ORIGINAL ARTICLE

Wet Form Age-Related Macular Degeneration Two Years Treatment Results Using Anti VEGF drugs

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SUMMARY

Aim: The aim of the study was to establish the efficacy of anti VEGF (Vascular Endothelial Growing Factor) drugs in the treatment of wet form ARMD (Age-Related Macular Degeneration) in everyday clinical practice in the Department of Ophthalmology, Faculty Hospital, Hradec Králové, Czech Republic, E.U., in patients registered in the Czech national registry AMADEUS.
Material and methods: Retrospective study with 24 months follow-up period. In the group were evaluated 143 eyes of 140 patients, out of them were 77 women (65.8 %), of average age 73.09 (71.69 – 74.48) years, and 40 men (34.2 %) of average age 74 (58 – 85) years. All of the patients were completely examined before the beginning of the treatment; during the treatment were, except the standardized eye examination, in patients treated with ranibizumab the color fundus photography and Optical Coherence Tomography (OCT) with measuring of the central retinal thickness performed every three months at least. The patients treated by pegaptanib were examined every six weeks before the drug application. The fluorescence angiography (FA) was performed at the beginning of the treatment to establish the type and extension of the choroidal neovascularization and during the treatment in case of necessity to establish the activity of the choroidal neovascular membrane (CNV). The treatment by ranibizumab was in the regimen PRN (pro re nata), and pegaptanib was applied every six months during the first year with the follow-up evaluation of the findings. The treatment evaluations were performed at 12 and 24 months.
Results: During the two years follow – up period, the authors noticed in patients treated with ranibizumab loss of 5.12 letters of ETDRS optotypes in case of mostly classical CNV, in occult CNV loss of 5.45 letters, and in minimally classical CNV loss of 2.83 letters. In three evaluated eyes with classical CNV in patients treated with pegaptanib we noticed after 2 years loss of 6.67 letters, in eleven eyes with occult CNV we established loss of 9.91 letters, and in two eyes with minimally classical CNV the average bestcorrected visual acuity (BCVA) remained unchanged. The pegaptanib treatment results may be influenced by small number of evaluated patients. The visual acuity changes during the two years treatment were not statistically significant. We noticed the decrease of average CRT (central retinal thickness) in all types of CNV treated both with ranibizumab and pegaptanib after the two years follow up. To reach these results, an average of 5.51 applications of ranibizumab and 9 applications of pegaptanib during the two years were used.
Conclusion: In the followed-up group we found, comparing to the natural course of neovascular form of ARMD, retarding of the BCVA decrease during the two years treatment with VEGF inhibitors in everyday clinical practice. Better results were achieved with ranibizumab treatment, however the differences were not statistically significant.

Key words: age related macular degeneration, AMADEUS Czech national registry, ranibizumab, pegaptanib

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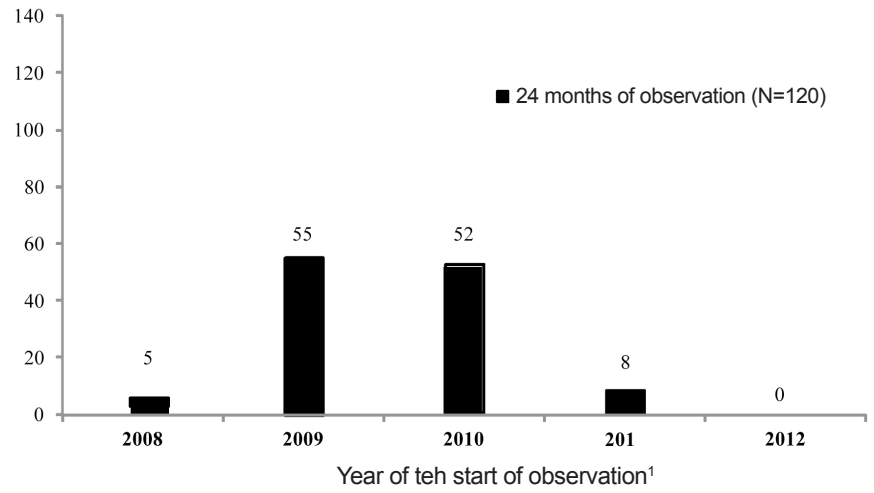
INTRODUCTION

