The efficacy of ranibizumab treatment in clinical practice in patients with the wet form of age-related macular degeneration. The results of the Czech National Registry

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Aims. The aim of this communication was to evaluate ranibizumab in the treatment of wet age-related macular degeneration.

Methods. Anonymised data on treatment efficacy and safety were consecutively entered into the Czech national database. From 01/09/2008 to 25/10/2011, 671 patients/685 eyes treated with ranibizumab monotherapy were entered in the registry. 454 ranibizumab treated eyes and 444 patients were monitored for 12-months. The dependent variable used to monitor disease progression and treatment results was change in visual acuity in the ETDRS (Early Treatment Diabetic Retinopathy Study) chart over time.

Results. After 12 months of treatment, a loss of < 15 letters in the ETDRS chart was found in 81.5% of eyes treated with ranibizumab. A gain of ≥ 15 letters was found in 9.7% of eyes on ranibizumab. The results for our patients treated in clinical practice with ranibizumab were poorer than those in the SUSTAIN (Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration) study. A rationale for this was sought in a sub-analysis.

Conclusions. Sub-analysis demonstrated that treatment naive CNV (choroidal neovascularization), occult CNV and lower height of the macular oedema at the outset of the disease may be positive prognostic factors for final visual acuity in anti-VEGF (vascular endothelial growth factor) treated patients.

Key words: age-related macular degeneration, ranibizumab

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INTRODUCTION

AMD is subdivided into the dry form and the wet form. According to Bressler, 90% of legal blindness from AMD is caused by the wet form¹. Ranibizumab (Lucentis, Novartis Pharma AG) is today, the main treatment for this condition. The phase III clinical trials ANCHOR and MARINA evaluated the benefit of ranibizumab in a regular dose of 0.5 mg each month^{2,3}. The SUSTAIN study was designed to further evaluate the safety, tolerability, and efficacy of OCT / BCVA-guided, individualized, flexible PRN (as needed) dosing regimen for ranibizumab⁴. In the case of the latter, it is still under discussion whether it is possible to reduce the frequency of application without impact on the resulting VA.

The objective of this communication was to evaluate ranibizumab efficacy in PRN dosing regimen in the treatment of wet AMD in clinical practice.

MATERIALS AND METHODS

The treatment of patients with wet AMD is centralized into 9 tertiary referral centres in the Czech Republic (see Appendix). Anonymised data on treatment efficacy and safety have been consecutively entered into the national database AMADEUS since September 2008. The main aim of this registry is to collect basic epidemiologic data on patients diagnosed with wet AMD, document standard diagnostic and therapeutic patterns and assess treatment effectiveness in standard clinical practice. The data collection is independent of all treatment decisions; it does not affect a patient's access to treatment and fully complies with all ethical as well as legal requirements for non-interventional data collection in the Czech Republic. All patients have given written informed consent to the treatment, as well as data collection. The reported investigations were in accordance with the principles of the current version of the Declaration of Helsinki.

The data are recorded from the moment of diagnosis and start of treatment at regular 3-month intervals for half a year. In the following period, the record is filled in every 6 months. Each record presumes biomicroscopic examination of the eye fundus, determination of VA using the ETDRS chart and an OCT examination (OCT 3 Stratus). The first visit involves FA; ICG is used only if it is necessary for determining a diagnosis. Based on the examinations, mandatory and optional data are specified. The mandatory data always include VA expressed by the number of letters, the central thickness of macula in 1 mm of macula in μm and volume in 6 mm of macula in mm^3 . The first visit also involves determination of the type and size of the CNV using FA or ICG. Patients with a diagnosed wet form of AMD who comply with the State Institute of Drug Control criteria for initiation of treatment with ranibizumab are entered in the registry. Ranibizumab therapy is indicated in patients with AMD who are older than 50 years, with predominantly classic, minimally classic, or occult CNV reaching the subfoveal area, a VA score between 70-35 letters (20/40-20/200 Snellen equivalent), total macular lesion area ≤ 8 DA, submacular haemorrhage $\leq 25\%$ of the total macular lesion area. Minimally classic and occult CNV must show signs of activity in the form of the presence of hard exudates, subretinal haemorrhages or decrease in VA within the last 3 months by ≥ 10 letters of the ETDRS chart. If it is a patient's only well-seeing eye and the other eye is blind or almost blind, the VA score between 75-15 letters (20/40-20/400 Snellen equivalent) is acceptable. In clinical practice, the decision of regulatory health authorities and health insurance companies, mean that patients with a loss of ≥ 15 letters within 12 month are excluded from economically costly treatment. In patients treated with ranibizumab in a dose of 0.5 mg, there are two separate phases: the loading phase, followed by the PRN phase. In the loading phase, the patients receive 3 consecutive monthly injections of ranibizumab (month 0-2), followed by a PRN phase wherein further treatment is given between and including months 3 and 11 according to the re-treatment criteria. Re-treatment with ranibizumab is performed if the patient's VA worsened against VA recorded in the previous visit, and if there is a demonstrable macular oedema in OCT examination. The PRN method of application is also followed in the second year and all succeeding years of patient treatment.

