AFLIBERCEPT IN CLINICAL PRACTICE

Bajaček J., Bieliková A.

Department of Ophthalmology, Central Military Hospital Ružomberok, Head: kliniky MUDr. Bieliková Anna, PhD.

The authors of the study declare that no conflict of interest exists in the compilation and theme of this professional communication, and that it is not supported by any pharmaceuticals company.

MUDr. Juraj Bajaček
Oftalmologická klinika
Ústredná vojenská nemocnica SNP - FN
Generála Miloša Vesela 21
034 26 Ružomberok
e-mail: jbajacek@yahoo.com

SUMMARY

In this article we have tried to evaluate first clinical experience with the effectiveness and safety of aflibercept in the treatment of the wet form of age related macular degeneration in all types of subretinal neovascular membranes for the period of the first 10 months of treatment in our clinic.

Key words: aflibercept, wet age related macular degeneration, subretinal neovascular membrane

Čes. a slov. Oftal., 71, 2015, No. 2, p. 101–108

INTRODUCTION

VAge related macular degeneration (ARMD), in particular its advanced neovascular form, is one of the main causes of irreversible loss of sight in developed countries, and the third most common cause of irreversible loss of sight worldwide (2, 8). The majority of patients with untreated wet form ARMD experience progression to severe loss of central visual acuity in the afflicted eye within 2 years of determination of the diagnosis (1).

Wet form ARMD fundamentally impairs quality of life, both in connection with sight and otherwise, and has a substantial influence on the patient's independence, as well as on physical, emotional and social health (13). The economic burden in connection with loss of sight as a consequence of wet form ARMD is very large, involving ophthalmological healthcare, and also costs which are not directly connected with sight but are linked to falls and fractures and the ensuing afflictions, hospitalisation, care and home healthcare attendance (12).

According to the latest observations, a key role in the development of choroidal neovascularisation in the pathogenesis of wet form ARMD is played by two important proteins from the group of vascular endothelial growth factors (VEGF): VEGF-A and placental growth factor (PlGF). Anti-VEGF therapy currently represents the standard care for patients with wet form ARMD. In clinical practice, the used anti-VEGF therapies of pegaptanib sodium, ranibizumab and bevacizumab (used off-label = outside of approved indication) act against the growth factor VEGF-A and enable the patient to avoid loss of sight, and in many cases may even improve visual acuity. The results of clinical trials have demonstrated that a proactive approach to treatment (fixed monthly dosing) by intravitreal anti-VEGF therapy (ranibizumab or bevacizumab) brings better results of visual acuity than a reactive approach (treatment according to requirement, based on clinical criteria) within the first year (6).

Last year aflibercept was introduced in Slovakia. This is a soluble, fully humanised false receptor fusion protein, which is composed of parts of extracellular domains of natural receptors 1 and 2 for human VEGF, in connection with an Fc part of human immunoglobulin (Ig) G1 (14). Aflibercept binds to VEGF-A and PlGF with a higher affinity than ranibizumab (7, 9). This strengthened bonding affinity indicates that aflibercept may have a longer duration of effect and higher efficacy in the eye, which enables less frequent dosing and a reduction of the burden of regular monthly monitoring of patients with wet form ARMD.

On the basis of the positive results from registration studies on patients with wet form ARMD, the improved mechanism of the effect of aflibercept and its categorisation for treatment of wet form ARMD since October 2013 in application centres in Slovakia, we decided to evaluate its benefits in clinical practice at our workplace. In the following case reports we present examples of the efficacy and safety of aflibercept after 10 months of treatment of newly diagnosed wet form ARMD, as well as on a patient with a refractive subretinal neovascular membrane who reacted sub-optimally to the previous anti-VEGF therapy. Central visual acuity was evaluated using an ETDRS optotype, and we evaluated central retinal thickness using spectral domain OCT.

Today injection solution of aflibercept is indicated for the treatment of wet form age related macular degeneration and other retinal diseases – macular edema as a consequence of central retinal vein occlusion and diabetic macular edema (14)

CASE REPORT 1

In September 2013, a 77 year old patient came to our outpatient clinic for an OCT examination, who had been sent by the district ophthalmologist due to suspicion of a subretinal neovascular membrane (SRNM) in the right eye. The patient stated that he had suffered progressive deterioration of vision in the right eye for approximately six months, and metamorphopsia persisting for about one month. In the first examination we conducted, we determined the following central visual acuity (CVA) in the right eye: 20/80 – 52 letters of ETDRS optotype, in the left eye CVA: 20/25 – 79 letters of ETDRS optotype and positive test on an Amsler grid. Numerous hard and soft drusens, edema and ablation of the neuroretina can be seen fundoscopically in the centre of the macular region (MR) (fig. 1). On the OCT finding we find subfoveolar ablation of the retinal pigment epithelium (RPE) as well as serous ablation of the neuroretina with edema and pronounced defects in the RPE up to the periphery of the MR (fig. 2). We also conducted a FAG examination on the patient, which confirmed predominant classic SRNM (fig. 3a + 3b). We prescribed intravitreal treatment with aflibercept in a dosing regime once every 4 weeks during the first 3 months of treatment for

