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Case series

Switching therapy in patients with age-related macular degeneration, diabetic macular edema and cistoid macular edema due to retinal vein occlusion

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Summary

Introduction. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents has revolutionized the management of age-related macular degeneration (AMD), diabetic macular edema (DME), macular edema in retinal vein occlusions (RVO), and other retinal diseases accompanied by neovascular and macular edema. The aim of the study is to show the effect of switching from bevacizumab to aflibercept in patients with recalcitrant wet AMD as the best clinical approach and regimen for patients with neovascular and macular edema accompanied retinal diseases.

Methods. All our patients received the intravitreal injections of 1.25 mg (0.1 mL) bevacizumab as the first treatment option, and we switched to aflibercept or triamcinolon acetonid when the therapy including bevacizumab seemed not to be effective enough, according to visual acuity and optical coherent tomography (OCT) findings.

Case presentations. We presented four cases: two patients with wet AMD, one patient with macular edema due to central retinal vein occlusion (CRVO) and one patient with DME in non-proliferative diabetic retinopathy (nPDR). The majority of our patients felt visual and anatomical improvement. Some patients felt anatomical improvement although their visual acuity did not improve. Switch to aflibercept had prolonged the positive effect of bavacizumab for approximately 2 months. When regular therapy including bevacizumab was reintroduced, the therapeutic effect would be prolonged. The effective clinical approach was not only the switching therapy but the combination therapy as well. Individual treatment approach and pro re nata regimen were most commonly used in our patients.

Conclusion. Switching anti-VEGF drug showed positive results in patients with refractory or recurrent wet AMD and macular edema.

Keywords: vascular endothelial growth factor agents, wet age-related macular degeneration, macular edema, switching therapy

Introduction

The list of diseases having angiogenesis as an underlying mechanism is becoming larger and larger every year. By using new medical treatments that either inhibit or stimulate angiogenesis, doctors have managed to prolong the lives of cancer patients, prevent limb amputations, reverse vision loss, and improve general health [1]. In ophthalmology, intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents have revolutionized the management of age-related macular degen-

eration (AMD), diabetic macular edema (DME), macular edema in retinal vein occlusions (RVO), and other neovascular and macular edema accompanied retinal diseases [2, 3]. In patients with recalcitrant AMD, despite prior anti VEGF treatments, intravitreal aflibercept can result in short-term anatomic improvement, reduction in subretinal fluid (SRF) and Pigment epithelium detachment (PED) dimensions, while preserving visual acuity [4, 5]. In Serbia, all patients are concerned with the cost and number of injections needed for successful treatment. Along with the fear of injections, patients are worried about losing their vision, the possibility of disease recurrence, as well as about the impact on family/social life. Some of the patients have difficulties in attending their clinic appointments. In Serbia, patients are also worried about the cost of treatment, because there is no reimbursement. Therefore, the aim of the treatment is to try and optimize visual and anatomical outcomes, while at the same time reducing the overall burden of the disease, as well as the number of injections.

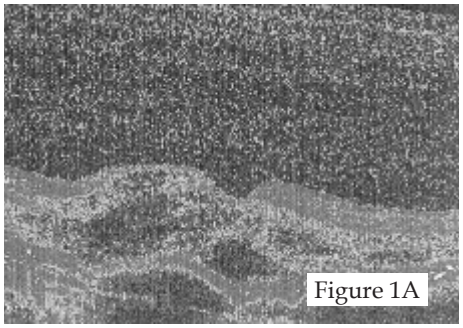
The aim of the study is to show the effect of switching from bevacizumab to aflibercept in patients with recalcitrant wet AMD, as well as to present the best clinical approach and regimen for patients with neovascular and macular edema accompanied retinal diseases.

