ORIGINAL ARTICLE

Ranibizumab in the ARMD Wet Form Treatment – Two Years Results Obtained from the AMADEuS Registry

Matušková V.[1], Kolář P.[1], Vysloužilová D.[1], Vlková E.[1], Dušek L.[2], Kandrnal V.[2], Jarkovský J.[2], Uher M.[2]

[1]Eye clinic of Medical Faculty, Masaryk University and University Hospital Brno, Head of the Clinic: E. Vlková, .
[2]Institute of Biostatistics and Analyses, Masaryk University Brno, director L. Dušek

SUMMARY

Aim: The aim of this study was the retrospective follow up of Age-Related Macular Degeneration (ARMD) wet form patients treated with ranibizumab during 24 months period. The data were recorded into the AMADEuS (Age-related MAcular DEgeneration in patientS in the Czech Republic) Registry and after their evaluation compared with treatment results obtained from other departments of ophthalmology collaborating in the AMADEuS project or results of some foreign studies as well.
Patients and methods: The group consisted of patients registered since October 1, 2008 until June 11, 2012, followed up for 24 months period. There were 90 eyes of 89 patients. All patients were completely examined in the Macular ambulance of the Department of Ophthalmology in the Faculty Hospital Brno-Bohunice, Czech Republic, E.U., and consequently the ranibizumab (Lucentis, Novartis) was applied intravitreally in three initials doses one month apart. Thereafter, ranibizumab was applied "on demand". In 43.3 % of eyes the mostly classical, in 27.8 % of eyes occult, and in 28.9 % of eyes the minimally classical choroid neovascular membrane was present. The initial visual acuity was in 3.3 % of eyes in the range 15 – 30 letters of ETDRS optotypes (20/500 – 20/200), in 61.1 % of eyes in the range 31 – 60 letters (20/200 – 20/63), and the visual acuity better than 61 letters of ETDRS optotypes (better than 20/63) was in 35.6 % of eyes.
Results: The average initial best-corrected visual acuity (BCVA) in our group of patients was 54.2 letters of EDTRS (SD ± 14.4). At the visit at three months after the start of the treatment the BCVA was 59.6 letters of EDTRS (SD ± 15.0), at the visit after 6 months 57.3 letters of EDTRS (SD ± 14.7), after one year of the study 54.8 letters of EDTRS (SD ± 16), after 18 months of the study 53.4 letters of EDTRS (SD ± 16,8), and after 24 months of the study was the BCVA 51.7 letters of EDTRS (SD ± 16.9). The average CRT (central retinal thickness) value by means of the OCT (optic coherence tomography) examination was at the beginning of the treatment 311.4 μm (SD ± 117.9), after 3 months of treatment 233.5 μm, (SD ± 85.4), after 6 months of treatment 262.2 μm, (SD ± 102,4), after 12 months 261 μm (SD ± 88,4), after 18 months 254.9 μm (SD ± 70.0), and after 24 months 249 μm (SD ± 87.5). The average number of ranibizumab doses during the follow-up period was 5.6. After the 24 months follow-up period, the gain of 15 or more letters of EDTRS was recorded in 11.1 % of patients, the gain of 1 – 14 letters of EDTRS optotypes was recorded in 32.2 % of patients, the decrease of 14 or less letters of EDTRS optotypes was found in 21.2 % of patients, and the decrease of 15 or more letters was found in our group in 22.2 % of patients.
Conclusion: The ARMD wet form treatment using ranibizumab is up to date the most effective available therapy. The AMADEuS registry is of great importance in the reviewing of the effectiveness of the ARMD wet form treatment.

Key Words: ARMD, register, Amadeus, ranibizumab, wet form, treatment

First author:
Dr. Veronika Matušková
Eye Clinic, University Hospital Brno and Medical Faculty of Masaryk University
Jihlavská 20
625 00 Brno
e-mail: v.matuskova@email.cz

INTRODUCTION

Age-related macular degeneration (ARMD) is the most frequent cause of severe damage to central visual acuity in patients aged over 60 years in developed countries. ARMD causes loss of central visual acuity in 20% of persons aged over 75 years. The dry form affects 85% of patients, the wet form appears in 15% of patients [3,6,11,13,15,16].

The wet form of ARMD is characterised by the presence of choroidal neovascular membranes (CNV). A key role in the pathogenesis of CNV is played by the vascular endothelial factor (VEGF).

Today photodynamic therapy with verteporfin and intravitreal application of anti-VEGF substances is routinely used in the treatment of the wet form of ARMD [2,12,14,17,18,19,22].