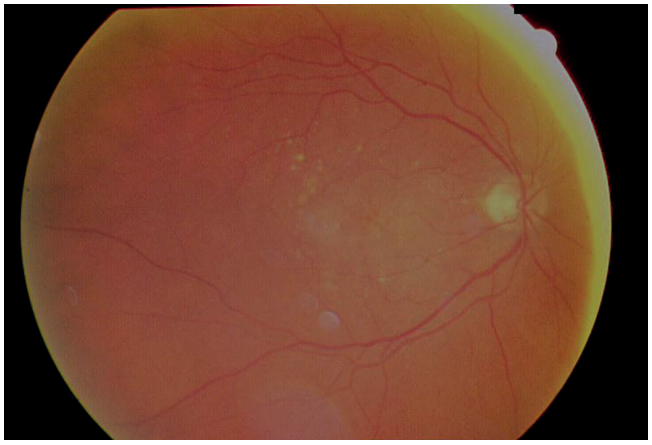

Fig. 1 Colour image of fundus of right eye. Numerous hard and soft drusens with edema are visible in the macular region

the patient, after which a further 3 doses were administered at intervals of 8 weeks. At the final follow-up examination one month after the sixth application, the patient reported to the clinic in August 2014 with CVA of 20/63 – 62 letters of ETDRS optotype, on the OCT finding a slight regression of ablation of the RPE is visible, with pronounced regression of the serous ablation of the neuroretina with residual edema and a more visible foveolar depression (fig. 4). Continuation with intravitreal treatment with aflibercept at intervals of 8 weeks was ordered for the patient.

CASE REPORT 2

In June 2011, an 80 year old patient came to our outpatient clinic, sent from another application centre for the purpose of continuing anti-VEGF therapy in the left eye. At the primary workplace, the patient was applied 10x pegaptanib intravitreally at intervals of 6 weeks for classic SRNM, with stable central visual acuity (CVA 20/32 – 72 letters of ETDRS optotype) and retinal thickness on OCT (fig. 5). In the right eye the patient had long-term reduced vision – fingers in front of eye, due to scarry stage of SRNM. Following an angiographic examination (fig. 6, fig. 7a + 7b), we prescribed intravitreal treatment with ranibizumab at intervals of 4 weeks for the patient. Over the course of 2 years the patient was applied a total of 15 doses of ranibizumab, with progressively deteriorating CVA to 20/145 – 41 letters of ETDRS optotype, in which pronounced atrophic changes in the retinal pigment

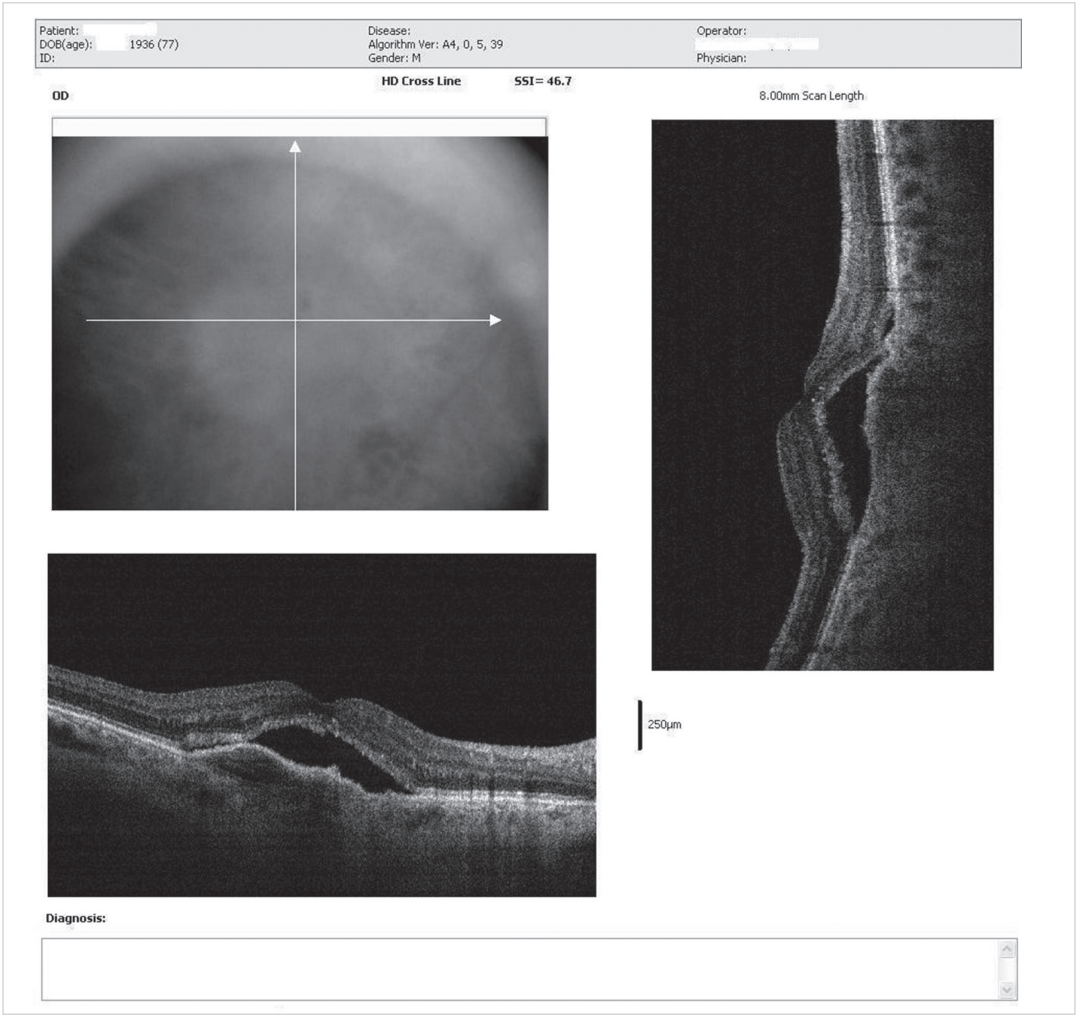

Fig. 2 OCT image (HD cross-line) of right eye. Subfoveolar pronounced serous ablation of the neuroretina with edema and with ablation of the RPE