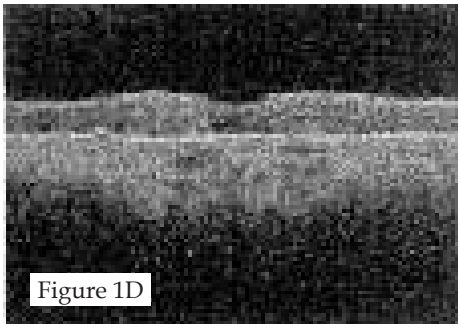
Methods

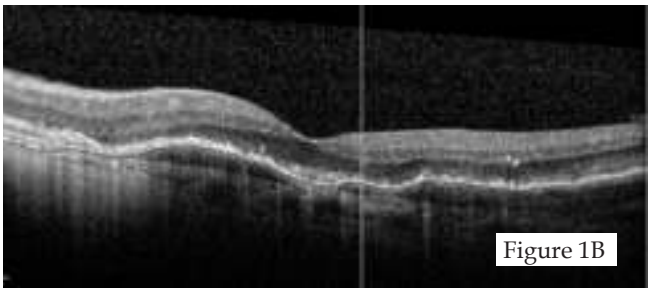
We presented four cases, two patients with wet AMD, one patient with macular edema due to CRVO, and one patient with DME in non-proliferative diabetic retinopathy (nPDR). The written informed consent was obtained from all patients prior to treatment. The study was conducted according to WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Furthermore, the study protocol was approved by the Ethics Committee of the Clinic for Eye Diseases at the Clinical Centre of Serbia, where patients were treated. All patients received intravitreal injection (IVI) of bevacizumab (1.25 mg/0.1 mL; Avastin; Roche, Switzerland), as a primary therapy. The strategy for the injection was based on an "as needed" or „pro re nata" (PRN) regimen. Spectral domain optical coherence tomography (SD-OCT, Copernicus, Optopol Technologies, Zawierci, Poland) was performed once a month for the purpose of evaluation, and IVI of anti-VEGF antibody treatment was applied in the case of recurrence of retinal bleeding or fluid accumulation on SD-OCT. All the patients had been followed up at the OCT for at least 4 to 6 weeks. In all of them, we switched the therapy from one anti-VEGF drug, bevacizumab, (Avastin- Roche, Basel, Switzerland) to aflibercept (Eylea-Bayer, Barmen, Germany) or to triamcinolone acetonide (Kenalog- Bristol-Myers Squibb, Italy), the corticosteroide, or dexamethasone intravitreal implant (Ozurdex-Allergan, Dublin, Ireland). Effects of anti-VEGF drugs and corticosteroids on visual acuity were recorded by using Snellen chart, while the effects on macular anatomy were recorded by SD-OCT. Our patients were evaluated every month and were injected every 4 to 8 weeks, according to a PRN regimen. The patients received an intravitreal injections of 1.25 mg (0.1 mL) of bevacizumab (Avastin®) as the first treatment option, and the therapy was switched to aflibercept (Eylea®) or triamcinolon acetonid when the therapy with bevacizumab seemed not to be effective enough, according to visual acuity and SD-OCT findings. Due to precautionary measures, we estimated the potential ocular and systemic side effects of administered medications in all our patients.

Case presentations

Case 1. A 77-year-old man presented with an acute deterioration of central vision in the left eye lasting for about 3 weeks and poor vision in the right eye due to wet AMD. Best corrected visual acuity (BCVA) was 3/60 in the right eye and 0.1 in the left eye. Fundus examination revealed fibrovascular scar in his right eye and active subretinal neovascularisation in his left eye (Figure 1A). The patient was treated with intravitreal bevacizumab (1.25 mg). He received nine injections of bevacizumab in his left eye during the period of one month and his BCVA improved, (the recorded value was 0.3) and stayed stable (Figure 1 B). He missed one visit due to the flood in the city where he lived and attended the next visit with huge pigment epithelial detachment







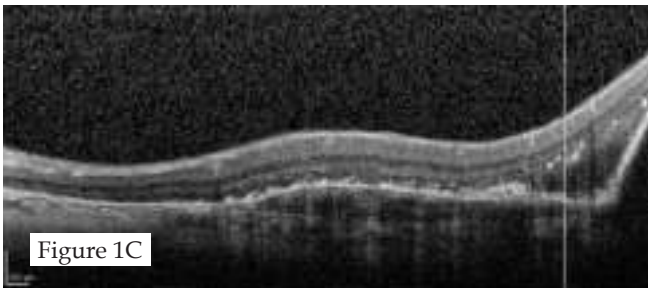
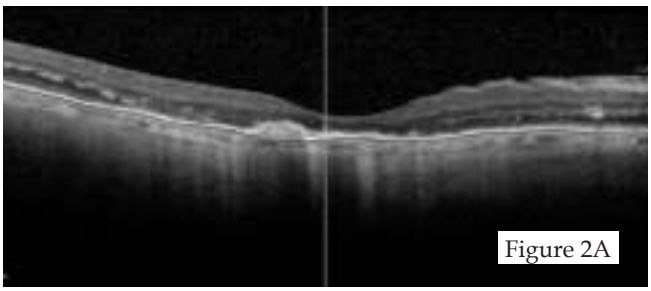


Figure 1. Optical coherence tomography (OCT) scans demonstrating the layers of the retina at the fovea in cross-section of the right eye before anti-VEGF treatment [A] and after anti-VEGF treatment [B, C, D]. There is resolution of the macular haemorrhages and subretinal fluid.

