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Combined therapy in exudative age-related macular degeneration

Złożone leczenie wysiękowej postaci zwyrodnienia plamki związanego z wiekiem

Figurska Małgorzata, Wierzbowska Joanna, Robaszkiewicz Jacek

Department of Ophthalmology, Military Health Service Institute in Warsaw
Head: Professor Andrzej Stankiewicz, MD, PhD

Summary: Purpose: Therapeutic options in active exudative age-related macular degeneration (AMD) are following means used to destroy the choroidal neovascularization (CNV) lesion: laser photocoagulation, radiotherapy, transpupillary thermotherapy, photodynamic therapy (PDT) or removal of neovascular membrane through vitreoretinal surgery. Another possibility is to suppress the development of neovascularization through intravitreal administration of anti-VEGF agents: ranibizumab, bevacizumab (off-label), sodium pegaptanib or steroids (off-label).
The aim of this paper is to present the early phase of treating exudative AMD with combined therapy: photodynamic therapy with intravitreal ranibizumab injection.
Material and methods: Our observation is based on three clinical cases. Observations are being carried out on larger patient groups according to the treatment scheme presented in this paper.
Results: In the three cases described one PDT procedure and the saturation phase of three ranibizumab injections allowed a significant improvement in visual acuity and closure of CNV leakage confirmed by fluorescein angiography (FA) and optical coherence tomography (OCT). Treatment is being continued according to AMD activity: next PDT in case of leakage in FA, another ranibizumab injection according to PRONTO study reinjection criteria.
Conclusions: The pathomechanism of exudative AMD confirms reasonability of combined treatment. Considering the stages of neovascularization in exudative AMD, VEGF inhibition combined with PDT has a synergistic action and increases the effectiveness of both therapies alone. Large clinical studies (FOCUS) show that combined therapy reduces the number or required PDT procedures. In combined therapy modification of PDT parameters should be considered: reduction of energy and laser exposure time.

Słowa kluczowe: wysiękowa postać zwyrodnienia plamki związanego z wiekiem (AMD), terapia łączona, terapia fotodynamiczna, ranibizumab.
Key words: exudative form of age-related macular degeneration (AMD), combined therapy, photodynamic therapy, ranibizumab.

Age-related macular degeneration (AMD), is a disease of the central retina, a region characterized by a high concentration of photoreceptors, responsible for sharp vision and perception of contrast. It affects the retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaries, leading to their destruction. The exudative form of AMD makes up 15% of all AMD cases, but in 90% of cases it leads to loss of central vision. Effective treatment of AMD, especially of the particularly dangerous exudative form, remains a problem. According to most recent research, the development of choroidal neovascularization (CNV), is to a high degree a dynamic repair process, an effect of the action of specific inflammation factors, which are stimulated by antigen deposits of Bruch's membrane, vascular endothelial growth factors (VEGF) (1,2,3). Therapeutic options in active exudative AMD are following means used to destroy the CNV lesion: laser photocoagulation, radiotherapy, transpupillary thermotherapy, photodynamic therapy (PDT) or removal of neovascular membrane through vitreoretinal surgery. Another possibility is to suppress the development of neovascularization through intravitreal administration of anti-VEGF agents: ranibizumab, bevacizumab (off-label), sodium pegaptanib or steroids (off-label).

The aim of this paper is to present the early phase of treating exudative AMD with combined therapy: photodynamic therapy with intravitreal ranibizumab (Lucentis®, Novartis, Basel, Switzerland) injection, based on three clinical cases. Observations are being carried out on larger patient groups according to the treatment scheme presented in this paper.

Case 1

The patient, a 70-year-old man, reported to the Ophthalmology Clinic due to decreased vision and metamorphopsia in the right eye. A full ophthalmological examination was performed with assessment of visual acuity on Early Treatment of Diabetic Retinopathy Study (ETDRS) charts: Vod 0.20 (50 letters), Vos 0.80 (79 letters), slit lamp examination of posterior and anterior segment, retinoscopy, aplanation tonometry, fluorescein angiography – FA (Heidelberg Engineering HRA 2), and optical coherency tomography – OCT (SLO OCT OTI). In the macula of the right eye, ophthalmoscopy revealed a greyish focus with small hemorrhages at its border. FA of the right eye showed a classic focus of exudative AMD with increasing hyperfluorescence in late stages of the examination (Fig. 1, 2). Macula of the left eye was normal in FA.

