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The drug program for wet form of AMD – the effectiveness of treatments based on diagnostics tests and patients opinion

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HIGHLIGHTS

The effectivity appraisal conducted with follow up treatment patients (treated before implementing the drug program) indicates the disease standstill and improvement in acuity of vision.

ABSTRACT

In people over 45 AMD is considered main reason for decrease in acuity of vision and blindness (amaurosis/ablepsia/typhlosis). The wAMD treating may require an immediate using of anti-VEGF eye injections (into the vitreous cavity). The AMD treatment program with ranibizumab and aflibercept has been available in Poland since 2015. The research aim was to evaluate the efficiency of the AMD treatment program in 98 patients participated in the AMD treatment program. Patients have been examined using diagnostic trials and diagnostic survey.

Key words: wet form of AMD, drug program, ranibizumab, aflibercept, visual acuity

INTRODUCTION

Age-related macular degeneration (AMD) is the major cause of severe vision loss and blindness in people over 45 years of age, particularly in developed countries. The disease affects the part of the retina responsible for central vision [1]. AMD involves the outer layers of the retina, retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris (CC). Abnormalities in retinal metabolism lead to the accumulation of extracellular material that deposits between the retinal pigment epithelium (RPE) and Bruch's membrane. These deposits, called drusen, are associated with the early stages of dry AMD, and although at this stage disease develops asymptomatically, drusen may lead to visual defects (metamorphopsia), reduced contrast or color distortions [1].

The studies conducted by European ophthalmologists showed that AMD leads to permanent and irreversible changes in the retina and choroid, leading to a partial or almost completes loss of central vision [1]. Even people who are > 45 years old can suffer from AMD; disease prevalence in this group of patients is about 8%. The prevalence of AMD increases with age and in patients above 80 years is up to 40% [2]. Moreover, the epidemiological outlook of AMD is not optimistic, particularly in the European population [3].

The Amsler grid test, in which patients interpret the image (each eye is tested separately), helps detect early signs of macular degeneration, such as scotomas and distortions [4, 5].

Dry AMD is a chronic disease. Along with disease progression, the number of drusen increase and the areas of RPE gradually degenerate, leading to the late stage of dry AMD, i.e., geographic atrophy. Thus, patients report higher metamorphopsia and deterioration in near and far visual acuity, which eventually leads to central scotoma. Although peripheral vision is preserved, daily activities are impaired to such an extent that patients are often diagnosed with functional blindness [6, 7].

Wet AMD, which develops in about 10% of patients, is far less common than the dry type, but its course is more rapid with significant deterioration of visual acuity leading even to complete blindness that affects the central visual field. Wet AMD is characterized by retinal pigment epithelial detachment associated with choroidal neovascularization, i.e., the proliferation of new, abnormal blood vessels that originate from the choroid through a break in the Bruch's membrane into the subretinal pigment epithelium or subretinal space [8].

Vascular proliferation can originate from choroidal or retinal vessels. In choroidal neovascularization, new blood vessels penetrate the natural barrier, which is the Bruch's membrane, and grow under the retinal pigment epithelium [1, 6]. Moreover, retinal neovascularization can affect choroid vessels leading to pathological retinal-choroidal anastomoses [9]. Regardless of the origin, newly formed blood vessels leak because of structural abnormalities and lack of tight junctions between their walls. This may lead to serious complications such us hemorrhagic detachment of the retinal pigment epithelium and the inner sensory layer of the retina, subretinal, intraretinal or vitreous hemorrhages, subretinal lipid exudates, or, sporadically, to exudative retinal detachment. Disciform scars, associated with deep and irreversible vision loss, represent the end-stage of neovascularization [6, 10].

Currently, intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors are the first treatment offered to patients with wet AMD. This symptomatic therapy helps close or limit the leakage from newly formed choroidal vessels and slows down central retinal degeneration with associated loss of vision [11].

