Invited review article/Vabljeni pregledni prispevek

NEW DEVELOPMENTS IN THE MANAGEMENT OF AGE-RELATED MACULAR DEGENERATION

NOVOSTI PRI OBRAVNAVI STAROSTNE DEGENERACIJE MAKULE

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Ključne besede: *starostna degeneracija makule; horoidalna nevrovaskularizacija; fotodinamična terapija; verteporfin*

Abstract – Background. *Age-related macular degeneration (AMD) is one of the most important challenges that ophthalmologists are facing in this century. If unrecognized, AMD can lead to rapid vision loss having a severe impact on the daily life of affected patients by reducing functional abilities. AMD is the leading cause of blindness in elderly people in industrialized countries, a fact many people are not aware of.*

Conclusions. *To date treatment options are only available in the late stages of AMD. In the neovascular form, thermal coagulation of choroidal neovascularization (CNV) is still the treatment of choice if the centre of the fovea is not involved. However, this treatment is suitable for only a small number of patients.*
Recently, photodynamic therapy (PDT) was introduced as a new treatment modality consisting of an intravenous infusion of a photosensitizing drug (verteporfin) which is then activated by a low-energy laser resulting in a specific occlusion of the CNV. PDT has been shown to reduce the risk of vision loss in subfoveal predominantly classic and occult CNV secondary to AMD.
Early detection, exact diagnosis, and prompt treatment of AMD therefore play an important role in managing patients with AMD in the future.

Izvleček – Izhodišča. *Starostna degeneracija makule (SDM) je eden od najpomembnejših izzivov za oftalmologe v tem stoletju. Nerazpoznana SDM lahko vodi v hitro izgubo vida, kar ima resen vpliv na vsakodnevno življenje za prizadetega bolnika, ker mu zmanjša delovne zmožnosti. SDM je vodilni vzrok slepote pri starejših ljudeh v industrijskih državah, česar se dosti ljudi ne zaveda.*

Zaključki. *Dosedanje možnosti zdravljenja so so bile na voljo le v poznih stadijih SDM. Pri neovaskularnih oblikah je termalna koagulacija horoidalne neovaskularizacije (CNV) še vedno terapija izbora, če center fovee ni prizadet. Seveda je tako zdravljenje primerno le za majhno število bolnikov.*
Pred kratkim je bila uvedena fotodinamična terapija (PDT) kot nov terapevtski način, ki se sestoji iz intravenozne infuzije fotosenzitivnega zdravila (verteporfin) in ga nato aktiviramo z nizko-energijskim laserjem, kar povzroči posebno zaporo CNV. PDT dokazano zmanjša ogroženost za izgubo vida pri subfoveolarni predominantno klasični in okultni CNV zaradi SDM.
Zgodnje odkritje, natančna diagnoza in takojšnje zdravljenje SDM bodo igrali pomembno vlogo pri obravnavi bolnikov s SDM tudi v prihodnosti.

Background

Age-related macular degeneration (AMD) is a progressive, degenerative disorder of the macula. It is the leading cause of severe visual impairment among people over 50 years of age in industrialized countries. In Europe the approximate number of affected people is 700,000. The risk of AMD rises rapidly with the increasing age (0.7–1.4% in people 65–75 years, 11–18.5% in people over 85 years) (1). As the mean age of western population rises, an increasing number of people will be at risk of developing AMD.

Clinical and angiographic findings in AMD

Two main forms can be distinguished, the non-neovascular or »dry«, and the neovascular or »wet« AMD. Drusen are the first clinical sign of AMD. However, hard drusen present also in eyes without AMD and, therefore, do not themselves characterize the disease (2, 3).

Non-neovascular AMD

About 80% of AMD cases are non-neovascular (4). Severe visual loss is rare in those forms. However, in a small number of patients, severe visual loss may occur due to central scotoma in geographic atrophy involving the fovea.