Age related macular degeneration (ARMD) is a degenerative disease of the retina, with the maximum number of changes in the macular area. It is the most frequent cause of practical blindness in the population aged over 65 years in developed countries (8). In the majority of patients a slowly developing "dry" atrophic form of ARMD occurs, but in approximately 10% a rapidly progressing "wet" form develops, together with a choroidal neovascular membrane (CNV), which is responsible for loss of sight in the majority of patients (1). The neovascular form of ARMD in its natural course leads to a loss of 2.7 rows of optotypes in one year and 4 rows of optotypes over 2 years (9). The standard treatment of wet form ARMD at present is application of drugs acting against vascular endothelial growth factor A (VEGF A). Photodynamic treatment with verteporfin is in decline due to its lower effectiveness.



Graph 1. Initiation of observation in patients with monotherapy of wet ARMD

The first anti VEGF preparation approved for clinical use is pegaptanib sodium (Macugen, Pfizer Inc.). This is an aptamer of ribonucleic acid, which binds to the isomer of VEGF A165, preventing binding to the receptor VEGFR-2 on endothelial cells (7). In the VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) it was determined that pegaptanib administered in a dose of 0.3 mg intravitreally in six-week intervals led to a loss of less than 15 letters in 70% of eyes over an observation period of one year, in comparison with 55% in the case of a placebo. In 6% an improvement of best corrected visual acuity (BCVA) was determined after one year by 3 or more rows of ETDRS optotypes (3). Another anti VEGF preparation approved for regular clinical use is ranibizumab (Lucentis, Novartis Pharma AG), a fragment of a humanised monoclonal antibody against a number of isoforms of VEGF A, covering VEGF165, VEGF121 and VEGF110 (5). In the clinical study Safety and Efficacy of a Flexible Dosing Regimen of Ranibizumab in Neovascular Age-Related Macular Degeneration (SUSTAIN), an average gain of +3.6 letters and an average reduction of CRT by 91.5 μm was determined over the course of 12 months of treatment, with an average number of 5.7 injections of ranibizumab administered within a pro re nata (PRN)

Table 1 a. Comparison of BCVA after one year of treatment according to individual types of CNV

			BCVA (ETDRS)			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**PC** **OC** **MC**	25 49 29	50.00 (46.73; 53.27) 53.98 (50.14; 57.82) 53.41 (47.90; 58.92)	50.04 (44.61;55.47) 49.43 (44.57; 54.29) 54.93 (49.40; 60.46)	1 0.07 0.47	0.04 (-4.39; 4.47) -4.55 (-8.96; -0.14) 1.52 (-3.99; 7.03)
Pegaptanib monotherapy – average (CI)	**PC** **OC** **MC**	3 11 2	49.00 (38.08; 59.92) 47.91 (37.68; 58.14) 50.00 (35.60; 64.40)	46.00 (31.55; 60.45) 42.55 (31.48; 53.62) 49.00 (11.76; 86.24)	1 0.29 0.66	-3.00 (-25.97; 19.97) -5.36 (-16.06; 5.34) -1.00 (-8.84; 6.84)

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 1b. Comparison of BCVA after one year of treatment according to size of lesion

			BCVA (ETDRS)N			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	13 80 10	52.31 (45.16; 59.46) 53.70 (50.84; 56.56) 46.80 (39.20; 54.40)	51.31 (40.67; 61.95) 53.70 (48.07; 55.09) 47.30 (40.40; 54.20)	0.656 0.205 0.918	-1.00 (-10.53; 8.53) -2.13 (-5.27; 1.01) 0.50 (-9.34; 10.34)
Pegaptanib monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	0 12 4	- 47.42 (38.52; 56.32) 51.25 (34.57; 67.93)	- 38.67 (29.01; 48.33) 60.00 (55.00; 65.00)	- 0.065 0.465	- -8.75 (-16.08; -1.42) 8.75 (-12.48; 29.98)

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 2a. Comparison of CRT after one year of treatment according to type of CNV