Treatment of the wet AMD involves properly timed administration of intravitreal anti-VEGF injections. Treatment program with ranibizumab and aflibercept for patients with wet AMD has been available in Poland since 2015 when the Ministry of Health approved these two drugs.

OBJECTIVES

The study aimed to evaluate the effectiveness of the drug program in patients with wet AMD.

MATERIALS AND METHODS

The study included 98 patients with wet AMD who had been enrolled to the drug program at the Ophthalmology Clinic of The St. Barbara Provincial Specialist Hospital No. 5 in Sosnowiec.

Patients were divided into four groups:

- **study group 1 – patients continuing treatment:** 19 patients, including 13 women (10 right eyes and 3 left eyes) aged 67–92 years and 6 men (2 right eyes and 4 left eyes) aged 68–81 years
- **study group 2 – patients starting under a standardized T&E regimen:** 27 patients, including 9 women aged 69–92 years and 18 men aged 63–90 years
- **study group 3 – patients starting aflibercept treatment:** 34 patients, including 20 women aged 61–93 years and 14 men aged 61–88 years
- **study group 4 – patients starting ranibizumab treatment:** 18 patients, including 9 women aged 60–96 years and 9 men aged 61–86 years.

The mean age of study participants in each group is presented in table 1.

TABLE 1

The mean age of participants in each study group.

Sex	Number of patients	Mean age (years)	Group 1	Group 2	Group 3	Group 4
Women	51	76.7	79.8	75.4	75.2	76.3
Men	47	75.6	75.5	74.9	76.2	75.8

The mean length of the disease differed between female and male study participants and amounted to 3.2 years in women and 2.5 years in men (p = 0.031). The mean duration of the disease was 2.87 years (SD = 1.68). Two research methods were used in the study: diagnostic tests and a diagnostic survey in the form of a questionnaire.

Methods of diagnostic tests

Visual acuity in selected groups was tested with Snellen chart with optotypes and constant lighting. The test was always performed before other examination to ensure that patient's eyes were not tired. Visual acuity was measured without correction. Optical coherent tomography (OCT) was performed at each visit. To analyze treatment effects we selected OCT results from all study participants at qualification to the drug program and from the follow-up visits after the seventh aflibercept injection and the third ranibizumab injection.

Retinal thickness was measured in microns using a retina map scan with an aim to always perform sequential central macular scans. The results were obtained automatically using standardized-protocol database.

Author's survey questionnaire

Surveys were conducted in the same group of patients. The patients filled in the questionnaire at follow-up visits. The questionnaire contained 19 closed questions with one possible answer (except for two questions with several possible answers). Respondents assessed their participation in the drug program taking into account access to diagnostic tests and to appointments with ophthalmologists, as well as their satisfaction with treatment effects. Moreover, the respondents were asked if their families help them arrive for visits and do household chores.

First, the raw data was entered into Excel and then processed using Statistica v. 13.1.

RESULTS

Diagnostic tests results

The mean improvement in visual acuity was achieved in the following groups of men:

- group 3 – in the right eye by 4 lines
- group 1 – in the right eye by 2 lines
- group 2 – in both eyes by 2 lines.

In group 4, visual acuity in men was improved by 1 line for the right eye and 2 lines for the left eye. The greatest visual acuity improvement among women was reported in group 2 for the right eye (by 2 lines). In the group 1 (woman), the visual acuity improved by 1 line.

Among men, we reported no visual acuity deterioration in both eyes in either group.

Treatment effects on visual acuity in all four groups are summarized in table 2.

Survey results

All patients were satisfied with participation in the drug program, although their level of satisfaction varied. The majority of participants were very satisfied – 58 people (59%), 37 people (38%) declared moderate satisfaction, and 3 people (3%) were sufficiently satisfied.