The data obtained during the treatment of the wet form of ARMD by ranibizumab at our clinic was entered into the AMADEuS register of patients. The AMADEuS project (Age-related MAcular DEgeneration in patientS in the Czech Republic) is focused on observing patients with the wet form of ARMD. The Czech Ophthalmological Society of the Czech Medical Society of J.E. Purkyně (COS JEP) in co-ope-

ration with the Institute of Biostatistics and Analyses at Masaryk University (IBA MU) has constructed a nationwide information system for monitoring the epidemiology and treatment of ARMD. The project entitled AMADEuS is a multicentric non-interventional observation prospective study with the aim of improving patient care and unifying the criteria for observation of ARMD in actual clinical practice in the Czech Republic. The fundamental tool of the project is the clinical register, which gathers parametrical data from 10 specialised centres. The project monitors photodynamic therapy with verteprofin (Visudyne) and treatment using preparations inhibiting VEGF, namely pegaptanib (Macugen) and ranibizumab (Lucentis) [5].

The primary aim of the AMADEuS project is to assess the available ARMD treatment in regular clinical practice. The secondary aim is to evaluate adherence to the guidelines recommended by the Czech Vitreoretinal Society (CVRS) and COS JEP, to obtain source materials for updating the guidelines for treatment of patients with ARMD in the Czech Republic, to standardise the therapeutic approaches in the incorporated centres, to evaluate the safety of the observed preparations, to create a model of prevalence of patients with wet form of ARMD in the Czech Republic over the next 3 years and to estimate the costs for treatment of the wet form of ARMD within the given period.

The AMADEuS project is under the patronage of COS at CLS JEP, the professional guarantors are Dr. Šárka Pitrová and Dr. Jiří Řehák. The technological background of the project and data analysis is provided by the IBA at Masaryk University in Brno (Dr. Ladislav Dušek and Dr. Vít Kandrnal). The AMADEuS project is supported by research grants from the Novartis company [8].

PATIENTS

The patients, who met the condition of 24-month observation, were included in the register from 1 October 2008 to 11 June 2012,. A total of 346 patients and 377 eyes were entered in the AMADEuS register as of the given date. There was a total of 89 patients (90 eyes) treated with ranibizmab over a two-year observation period. In this sample women represented 56.20% and men 43.8%. 11.2% of patients were aged under 60 years, with 21.3% aged between 60 and 70 years, 42.7% aged between 70 and 80 years and 24.7% aged over 80 years (graph 1).

In 43.3% of eyes predominantly classic CNV was present, in 27.8% occult CNV and in 28.9% minimally classic CNV (graph 2). A lesion smaller than 2 papillary diameters (PD) was described in 16.7 of eyes, lesion with a size of 2-5 PD in 71.1% of eyes and lesion larger than 5 PD in 12.2% of eyes (graph 3). Initial visual acuity within the range of 15-30 letters of ETDRS optotypes in our sample appeared in 3.3% of eyes, visual acuity of 31-60 letters was present in 61.1% of eyes and visual acuity of more than 61 letters of ETDRS optotypes was present in 35.6% of eyes (graph 4).

METHOD

Patients with the wet form of ARMD treated with ranibizumab over the course of 24 months were observed retrospectively. All of the patients were examined in the macular center of the Eye Clinic of the University Hospital Brno Bohunice. In each examination the patients' best corrected visual acuity (BCVA) was determined using the ETDRS optotypes, their intraocular pressure measured, the anterior segment of the eye was examined on a slit lamp (Zeiss SL120) and biomicroscopy of the fundus was performed in arteficial mydriasis using aspherical lenses (Ocular Instruments with an optical capacity of +60D or +78D). The diagnosis and type of CNV was determined on the basis of fluorescent angiography (Topcon TRC 50IX with the use of the display system ImageNet 2000).

Upon each visit an OCT examination was performed on all patients (optical coherent tomography using the instrument Zeiss Stratus III – fast macular scan and 6 mm cross hair scan). The patients underwent an intravitreal application of ranibizumab in the operating theatre of the Eye Clinic at the University Hospital Brno. Antibiotics were applied to the conjunctival sac 3x per day for 3 days before the IVT injection (ofloxacinum opht gtt 3 mg/ml or levoflaxacinum 5 mg/ml). The skin of the eyelids was disinfected using 10% povidone-iodine solution (Betadine) and the conjunctival sac was rinsed with 5% povidone-iodine solution. 0.5 mg of ranibizumab (0.05 ml of solution) was applied. The intravitreal application was performed under aseptic conditions under a surgical microscope. Half an hour after the intravitreal application of the medicament, the patient's intraocular pressure was measured, the entry wound was checked on a slit lamp and biomicroscopy of the fundus was performed. After the injection, the patient applied local antibiotics 3x per day for a further 3 days.