			CRT (μm)			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**PC** **OC** **MC**	19 39 21	365.6 (306.9; 424.4) 337.9 (309.5; 366.3) 331.4 (288.3; 374.5)	264.4 (225.5; 303.4) 302.9 (273.5; 332.2) 304.3 (270.8; 337.7)	**0.022** **0.041** 0.114	-83.5 (-150.2; -16.7) -35.7 (-70.1; -1.3) -41.8 (-96.8; 13.2)
Pegaptanib monotherapy – average (CI)	**PC** **OC** **MC**	0 3 0	- 360.6 (285.3; 435.8) -	- 228.8 (171.2; 286.3) -	- 0.109 -	- -131.0 (-226.3; 35.7) -

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 2b. Comparison of CRT after one year of treatment according to size of lesion

			BCVA (ETDRS)N			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	11 62 6	371.8 (318.5; 425.0) 338.0 (311.2; 364.8) 337.1 (280.2; 394.1)	304.9 (261.8; 348.0) 292.5 (270.0; 314.9) 285.3 (203.1; 367.5)	0.083 0.005 0.600	-69.9 (-131.0; -8.8) -47.4 (-78.9; -16.0) -24.7 (-151.5; 102.1)
Pegaptanib monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	0 2 1	- 401.3 (345.0; 457.5) -	- 242.5 (200.9; 284.1) -	- 0.180 -	- -177.5 (-225.5; -129.5) -

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 3a. Comparison of BCVA after 24 months according to individual types of CNV

			BCVA (ETDRS)			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**PC** **OC** **MC**	25 49 29	50.00 (46.73; 53.27) 53.98 (50.14; 57.82) 53.41 (47.90; 58.92)	44.88 (37.35; 52.41) 48.53 (42.92; 54.14) 50.59 (42.59; 58.59)	0.3 0.07 0.92	-5.12 (-11.45; 1.21) -5.45 (-10.90; 0.00) -2.83 (-9.73; 4.07)
Pegaptanib monotherapy – average (CI)	**PC** **OC** **MC**	3 11 2	49.00 (38.08; 59.92) 47.91 (37.68; 58.14) 50.00 (35.60; 64.40)	42.33 (23.93; 60.73) 38.00 (22.63; 53.37) 50.00 (40.20; 59.80)	1 0.33 1	-6.67 (-35.50; 22.16) -9.91 (-23.20; 3.38) 0.00 (-19.60; 19.60)

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 3b. Comparison of BCVA after 24 months according to size of lesion

			BCVA (ETDRS)			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	13 80 10	52.31 (45.16; 59.46) 53.70 (50.84; 56.56) 46.80 (39.20; 54.40)	55.46 (44.44; 66.48) 48.03 (43.44; 52.62) 40.40 (33.68; 47.12)	0.31 0.03 0.12	3.15 (-8.02; 14.32) -5.68 (-9.70; -1.66) -6.40 (-15.77; 2.97)
Pegaptanib monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	0 12 4	- 47.42 (38.52; 56.32) 51.25 (34.57; 67.93)	- 35.83 (22.48; 49.18) 53.75 (40.87; 66.63)	- 0.27 0.56	- -11.58 (-24.63; 1.47) 2.50 (-6.89; 11.89)

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 4a. Comparison of CRT after 24 months according to type of CNV

			CRT (µm)			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**PC** **OC** **MC**	17 34 24	365.6 (306.9; 424.4) 337.9 (309.5; 366.3) 331.4 (288.3; 374.5)	313.7 (271.2; 356.1) 276.5 (244.3; 308.7) 302.0 (263.1; 340.9)	0.48 0 0.28	-41.1 (-111.8; -29.6) -74.3 (-119.4; -29.2) -34.4 (-90.3; 21.5)
Pegaptanib monotherapy – average (CI)	**PC** **OC** **MC**	0 3 0	- 360.6 (285.3; 435.8) -	- 227.8 (184.3; 271.3) -	- 0.1 -	- -131.3 (-150.3; 112.4) -

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 4b. Comparison of CRT after 24 months according to size of lesion