(PED) on the SD-OCT and BCVA 0.2 in his left eye (Figure 1C). We decided to switch therapy to aflibercept (Eylea®) and after only one injection in his left eye, his BCVA improved reaching 0.4, while PED disappeared. The follow-up was performed every four weeks and his vision had continuously been stable during the follow-up period of three months (Figure 1D).

Case 2. A 76-year-old woman was admitted to hospital due to loss of vision in the right eye that had begun a week earlier. Her BCVA was 0.5 in the right eye and fundus examination revealed wAMD. In the left eye, she had dry AMD and BCVA was 0.8. She was treated with intravitreal bevacizumab (1.25 mg), three injections every four weeks (Figure 2A). Visual acuity and OCT findings did not change, so it was decided to swich therapy to aflibercept (2 mg), two injections every four weeks (Figure 2B). After the treatment with intravitreal aflibeccept injections, there was anatomical improvement, visible on OCT, but her BCVA did not change. Due to the fact that she did not feel visual improvement, the patient was not satisfied with the result of the treatment, although there was a continuous anatomical improvement during the follow-up period lasting for three months.

Case 3. A 35-year-old male was hospitalized due to an acute, painless decrease in vision in his left eye during skiing on a very cold weather. Fundus examination revealed central retinal vein occlusion (CRVO) with pronounced macular edema and decrease in BCVA to 0.3 on the



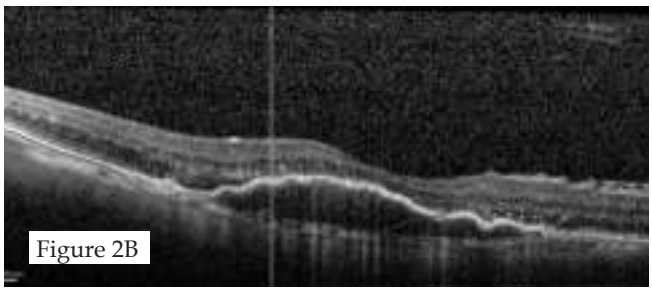
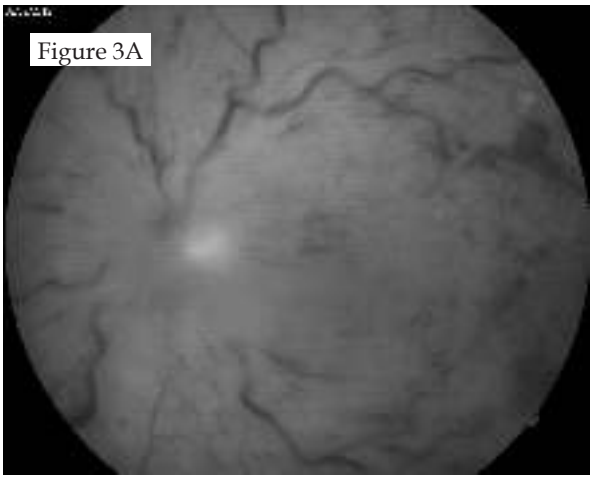
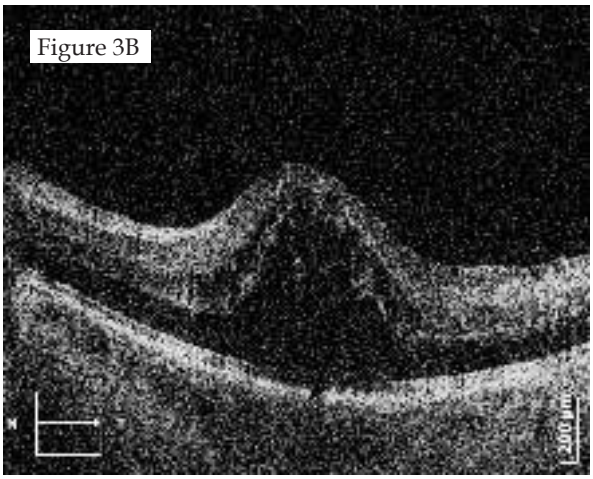


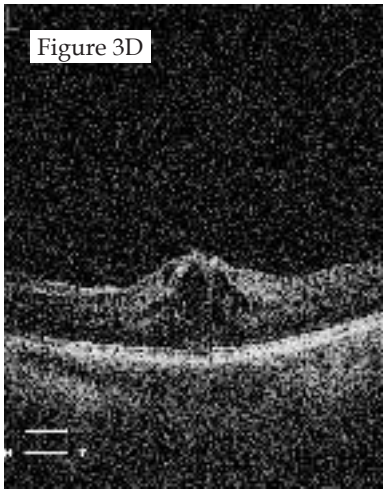
Figure 2. Optical coherence tomography (OCT) of the right eye after injection of bevacizumab intravitrealy [A], the same eye after aflibercept intravitrealy [B]. There is a resolution of RPE ablation [B].