Definitions

Non-neovascular AMD is characterized by one or more of the following items (2, Table 1).
Early AMD:
- drusen (≥ 63 μm) that might be confluent,
- areas of increased pigment,
- areas of depigmentation.

Table 1. *Definitions of early age-related maculopathy (ARM) and late age-related macular degeneration (AMD) (2).*

Razpr. 1. *Definicija zgodnje starostne bolezni makule (ARM) in kasne starostne degeneracije makule (AMD).*

Early ARM / Zgodnji ARM
Drusen ≥ 63 µm, confluent drusen / Drusen ≥ 63 µm, confluent drusen Hyperpigmentation of the RPE / Hiperpigmentacija RPE Hypopigmentation of the RPE / Hipopigmentacija RPE
Late AMD / Kasna AMD
RPE atrophy (≥ 175 µm) / Atrofije (≥ 175 µm) Geographic atrophy / Prevod Exudative AMD / Prevod Fibrous scar / Prevod

Late AMD: geographic atrophy characterized by any sharply delineated round or oval area of hypopigmentation or absence of the retinal pigment epithelium (RPE) at least 175 µm in diameter.

Treatment

At present, no proven treatment is available for the non-neovascular AMD. However, there is first evidence that the intake of antioxidants (5) may reduce the progression of AMD. Monitoring of non-neovascular AMD with high risk characteristics of progression to neovascular forms is important. Progression of the disease occurs in 10 to 20% of patients.

Risk factors

At especially high risk of developing neovascular AMD, are patients with RPE clumping, large soft drusen, and if one eye already has CNV. Once the first eye is affected by CNV, there is a greater than 40% risk of developing CNV in the fellow eye within 5 years. Risk factors indicating the development of CNV in the fellow eye are the presence of five or more drusen, one or more large drusen or confluent drusen, focal hyperpigmentation, and systemic hypertension (6).

Neovascular AMD

Neovascular AMD is caused by choroidal neovascularization (CNV). The detailed mechanisms underlying the development of neovascular AMD are still not known, although a number of events in the development of CNV have been identified. Abnormal new blood vessels proliferate from the choriocapillaris, extending through Bruch's membrane into the space under the RPE or the neurosensory retina where they can leak serous fluid, lipids, and blood. Finally fibrovascular tissue develops, leading to irreversible severe loss of vision. Neovascular AMD accounts for approximately 90% of all cases with severe vision loss in AMD (7).

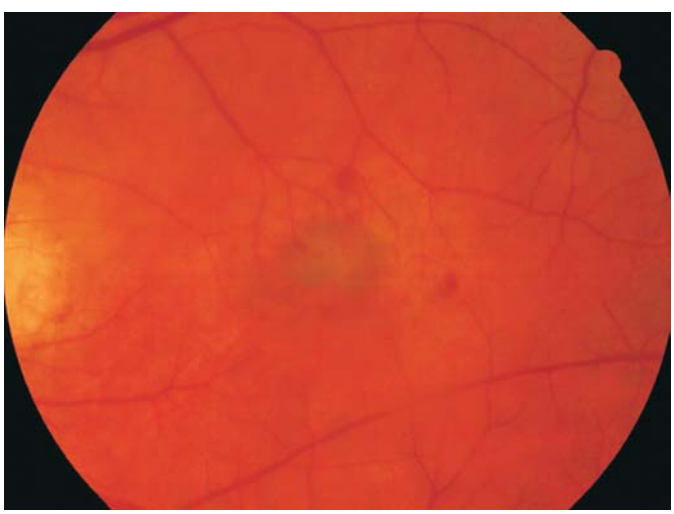

Figure 1a. *Neovascular AMD with serous detachment of the neurosensory retina and haemorrhages.*

Sl. 1a. *Neovaskularna SDM s seroznim odstopom nevrosenzorne mrežnice in krvavitve.*