The basic characteristics of patients used for description of disease progression and treatment results were changes in VA in the ETDRS chart over time. Based on the criteria applied in the MARINA study, the criteria for evaluation of patient conditions according to change in ETDRS were:

Significant worsening of VA: decrease by ≥ 15 letters, mild worsening of VA: decrease by 0-14 letters, mild improvement of VA: increase by 1-14 letters, significant improvement of VA: increase by ≥ 15 letters.

The same evaluation criteria of change in ETDRS were applied to all check-up examinations of patients^{3,5}.

The data were described using standard parametric and non-parametric statistics – the means, standard deviation,

median and percentiles for continuous data, percentages or frequencies for categorical data. The statistical significance of differences between groups was evaluated using the Mann-Whitney U test for continuous data and Fisher's exact test for categorical data. Changes in values of continuous variables over time were evaluated using the Wilcoxon paired test. The analysis was performed using the software PASW Statistics 19.0.1. (SPSS, Inc. 2010) and performed by the Institute of Biostatistics and Analyses at Masaryk University, Brno, operating independently of any AMD treating centre.

RESULTS

From 01/09/2008 to 25/10/2011, 671 patients and 685 eyes treated with ranibizumab monotherapy were entered in the registry. The right eye was treated 342 times, the left eye 343 times. The population included 38.2% men, average age 73 years (SD: 8.6) and 61.8% women, average age 74 years (SD: 8.2).

The average baseline VA of those patients was 51.6 (SD: 19.2) letters of the ETDRS chart with a median of 53 letters (5 and 95% percentiles: 22 - 74). 11.2% of patients had VA 15-30 letters, 60.4% had VA 31-60 letters and 28.3% had VA ≥ 61 letters.

A minimum of 3 injections was given to each patient. On average, 4.3 injections of ranibizumab were applied per patient (SD: 1.2) with a median of 4 injections (5 and 95% percentiles: 3 - 6). A 12-month monitoring period was accomplished with 454 patients treated with ranibizumab monotherapy. The reasons for discontinuation of ranibizumab treatment during the first year were complications of the treatment (Table 1), but also the measures of regulatory authorities and health insurance companies which deny patients with a loss of ≥ 15 letters within 12 month economically costly treatment. The average resulting VA of 454 patients treated for 12 months with ranibizumab was 50.5 letters in the ETDRS chart (SD: 17.9) with a median of 52 letters (5 and 95% percentiles: 19 - 77). VA 15-30 letters was seen in 13.4% of patients, VA 31-60 letters was seen in 55.3% of patients and VA ≥ 61 letters was seen in 29.3% of patients. Deterioration of VA by ≥ 15 letters was found in 18.5% of patients and deterioration of VA by 0-14 letters was found in 38.3% of

Table 1. Complications of the treatment.

	Frequency of complications
Subretinal fibrosis	5
Decreased visual acuity	5
Blurred of vision	4
Red eye	2
Retinal haemorrhages	2
Cataract	1
Dry eye	1
Pain of eye	1
Hypertension	1
Others	6

Fig. 1. Macular oedema height measured in OCT at the initiation of the therapy.

patients. Improvement in VA by 1-14 letters occurred in 33.5% of patients and improvement in VA by ≥ 15 letters was seen in 9.7% of patients. Loss of < 15 letters in the ETDRS chart occurred in 81.5% of ranibizumab-treated patients.