Snellen chart (Figure 3A, B). He was previously healthy, but hematological examination showed positive antiglicoprotein and anticardiolipin antibody IgM class, so he was diagnosed with primary antiphospholipid syndrome. The patient had been treated with nadroparin (Fraxiparine) 0.3 ml 2 times subcutaneously for 5 months, than one month with Warfarin (Farin) 10 mg per os, and finally he had been receiving Aspirin 100 mg for the next four months. Due to the failure of vision caused by macular edema, the patient received nine intravitreal injections of bevacizumab (1.25 mg) in 4-6 week intervals and was switched to triamcinolone-acetonide and later on to aflibercept. Due to a recurrent macular edema, we switched therapy from bevacizumab to triamcinolon-acetonide and aflibercept, and the patient received twenty one intravitreal injections of bevacizumab, one intravitreal injection of triamcinolon-acetonide (post-treatment complications with increased intraocular pressure lasting for six months), and seven intravitreal injections of aflibercept. Improvement of visual acuity and OCT findings after intravitreal administrations of bevacizumab after aflibercept indicated that aflibercept prolonged the efect of bevacizumab (Figure 3C-E). During the five-year follow-up, visual acuity in the left eye remained 1.0 per Snellen, hemorrhages were resorbed and, after the last application of aflibercept, did not recur (Figure 3D).

Case 4. A 55-year old female, with a history of uncontrolled Type 2 diabetes and with hemoglobin A1c values as high as 11%, was referred to for the management of diabetic macular edema (DME). On initial presentation, visual acuity







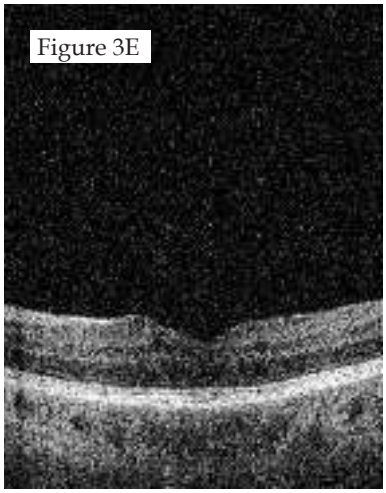
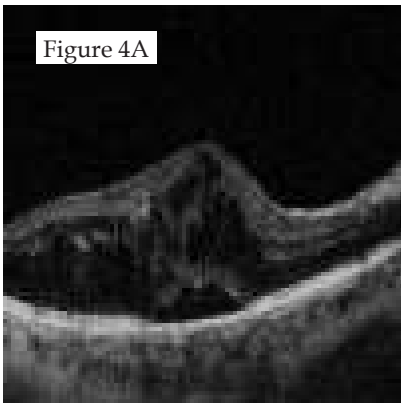


Figure 3. Color fundus [A]; photograph and optical coherence tomography (OCT) scans of the patient's left eye before anti-VEGF treatment [B] and after anti-VEGF treatment [C, D, E]. There is resolution of the macular edema.



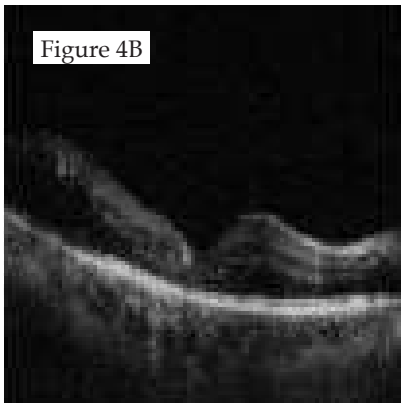


Figure 4. Optical coherence tomography (OCT) scans of a patient's left eye before anti-VEGF treatment [A] and after anti-VEGF treatment [B]. There is resolution of intraretinal and subretinal fluid.

was 0.7 in the right and 0.3 in the left eye. Clinical examination and fundus photographs revealed non-proliferative diabetic retinopathy in both eyes, as well as chronic DME. The patient received five injections of bevacizumab, but her BCVA and OCT did not change, so we switched therapy to dexamethasone intravitreal implant (Ozurdex®) (Figure 4). A month later, visual acuity improved from 0.3 to 0.5 in the left eye, but after three months she came back with DME and BCVA 0.4. She received aflibercept and the visual acuity improved to 0.7. It had stayed stable for three months when aflibercept intravitrealy was again administered and it had not changed for the next four months.