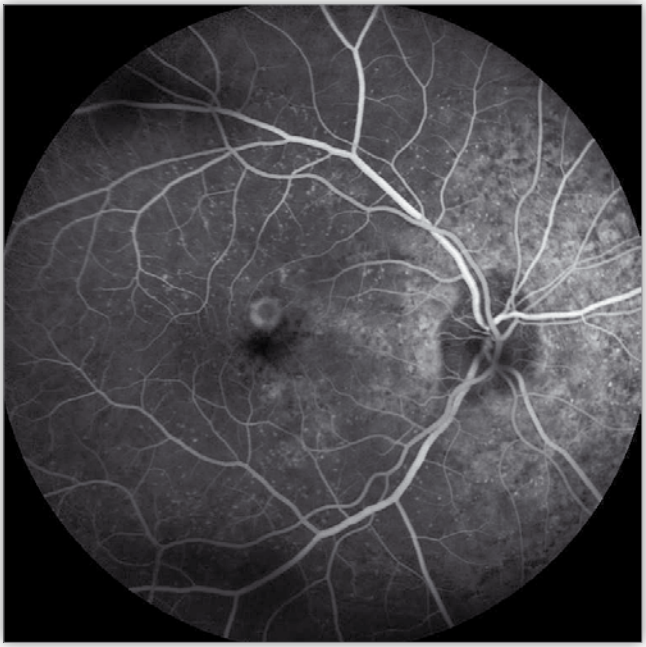

Fig. 1. Case 1. FA of the right eye (early phase) before treatment: in the macula focus of classic CNV.
Ryc. 1. Przypadek 1. AF prawego oka (faza wczesna) przed leczeniem: w plamce typowe ognisko neowaskularyzacji naczyniówkowej (CNV).

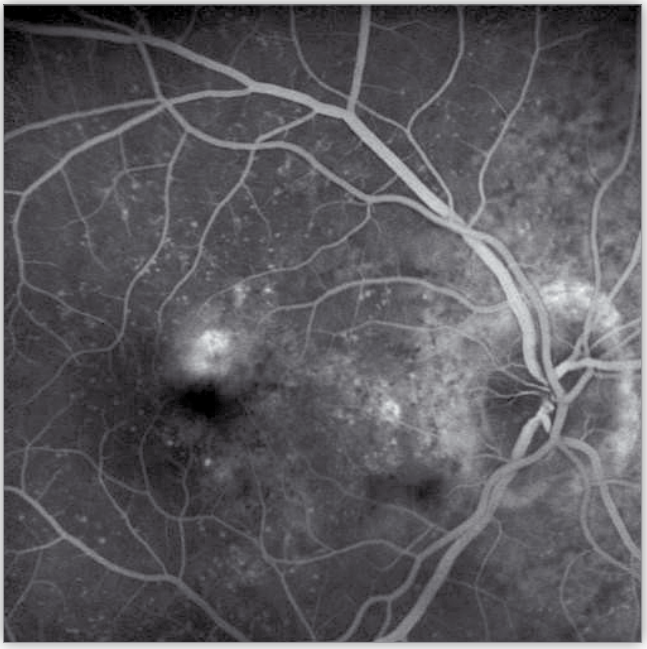

Fig. 2. Case 1. FA of the right eye (late phase), before treatment: increasing hyperfluorescence of CNV focus.
Ryc. 2. Przypadek 1. AF prawego oka (faza późna) przed leczeniem: wzrost hiperfluorescencji w ognisku CNV.

In OCT of the right eye, a distortion of the RPE-choriocapillary stripe was visible, which is typical for classic exudative AMD with subretinal fluid and increased retinal thickness in the foveola of 245 μm (Fig. 3). OCT of the left eye was normal. The patient was qualified for combined therapy: photodynamic therapy and intravitreal ranibizumab injections. PDT was performed according to standard preparation and dosage of verteporfin (Visudyne®; Novartis Pharma AG, Basel, Switzerland) solution (2 mg/ml, 6

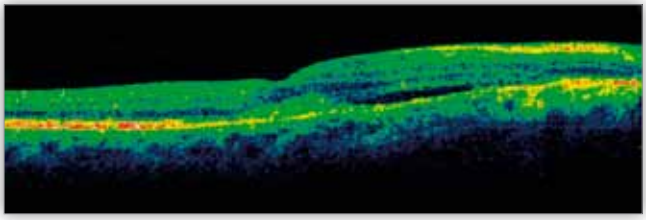

Fig. 3. Case 1. OCT of the right eye before treatment: distortion of the RPE/ choriocapillary stripe (focus of CNV), subretinal fluid.
Ryc. 3. Przypadek 1. OCT prawego oka przed leczeniem: zniekształcenie RPE/ pas choriokapilarów (ognisko CNV), płyn podsiatkówkowy.

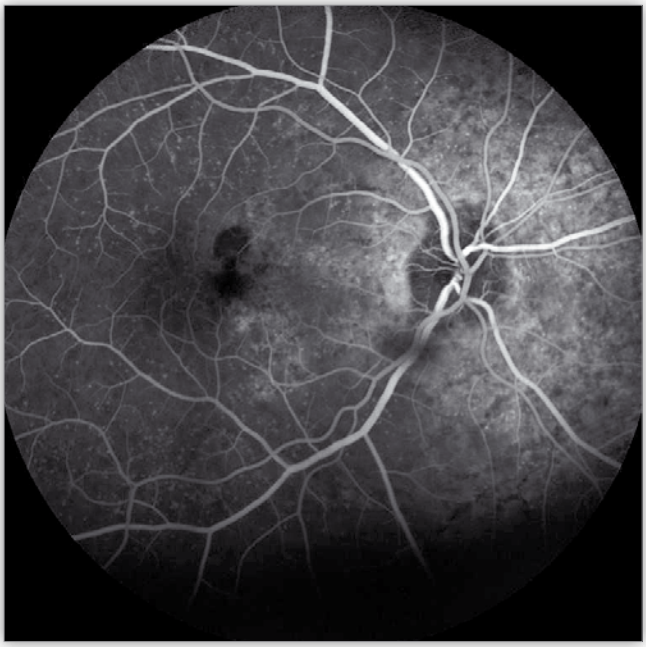

Fig. 4. Case 1. FA of the right eye (early phase) after PDT and the first ranibizumab injection: without CNV focus, hypofluorescence in the fovea.
Ryc. 4. Przypadek 1. AF prawego oka (faza wczesna) po PDT i pierwszej iniekcji ranibizumabu: bez ogniska CNV, hipofluorescencja w dołeczku.