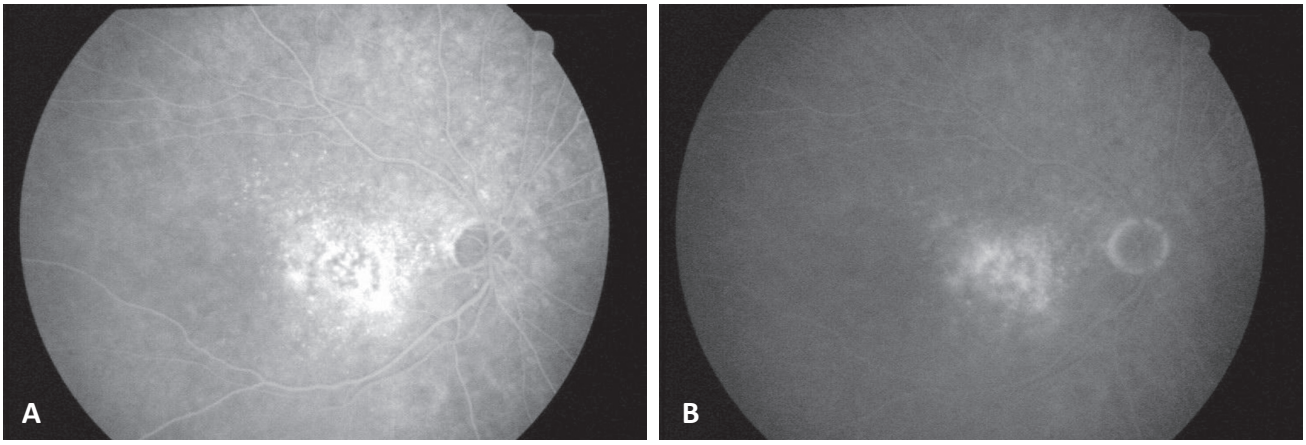

Fig. 3a, b FAG images of right eye. In the MR there are numerous hyperfluorescent deposits due to stasis and seepage of the contrast substance in places of edema and ablation of the neuroretina. Hyperfluorescent drusens are visible in the surrounding area

epithelium (RPE) persisted on the OCT finding, with edema of the neuroretina with maximum in the lower nasal sectors and up to macrocystic changes in the area of the fovea (fig. 8). With regard to the deteriorating vision, the progression of the finding on OCT (fig. 9) and the possibility of ordering a new available anti-VEGF therapy for wet form ARMD, after a control angiographic examination we indicated the patient for intravitreal treatment with aflibercept 2 mg in a dosing regimen of once per 4 weeks over the course of 3 months of therapy, after which there followed a further 3 doses at