Discussion

Anti-VEGF therapy has become the standard of care for the treatment of wet AMD and many other retinal diseases, such as diabetic retinopathy and retinal vein occlusion. Different strategies for the use of pro re nata (PRN) treat and extend (T&E), and monthly regimens with intravitreal anti-VEGF agents (bevacizumab, ranibizumab or aflibercept) in patients with retinal diseases such as neovascular AMD, diabetic macular edema and macular edema due to retinal vein occlusion, have been discussed world-wide [6-8]. The main focus of our study was to present the effectiveness and visual outcomes of PRN, as well as the importance of switch therapy and individual approach. Switching anti-VEGF drug has showed positive results in patients with refractory or recurrent wet AMD and macular edema [9-12]. There were visual and anatomical improvements in the majority of our patients. Some patients felt anatomical improvements although their visual acuity did not improve. Switching to aflibercept had prolonged the positive drug effect for approximately 2-4 months. When regular therapy with bevacizumab was reintroduced, the therapeutic effect would be prolonged. The effective clinical approach in our patients was not only switching therapy but combination therapy as well. Individual treatment approach and PRN regimen were most commonly used as effective treatment regimes in our patients. Nowadays, there is an increasing interest in establishing a regimen that offers the best visual outcome in conjunction with reduced injection frequency. Furthermore, the reduction in treatment burden by individualizing treatment and minimizing the number of injections, as well as cost reduction, are of considerable interest.

Conclusion

Switching anti-VEGF drug showed positive results in patients with refractory or recurrent wet AMD and macular edema. The PRN regimen requires frequent clinic visits to monitor disease status. Intravitreal treatment, switching therapy and combination therapy can have positive effects on visual outcomes and treatment cost in the selected group of patients.

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Ethical approval. The Ethics Committee of the Clinic for Eye Diseases, Clinical Centre of Serbia, Belgrade approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest

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Zamena bevacizumaba aflibercеptom kod bolesnika sa senilnom degeneracijom žute mrlje, dijabetesnim makularnim edemom i cistoidnim makularnim edemom zbog retinalne venske okluzije

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Uvod. Intravitrealna injekcija anti-vaskularnih endotelijalnih faktora rasta (anti-VEGF) je napravila revoluciju u lečenju senilne degeneracije makule (SDM), dijabetesnog makularnog edema (DME), makularnog edema uzrokovanog okluzijom retinalnih venskih krvnih sudova (RVO) i drugim retinalnim bolestima koje su praćene neovaskularnim i makularnim edemom. Cilj ove serije prikaza slučajeva je da pokaže efekat zamene bevacizumaba aflibercеptom kod pacijenata sa rekurentnom vlažnom formom SDM, kao i najbolji klinički pristup i režim za pacijente sa neovaskularnim i makularnim edemom udruženim sa retinalnim bolestima.

Metode. Kao terapiju, svi naši pacijenti su dobili intravitrealnu injekciju 1,25 mg (0,1 ml) bevacizumaba kao prvu opciju lečenja, a kada se terapija bevacizumabom činila nedovoljno efikasnom na osnovu nalaza vidne oštrine i optički koherentne tomografije zamenili smo ga aflibercеptom ili triamcinolon acetonidom.

Prikazi bolesnika. Prikazana su četiri bolesnika, dva sa SDM, jedan sa makularnim edemom usled RVO i jedan slučaj sa DME i neproliterativnom dijabetesnom retinopatijom (nPDR). Kod većine pacijenata došlo je do poboljšanja oštrine vida i anatomskog poboljšanja. Neki pacijenti su imali anatomsko poboljšanje, mada se njihova oštrina vida nije poboljšala. Zamena aflibercеptom je produžila pozitivno dejstvo leka tokom približno dva meseca, i ako bi se redovna terapija bevacizumabom ponovo uvela, terapijski efekat bevacizumaba bi nastavio da se produžava. Efikasan klinički pristup kod naših pacijenata možda nije samo zbog zamene terapije, već zbog kombinovanja nekoliko terapija zajedno. Pristup individualnom lečenju i pro re nata (PRN), po potrebi, bili su najčešće korišćeni u efikasnom režimu lečenja naših pacijenata.

Zaključak. Zamena anti-VEGF terapije je pokazala pozitivne rezultate kod pacijenata sa refraktarnom i rekuretnom vlažnom formom SDM i makularnog edema.

Ključne reči: vaskularni endotelijalni faktor rasta, eksudativna (vlažna forma) senilne degeneracije makule, makularni edem, zamena terapije