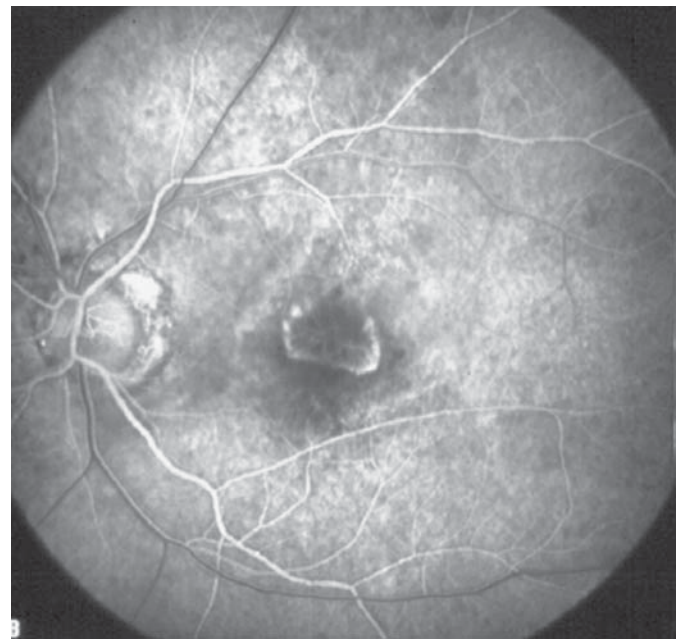

Figure 1b. *Fluorescein angiography in the early phase reveals a subfoveal, classic, well-defined CNV.*

Sl. 1b. *Fluoresceinska angiografija odkrije v zgodnji fazi subfovealno, klasično, dobro omejeno CNV.*