The results of the ranibizumab treated patients in the AMADEUS registry were not as good as we had hoped. We performed a subanalysis of the patients of the AMADEUS registry from 01/09/2008 to 25/10/2011 to determine the cause.

We found that from 01/09/2008 to 25/10/2011, some patients were not treated with ranibizumab but still being treated with pegaptanib in fixed dosing regimen (1 injection per 6 weeks). From 01/09/2008 to 25/10/2011 the 12-month monitoring period was accomplished with 196 pegaptanib treated eyes and 195 patients; the right eye was treated 97 times, the left eye 99 times. The population included 43.1% men, average age 73 years (SD: 9.7) and 56.9% women, average age 74 years (SD: 10.5). The average baseline VA of the pegaptanib treated patients was 52.5 (SD: 15.5) letters of the ETDRS chart with a median of 55 letters (5 and 95% percentiles: 25 - 74). 10.7% of patients had VA 15-30 letters, 55.1% had VA 31-60 letters and 34.2% had VA ≥ 61 letters. On average, 8.7 pegaptanib injections were applied per patient (SD: 0.5) with a median of 9 injections (5 and 95% percentiles: 8 - 9).

The average resulting VA of 196 patients treated with pegaptanib was 51 letters in the ETDRS chart (SD: 18) with the median of 53 letters (5 and 95% percentiles: 20 - 75). VA 15-30 letters was seen in 14.3% of patients, VA 31-60 letters was seen in 53.1% of patients and VA ≥ 61 letters was seen in 31.6% patients.

Deterioration of VA by ≥ 15 letters occurred in 14.3% of treated patients and deterioration of VA by 0-14 letters occurred in 41.3% of the pegaptanib-treated patients. Improvement in VA by 1-14 letters occurred in 34.2% of patients and improvement in VA by ≥ 15 letters was seen in 10.2% of patients. Loss of < 15 letters was found in 85.7% of the pegaptanib-treated patients. While the results of ranibizumab-treated patients were not good, the results of pegaptanib-treated patients were. This was the reason for analysing selected parameters in the two groups.

We revealed interesting findings in baseline macula thickness, type and size of CNV and incidence of the newly diagnosed, treatment-naïve CNV in the ranibizumab and pegaptanib treated groups.

The average baseline macula thickness of patients treated with ranibizumab was 350.9 μm (SD: 122.7) with a median of 331.5 μm (5 and 95% percentiles: 187.0 - 590.0) and the average volume of macula was 8.4 mm^3 (SD: 1.8) with a median of 7.9 mm^3 (5 and 95% percentiles: 6.2 - 12.1). The average baseline macula thickness of patients treated with pegaptanib was 317.2 μm (SD: 109.1) with a median of 306.5 μm (5 and 95% percentiles: 174.0 - 533.0) and the average volume of macula was 8.1 mm^3 (SD: 1.7) with a median of 7.7 mm^3 (5 and 95% percentiles: 6.2 - 11.3). Analysis of the data array revealed a different height of baseline macular oedema in patients treated with ranibizumab and pegaptanib. Macular oedema height measured in OCT at the initiation of the therapy is illustrated in Fig. 1. CNV with macular oedema up to 244 μm were treated with ranibizumab in 16.5% and with pegaptanib in 28.0%. CNV with macular oedema from 244 μm to 343 μm were treated with ranibizumab in 36.6%

Table 2. Use of ranibizumab and pegaptanib depending on the type and size of CNV.

Type of CNV	Size of CNV	N	Ranibizumab (N = 685)	Pegaptanib (N = 196)
PC	< 2 PD	36 (20.0%)	31 (86.1%)	5 (13.9%)
	2 - 5 PD	127 (70.6%)	113 (89.0%)	14 (11.0%)
	> 5 PD	17 (9.4%)	16 (94.1%)	1 (5.9%)
	Total	180 (100.0%)	160 (88.9%)	20 (11.1%)
OC	< 2 PD	149 (28.0%)	114 (76.5%)	35 (23.5%)
	2 - 5 PD	350 (65.8%)	240 (68.6%)	110 (31.4%)
	> 5 PD	33 (6.2%)	24 (72.7%)	9 (27.3%)
	Total	532 (100.0%)	378 (71.1%)	154 (28.9%)
MC	< 2 PD	28 (16.6%)	24 (85.7%)	4 (14.3%)
	2 - 5 PD	123 (72.8%)	106 (86.2%)	17 (13.8%)
	> 5 PD	18 (10.7%)	17 (94.4%)	1 (5.6%)
	Total	169 (100.0%)	147 (87.0%)	22 (13.0%)