			CRT (µm)			
	N		**Baseline**	**12 months**	**p[1]**	**Difference after 12 months**
Ranibizumab monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	11 62 6	371.8 (318.5; 425.0) 338.0 (311.2; 364.8) 337.1 (280.2; 394.1)	267.8 (240.7; 294.8) 301.0 (274.7; 327.4) 271.6 (204.8; 338.4)	0.02 0.04 0.25	-108.7 (-167.0; -50.5) -44.9 (-82.9; -6.9) -41.5 (-117.3; 34.3)
Pegaptanib monotherapy – average (CI)	**< 2 PD** **2 – 5 PD** **> 5 PD**	0 3 0	- 401.3 (345.0; 457.5) -	- 247.4 (204.1; 290.7) -	- 0.07 -	- -104.5 (-158.8; -50.2) -

1Statistical significance of Wilcoxon test for change from beginning of observation

Table 5. Overview of number of applications during first and second year of treatment

		Therapy during first year		Therapy during second year		Therapy over two years
	N	**Number of doses:** average (95% CI) / median (5%; 95% perc.)	N	**Number of doses:** average (95% CI) / median (5%; 95% perc.)	N	**Number of doses:** average (95% CI) / median (5%; 95% perc.)
Ranibizumab monotherapy	103	4.05 (3.80; 4.30) / 4 (3; 6)	103	1.47 (1.16; 1.78) / 1 (0; 4)	103	5.51 (5.04; 5.98) / 5 (3; 10)
Pegaptanib monotherapy	16	9.00 (9.00; 9.00) / (9 (9; 9)	16	-	16	9.00 (9.00; 9.00) / (9 (9; 9)

1Statistical significance of Wilcoxon test for change from beginning of observation

treatment scheme (4). In the clinical study Prospective OCT Imaging of Patient with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO), an improvement of BCVA by 9.3 letters and an average reduction of CRT by 178 μm was determined over 12 months with an average number of 5.6 injections (2).

In the Czech Republic, treatment of the wet form of ARMD is concentrated in 10 centres (University Hospital Brno, University Hospital Hradec Králové, University Hospital Vinohrady Prague, University Hospital Olomouc, University Hospital Ostrava, University Hospital Plzeň, Masaryk Hospital Ústí nad Labem, Central Military Hospital Prague – Střešovice, General University Hospital Prague and Hospital České Budějovice). The effectiveness and safety of treatment is monitored in the AMADEUS register, the aim of which is to obtain fundamental epidemiological information about patients with wet form of ARMD, about standard procedures of evaluating of treatment and the results of treatment in regular clinical practice. Patients have been included in the register after a diagnosis has been safely determined and the indication criteria for treatment evaluated. Gathering of data is fully anonymous, retrospective and does not in any way influence medical decisions or the availability of treatment for patients.

The aim of our investigation was to determine the efficacy of anti VEFG drugs in the treatment of age related macular degeneration in regular clinical practice at the Eye Clinic at University Hospital Hradec Králové in patients included in the AMADEUS national register.

METHODOLOGY

In the population, patients included in the AMADEUS national register were retrospectively assessed, with an observation period of 24 months. The patients were progressively included in observation from 2008 to 2011 (graph 1). The inclusion criteria for observation were the minimum age of 55 years, presence of wet ARMD of all types of CNV, previously uninfluenced by other treatment, BCVA within the range of 70-35 letters of ETDRS optotypes (Snellen's equivalent 20/40-20/200). Further criteria for application of ranibizumab or pegaptanib were size of lesion up to 8 diameters of disc of optic nerve (DD). In the case of occult CNV, treatment was commenced upon demonstration of activity of CNV (reduction of BCVA by two or more rows of optotypes within 3 months, presence of haemorrhage or hard exudates in macula). The indication criteria for this treatment reimbursed from the public health insurance are limited by the indication limits of reimbursement, which are stipulated by the State Institute for Drug Control (SÚKL). Patients were not included in the observation if they had a different cause of origin of CNV (myopia, angioid streaks ...), upon inflammatory affliction of the treated eye, if fibrosis of CNV predominated and upon demonstrated allergy to anti VEGF substances or fluorescein.