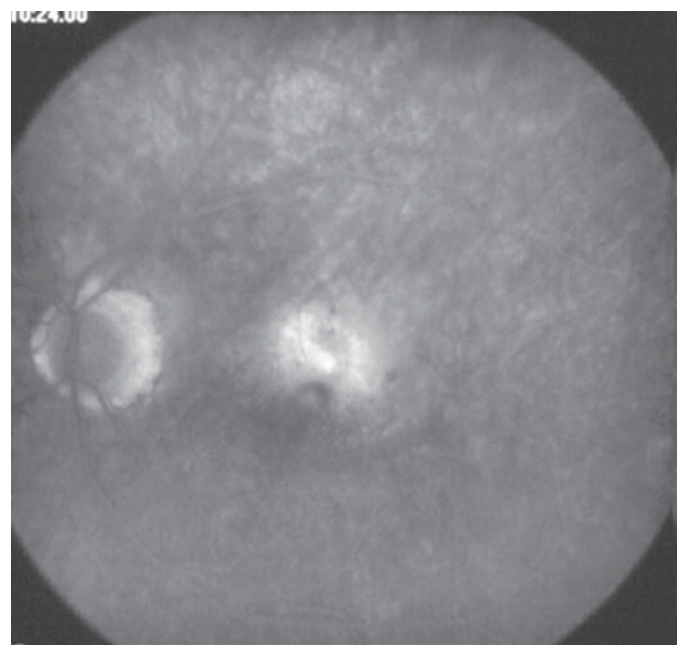

Figure 1c. *The late frame shows the leakage of dye from the CNV.*

Sl. 1c. *Pozna zgradba prikaže puščanje kontrasta iz CNV.*

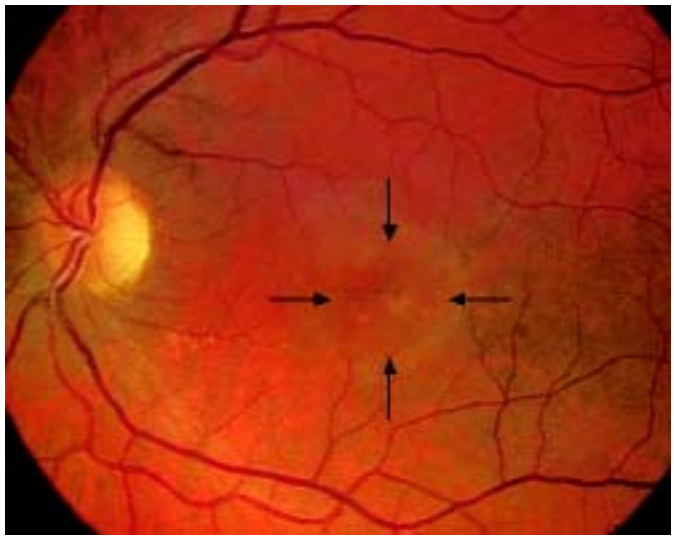

Figure 2a. *The patient presented with recent deterioration in visual acuity and metamorphopsia due to neovascular AMD with subretinal fluid (arrows), VA 20/50.*

Sl. 2a. *Bolnik se je predstavil z nedavno poslabšano vidno ostrino in metamorfopsijo zaradi neovaskularne SDM s subretinalno tekočino (puščice), VA 20/50.*

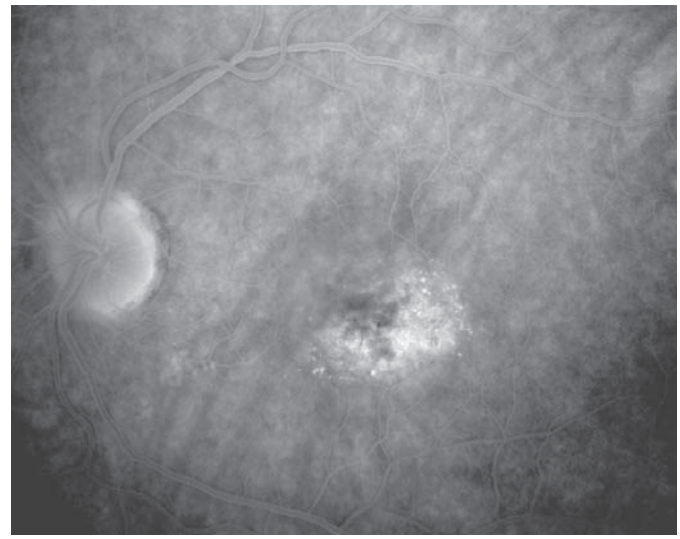

Figure 2b. *Fluorescein angiography shows late leakage, staining, and speckled hyperfluorescence corresponding to occult CNV.*

Sl. 2b. *Fluoresceinska angiografija prikaže pozno puščanje, barvanje in pikaste hiperfluorescence, ki ustrezajo okultni CNV.*

The Macula Photocoagulation Study Group reported that 12% of patients with extrafoveal CNV in one eye, and 49% of patients with CNV in both eyes, went legally blind within 5 years (8). The risk of vision loss is, of course, highest in eyes with subfoveal lesions with approximately 70% becoming legally blind within 2 years (9).
Over 70% of extrafoveal lesions become subfoveal within one year of diagnosis (10).
The main symptoms of neovascular AMD are a sudden loss of central vision, metamorphopsia, decreased contrast sensitivity, decreased color vision, central scotoma, and photopsia.

Definitons

Neovascular AMD is characterized by one or more of the following morphological findings (2, Table 1):
- detachment of the neurosensory retina,
- RPE detachment,
- subretinal or sub-RPE neovascular membrane,
- sub- or intraretinal hemorrhages,
- hard exudates (lipids),
- scar/glial tissue or fibrin-like deposits.

Diagnosis

Fundus biomicroscopy via a dilated pupil and fluorescein angiography are the most important tools in making the exact diagnosis of AMD stage. At present, all therapeutic strategies are based on it. Fluorescein angiography provides the classification of AMD. Indocyanin green angiography may provide further information, but is not used for decision making of about the PDT treatment.

Fluorescein angiographic features

Fluorescein angiography is necessary for determining the pattern (classic or occult), the boundaries (well- or poorly defined), and the location of the lesion with respect to the centre of the foveal avascular zone (FAZ).

