(38)

Efficacy of intravitreal aflibercept in patients with exudative age-related macular degeneration

Ocena skuteczności leczenia doszklistkowymi iniekcjami afliberceptu chorych na wysiękową postać zwyrodnienia plamki związanego z wiekiem

Joanna Dolar-Szczasny, Anna Święch-Zubilewicz, Jerzy Mackiewicz

Department of Retinal and Vitreal Surgery, Medical University of Lublin, Poland
Head: Jerzy Mackiewicz, PhD, MD

Abstract: Aim of the study: To evaluate the efficacy of intravitreal aflibercept administered to patients with exudative age-related macular degeneration.
Materials and methods: 70 patients with exudative age-related macular degeneration confirmed clinically and in additional diagnostic procedures (fluorescein angiography and spectral domain-optical coherence tomography) were enrolled. All patients were administered three doses of intravitreal aflibercept at one-month intervals. Some patients (seven) received an additional injection of the drug two months after the last of the three injections. The best-corrected visual acuity and the optical coherence tomography findings were assessed at baseline and after the treatment.
Results: At baseline, the mean best corrected visual acuity was 0.20. After the injection of aflibercept it improved to the mean value of 0.32 with the difference being statistically significant ($p < 0.001$, Student's t-test). The mean central subfield thickness at baseline was 311.4 μm. It decreased to mean value of 254.5 μm with the difference being statistically significant ($p<0.001$, Student's t-test).
Conclusions: Intravitreal injections of aflibercept improved clinical and anatomical parameters in patients with exudative age-related macular degeneration in the initial phase of treatment.

Key words: aflibercept, age-related macular degeneration (AMD), vascular endothelial growth factor (VEGF), intravitreal injections.

Abstrakt: Cel pracy: ocena skuteczności afliberceptu podawanego doszklistkowo u chorych na wysiękową postać zwyrodnienia plamki związanego z wiekiem.
Materiał i metody: badaniem objęto 70 chorych na wysiękową postać zwyrodnienia plamki związanego z wiekiem potwierdzoną badaniem klinicznym oraz badaniami dodatkowymi: angiografią fluoresceinową i spektralną optyczną koherentną tomografią. Wszyscy chorzy otrzymali 3 dawki afliberceptu podane doszklistkowo w comiesięcznych odstępach. U części chorych (7) podano dodatkową iniekcję leku po 2 miesiącach od 3. iniekcji. Analizie poddano najlepiej skorygowaną ostrość wzroku oraz wyniki badań optycznej koherentnej tomografii dna oka przed leczeniem i po nim.
Wyniki: u badanych średnia skorygowana ostrość wzroku w momencie kwalifikacji do leczenia wyniosła 0,20. Po podaniu iniekcji afliberceptu wynosiła średnio 0,32 i była istotnie różna statystycznie ($p<0,001$, test t-Studenta). Średnia grubość centralna siatkówki przed leczeniem wynosiła 311,4 μm. Po leczeniu obniżyła się do średnio 254,5 μm i była istotnie różna statystycznie ($p<0,001$, test t-Studenta).
Wnioski: iniekcje doszklistkowe afliberceptu w początkowej fazie leczenia powodują poprawę parametrów klinicznych i anatomicznych u chorych na wysiękową postać zwyrodnienia plamki związanego z wiekiem.

Słowa kluczowe: aflibercept, zwyrodnienie plamki związane z wiekiem (AMD), śródbłonkowy czynnik wzrostu naczyń (VEGF), iniekcje doszklistkowe.

Introduction

Exudative age-related macular degeneration (Age-related Macular Degeneration – AMD) is responsible for 80% of cases of severe visual impairment associated with AMD (1).