mg/m^2), 15 minutes after start of the infusion, with a 689 nm laser (Opal Photoactivator, Coherent), exposure time 83 seconds, energy 50 J/cm^2. Diameter of the laser focus was calculated by adding a 1000 μm margin of healthy tissue to lesion size. Three days later 0.5 mg of ranibizumab was administered to the vitreous body of the right eye. A month later the first full follow-up was performed. Visual acuity of the right eye improved to 68 ETDRS letters (0.40). Angiography of the right eye showed no leakage in place of previous CNV focus (Fig. 4, 5). In OCT subretinal fluid had receded, fovea contour was restored and retinal thickness in the foveola was reduced to 195 μm (Fig. 6). Two more 0.5 mg ranibizumab doses were administered to the right eye in monthly intervals. The next control angiography 3 months after PDT showed no leakage, so the patient wasn't qualified for another treatment. Visual acuity after loading phase was 0.625 (75 letters). Due to no indicators of active exudative process found in OCT, further procedure will be based on PRONTO study reinjection criteria (Fig. 7) (4). Further ranibizumab injections are planned if monthly follow-up shows 1) deterioration of visual acuity by 5 letters or macular fluid in OCT, 2) increase in central

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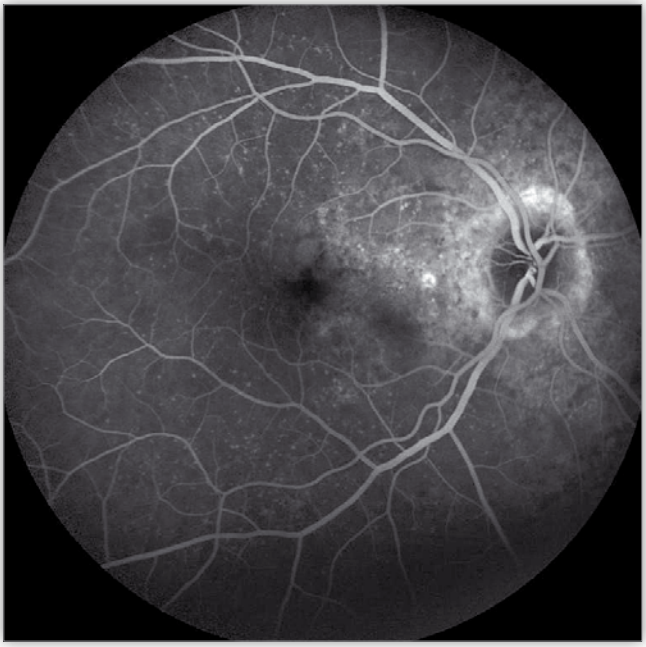

Fig. 5. Case 1. FA of the right eye (late phase) after PDT and the first ranibizumab injection: without hyperfluorescence typically for the leakage.
Ryc. 5. Przypadek 1. AF prawego oka (faza późna) po PDT i pierwszej iniekcji ranibizumabu: hiperfluorescencja typowa dla przecieku.

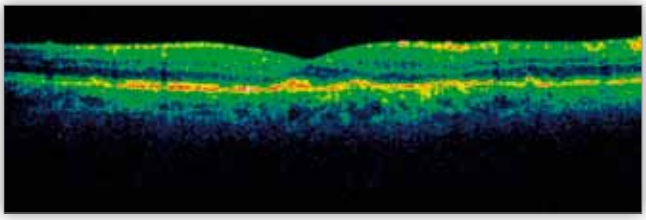

Fig. 6. Case 1. OCT of the right eye after PDT and first ranibizumab injection: fovea contour persist, without subretinal fluid.
Ryc. 6. Przypadek 1. OCT prawego oka po PDT i pierwszej iniekcji ranibizumabu: kontur dołeczka zachowany, bez płynu podsiatkówkowego.

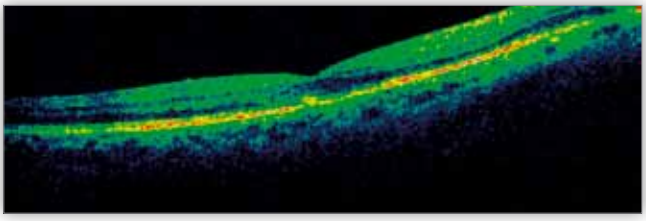

Fig. 7. Case 1. OCT of the right eye after ranibizumab saturation phase: without CNV activity.
Ryc. 7. Przypadek 1. OCT prawego oka po podaniu ranibizumabu w fazie wysycenia: bez czynnej CNV.

retinal thickness by 100 μm or more, 3) new CNV lesion, 4) new hemorrhage in the macula, or 5) subretinal fluid will persist. Another PDT procedure will be performed if there is leakage in FA. The patient remains under planned one year observation.