Classic CNV

The angiogram shows a pattern characterized by a bright area of fluorescence in the early phase and the leakage of fluorescein at the boundaries of the bright area in the mid- and late-phase (Figure 1a, 1b, 1c).
Extrafoveal lesions are located at least 200 μm from the geometric centre of the FAZ. Juxtafoveal lesions are located 1 to 199 μm from the centre of the FAZ. Subfoveal lesions extend directly beneath the centre of the FAZ.

Occult CNV

Two fluorescein patterns can be distinguished.
- The angiogram shows a late leakage of undetermined source at the level of the RPE (Figure 2a, 2b) with no evidence of classic CNV or a pattern of fibrovascular RPE detachment.
- A fibrovascular RPE detachment is characterized by an irregular elevation of the RPE showing a stippled fluorescence within 1 to 2 minutes, and a persistent staining or leakage in the late phase.

Predominantly classic CNV

If the classic CNV is occupying ≥ 50% of the entire lesion area and is extending under the centre of the foveal avascular zone, it is defined as predominantly classic CNV (Figure 3a, 3c).

Minimally classic CNV

The area of classic CNV is occupying < 50%, but > 0% of the area of the entire lesion (Figure 4a, 4b, 4c).

PDT-treatment of neovascular AMD

The MPS reported a treatment benefit with thermal laser coagulation for well-defined extra- and juxtafoveal CNV (11, 12). This is still the gold standard of therapy if the centre of the

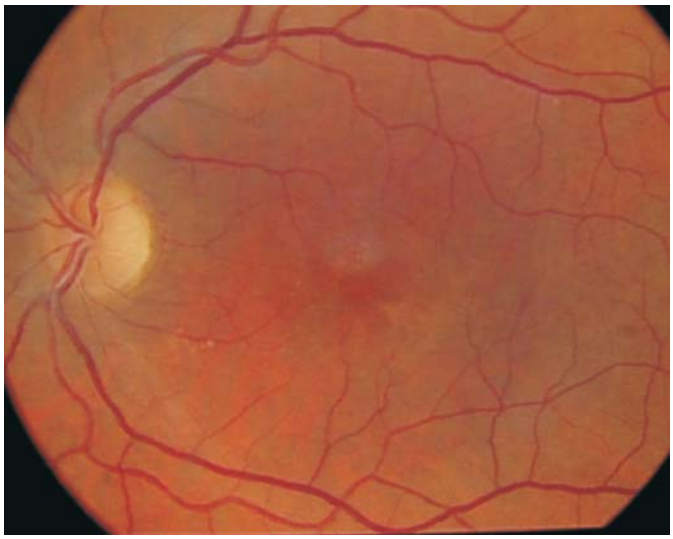

Figure 2c. *Three months after PDT fluid is absorbed, VA 20/40.*

Sl. 2c. *Tri mesece po PDT je tekočina absorbirana, VA 20/40.*

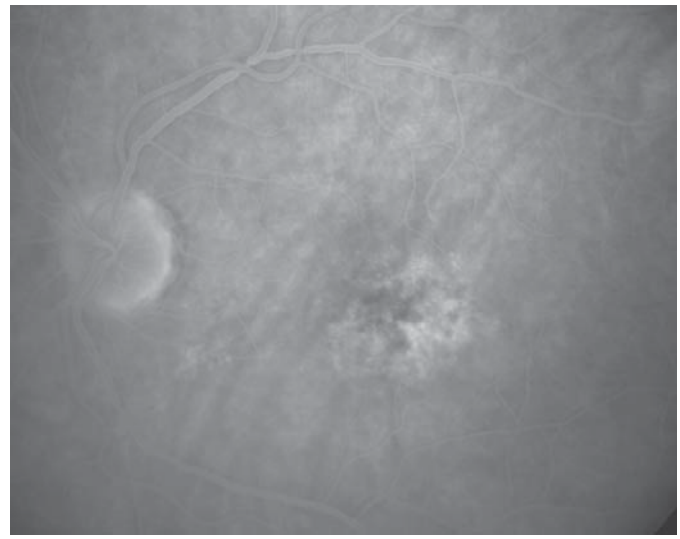

Figure 2d. *Fluorescein angiography shows a window defect and some staining, but no dye leakage.*

Sl. 2d. *Fluoresceinska angiografija kaže okno – defekt in malo barvanja, brez puščanja kontrasta.*

fovea is not involved. However, CNV recurrence rates following laser treatment range from 39% to 76%, with the most occurring within the first 2 years (1). PDT treatment has presently not been evaluated for extra- or juxtafoveal CNV.