Moreover, participants assessed their treatment results. In majority, treatment results were positively assessed by 78 participants (79.59%), including 36 women (36.73%) and 42 men (42.86%). Only 20 respondents (20.41%) negatively assessed treatment results, including 15 women (15.31%) and 5 men (5.1%). A statistical relationship was found between the declared satisfaction with therapy and respondents' sex (p = 0.021). A total of 46% of women and 54% of men were satisfied with the treatment results.

The availability of medical appointments and diagnostic tests as well as own level of knowledge about AMD were positively assessed by all respondents. However, as many as 82% of study participants had not been treated with intravitreal injections before joining the AMD drug program. A total of 94% of respondents were satisfied with the method of administering the drug, whereas 6% did not like too frequent visits to the ophthalmology clinic. The majority of participants taking part in the program came alone for tests and intravitreal injections. According to 60% of patients, frequent visits to the clinic were not a problem, but for 40% of the respondents, including 33% men and 67% women, it was so burdensome that they needed assistance from family members to arrive at the clinic for intravitreal injection or follow-up tests, and this result was statistically signifi-

TABLE 2

Analysis of the study groups treated in the drug program.

Groups	mean age in each group	mean visual acuity at baseline	mean visual acuity at baseline	mean retinal thickness at baseline	mean retinal thickness at baseline	number of injections	number of injections	mean visual acuity after the seventh and third injection in the group 4	mean visual acuity after the seventh and third injection in the group 4	mean retinal thickness after the seventh and third injection in the group 4	mean retinal thickness after the seventh and third injection in the group 4
		OP	OL	OP	OL	OP	OL	OP	OL	OP	OL
Women	**76.7**										
Group 1 – patients continuing treatment	**79.8**	**0.2**	**0.1**	**400.6**	**513.33**	**7.8**	**7.66**	**0.27**	**0.28**	**370.2**	**381**
Group 2 – patients treated with aflibercept under a standardized T&E regimen	**75.4**	**0.32**	**0.225**	**447**	**403.25**	**7**	**7.25**	**0.474**	**0.33**	**307.2**	**309.5**
Group 3 – patients treated with aflibercept	**75.2**	**0.4**	**0.308**	**343.5**	**409**	**7.75**	**8**	**0.436**	**0.283**	**288**	**299.3**
Group 4 – patients treated with ranibizumab	**76.3**	**0.42**	**0.35**	**389.85**	**377.5**	**4.29**	**4.5**	**0.406**	**0.375**	**344.85**	**291**
Men	**75.6**										
Group 1 – patients continuing treatment	**75.5**	**0.35**	**0.325**	**313.5**	**386.5**	**7.5**	**6.25**	**0.5**	**0.356**	**258.5**	**299.25**
Group 2 – patients treated with aflibercept under a standardized T&E regimen	**74.9**	**0.26**	**0.295**	**393.7**	**388.6**	**7.2**	**7.5**	**0.43**	**0.547**	**331.5**	**300.4**
Group 3 – patients treated with aflibercept	**76.2**	**0.2**	**0.2**	**344.3**	**426.75**	**7**	**7.75**	**0.6**	**0.21**	**299**	**340.5**
Group 4 – patients treated with ranibizumab	**75.8**	**0.26**	**0.26**	**341**	**459**	**4.8**	**4**	**0.36**	**0.412**	**292.5**	**337.5**

Orange color indicates improvement, red color indicates deterioration.
OP – right eye; OL – left eye.

cant (p = 0.018). Moreover, we found a correlation between the need for help from the patients' family members and age: patients aged 61–80 years required much more help than the younger ones (p = 0.009). Moreover, more than half of the respondents (55%) received assistance from family members in doing household chores (fig. 1). The average rating of satisfaction with such help was 9.55 (SD = 1) on a 10-point scale, but 16 women and 5 men could not receive help from family members, because they lived in single-person households.