The patients signed an informed consent to treatment. Treatment with pegaptanib was applied with adherence to the standard dosing interval of intravitreal application every 6 weeks according to the Summary of Product Characteristics (SPC). Treatment with ranibizumab was within the dosing regimen for PRN, i.e. after the first three injections after a month there followed a further injection after deterioration of the disease. The criterion for replication was deterioration of BCVA by more than 5 letters of ETDRS optotypes in connection with macular oedema confirmed on OCT, or the presence of haemorrhage or hard exudates in the macula. Regular checks during the course of treatment were conducted at the Eye Clinic of the University Hospital Hradec Králové at least every three months. Patients treated with pegaptanib were checked every 6 weeks during the course of treatment, patients treated with ranibizumab, in addition to checks at our clinic, were observed every month in the outpatient clinics of district ophthalmologists or diagnostic centres, and in the case of deterioration of BCVA by more than one row of optotypes were indicated for acute examination at our clinic. During the course of observation an examination of BCVA was conducted on patients using ETDRS Snellen charts, as well as an examination of the anterior ocular segment on a slit lamp, measurement of intraocular pressure, examination of posterior ocular segment biomicroscopically, colour fundus photography, and OCT focusing on central retinal thickness (CRT). Fluorescein angiography was performed at the beginning of observation with the aim of determining the type and size of choroidal neovascularisation and during the course of treatment in the case of necessity to verify CNV activity. During the treatment with ranibizumab, OCT was performed during the observation phase of treatment in order to determine the activity of the disease. Evaluation of the treatment was conducted after 12 and 24 months.

The aim of monitoring was to determine the effectiveness of treatment of wet form of ARMD using VEGF inhibitors in regular clinical practice, depending on the type of CNV and the size of the lesion. A statistical evaluation was conducted using a Kruskal Wallis H test, Wilcoxon test and Man Whitney U test. Statistical significance was on the level of $p = 0.05$. The analysis was conducted with the use of SPSS 19.01.1. (IBM Corporation, 2010). The statistical evaluation of the population was conducted by the Institute of Biostatistics and Analysis at Masaryk University, Brno.

RESULTS

In the sample group we retrospectively evaluated 143 eyes of 140 patients, of whom 77 were women (65.8%) with an average age of 73.09 years (71.69-74.48) and 40 men (34.2%) with an average age of 74 years (58-85). From this population 120 eyes of 117 patients were treated with monotherapy and 23 eyes of 23 patients were with a change of treatment in the course of the observation period. The study presents the results of the patients with mono-

therapy. None of the patients from the population who underwent treatment by photodynamic therapy (PDT) with verteporfin were evaluated. Of a total number of 119 eyes, 103 eyes were treated with ranibizumab and 16 eyes were treated with pegaptanib. Table 1a presents the initial values of BCVA for the groups of patients treated with ranibizumab and pegaptanib, divided according to types of CNV, and their comparison with values of BCVA in the 12th month of observation. Table 1b presents the values of one-year observation divided according to size of lesion. Table 2a presents the values of CRT determined on OCT in one-year observation according to type of CNV and table 2b according to size of lesion. Table 3a shows the values of BCVA in month 24 according to types of CNV, and table 3b shows the values according to the size of lesion. Table 4a presents the values of CRT in 24-month observation according to the type of CNV and table 4b according to the size of lesion. Table 5 shows the average numbers of injections of ranibizumab and pegaptanib for the first and second year of treatment.