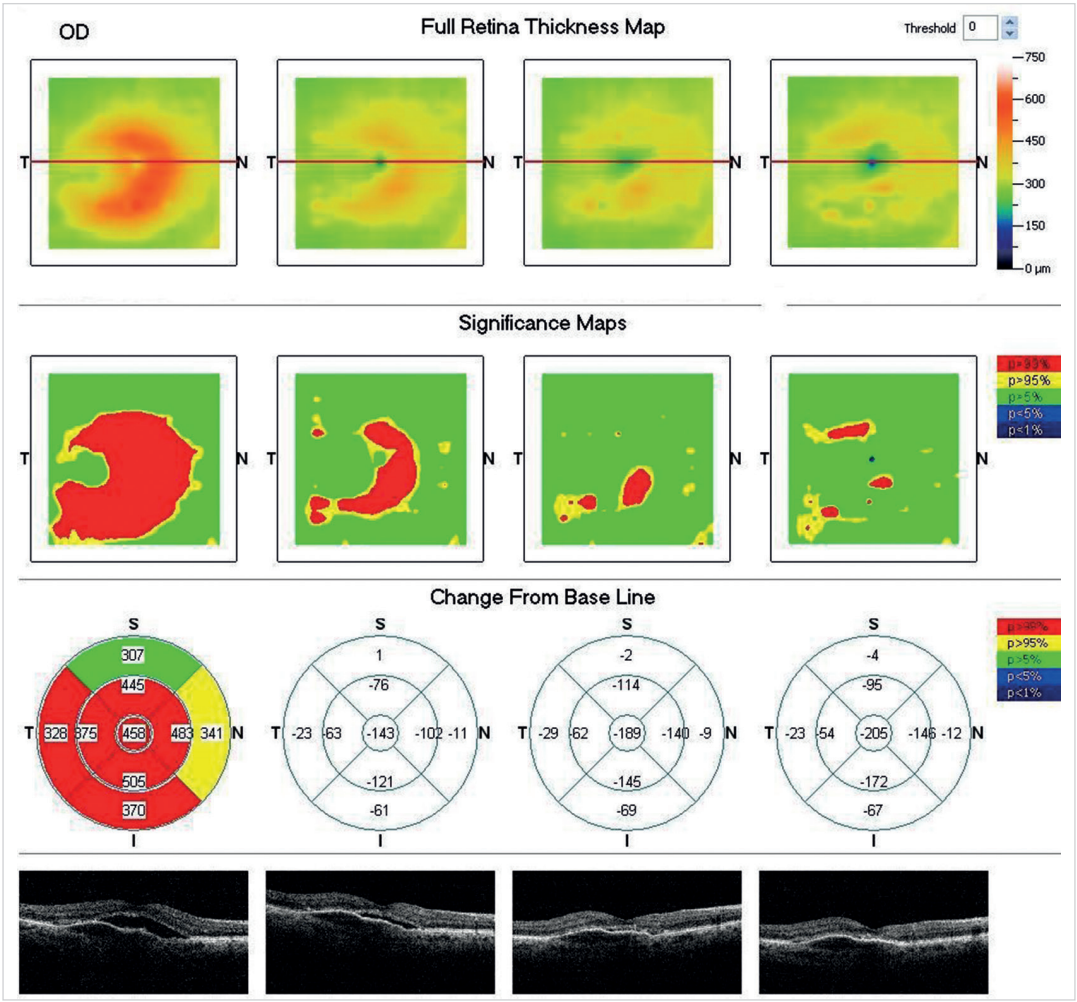

Fig. 4 OCT image of right eye (comparative map after 10 months from the beginning of treatment with aflibercept). Pronounced regression of edema and serous ablation of the neuroretina. CRT – 205 µm. Ablation of RPE persists

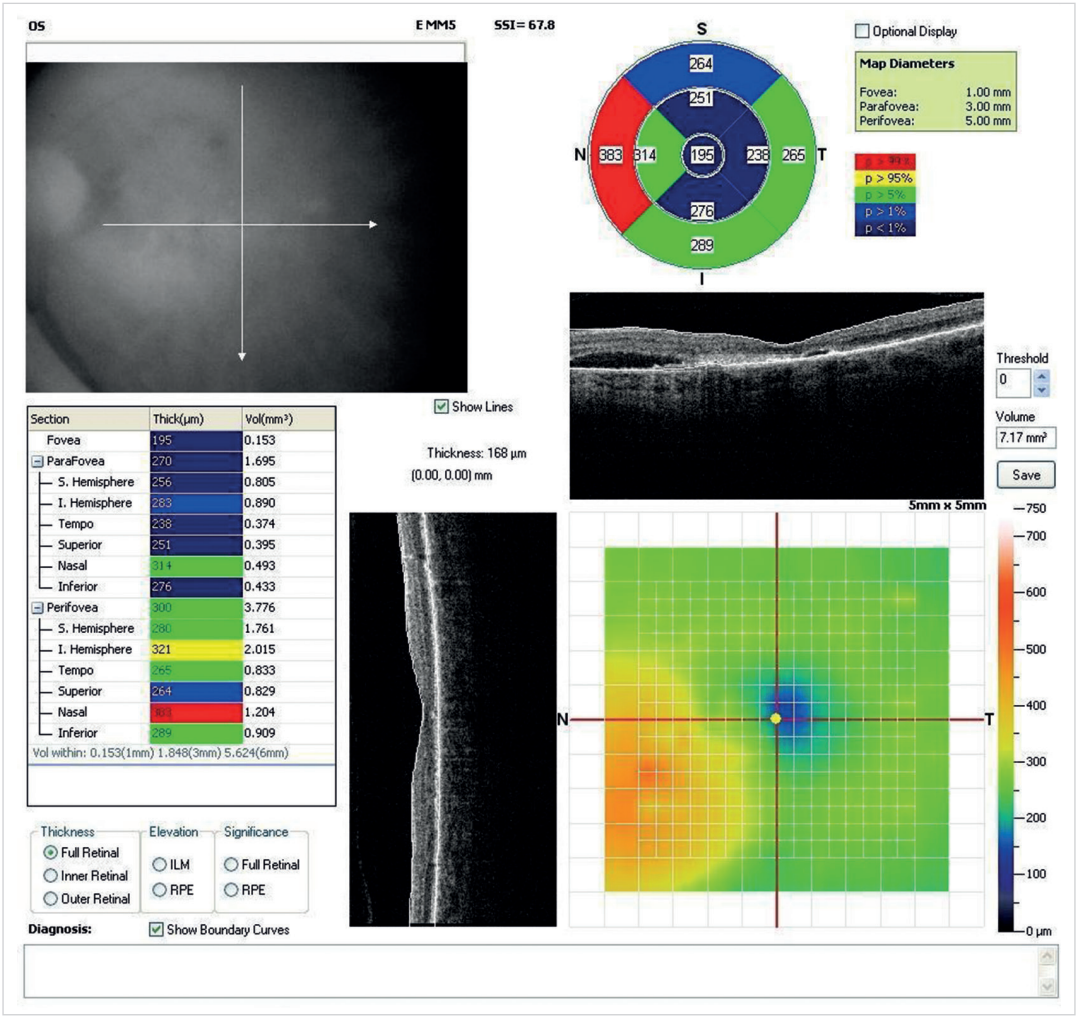

Fig. 5 OCT image (map) of left eye. Pronounced defects, atrophic changes of RPE predominantly subfoveolar, with edema and serous ablation of neuroretina predominantly in nasal sectors.
Finding after 10 intravitreal applications of pegaptanib

intervals of 8 weeks. At the last follow-up examination after 6 doses of aflibercept, the patient had visual acuity of CVA 20/63 – 62 letters of ETDRS optotype, and on the OCT finding regression of the edema of the neuroretina is visible (fig. 10). With regard to the improvement of the anatomical and functional finding, continuation of intravitreal therapy with aflibercept at an interval of 8 weeks was ordered for the patient.