Patients were asked about their visual acuity improvement (fig. 2). The average improvement assessed by respondents (N = 88) occurred after 3.7 injections (SD = 1.7). No statistical correlation was found between respondents' sex and satisfaction with help from family members as well as between respondents' sex and the number of injections leading to vision improvement. Moreover, there were no statistically significant differences between visual acuity and retinal thickness and the level of patients' satisfaction with treatment results.

FIGURE 1

Assessment of the help from family members (N = 98).

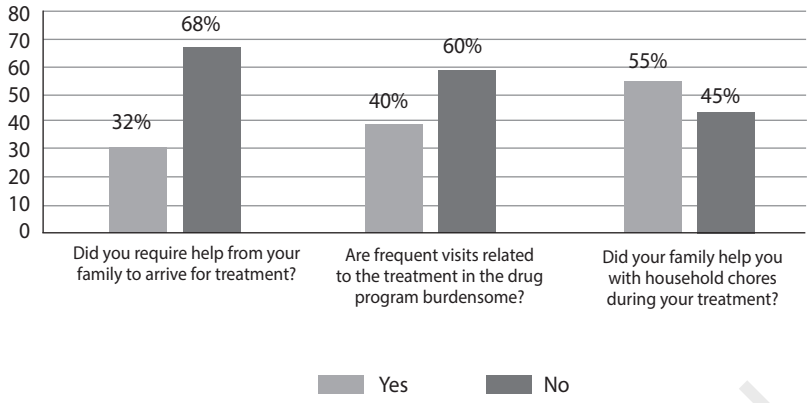
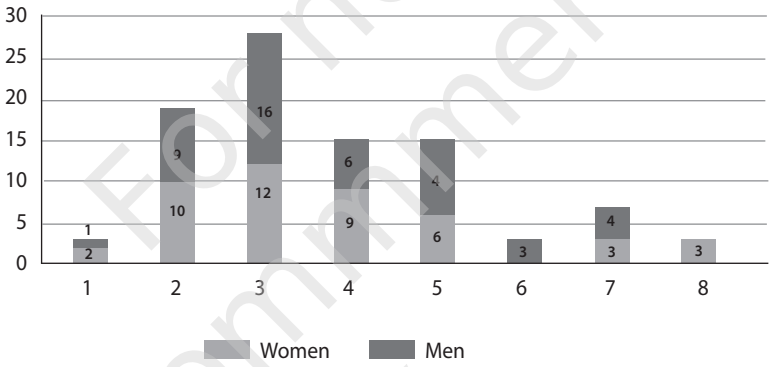


FIGURE 2

Subjective visual acuity improvement in relation to the number of injections (N = 98).



DISCUSSION

Since the first OCT device, there has been a rapid development in diagnostic techniques enabling early AMD detection and many studies on effective AMD prevention and treatment have been carried out. In Poland, studies on AMD diagnostics and treatment have been carried out since 2005 [12].

A real revolution in ophthalmology was the discovery of VEGF inhibitors, which slow down the formation and growth of new vessels, allowing patients not only to maintain visual acuity, but also to improve visual functions. This treatment is relatively new and involves ranibizumab, approved in 2006 for the treatment of wet AMD, and aflibercept, approved in 2015. Anti-VEGF therapy has become the gold standard in the treatment of AMD [13].

Studies have shown that treatment with anti-VEGFs is associated with continuous and repeatable administration of intravitreal injections, depending on disease symptoms, for the rest of patient's life. In 2015, Polish treatment program for wet AMD was introduced in Poland not only because anti-VEGFs had been found effective but also to establish one treatment plan. We assessed treatment results, including visual acuity and retinal thickness, compared to the effectiveness of anti-VEGF therapy. Two-thirds of the study participants observed improved visual acuity, a result worth emphasizing, as for the majority of patients maintaining visual acuity is a priority. We reported no significant correlations between retinal thickness and vision improvement.