The introduction of vascular endothelial growth factor (VEGF) inhibitors was a breakthrough in the treatment of exudative AMD. The first approved drug was pegaptanib sodium (Macugen), which is a selective RNA aptamer inhibiting a VEGF165 isoform. In 2005, a report of Rosenfeld (2) was published addressing the efficacy of a humanized monoclonal antibody, bevacizumab (Avastin) in exudative AMD. One year later, ranibizumab (Lucentis), a Fab fragment of this antibody was launched. Recently, a new product, aflibercept (Eylea) was approved for treatment of exudative AMD. It is a recombinant fusion protein binding all VEGF-A isoforms as well as placental growth factor (PIGF), which is also involved in neovascularization process. Different studies have shown that aflibercept shows much higher affinity to VEGF than previously used products (3). Furthermore, it remains active in vitreous humor significantly longer than ranibizumab (4). This enabled the development of a new treatment algorithm involving less frequent intravitreal injections, the efficacy of which was confirmed in two large clinical

trials, VIEW1 and VIEW2. These studies demonstrated that dosage regimen including maintenance doses of aflibercept administered every two months after the initial loading dose of three injections administered at one-month intervals is as effective as a monthly ranibizumab injections (5).

We decided to assess the initial treatment phase of patients with neovascular AMD according to the protocol including three intravitreal injections of aflibercept administered at one-month intervals, followed by maintenance doses administered every two months.

Aim of the study

The aim of the study was to evaluate the efficacy of intravitreal aflibercept injections administered to patients with exudative AMD.

Material and methods

70 patients with exudative AMD treated at the Department of Retinal and Vitreal Surgery of the Medical University of Lublin were enrolled. The group consisted 39 women (56%) and 31 men (44%), who were treatment naive (55 patients) or who continued treatment (15 patients) after previous therapy with another anti-VEGF agent (ranibizumab or bevacizumab). The mean age was 67 years (age range of 55 to 83 years). All enrolled patients met the eligibility criteria set out by the National Health Fund i.e.: visual acuity range from 0.1 to 0.5 and age over 50 years. Patient with predominantly hemorrhagic and atrophic lesions were excluded from the study.

The study was conducted from May 2014 till March 2015; the treatment and follow-up lasted for 10 months altogether. The patients were treated according to the regimen recommended by the manufacturer: three initial injections of 2.0 mg aflibercept administered once a month, followed by injections of 2.0 mg aflibercet admininstered every two months, in case of clinically confirmed disease progression. The total number of injections administered over the study was 220. 60 patients received three injections, and 10 patients received four injections.

As a part of eligibility assessment, all treated patients had the best-corrected visual acuity (BCVA) measured using Snellen charts. Additionally, spectral domain-optical coherence tomography (SD-OCT; Zeiss Cirrus) and fluorescein angiography (FA; OPTOS 200Tx) were performed. The interval between the screening visit and first aflibercept injection ranged from 2 to 3 months. After the third injection patients were scheduled for follow–up visits at 4-week intervals. During follow-up visits BCVA re-assessed and SD OCT was performed to evaluate retinal structure, allowing appreciation of changes in central subfield thickness (CST). Statistical analysis was performed with paired Student t tests.

Results

The baseline BCVA assessed during screening in the study group ranged from 0.1 to 0.5 (mean, 0.20; median, 0.175). After the treatment (administration of 3-4 intravitreal injections of aflibercept), BCVA ranged from 0.1 to 0.8 (mean, 0.32; median, 0.30). The difference was statistically significant ($p<0.001$, Student's *t*-test), as compared to the results obtained prior to the treatment (Fig. 1). The mean BCVA gain in patients receiving aflibercept as the first line treatment and previously treated with other anti-VEGF agents was 0.1 and 0.04, respectively. The mean CST assessed using OCT at baseline was 311.4 (range 216-363) μm. It decreased to 254.5 μm (range 180–314) following the injections, and the difference between the two timepoints was statistically significant ($p<0.001$, Student's *t*-test) (Fig. 2).

Furthermore, the SD-OCT performed upon treatment completion (i.e. administration of three or four injections) demonstrated lack of subretinal fluid and intraretinal edema in 44 patients (63%) (Fig. 3).