and with pegaptanib in 32.1%. CNV with macular oedema above 343µm were treated with ranibizumab in 43.3% and with pegaptanib in 33.6%. Apparently, the larger the macular oedema at diagnosis, the more often was ranibizumab opted for treatment. The ranibizumab-treated patients had statistically significantly higher baseline macular oedema than the pegaptanib-treated group ($P = 0.001$).

In the group treated with ranibizumab, 378 patients (55%) had occult CNV, 147 patients (22%) had minimally classic CNV and 160 patients (24%) had predominantly classic CNV. CNV in 628 (92%) patients treated with ranibizumab was ≤ 5 DA. In the group treated with pegaptanib, 154 patients (79%) had occult CNV, 22 patients (11%) had minimally classic CNV and 20 patients (10%) had predominantly classic CNV. CNV in 185 (94%) patients treated with pegaptanib was ≤ 5 DA. Use of ranibizumab and pegaptanib depending on the type and size of CNV is shown in Table 2. Analysis of the data showed that the group treated with pegaptanib had a statistically significantly higher proportion of occult CNV than the group treated with ranibizumab ($P < 0.001$) and statistically significantly lower proportion of minimum and predominantly classic CNV ($P < 0.001$).

The analysis also showed that in the 685 patients treated with ranibizumab, 584 patients (85.3%) were newly diagnosed, treatment-naïve patients. 101 patients (14.7%) in this group had had prior therapy before the ranibizumab treatment (laser, PDT, bevacizumab). In the 196 patients treated with pegaptanib, 179 (91.3%) were newly diagnosed and treatment-naïve. 17 patients (8.7%) in this group had had previous therapy before the pegaptanib treatment (laser, PDT, bevacizumab). Compared to the ranibizumab-treated patients, in the pegaptanib-treated patients, the number of newly diagnosed, treatment-naïve patients was statistically significantly higher ($P = 0.032$).

DISCUSSION

We were unpleasantly surprised that the results of our patients treated in the PRN dosing regimen in clinical practice with ranibizumab were worse than the results

in the PRN dosing regimen in the SUSTAIN study. In the latter, by month 12, 92.5% of patients had lost <15 ETDRS letters from the baseline and 19.3% of patients had a VA gain of ≥ 15 ETDRS letters⁴. Equally surprising was the finding that the results for our patients treated in clinical practice with pegaptanib were better than the results in the VISION study. In the VISION study, in treatment with pegaptanib in a dose of 0.3 mg every 6 weeks after 54 weeks, loss of VA < 15 ETDRS letters was found in 70% of patients, and 6% of patients had a VA gain of ≥ 15 ETDRS letters^{6,7}.

There was no statistically significant difference between the ranibizumab and pegaptanib treated groups in baseline VA ($P = 0.212$). Yet the ranibizumab treated group failed to meet the expectations of treatment efficacy while the pegaptanib-treated group did. We believe the reasons for these results are the findings in a subanalysis of the groups: the differences in number of patients, baseline macula thickness, type and size of CNV and incidence of newly diagnosed, treatment-naïve CNV in the two treatment groups.

In particular, patients for treatment with either ranibizumab or pegaptanib were not evenly distributed as in a clinical trial. They were selected for either treatment. The unequal distribution in the two groups is self evident. Ranibizumab was used to treat 685 patients while pegaptanib was used to treat only 196 patients. There are other major differences between groups.

In the pegaptanib-treated group, 79% of patients had occult CNV, while in the ranibizumab-treated group only 55% of patients had. In the pegaptanib-treated group compared to the ranibizumab-treated group, the share of occult CNV was statistically significantly higher ($P < 0.001$). Sarks⁸ and Killingsworth⁹ demonstrated histologically that the onset of CNV is characterized by intrachoroidal followed by sub-RPE fibrovascular proliferation. Occult CNV which is fibrovascular tissue in the sub-RPE space, may in part represent an earlier stage of CNV because it is in the same tissue plane. Occult CNV as an earlier stage of the disease is assumed to be associated with less damage to photoreceptors in macula and successful treatment provides greater improvement expectancy¹⁰.