Yuzawa et al., who assessed quality of life in the treatment of patients with AMD, showed adverse impact of AMD on quality of life, comparable to serious cardiovascular or neoplastic diseases. The authors recommended paying particular attention to visual acuity, and not to retinal thickness. Preservation of vision is very important for patients, because it has the greatest impact on their mental state and ability to function independently in everyday life [14]. In our study all participants declared satisfaction with

the treatment, so we can assume that their quality of life has improved. Moreover, patients treated for dry AMD also declared improved quality of life, visual acuity and mental health. Brzuzy [15] assessed quality of life of blind, visually impaired and healthy people based on 15 selected areas. The author showed that people with visual impairment assessed their quality of life much worse than healthy people. Interestingly, when analyzing different aspects of life, patients with visual impairment reported a significantly lower quality of life in terms of health assessment, life achievements, earnings, savings and housing. However, healthy study participants declared the lowest quality of life with regard to satisfaction with children, place of residence, friends and acquaintances. On the other hand, Cardinali [16], who examined elderly people with acquired visual impairment, proved that this dysfunction negatively affects life satisfaction and contributes to the development of depression. Moreover, it has been shown that AMD increases anxiety and leads to social isolation [17].

In our study, men were statistically more satisfied with treatment results. This finding has been confirmed by other studies conducted among patients with different chronic diseases. For instance, women with cardiovascular diseases were less satisfied than men with the quality of medical services and communication with physicians [18]. Similar results were obtained by researchers from Qatar who reported that men were more satisfied with psychiatric treatment than women [19]. This can be explained by the fact that women's participation in the clinical trials is much lower than men [20] and consequently, women may be less motivated to undertake therapy and modify lifestyle [21].

The social audit of AMD treatment was a very important project carried out in Poland as part of the Citizens for Democracy program financed by EEA funds. Within the project, AMD treatment of Polish patients was assessed before introducing the drug program. The results of the survey conducted by Kieszkowska-Grudny indicate patients' difficulties in access to treatment and diagnostic tests. Besides, public healthcare patients had to wait longer for intravitreal injections than private patients. According to the report, patients' knowledge of AMD was low. A significant disadvantage was also the inability to continue the treatment [11].

Our study confirms that before implementation of the drug program, access to AMD treatment was difficult. In the survey, patients expressed their satisfaction with participation in the program, as well as with treatment results. Their high level of satisfaction was probably associated with easier access to ophthalmologists (they did not wait long for the appointments), faster diagnostic tests and treatment, and access to educational materials and information on the disease. These are the most important factors influencing patients' satisfaction with healthcare. Frequent visits to the clinic were not burdensome for people participating in our study, as the treatment process was well organized. Moreover, our study shows that the majority of patients came for tests or intravitreal injections on their own, whereas the rest of the patients received help from their family members. For many patients, family help is invaluable [22], but it seems that asking for help is very often difficult. However, it is worth emphasizing that some studies indicate high levels of stress among people looking after AMD patients [23].

CONCLUSIONS

1. Our evaluation of treatment results in patients who continue the treatment (treated before the implementation of the drug program) shows that AMD progression stopped and visual acuity improved. This result justifies the decision to qualify patients with AMD to the drug program.
2. After comparing the results of treatment with aflibercept with and without T&E regimen, we found no significant differences in inhibiting disease progression and improving visual acuity. Moreover, the conducted analysis showed no significant differences in improving visual acuity and inhibiting disease progression between aflibercept and ranibizumab.
3. All respondents were satisfied with participating in the drug program and the majority of them declared a high level of satisfaction. This is probably due to the fact that drug program participants had easier access to ophthalmologists (they did not wait long for the appointments), faster diagnostic tests and treatment, and access to educational materials and information on the disease.
4. All respondents were satisfied with treatment effects, regardless of the diagnostic tests results, even those with deteriorated visual acuity.
5. Statistically, more men than women were satisfied with treatment effects, which is probably due to the fact that improvement in visual acuity was higher in men than in women.
6. Every third patient treated in the AMD drug program required help from family in commuting to injections and to follow-up visits.

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The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.