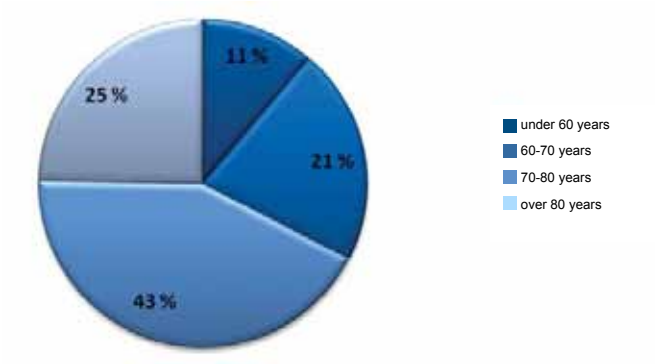
The obtained data was entered in the AMADEuS register (http://amadeus.registry.cz). Upon the first entry of the patient into the register, the patient was provided with anonymity and allocated a number in the form of (AMD-B-***). The data was entered at the commencement of treatment after 3, 6, 12, 18, and 24 months. Upon the initial visit the health insurance company, district of residence, length of subjective complaints and date of commencement of treatment (fig. 1) were entered. BCVA was recorded upon the completion of each form. If the patient read at least 20 letters from a distance of 4 metres on ETDRS optotypes, the patient was allocated an added bonus of 30 letters. If the patient read less than 20 characters from a distance of 4 metres (i.e. less than 4 whole rows), the patient was placed at a distance of 1 m from the ETDRS optotypes, the number of letters read from 1 m was added to the number of letters read from 4 m.

The type of lesion, size of lesion, intraocular pressure value, angiographic finding, values measured by OCT examination (central macular thickness [μm], macular volume [mm3]), presence of metamorphopsias and degree of subjective complaints were also entered in the electronic form. Any undesirable side effects were also recorded (fig. 2).

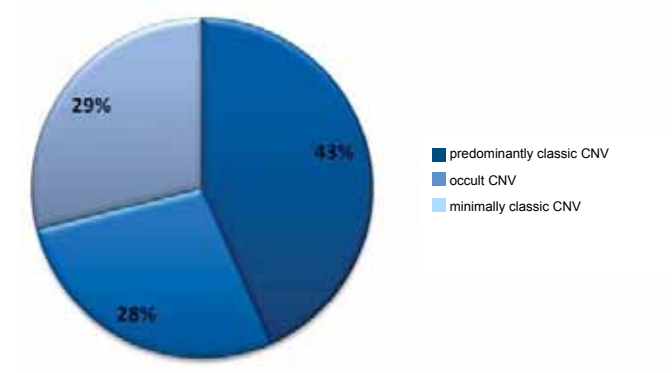
RESULTS

The average initial BCVA in our patients was 54.2 ETDRS letters (20/80) (SD ± 14.4), at the check-up 3 months after the beginning of treatment 59.6 (20/63) (SD ± 15.0), at the check-up after 6 months 57.3 (20/63) (SD ± 14.7), after 1 year of observation 54.8 (20/80) (SD ± 16.0), after 18 months of observation 53.4 (20/80) (SD ± 16.8) and after 24 months of observation from the beginning of treatment BCVA was 51.7 ETDRS letters (20/100) (SD ± 16.9) (graph 5).

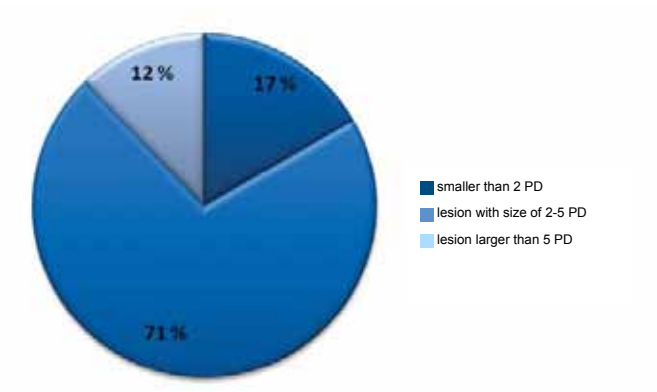
The average CRT value on OCT at the beginning of treatment was 311.4 μm (SD ± 117.9), after 3 months of treatment 233.5 μm (SD ± 85.4), after 6 months of treatment 262.2 μm (SD ± 102.4), after 12 months 261 μm (SD ±