Subanalysis also revealed that occurrence of newly diagnosed, treatment naïve patients was statistically significantly higher in pegaptanib-treated patients ($P = 0.032$).

Quiram evaluated the efficacy of pegaptanib in 90 eyes of 90 patients with newly diagnosed, treatment naïve CNV lesions. Of the 90 patients, 20% gained ≥ 3 lines of vision. Quiram presumes that if CNV is diagnosed early and it has not been treated yet, the time of its growth is shorter, damage to macula is lower and successful therapy increases a chance of a favourable therapeutic result¹¹.

The difference in the baseline thickness of macula in patients treated with ranibizumab and pegaptanib was also statistically significant. The ranibizumab-treated patients had statistically significantly higher baseline macular oedema than the pegaptanib-treated group ($P = 0.001$). We found nothing in the literature which would explain unambiguously the relation of the baseline macular oedema height and the resulting VA. We presume that macula oedema height relates to CNV activity. We assume that the higher the macular oedema, the greater the activity of CNV. We presume that greater CNV activity may be related to more aggressive damage to macula and a worse therapeutic result, as measured by the VA level.

We think that newly diagnosed, treatment naïve CNV, occult CNV and lower baseline macular oedema could be positive prognostic factors of visual function in the treatment of the wet form of AMD.

A subanalysis of data in our array demonstrated that pegaptanib compared to ranibizumab was statistically significantly used more often in occult CNV, newly diagnosed, treatment naïve patients and CNV with lower baseline macular oedema. We assume that this could be the reason why after the 12-month treatment loss of < 15 ETDRS letters was seen in 85.7% of pegaptanib patients and only in 81.5% of ranibizumab-treated patients. We assume that this may explain why the results of pegaptanib-treated patients are better than those of the VISION study, and the results of the ranibizumab-treated patients were worse than the results of the SUSTAIN study.

It is also a fact that in our population of ranibizumab-treated patients, the average number of injections per 12-month therapy was 4.3. The question is whether this fact contributed to the worse results of the ranibizumab-treated patients. It is true that this number is lower than in the SUSTAIN study, where the average number of injections per 12 month was 5.7. However, in a clinical trial, patients are treated, whether their visual acuity improves or worsens. In clinical practice in the Czech Republic, one of the decisions of regulatory authorities and health insurance companies is that patients with a loss of ≥ 15 letters within a 12 month are excluded for economic reasons. In the treatment therefore there are only favourable responders. These patients do not need such frequent application of ranibizumab which has an impact on the average number of injections applied in a file per 12 months.

Pagliarini also evaluated the effectiveness and safety profile of ranibizumab 0.5 mg in patients with the wet form of AMD in routine clinical practice. A mean of 6.2 ranibizumab injections was administered during the study (first year: 4.4; second year: 1.8) over 2 years¹².

CONCLUSIONS

Based on this evaluation, we conclude that occult CNV, newly diagnosed, treatment naïve CNV and CNV with lower baseline macular oedema if using an anti-VEGF therapy have a better prospect for as measured by the VA level. However, to confirm whether the type of CNV, newly diagnosed, treatment naïve CNV and height of the baseline macular oedema really represent a prognostic factor in the treatment of wet AMD, other clinical studies will be necessary.

ABBREVIATIONS

AMD, Age-related macular degeneration; ANCHOR, ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in Age-Related Macular Degeneration; MARINA, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration; CNV, Choroidal neovascularization; SUSTAIN, Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; OCT, Optical coherence tomography; BCVA, Best corrected visual acuity; PRN, Pro re nata; VA, Visual acuity; AMADEUS, Age related MACular DEgeneration in patientS in the Czech Republic; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, Fluorescein angiography; ICG, Indocyanine green angiography; DA, Disc area; SD, Standard deviation; PDT, Photodynamic therapy; VISION, VEGF Inhibition Study In Ocular Neovascularization; VEGF, Vascular endothelial growth factor.

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