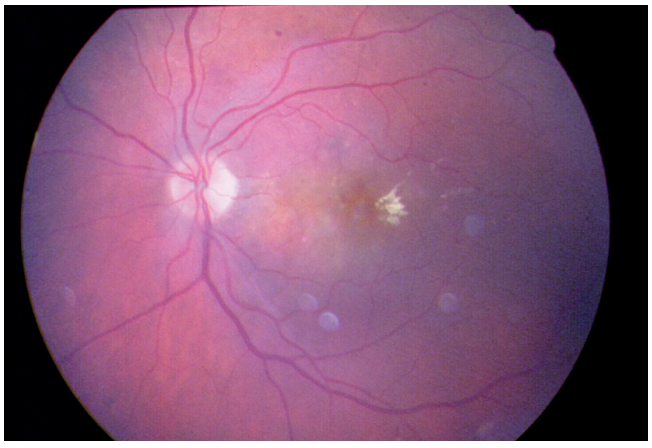

Fig. 6 Colour image of left eye with classic SRNM

DISCUSSION

NOn the basis of the results of the clinical trials of the 3rd phase VIEW1 and VIEW2 on newly-diagnosed patients with wet form ARMD, aflibercept 2 mg applied every 2 months (after 3 initial doses once per month) has statistically comparable and clinical equivalent efficacy as ranibizumab 0.5 mg administered once per month, in the sense of prevention of loss of sight, improvement of visual acuity, reduction of the scope of choroidal neovascularisation, reduction of retinal thickness and reduction of the amount of fluid in the retina after 1 year (3). In the 52nd week, upon therapy with aflibercept in the aforementioned dosing regimen, the average change of visual acuity was +8.4 letters on ETDRS optotype in comparison with the initial value (3). The functional and anatomical results of treatment of wet form ARMD were attained with a significantly lower number of injections of aflibercept in the first year (7.6 injections of aflibercept versus 12.3 injections of ranibizumab), and these results were maintained also in

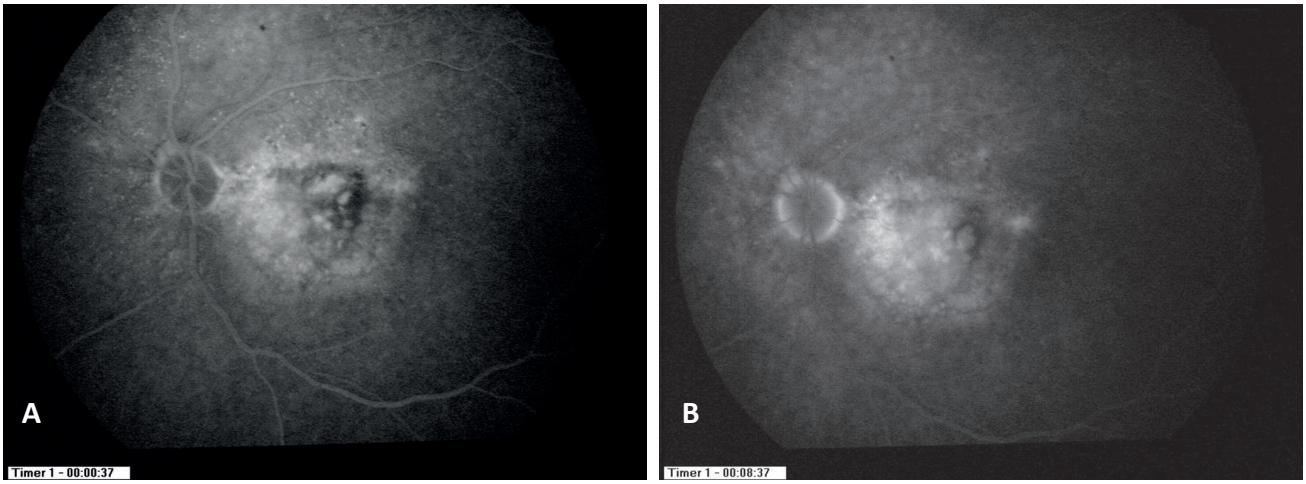

Fig. 7a, b FAG images of left eye with classic SRNM

the second year of treatment with a significantly lower number of injections of aflibercept (4.2 injections of aflibercept versus 4.7 injections of ranibizumab) (14 ,11). The safety of aflibercept was comparable with ranibizumab after two years of observation (11).

The presented case report, as well as our practical experiences with aflibercept in the treatment of other newly-diagnosed patients with wet form ARMD with occult or predominantly classic SRNM are similar in the result of the efficacy of aflibercept from clinical trials, and in certain cases exceed these trials.