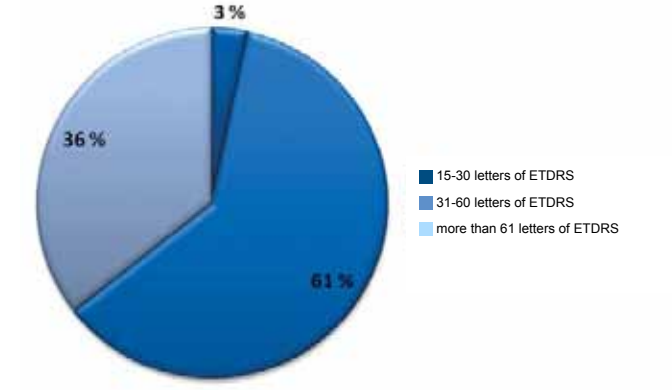
Graph 1 Characteristics of group of patients according their age



Graph 2 Characteristics of group of patients according to type of CNV



Graph 3 Characteristics of group of patients according to size of lesion



Graph 4 Characteristics of group of patients according to initial visual acuity

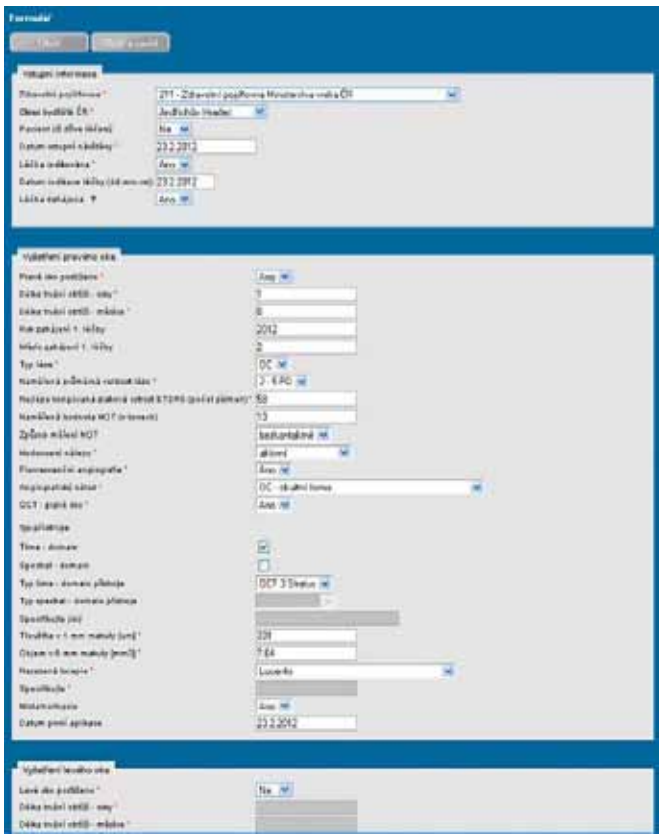


Fig. 1 Entering of patient's first visit into AMADEuS register

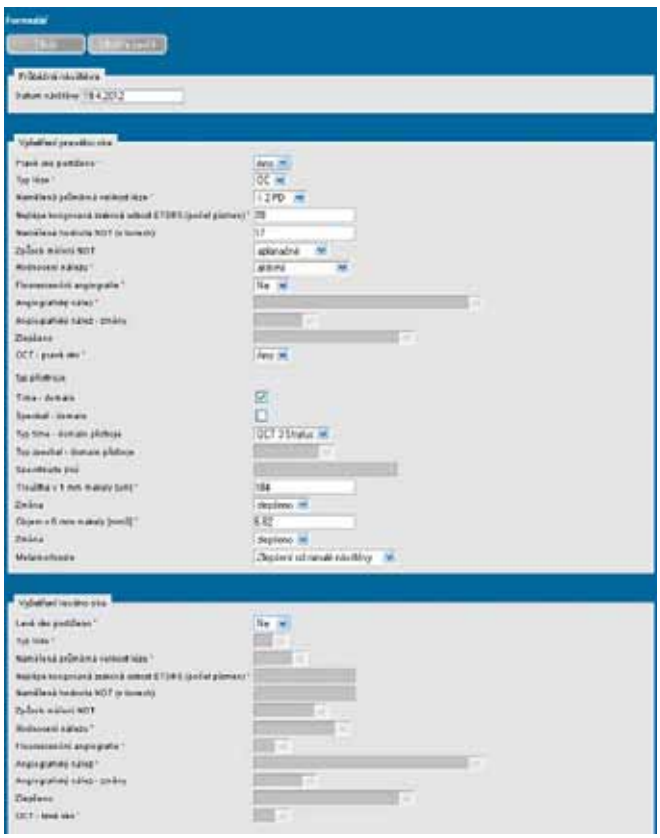
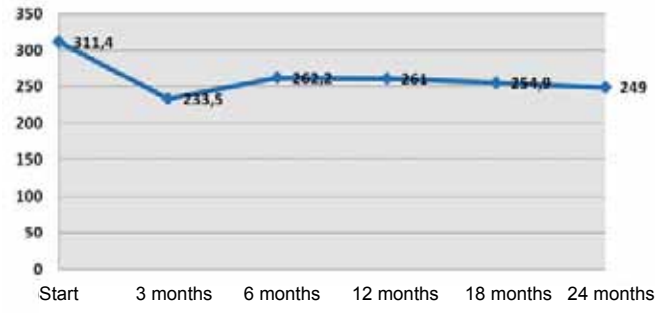
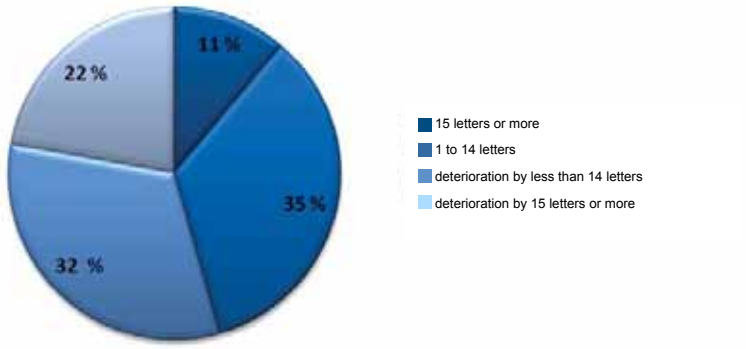