No significant ocular complication was observed over the study, except for intraconjunctival hemorrhage in 16 cases (7% of injections). No systemic complications were noted, either.

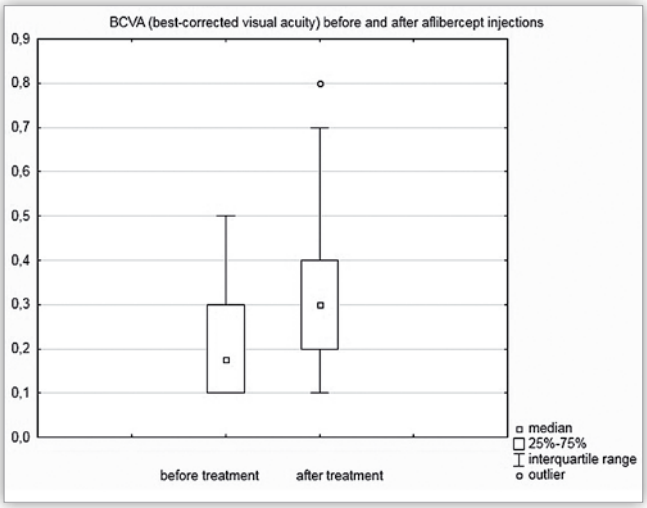

Fig. 1. Best-corrected visual acuity at baseline and after aflibercept treatment.

Ryc. 1. Najlepsza skorygowana ostrość wzroku – wartości wyjściowa i po zakończeniu leczenia.

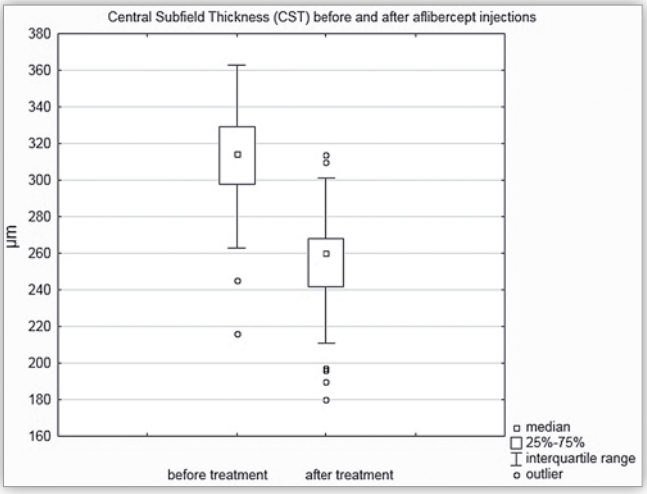

Fig. 2. Central subfield thickness in OCT at baseline and after aflibercept treatment.

Ryc. 2. Poddołkowa grubość siatkówki w obrazie badania OCT – wartości wyjściowa i po zakończeniu leczenia.