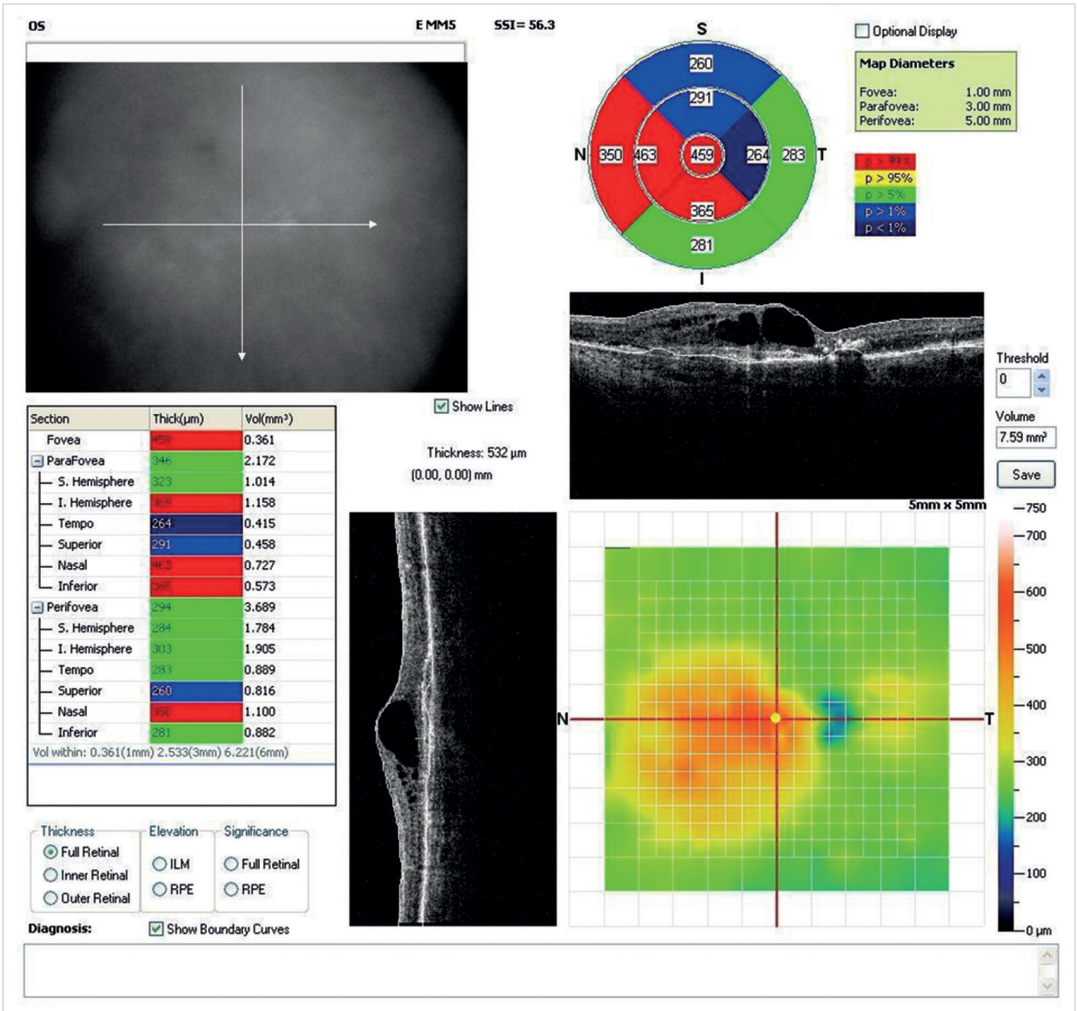

Fig. 8 OCT image (map) of left eye. Pronounced edema of neuroretina with macrocystic mutation in place of fovea. Pronounced atrophic changes of RPE to incipient fibrotic mutation. Finding after 15 intravitreal doses of ranibizumab