Fig. 2 Entering of check-up visit into AMADEuS register

Graph 5 Development of best corrected visual acuity (BCVA) over 24 months of observation



Graph 6 Development of central retinal thickness (central retinal thickness - CRT) over 24 months of observation



Graph 7 Best corrected visual acuity (BCVA) after 24 months of observation 11% 15 letters or more

88.4), after 18 months 254.9 µm (SD ± 70.0) and after 24 months 249 µm (SD ± 87.5) (graph 6).

The average number of doses of ranibizumab was 5.6 during the observation period. The application of 3 doses of ranibizumab was necessary in 23.3% of patients, in 22.2% we applied 4 doses, in 15.6% of patients 5 and 6 doses, 4.4% of patients received 7 doses, 5.6% received 8 doses, 2.2% 9 and 10 doses, 4.4% 11 doses and 1.1% of patients received 13 doses.

After the 24-month observation period a gain of 15 or more ETDRS letters was recorded in 11.1% of patients, a gain of 1 to 14 ETDRS letters in 34.4% of patients, a decline of less than 14 letters of ETDRS optotypes was observed in 32.2% of patients and a decline of more than 15 ETDRS letters occurred in 22.2% of patients in our sample (graph 7). Residual activity of the disorder after 2 years of treatment was observed in 24.4% of patients.

DISCUSSION

The vascular endothelial growth factor (VEGF) is a signal protein which stimulates the new formation of blood vessels. There are a number of basic subtypes of VEGF molecules (VEGF-A, VEGF-B, VEGF-C, VEGF-D). The VEGF-A molecule has a number of isoforms (VEGF A121, 145, 165, 183, 189, 206), which differ from one another in terms of the size of the molecule.

The humanised antibody blocking VEGF-A is known as bevacizumab (Avastin, Roche) and has a molecular mass of 148 kD. However, the original experiments with bevacizumab on animal retinas demonstrated that this antibody does not penetrate through all layers of the retina. As a result, further considerable financial resources were spent on the development of a smaller molecule. Ranibizumab (Lucentis, Novartis) is a recombinant humanised fragment of the original bevacizumab molecule, which blocks all isoforms of the VEGF-A molecule in the same manner as bevacizumab [2, 14, 18, 19].

The gene sequence for the part of the molecule balancing VEGF-A was extracted from the precursor and inserted into the vector Escherichia coli in order to create a recombinant of the human fragment (rhuFab). This process removed the Fc part of the antibody, thus reducing the immunogenic potential and reducing the size of the molecule. The molecular mass is 48 kD. On animal models it was demonstrated that reduction of the size of the molecule enabled penetration through all layers of the retina [7].

Ranibizumab blocks the part of the VEGF-A molecule which serves to link to the VEGF receptor 1 in the endothelial cells. By doing so it reduces the proliferation of endothelial cells, reduces the vascular permeability of blood vessels and halts the formation of new blood vessels. Thanks to its low molecular mass, ranibizumab is capable of penetrating into all layers of the retina [2].

The biological half-life of ranibizumab in the vitreous area is 10 days [2]. Some publications state a shorter biological half-life of 7 days [20]. Ranibizumab has a rapid systemic elimination and a short systemic half-life (~ 2 hours) [10].