Case 2

The patient, a 69-year-old woman, reported to the Ophthalmology Clinic due to deterioration of vision in the left eye, which had begun a few months before. The patient received latanoprost drops in both eyes as treatment of primary open

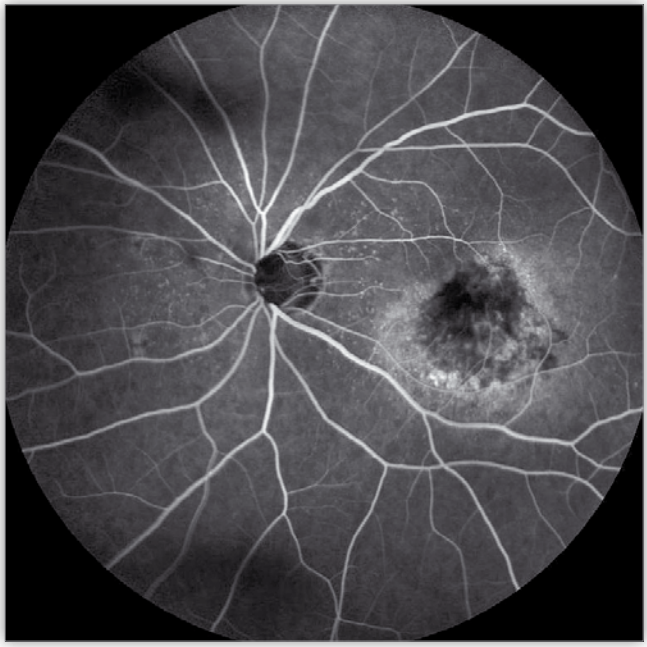

Fig. 8. Case 2. FA of the left eye (early phase) before treatment: in the macula hyperfluorescence focus.
Ryc. 8. Przypadek 2. AF lewego oka (faza wczesna) przed leczeniem: w plamce ognisko hiperfluorescencji.

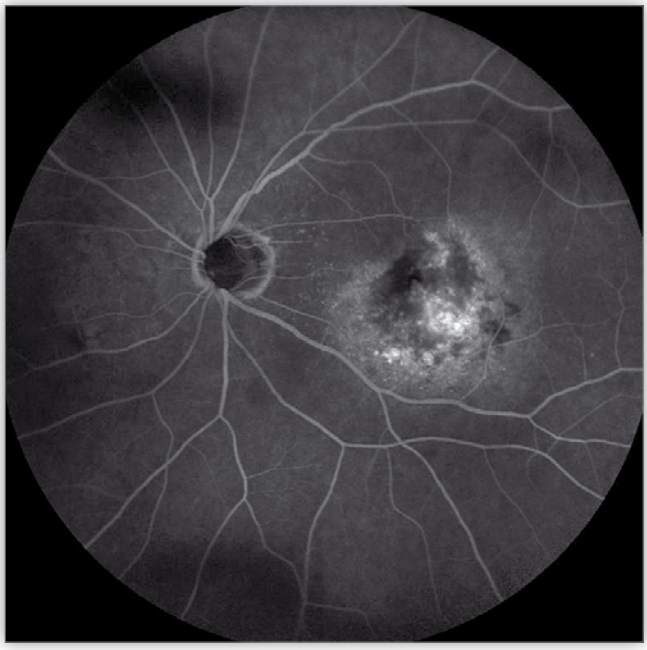

Fig. 9. Case 2. FA of the left eye (late phase) before treatment: increasing hyperfluorescence with CNV focus, borders blurring.
Ryc. 9. Przypadek 2. AF lewego oka (faza późna) przed leczeniem: wzrost hiperfluorescencji z ogniskiem CNV o zatartych granicach.

angle glaucoma. A full ophthalmological examination was performed with assessment of visual acuity on ETDRS charts: Vod 0.80 (81 letters), Vos 20 letters, examination of posterior and anterior segment, FA and OCT. No abnormalities were found in the macula of the right eye. In the macula of the left eye a grey, elevated degenerative lesion was present, which corresponded to advanced exudative AMD. FA of the left eye showed a focus of growing hyperfluorescence with borders blurring in late stages of the examination (Fig. 8, 9). In OCT of the left eye

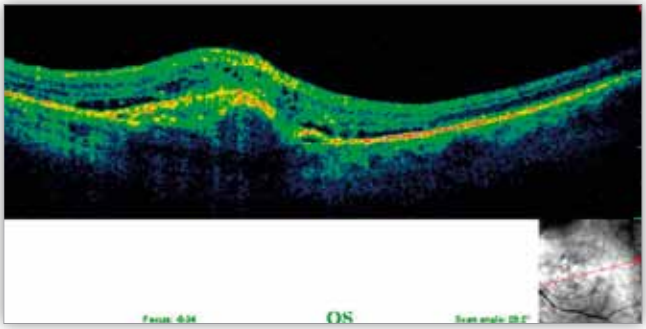

Fig. 10. Case 2. OCT of the left eye before treatment: distorted reflection stripe from RPE/choriocapillary layer with PED foci, subretinal fluid, retinal edema.

Ryc. 10. Przypadek 2. OCT lewego oka przed leczeniem: zniekształcone odbicie od paska RPE/ warstwa choriokapilarów z ogniskami PED, płyn podsiatkówkowy, obrzęk siatkówki.