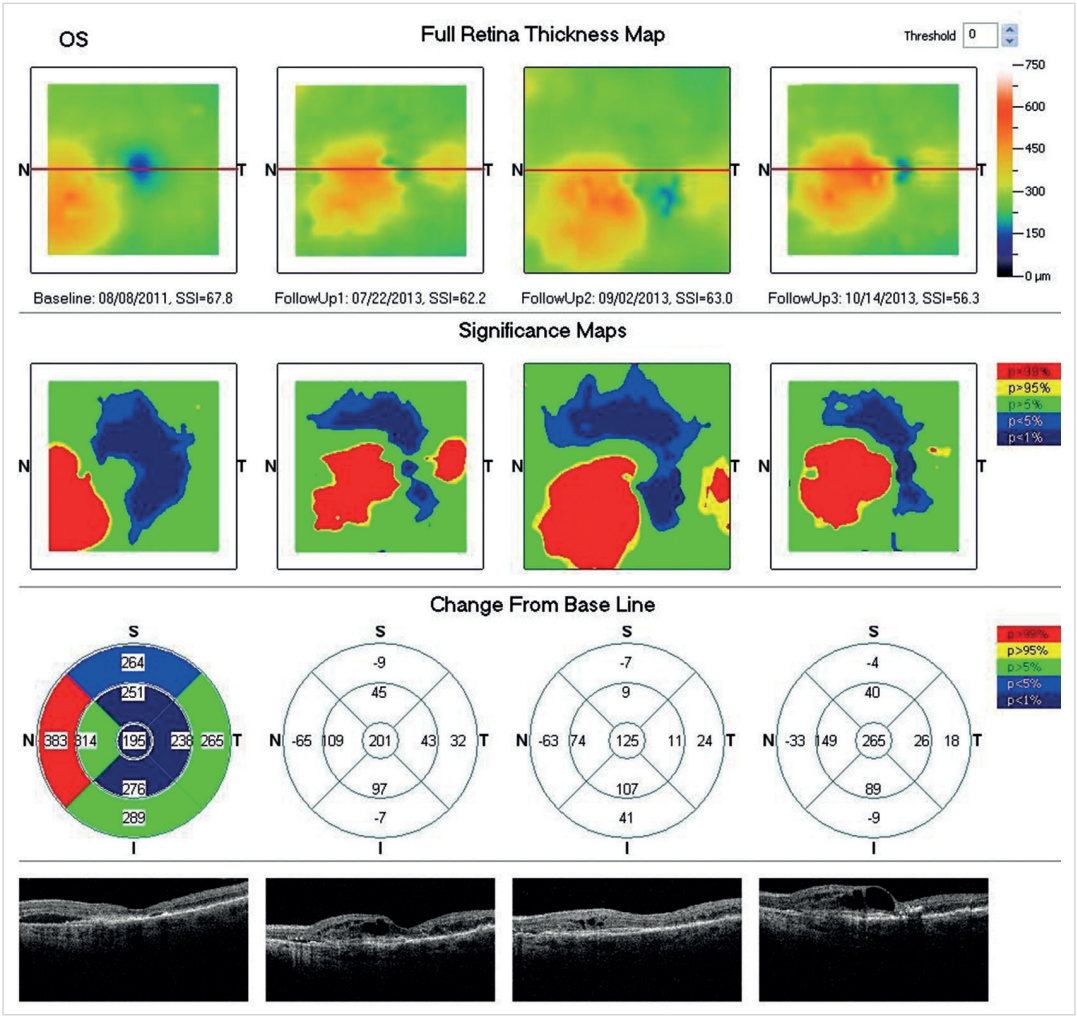

Fig. 9 OCT image (comparative – after 2 years of treatment with ranibizumab). Progression of edema of neuroretina and retinal thickness – CRT: +265 µm

Recently primary data from a number of studies has been published, demonstrating the clinical benefit of the use of aflibercept also on patients with a sub-optimal response to previous anti-VEGF therapy (4, 15, 16). In an endeavour to achieve an improvement in visual acuity, to treat patients who were not responding or not responding sufficiently to therapy, as well as in an endeavour to manage tachyphylaxis and reduced biological efficacy following repeated administration of intravitreal injections, a switch of therapeutic substances is applied in practice. In comparison with other anti-VEGF substances used in the treatment of neovascular ARMD, aflibercept, thanks to its unique structure, has different bonding properties – a higher affinity and broader scope not only to all isoforms of VEGF-A, but also to PlGF (7). Data demonstrating the clinical benefit is available, covering stabilisation or improvement of visual acuity and improvement of the anatomical finding on OCT, or prolonging of the intervals between injections following switching of therapy to aflibercept in the case of a sub-optimal response to other anti-VEGF substances (4, 5, 10, 15, 16).

According to our experiences to date, switching of therapy to aflibercept in patients with a sub-optimal response to other anti-VEGF substances at our workplace has led to an improvement of the anatomical finding and to stabilisation or improvement of visual acuity after the first 3 introductory injections. Since the recommended two-month dosing regimen (after the introductory monthly doses) in the first year of treatment of ARMD does not require monitoring during the period between injections of aflibercept, the patients did not need to report to the clinic every month, which relieved the burden on both doctors and patients in connection with monthly monitoring and treatment of wet form ARMD.

CONCLUSION

Despite the short observation period, experiences to date with aflibercept in the treatment of wet form ARMD have demonstrated good efficacy and safety on newly-diagnosed patients with all types of SRNM, which it is necessary to verify in practice from a long-term perspective. In the case of patients for whom previous anti-VEGF therapy has been switched to aflibercept, we observed a stabilisation and improvement of the anatomical and functional finding. Up to this point no serious adverse effects have been manifested in treatment with aflibercept. The dosing regimen of aflibercept in the treatment of wet form ARMD has advantages in terms of the reduced need for monitoring, greater comfort for the patient