The effectiveness of ranibizumab in minimally classic and occult CNVs was tested in the MARINA clinical trial (Ranibizumab for neovascular age-related macular degeneration).

A total of 716 patients were included in the study. In the group of patients (n = 238) receiving 0.5 mg of ranibizumab per month, a loss of less than 15 letters was attained in 94.6% of patients after 12 months. In the group receiving the placebo, a loss of visual acuity of less than 15 letters of ETDRS optotypes was observed in 62.2% of subjects. An improvement of visual acuity by more than 15 letters was recorded in 33.8% of patients receiving 0.5 mg of ranibizumab, and in the group receiving the placebo such

Table 1 Overview of studies with ranibizumab in the treatment of wet form of ARMD

	Type of CNV	Number of patients	Loss of less than 15 letters	Gain of more than 15 letters	Gain
UH Brno	**All types**	89	77,8	11,1	-2,5
Marina	**Minimally classic or occult**	240	90,0	33,3	6,6
Anchor	**Classic**	140	89,9	41,0	10,7
PIER	**All types**	61	90,0	8,2	-2,3
Placebo (Marina)	**Minimally classic or occult**	238	52,9	3,8	-14,9
PDT (Anchor)	**Classic**	143	65,7	6,3	-9,8

Table 2 Comparison of initial VA in our patients and in the Amadeus register

Initial VA	UH Brno	Amadeus Register
< 14 letters	2.80%	6.30%
15-30 letters	16.80%	16.70%
31-60 letters	53.30%	51.30%
61 or more letters	27.1%	25.70%

Table 3 Change of BRVA after 24-month observation period in our patients and in the Amadeus register

Change	UH Brno	Amadeus Register
Gain of 15 or more letters	2.80%	6.30%
Gain of 1 to 14 letters	16.80%	16.70%
Loss of 0 to 15 letters	53.30%	51.30%
Loss of 15 or more letters	27.1%	25.70%

an improvement was present in only 5.0% of patients. The average increase in visual acuity in the group treated with ranibizumab was 6.6 letters of ETDRS optotypes. The gain of letters was maintained throughout the entire observation period of 24 months. By contrast, in the group with the placebo there was a deterioration of visual acuity by 10.4 letters of ETDRS optotypes. The average number of doses of 0.5 mg of ranibizumab per patient was 21.7 [21].

The benefit of ranibizumab in the treatment of classic membranes was examined in the ANCHOR study (Anti-VEGF body Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration). A total of 423 patients were included in the study. A loss of less than 15 letters of ETDRS optotypes was recorded in 96.4% of patients receiving 0.5 mg of ranibizumab. An improvement of VA by more than 15 letters of ETDRS optotypes was recorded in 40.3% of patients. The average gain of letters in the group treated with ranibizumab was 11.3 letters [4].

A gain of more than 15 letters was attained in the Marina study in 33.3% of patients, and in as many as 41.0% in the Anchor study, whilst in our sample we attained this improvement in 11% of patients. The average gain of letters in the Anchor study was 10.7 ETDRS letters, with 6.6 letters in the Marina study and a loss of 2.5 letters in our study. The superior results in comparison with ours were attained most probably due to the stricter intake criteria of both of the above cited clinical trials, i.e. lesion with a maximum size of 5400 μm, BCVA between 20/40 (0.5) and 20/320 (0.06), an absence of structural disorder in the fovea and regular application of ranibizumab at an interval of 4 weeks over a period of 2 years. In the Marina study 80% of patients read more than 45 letters of ETDRS optotypes on their initial visit.

Our group of patients covered a spectrum corresponding to clinical practice, i.e. larger and more aggressive lesions (e.g. 12.5% of patients with a lesion larger than 5 PD). A further large difference is the dosing scheme of ranibizumab.

In the Marina and Anchor studies, ranibizumab was administered monthly, in our patients it was administered "on demand". There remains the undeniable fact that the greatest effect on improving BCVA is produced by monthly administration of ranibizumab. With regard high financial demand of this treatment, there is an endeavour to find the optimum dosing scheme for administration of ranibizumab. The effectiveness of quarterly administration of ranibizumab was evaluated in the PIER study (Randomised, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration). Ranibizumab was first of all administered monthly for a period of 3 months and subsequently administered quarterly. The study included a total of 184 patients. Over 24 months of observation 8.2% of patients treated with 0.5 mg of ranibizumab gained more than 15 letters. During the observation period there was a decline by 2.3 letters of ETDRS optotypes in the group of patients receiving 0.5 mg of ranibizumab [1]. This result is in accordance with our observations.