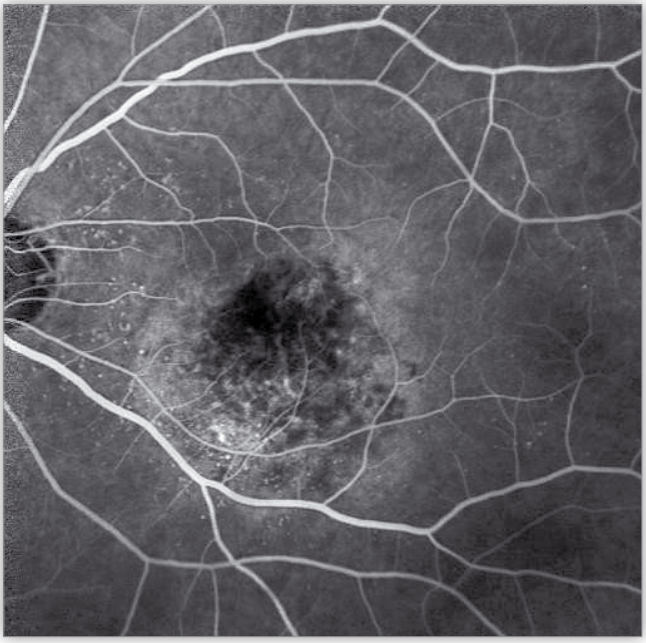

Fig. 11. Case 2. FA of the left eye (early phase) after PDT and first ranibizumab injection: in the macula non homogeneous hyperfluorescence.

Ryc. 11. Przypadek 2. AF lewego oka (faza wczesna) po PDT i pierwszej iniekcji ranibizumabu : w plamce homogeniczna hiperfluorescencja.

intraretinal edema (central retinal thickness up to 670 μm), distorted reflection stripe from RPE/choriocapillary layer with pigment epithelial detachment (PED) foci, subretinal fluid were found (Fig. 10). The patient was qualified for combined therapy: photodynamic therapy and intravitreal ranibizumab injections. PDT was performed according to standard procedure. Diameter of the laser focus was calculated by adding a 1000 μm margin of healthy tissue to lesion size. Three days later 0.5 mg of ranibizumab was administered to the vitreous body of the left eye. A month later the first full follow-up was performed. Visual acuity in the left eye improved by 14 letters to a value of 34 letters. Angiography of the left eye showed a considerable reduction of leakage in the CNV lesion area (Fig. 11, 12). In OCT subretinal fluid had receded, fovea contour was restored and central retinal thickness was reduced to 215 μm (Fig. 13). Two more 0.5 mg ranibizumab doses were administered to the right eye in monthly intervals, according to the loading phase

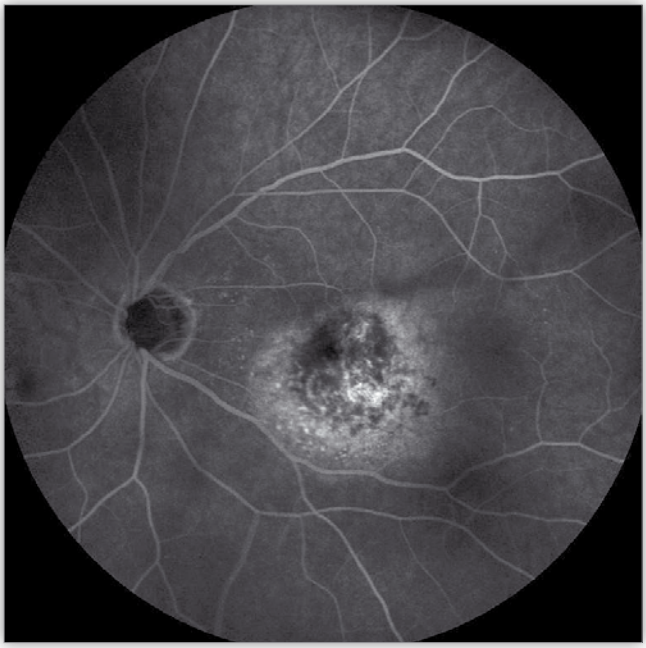

Fig. 12. Case 2. FA of the left eye (late phase) after PDT and first ranibizumab injection: in the macula hyperfluorescence without intensive leakage like before treatment.

Ryc. 12. Przypadek 2. AF lewego oka (faza późna) po PDT i pierwszej iniekcji ranibizumabu: w plamce hiperfluorescencja bez intensywnego przecieku, jaki był widoczny przed leczeniem.

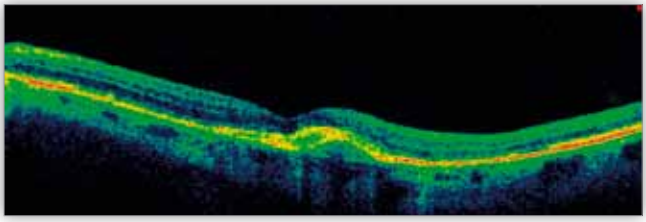

Fig. 13. Case 2. OCT of the left eye after PDT and the first ranibizumab injection: fovea contour mostly restored, without subretinal fluid and retinal edema.

Ryc. 13. Przypadek 2. OCT lewego oka po PDT i pierwszej iniekcji ranibizumabu: kontur dołeczka przywrócony w dużej części, bez płynu podsiatkówkowego i obrzęku siatkówki.