ISSN 0023-2157 Index 362646

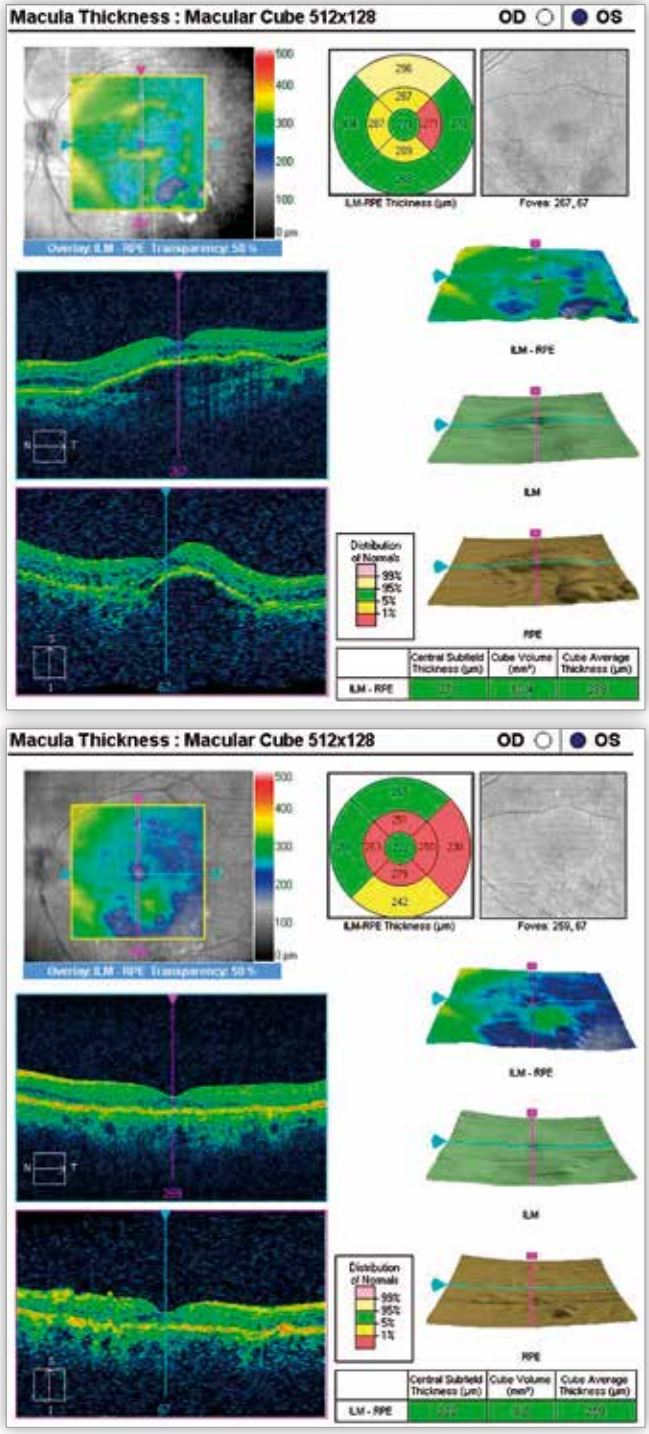

Fig. 3. 63 year-old woman; OCT scans: BCVA=0.2 and subretinal fluid before treatment (A), BCVA=0.5 and lack of subretinal fluid after treatment (B).

Ryc. 3. Pacjentka lat 63, obraz badania OCT. Przed rozpoczęciem leczenia (A) Vis c.c. = 0,2 i płyn podsiatkówkowy. Po zakończeniu leczenia (B) Vis c.c. = 0,5, płyn podsiatkówkowy uległ wchłonięciu.

Discussion

Anti-VEGF agents are used in long-term treatment of exudative AMD. It requires a repeated administration of the drug as an intravitreal injection for even as long as several years. This gave rise to the to attempts to develop a new formulation which lasts longer, thus reducing the total number of injections. A number of reports indicate good results of aflibercept administered intravitreally to patients with AMD and other retinal disorders requiring anti-VEGF therapy (6–10).

Our efficacy study of intravitreal aflibercept during the initial phase of exudative AMD treatment confirmed its efficacy in terms of both functional (BCVA) and anatomical (OCT) outcomes. In most patients visual acuity gain and the morphological improvement were achieved, which manifested in OCT as a reduction or a complete resolution of subretinal fluid and intraretinal edema (63% of patients). Similarly, in VIEW1 and VIEW2 trials, persistent intra- or subretinal fluid one year after treatment was shown in 27.6% and 32.3% of patients, respectively (5). Only a minority of our patients needed a subsequent (fourth) dose of aflibercet, administered two months after the loading dose. It is believed that the decreased number of injections in exudative AMD is due to the pharmacokinetic properties of the drug and that after the three loading doses administered at monthly intervals, subsequent injections can be performed every two months, if necessary. We discontinued treatment in our patients, having confirmed a complete reabsorption of subretinal fluid and resolution of intraretinal edema. Preliminary observations in this group are in line with the reports on possible reduction in the number of injections with aflibercept. It should be noted, though, that we focused only on the initial phase of treatment, which covers a few-month long follow-up period.