The greatest gain in ETDRS letters was attained in the Anchor study, i.e. the study with more aggressive lesions (with predominantly classic CNV). The resulting visual acuity is therefore fundamentally influenced not only by the type of CNV, but an important role here is played also by other factors (atrophy of RPE – retinal pigment epithelium, percentage representation of fibrotisation, size of accompanying subretinal haemorrhage and initial BCVA). A comparison of our results with the results of the individual clinical trials is presented in table 1.

If we compare the visual acuity (VA) in our patients and in the above-mentioned studies, we observe a sharp improvement of VA in all groups in the first 3 months of treatment. In our patients and in the PIER study the initial improvement is followed by a gradual deterioration of VA, after 12 months of observation visual acuity corresponds to the initial value, and during the second year of observation there is a visible slight loss of letters of ETDRS optotypes.

Upon monthly administration of ranibizumab (MARINA, ANCHOR), following an initial rapid improvement in the first three months there is a further gradual improvement up to 12 months of observation, whilst during the second year of observation it is possible

to observe a slight decline in the gain of ETDRS letters.

The VA curve inversely corresponds to the CRT curve. We see the maximum decline in our patients after 3 months of treatment, after which there is a slight increase in CRT in the period up to 12 months, and in the second year of the observation there is an observable further slight decline of CRT. After an initial decline, the CRT value never reaches the initial values. Primarily during the second year of observation there is a visible deterioration of VA together with a decline of CRT, which means that there is probably a progression of RPE atrophy or fibrotisation of the lesion in these patients.

Upon an evaluation of the development of visual acuity in patients with the "shame" treatment in the Marina study, there is a perceptible rapid deterioration of VA during the observation period. In the first year there is a loss of 10.4 ETDRS letters, in the second year the deterioration of visual acuity is less pronounced and at the end of the two-year observation period reaches a loss of 15 ETDRS letters. In an endeavour to attain the best possible results in patients with the wet form of ARMD it is necessary to keep in mind not only effective and sufficient dosing of ranibizumab, but also timely commencement of treatment. A delay in the commencement of treatment by 6 months represents a loss of almost 7 letters of ETDRS optotypes for the patient [21].

In the group of all patients treated with ranibizumab entered in the AMADEuS register as of 11 June 2012, initial visual acuity was within the range of 15-30 letters of ETDRS optotypes in 16.7% of eyes, 31-60 letters in 51.3% and more than 61 letters of ETDRS optotypes were read by 25.7% of eyes [9].

The distribution of initial visual acuity in the observed patients is very similar to the distribution in the group of patients from all the centres of the AMADEuS register (see table 2). The largest difference is in the number of patients in the group with visual acuity of 14 ETDRS letters or less, 6.3% versus 2.8%. This fact may be connected with the use of other therapeutic options in classic CNV, i.e. with PDT (photodynamic therapy with Visudyn). In our clinic we still use this treatment routinely, primarily in extensive and highly active classic CNVs.

In the group of all patients treated with ranibizumab entered in the AMADEuS register as of 11 June 2012 with a 24-month observation period, a gain of 15 or more ETDRS letters was observed in 11.2% or patients, a gain of 1 to 14 ETDRS letters in 29.7% of patients, a decline of less than 14 letters of ETDRS optotypes was present in 53.3% of patients and a decline of more than 15 ETDRS letters occurred in 30.8% of patients in the entire AMADEuS group. The activity of the disorder was described in 26.4% of patients (table 3).

BCVA of our patients corresponds in its results to the overall AMADEuS group, whilst slightly better results were attained in the group with a gain of 1 to 14 ETDRS letters and in the group with a loss of more than 15 ETDRS letters. This fact may again connect to the fact that PDT with verteporfin was used in the treatment of very aggressive lesions.

In the AMADEuS register the average number of doses of ranibizumab was 5.4 over 24 months. 3 doses of ranibizumab were required for stabilisation or improvement in 25.6% of patients, in 22.6% of patients 4 doses were applied, in 18.5% of patients 5 doses were required, in 13.8% 6 doses, in 5.1% 7 doses and in 4.6% of patients 8 doses were required. In the group of patients in which progression of the disorder occurred (decrease of ETDRS by more than 15 letters), 3 doses were applied in 23% of patients, 4 doses in 17.6%, 5 doses in 14.9%, 6 doses in 17.6%, 7 doses in 14.9% and 8 doses were required in 5.4% of patients. The average number of doses of ranibizumab in our patients was 5.6 over 24 months, which corresponds with the result of the AMADEuS register. It is visible that the difference of our patients and the group of the AMADEuS register overall is rather in the initial characteristics of the patients (number of aggressive lesions, initial BCVA) than in the method of available treatment.