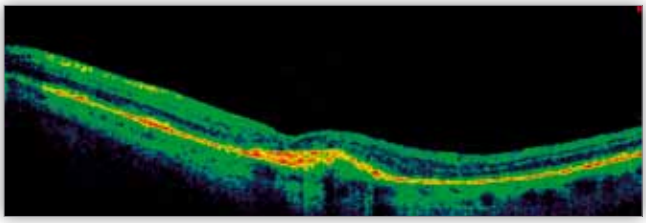

Fig. 14. Case 2. OCT of the left eye after ranibizumab saturation phase: without CNV activity, subretinal scar.

Ryc. 14. Przypadek 2. OCT lewego oka po podaniu ranibizumabu w fazie wysycenia: bez czynności CNV, blizna podsiatkówkowa.

of treatment. The next control angiography 3 months after PDT showed no leakage, so the patient wasn't qualified for another treatment. Due to no indicators of active exudative process found in OCT, further procedure will be based on PRONTO study reinjection criteria (Fig. 14). Current visual acuity of the left eye is 34 letters. Another PDT procedure will be performed if there is leakage in FA. The patient remains under planned one-year observation.

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Case 3

The patient, a 68-year-old man, reported to the Ophthalmology Clinic due to decreased vision in the left eye. An ophthalmological examination was performed with assessment of visual acuity on ETDRS charts: Vod 20/250, Vos 0.20 (52 letters), examination of posterior and anterior segment, FA and OCT. In the macula of the right eye a scar formed in course of exudative AMD was seen. In the macula of the left eye, ophthalmoscopy revealed a greyish focus with small hemorrhages at its border.

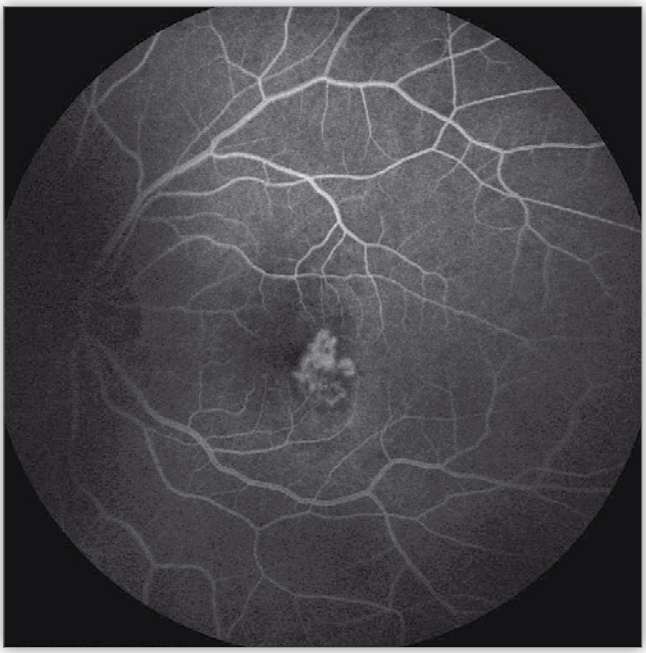

Fig. 15. Case 3. FA of the left eye (early phase) before treatment: in the macula focus of classic CNV.

Ryc. 15. Przypadek 3. AF lewego oka (faza wczesna) przed leczeniem: w plamce typowe ognisko CNV.

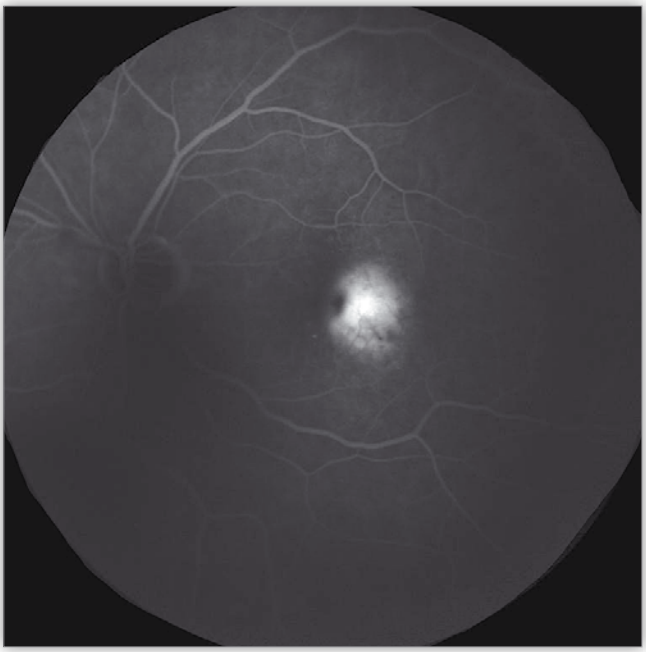

Fig. 16. Case 3. FA of the left eye (late phase) before treatment: intensive hyperfluorescence of active CNV focus.

Ryc. 16. Przypadek 3. AF lewego oka (faza późna) przed leczeniem: intensywana hiperfluorescencja aktywnego ogniska CNV.