Further studies in patients previously treated with intravitreal injections of other anti-VEGF agents should be conducted. However, our preliminary results suggest slightly worse outcomes in these patients, which is probably due to recalcitrant nature of some wet AMD forms.

Conclusions

Aflibercept is an effective intravitreal drug for the treatment of exudative AMD. It improves visual acuity or reduces vision loss in a significant number of patients during the first year of treatment. Additionally, it resolves retinal edema and subretinal fluid, either partially or completely. Eylea has an excellent safety profile. However, the long-term effects of the drug are still unknown, so further studies with longer follow-up are required.

References:

1. Jager RD, Mieler WF, Miller JW: *Age-related macular degeneration*. N Engl J Med. 2008; 358: 2606–2617.
2. Rosenfeld PJ, Moshfeghi AA, Puliafito CA: *Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration*. Ophthalmic Surg Lasers Imaging. 2005; 36: 331–335.
3. Holash J, Davis S, Papadopoulos N, Croll SD, Ho L, Russell M, et al.: *VEGF-Trap: A VEGF blocker with potent antitumor effects*. Proc Natl Acad Sci U S A. 2002; 20, 99: 11393–11398.
4. Stewart MW, Rosenfeld PJ: *Predicted biological activity of intravitreal VEGF Trap*. Br J Ophthalmol. 2008; 92: 667–668.
5. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al.: *VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration*. Ophthalmology. 2012; 119: 2537–2548.

6. Rejdak R, Szkaradek M, Taslaq W, Kałuzny JJ, Grieb P, Jünemann AG: *Nowy lek VEGF Trap-Eye – Eylea – i jego wykorzystanie w leczeniu zwyrodnienia plamki związanego z wiekiem, zakrzepu żyły środkowej siatkówki, cukrzycowego obrzęku plamki oraz neowaskularyzacji w przebiegu krótkowzroczności*. Klin Oczna. 2012; 114: 308–310.
7. Koizumi H, Kano M, Yamamoto A, Saito M, Maruko I, Sekiryu T, et al.: *Aflibercept therapy for polypoidal choroidal vasculopathy: short-term results of a multicentre study*. Br J Ophthalmol. 2015 Mar 16. pii: bjophthalmol-2014-306432 [Epub ahead of print]
8. Ikuno Y, Ohno-Matsui K, Wong TY, Korobelnik JF, Vitti R, Li T, et al.: *MYRROR Investigators*. Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularization: The MYRROR Study*. Ophthalmology. 2015 Mar 4. pii: S0161-6420(15)00098-6 [Epub ahead of print]
9. Călugăru D, Călugăru M: *Intravitreal Aflibercept for Macular Edema Secondary to Central Retinal Vein Occlusion: 18-Month Results of the Phase 3 GALILEO Study*. Am J Ophthalmol. 2015; 159: 607–608.
10. Yuzawa M, Fujita K, Wittrup-Jensen KU, Norenberg C, Zeitz O, Adachi K, et al.: *Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration*. Ophthalmology. 2015; 122: 571–578.

The study was originally received 20.04.2015 (KO-00007-2015)/
Praca wpłynęła do Redakcji 20.04.2015 r. (KO-00001-2015)
Accepted for publication 03.11.2015/
Zakwalifikowano do druku 03.11.2015 r.

Reprint requests to (Adres do korespondencji):
dr n. med. Joanna Dolar-Szczasny
Department of Retina and Vitreal Surgery of Medical University in Lublin, Poland
ul. Chmielna 1,
20-149 Lublin, Poland
e-mail: joannaszczasny@op.pl

ISSN 0023-2157 Index 362646