CONCLUSION

Treatment of the wet form of ARMD using ranibizumab is currently the most effective available therapy. Upon an assessment of the effectiveness of this treatment, a useful tool is the nationwide AMADEuS register. This enables mapping of the number of patients, the stage of their disorder and a comparison of the effectiveness of treatment in individual centres. These observations lead to an improvement in care of patients with the wet form of ARMD. Last but not least, the register is useful in recording the number of patients with the wet form of ARMD and in estimating the financial costs required for this treatment.

LITERATURE

1. Abraham, P., Yue, H., Wilson, L.: Randomized, double-masked, sham--controlled trial of ranibizumab for neovascular age-related macular degeneration, PIER study year 2, Am J Ophthalmol, 150, 2010; 3: 315–324.
2. Blick, S., Keating, G., Wagstaff, A.: Ranibizumab, Adis Drug Profile, 67, 2007; 8: 1199–1206.
3. Boguszaková , J., Sklivec a sítnice In Kuchynka P.: Oční lékařství, Praha, Grada, 2007, Praha, s 316–324.
4. Brown, D. M., Michels, M., Kaiser, P., K. et al.: for the ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular agerelated macular degeneration: Two-year results of the ANCHOR study, Ophthalmology, 116, 2009, 1: 57–65.
5. Dušek, L., Pitrová, Š., Řehák, J. et al.: Informační zázemí České oftalmologické společnosti ČLS JEP pro monitoring a hodnocení léčby vlhké formy věkem podmíněné makulární degenerace - národní projekt AMADEUS. Čes a Slov Oftalmol, 66, 2010, 3: 99–109.
6. Ernest, J., Fišer, I., Kolář, P.: Věkem podmíněná makulární degenerace. Praha, Česká vitreoretinální společnost, 2007; 88 s.
7. Ferrara, N., Damico,L., Shams, N. et al.: Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration, Retina, 26, 2006; 8: 859–870.
8. http://amadeus.registry.cz/.
9. http://amadeus.registry.cz/index.php?-pg=vysledky-a-publikace--analyticka--zprava-cerven-2012.
10. Chen, Y., Wiesmann, Ch., Germaine, F. et al.: Selection and Analysis of an Optimized Anti-VEGF Antibody: Crystal Structure of an Affinity-matured Fabin Complex with Antigen, J Mol Biol, 1999; 293, 865 –881.
11. Kolář, P.: Klasifikace a klinický obraz VPMD In Kolář., P: Věkem podmíněná makulární degenerace, Praha, Grada, 2008, s 59–74.
12. Kolář, P., Vlková, E., Vižďová, D.: Fotodynamická terapie s preparátem Visudyne v léčbě vlhké formy věkem podmíněné makulární degenerace – dvouleté výsledky. Čas Lék čes, 145, 2006; 10: 795 – 800.
13. Kolář, P.: Epidemiologie věkem podmíněné makulární degenerace. Čes a Slov Oftalmol, 66, 2010; 3: 127–130.
14. Kolář, P.: Ranibizumab u pacientů s vlhkou formou věkem podmíněné ma-

kulární degenerace – studie SUSTAIN. Farmakoterapie, 2009; 6: 579–580.
15. Kolář, P.: Věkem podmíněná makulární degenerace, Čas Lék čes, 144, 2005; 8: 516–520.
16. Kolář, P.: Věkem podmíněná makulární degenerace, Oftalmochirurgie, 3, 2008; 2: 9–21.
17. Kolář, P.: Macugen v léčbě vlhké formy věkem podmíněné makulární degenerace, Oftalmochirurgie, 3, 2008; 2: 37–42.
18. Kolář, P.: Ranibizumab (Lucentis) – nový lék k léčbě vlhké formy věkem podmíněné makulární degenerace. Praktické lékárenství, 2008; 6: 271–274.
19. Kolář, P.: Ranibizumab. Farmakoterapie. 2007; 5: 431–434.
20. Krohne, T. U., Liu, Z., Holz, F. G., Meyer, C.: Intraocular Pharmacokinetics of Ranibizumab Following a Single Intravitreal Injection in Humans. Am J Ophthalmol, 2012; 154: 682–686.
21. Rosenfeld, P. J., Brown, D. M., Heier, J. S., et al.: for the MARINA Study Group: Ranibizumab for Neovascular Age-Related Macular Degeneration The New England Journal of Medicine, 355, 2006; 14: 1419–1431.
22. Sivaprasad, S., Hykin, P., Saeed, A. et al.: Intravitreal pegaptanib sodium for choroidal neovascularisation secondary to age-related macular degeneration, Pan-European experience. Eye, 5, 2010, 24: 793–798.