DISCUSSION

The representation of both drugs with anti VEGF effects is unequal in our study population, with a substantial prevalence of indication of ranibizumab. We explain this by the endeavour to attain the best possible therapeutic effect, which has been confirmed in favour of ranibizumab by several clinical studies, despite the fact that these were not studies comparing both drugs directly with the same inclusion criteria (2, 3, 4). In our study population from regular clinical practice we found out the largest reduction of BCVA upon treatment with ranibizumab and pegaptanib in the first and second year in the case of occult CNV. However, this reduction was not statistically significant in comparison with the value of BCVA before treatment and was not larger than two rows of optotypes, which is still evaluated as stabilisation of BCVA in clinical trials. A more pronounced reduction of BCVA was observed upon treatment with pegaptanib in all types of CNV in the first and second year of treatment, although the differences were not statistically significant, and in the case of treatment with pegaptanib they might be influenced by the small number of patients. The average number of injections in the treatment with ranibizumab over two years was almost half in comparison with the two-year treatment with pegaptanib. In our population the PRN therapeutic scheme of ranibizumab was used, as in the PrONTO and SUSTAIN studies (2, 4). We explain the maintenance of initial BCVA without an average gain of letters in one year observation with reference to the smaller number of applications of ranibizumab. This is due to the longer interval between checks in regular clinical practice in comparison with clinical studies and the lower availability of treatment depending on the limited financial budget drawn from public health insurance. This influence became evident even more in the second year of the treatment. Maintenance of the baseline BCVA upon an average number of 9 injections of pegaptanib per year corresponds to the results of the V.I.S.I.O.N. study (3).

Despite the fact that we did not demonstrate maintenance of baseline BCVA upon treatment with ranibizumab or pegaptanib during the course of the two-year observation, we documented a reduction of CRT in all types of CNV, and in the case of the treatment with ranibizumab this decrease in occult CNV was statistically significant. This difference demonstrates that the resulting BCVA is not determined only by the presence and scope of macular swelling, but also by changes in actual CNV (cicatrical redevelopment of CNV) and the influence on photoreceptors and RPE cells.

The resulting visual acuity of patients treated with ranibizumab in the two-year observation was worst in the subgroup of patients with CNV with a size greater than 5 PD, which corresponds to the worse prognosis of patients with larger CNV. Patients with a lesion with a size of 2-5 PD treated with pegaptanib had worse visual acuity in the two-year observation than patients treated with ranibizumab, which we explain by the worse response to the selective VEGF inhibitor. It is not possible to conduct a comparison of the effect of pegaptanib on lesions with a size larger than 5 PD and smaller than 2 PD due to the small number of evaluated eyes. The reduction of CRT in all sizes of lesions, which was statistically significant in the case of patients with lesions with a size of up to 2 PD and 2-5 PD treated with ranibizumab does not lead to an improvement of BCVA in two-year observation, with the exception of the group of patients with a lesion smaller than 2 PD treated with ranibizumab. In these patients the reduction of CRT was the largest. Our finding confirms the fact that better results of an anti VEGF treatment are attained in the case of minor lesions. Decrease in BCVA in both treated groups is substantially slowed in comparison with the natural course of the neovascular form of ARMD (9).

The average number of doses of ranibizumab in our study population was 5.51 over 24 months, which is comparable to an average number of 5.4 injections in the entire AMADEUS group and with an average number of 5.6 injections stated by the authors from the Eye Clinic of Masaryk University and University Hospital Brno (6).The stated average numbers of applications are lower than the numbers of injections in the SUSTAIN or PrONTO clinical studies, but they correspond to the conditions of regular clinical practice in the Czech Republic. In the case of treatment with pegaptanib, we documented an average of 9 injections in the two-year observation, which means that treatment was not indicated in the second year in any of the observed patients, and the condition was evaluated as stable after the first year of treatment.

CONCLUSION

In the evaluated group we determined a slowing of the deterioration of BCVA during the course of two-year treatment with VEGF inhibitors in regular clinical practice, in comparison with the natural course of the neovascular form of ARMD. We attained better results upon treatment with ranibizumab, nevertheless the differences were not statistically significant. Despite the fact that we recorded an average deterioration of BCVA in all types of CNV upon treatment with ranibizumab or pegaptanib in the two-year observation, we also determined a reduction of CRT in all types of CNV. The resulting visual acuity in the case of a longer duration of the disease depends rather upon changes in CNV, diminution of photoreceptors and damage to RPE rather than retinal edema. We confirmed greater effectiveness of anti VEGF treatment in the case of smaller lesions. In the case of treatment with ranibizumab, resulting BCVA is dependent on the average number of applied injections, as demonstrated by the comparison of our results with the results of clinical studies. Our study demonstrates the benefit of the AMADEUS national register for the treatment of wet form of ARMD. The data recorded in the register serve for further rational use of the costly treatment of this disease.

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