FA of the left eye revealed a classic focus of exudative AMD with hyperfluorescence, which increased in late stages of the examination (Fig. 15, 16). The patient was qualified for combined therapy: PDT and intravitreal ranibizumab injections. PDT was performed according to standard procedure. Diameter of the laser focus was calculated by adding a 1000 μm margin of healthy tissue to lesion size. Three days later 0.5 mg of ranibi-

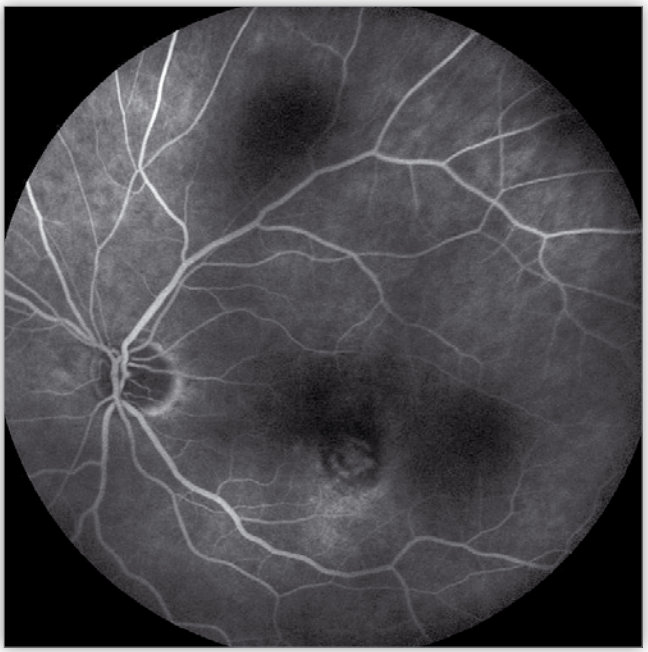

Fig. 17. Case 3. FA of the left eye (recirculation phase) after PDT and ranibizumab saturation phase: in the place of active CNV focus a little hyperfluorescence is observed.

Ryc. 17. Przypadek 3. AF lewego oka (faza recyrkulacji) po PDT i podaniu ranibizumabu w fazie wysycenia: obserwuje się małą hiperfluorescencję w miejscu aktywnego ogniska CNV.

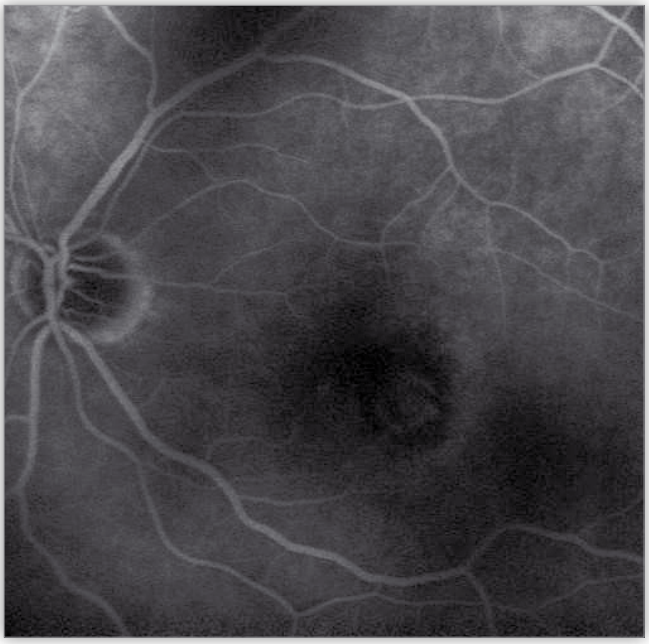

Fig. 18. Case 3. FA of the left eye (late phase) after PDT and ranibizumab saturation phase: the macula without leakage.

Ryc. 18. Przypadek 3. AF lewego oka (faza późna) po PDT i podaniu ranibizumabu w fazie wysycenia: plamka bez przecieku.

zumab was administered to the vitreous body of the left eye. A month later the first full follow-up was performed. Visual acuity in the left eye improved to 0.40 (65 ETDRS letters). Angiography of the left eye showed no leakage in place of previous CNV focus. Two more 0.5 mg ranibizumab doses were administered to the right eye in monthly intervals. The next control angiography 3 months after PDT showed no leakage, so the patient wasn't qualified for another treatment (Fig. 17, 18). Visual acuity of the left eye was 0.40 (67 letters), and had improved, compared to baseline, by 15 letters. Further procedure will be based on PRONTO study reinjection criteria. Another PDT procedure will be performed if there is leakage in FA. The patient remains under planned one-year observation.

Discussion

Combined therapy blocks the activity of exudative AMD on a few most important levels, which is of special importance in the early, striking phase of treatment. Combination of photodynamic therapy with anti-VEGF drugs blocks the release and action of vascular-endothelial growth factors after PDT procedure, create a chance to stop progressing loss of vision and even to reverse this process, and to reduce activity of the CNV focus. It definitely allows a reduction in numbers of procedures (intravitreal injections and PDTs), so it lowers treatment costs.

FOCUS study compared the effectiveness of combined therapy and verteporfin monotherapy in dominantly classic CNV. One week after PDT the patients received either ranibizumab injection or placebo. In 12-month follow-up (ranibizumab injections repeated monthly) stabilization of vision was found in 87.6% of patients, in the placebo group the result was 68%. In 24.8% of patients treated with ranibizumab vision improved by 15 letters or more, which was true for only 7.1% of PDT patients. Better results were found in patients who weren't treated with PDT before – improvement of 3 lines or more in 31%. After 12 months in the combined therapy group mean visual acuity improved by 4.9 letters, while in the PDT group it decreased by 8.2 letters. The mean number of PDT procedures per year in the combined therapy group was lowered to 1.3; in the PDT-only group it was 3.4 (5). Underway MONT BLANC and DENALI studies will probably have as positive results and confirm that polytherapy shortens the treatment and lowers its costs (as shown in FOCUS and PROTECT studies).