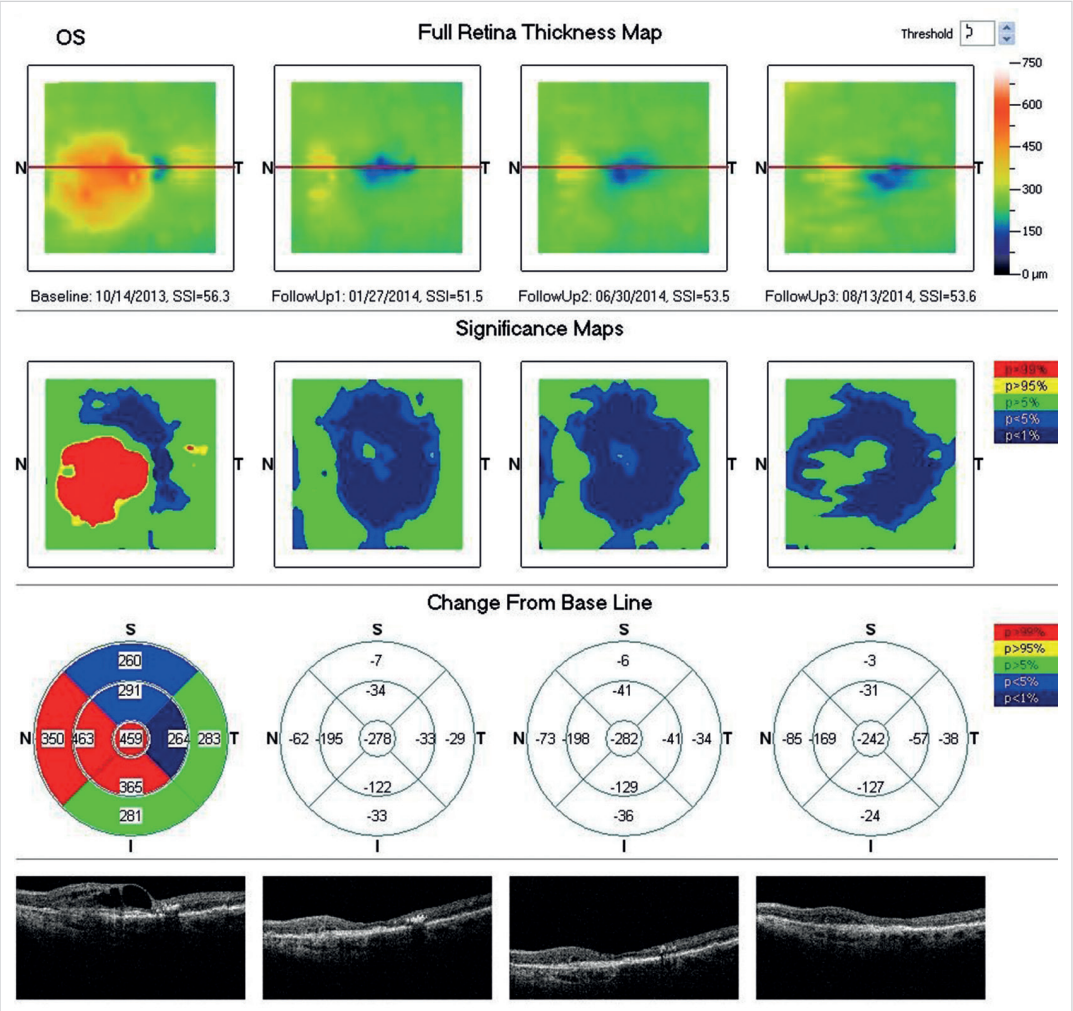

Fig. 10 OCT image (comparative – after 10 months of treatment with aflibercept). Regression of edema of neuroretina and retinal thickness – CRT: -242 µm

and doctor, and brings the possibility of a lower incidence of adverse effects in connection with intravitreal application, which reduces the working and economic burden of wet form ARMD on patients, doctors in application centres and the overall healthcare system. We expect that thanks to the possibility of a further prolonging of the intervals between injections of aflibercept, in the second year of treatment this burden will be reduced yet further.

LITERATURE

1. **Bressler, S.B., Bressler, N.M., Fine, S.L. et al.:** Natural course of choroidal neovascular membranes within the foveal avascular zone in senile macular degeneration. Am J Ophthalmol, 93(2); 1982: 157–163.
2. **Congdon, N., O'Colmain, B., Klaver, C.C. et al.:** Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol, 122 (4); 2014: 477–485.
3. **Heier, J.S., Brown, M.D., Chong, V. et al.:** Intravitreal aflibercept (VEGF Trap--Eye) in wet age-related macular degeneration. Ophthalmology, 119 (12); 2012: 2537–2548.
4. **Chang, A.A., Li, H., Broadhead, G.K. et al.:** Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. Ophthalmology, 121; 2014: 188–192.
5. **Cho, H., Weber, M.L., Shah, C.P. et al.:** Initial utilization of aflibercept in exudative age related macular degeneration. Eur J Ophthalmol, 24(4); 2014: 576–581.
6. **Martin, D.F., Maguire, M.G., Ying, G.S. et al:** Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med, 364(20); 2011: 1897–1908.
7. **Papadopoulos, N., Martin, J., Ruan, Q. et al.:** Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis, 15(2); 2012: 171–185.
8. **Resnikoff, S., Pascolini, D., Etya'ale, D. et al.:** Global data on visual impairment in the year 2002, Bull World Health Organ, 82(11); 2004: 844–851.
9. **Rudge, J.S., Holash, J., Hylton, D. et al.:** VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. Proc Natl Acad Sci U S A, 104(47); 2007: 18363–18370.
10. **Sawa, Y. et al.:** Short-term outcomes of aflibercept for recurrent neovascular

age-related macular degeneration in Japanese patients. E-poster PO-1531, World Ophthalmology Congress 2014, Tokyo, Japan, April 2–6, 2014.
11. **Schmidt-Erfurth, U. et al.:** Intravitreal aflibercept injection for neovascular age-related macular degeneration. Ninety-six week results of the VIEW studies. Ophthalmology, 121; 2014: 193–201.
12. **Schmier, J.K., Jones, M.L., Halpern, M.T.:** The burden of age-related macular degeneration. Pharmacoeconomics, 24(4); 2006: 319–334.
13. **Soubrane, G., Cruess, A., Lotery, A. et al.:** Burden and health care resource utilization in neovascular age-related macular degeneration: findings of a multicountry study. Arch Ophthalmol, 125(9); 2007: 1249–1254.
14. Eylea (aflibercept injekčný roztok v liekovke) Súhrn charakteristických vlastností lieku. Berlin, Nemecko: Bayer Pharma AG: 2014.
15. **Wykoff, C.C., Brown, D.M., Maldonado, M.E. et al.:** Aflibercept treatment for patients with exudative age-related macular degeneration who were incomplete responders to multiple ranibizumab injections (TURF trial). Br J Ophthalmol, 98(7); 2014: 951–955.
16. **Yonekawa, Y., Andreoli, C., Miller, J.B. et al.:** Conversion to aflibercept for chronic refractory or recurrent neovascular age-related macular degeneration. Am J Ophthalmol, 156(1); 2013: 29–35.

NOTIFICATION

We hereby inform you that on the day of 26 March 2015, at a ceremony held in the Theresian hall of the Břevnov monastery, Dr. Jaroslava Vladyková was awarded the honour of Knighthood of Czech Medicine. After Professor Ivan Karel she is the second ophthalmologist to be awarded this prestigious honour.

Journal editorial board