic viability and ergonomic benefits are clearly favourable in case of T&E, especially considering that the entire Europe is currently struggling with limited resources such as the shortage of doctors and funds, as well as difficulties typical for elderly patients. The treat-and-extend protocol that has been introduced and is being used in Europe, seems to be the best developed strategy that exists nowadays, as it permits to adjust the therapy to patient's individual needs and adjust the number of follow-up visits and injections accordingly to the activity of the disease and the patient's response to treatment. In conclusion, when searching for balance between the above-mentioned limitations and good treatment results both in the anatomical and functional aspects, it seems necessary to replace the current rigid protocol used in the first year and the PRN used in subsequent years with the more individualised treat-and-extend strategy.

CONCLUSIONS

The results of our study demonstrate that continuing with the combination of rigid + PRN protocols, which are the only ones currently available within the wAMD treatment programme refundable from public funds in the Polish health care system, not only causes difficulties for the patient and the physician, but also puts an unnecessary strain on the system, while failing to provide satisfactory therapeutic results.

Figures: from the author's own materials.

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Authors' contributions:
Jarosław Kocięcki: development of the study topic;
Wojciech Suda: selection of the study group, methodology, data analysis, writing the manuscript;
Agnieszka Lisiak: selection of the study group, methodology, data analysis, writing the manuscript.

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