Experience with PDT plus VEGF inhibitors combined treatment in other forms of AMD is limited. Patients qualified for TORPEDO study had following forms of AMD: 25 patients with occult CNV – 64% of eyes, RAP – 24%, the rest (3 eyes) with classic CNV focus. In all cases the treatment began with PDT according to the following parameters: 10-minute infusion of Visudyne solution in a dose of 6 mg/m^2, 15 minutes after start of the infusion exposure to 689 nm laser, time 42 seconds, energy 25 J/cm^2. The same day 0.5 mg of ranibizumab was administered intravitreally. Further injections were performed after 4 and 8 weeks. During the 24-month follow-up period further ranibizumab injections were performed according to the same criteria as those presented in our paper. Mean visual acuity in the treated group improved by 7.2 letters, mean retinal thickness decreased by 146 μm. Visual acuity improved by more than 3 lines in 16% of cases, by 1-3 lines in 20%, remained unchanged in 32%, deteriorated by 1-3 lines in 16%, by more than 3 lines also in 16%. A significant deterioration of vision was a result of vitreal hemorrhages, fibrosis, growth of previously small CNV foci. The mean number of injections in the first 12 months was 5.1 (3-9) and in 24-month observation 7.1 (3-13). A total number of 178 injections was performed without any adverse effects (6).

Ranibizumab monotherapy brings the best effects, when injections are repeated monthly (MARINA, ANCHOR studies) (7,8). On the other hand, AMD pathogenesis is more complex and can't be reduced to just VEGF action. Development of a subretinal neovascular membrane is a consequence of a cascade of ischemia, hypoxia, inflammation factors, vascular-endothelial growth factors together with atrophy of choroidal vasculature (1-3).

Combined therapy with VEGF inhibitors gives a possibility of blocking angiogenesis, reducing vessel leakage, of rapid absorption of subretinal fluid, which corresponds to improved visual acuity (9). The goal of photodynamic therapy is to selectively close or destroy choroidal neovascularization or a completely new microvascular net, while maintaining perfusion in deeper vessel layers. Photodynamic therapy causes a selective non-thermal thrombosis of choroidal neovascularization, while retine above it remains unaltered. The number of PDT procedures decreases from 3.5 in the first year of treatment to 0.1 in the fifth (10). PDT induces a proangiogenic response with heightened expression of VEGF (11). Because of this, a combination of PDT and anti-VEGF drugs can inhibit this process.

In TORPEDO and PROTECT studies photodynamic therapy was performed on the same day as ranibizumab injection (6,9). Earlier the safety of this procedure was tested in experiments on monkeys. Modified PDT parameters in the TORPEDO study allow to minimalize the risk of an extensive occlusion of choriocapillaries. It confirms earlier suggestions which pointed to considering lowering the energy dose and shortening laser exposure time when combining therapies. Cases of persisting or transient disturbances in choroidal collateral circulation after PDT have been described (12,13). In the TORPEDO study 66.7% of cases are eye with occult CNV, and especially in this form of exudative AMD a modification of PDT parameters is important (6).

Photodynamic therapy is also combined with bevacizumab injections. Potter et al. describe a reduction in bevacizumab injections in a period of 6 months from 5.1 (bevacizumab-only therapy) to 2.8 (bevacizumab and 25 J/cm^2 PDT) and 2.5 (bevacizumab and 12 J/cm^2 PDT). The patients were examined every month from the point of view of possible bevacizumab reinjection and every 3 months from the point of view or possible repeated combined therapy (14).

Several studies have documented hypoperfusion in the PDT-treated area, persisting for a few months (15). It has been proven that combined therapy extends the period of hypoperfusion. Extended hypoperfusion can help to reduce CNV recanalization and allows neurons to rebuild through reducing exposure to oxygen and free oxygen radicals.

Combined therapy is often used in proliferative and inflammatory diseases, for example in oncology or immunology. Exudative AMD is a disease which has a complex pathogenesis with proliferative and inflammatory factors involved. Photodynamic therapy is associated with chronic occlusion or disturbed

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perfusion in collateral choroidal vessels and induction of VEGF and inflammation factors through ischemia. It justifies using combined treatment in exudative AMD (16).

Conclusions

1. The pathomechanism of AMD confirms that combined treatment is justified.
2. Considering phases of neovascularization in exudative AMD, VEGF inhibition combined with photodynamic therapy has a synergistic action and increases the effectiveness of both therapies alone.
3. Large clinical studies (FOCUS) show that combined therapy doesn't statistically significantly improve treatment effects, but it reduces the number of PDT procedures required.
4. In combined therapy a modification of PDT parameters should be considered: reduction of both energy and laser exposure time.

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Reprint requests to/ Adres do korespondecji:
Małgorzata Figurska, MD
Department of Ophthalmology Military Medical Institute
Szaserów Str. 128
04-141 Warszawa
malgorzata-figurska@wp.pl