In subfoveal CNV, the MPS reported some treatment benefit with thermal laser coagulation for certain well-defined cases. Because of thermal destruction of the retinal tissue overlying the CNV, the treated patients suffered immediate loss of visual acuity, and the beneficial effects of treatment were not apparent until 12 to 24 months after laser therapy. Another limitation of laser coagulation is the high rate of CNV recurrence of over 50% having persistent or recurrent CNV within 3 to 5 years of treatment (13).

Recently, photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis AG) has shown substantial benefit as treatment modality for subfoveal CNV (14) preserving vision and contrast sensitivity. Verteporfin is the first light-activated drug approved for treatment of CNV secondary to AMD. Several other photodynamic agents are in development, part of them are being evaluated in clinical trials, but are not approved to date.

Verteporfin therapy is currently approved for the treatment of classic and predominantly classic subfoveal CNV (3a–d) as well as occult subfoveal CNV (2a–d, Figure 7). Clinical evidence for PDT efficacy is derived primarily from the TAP (15–17) and VIP (18, 19) trials. However, treatment outcomes are strongly influenced by correct patient selection. Therefore, identifying those patients who would most likely benefit from verteporfin therapy is essential.

Verteporfin therapy reduced the risk of moderate and severe visual loss in patients with classic CNV through 24 and 36 months of follow-up. At the month 24 examination, 15% of treated patients had severe vision loss, compared with 36% given placebo (15, 17). In addition, among patients presenting with predominantly classic CNV, verteporfin-treated patients have improved visual acuity. At 24 months, 9% of treated patients experienced at least three lines of vision gain compared with 4% in patients who received placebo (15).

On fluorescein angiography, eyes treated with verteporfin showed a greater chance of reduction in lesion growth and the absence of leakage than classic CNV.

The month 24 examination results from the VIP trial have shown benefits of PDT in patients with occult with no classic CNV, presenting with recent disease progression, defined as the presence of blood associated with CNV, growth of the lesion (an increase in lesion greatest linear dimension of at least 10%), or deterioration in visual acuity (a loss of at least one line) within the past 12 weeks. Subgroup analysis suggested that a greater benefit was achieved particularly in patients with either smaller lesions (≥ 4 disc areas), or lower levels of visual acuity (< 20/50) (18). In this group, 21% of the treated patients and 48% of patients who received placebo had severe vision loss at the month 24 examination.

Verteporfin therapy should also be considered for juxtafoveal lesions that are so close to the fovea that laser treatment would certainly extend under the centre of the FAZ if all other criteria were met.

However, PDT is not of value for minimally classic CNV (18, 19) because no significant visual acuity benefits were found (15).

Verteporfin therapy

PDT in subfoveal CNV represents a major therapeutic advance preserving the retinal tissue overlying the CNV. Verteporfin (benzoporphyrin derivative monoacid or BPD-MA) is a chlorin-type molecule derived from porphyrin, and exists as an equal mixture of two regioisomers, BPD-MA_C and BPD-MA_D. The drug is supplied as a lyophilized, freeze-dried cake that is reconstituted and diluted to a volume of 30 mL. Verteporfin treatment is mainly a two-step process in which the drug is first administered by intravenous infusion, transported via the plasma by low-density lipoproteins with preferential accumulation in the neovascular endothelial cells via LDL receptors. Then it is activated in the target area by a non-thermal laser light at the wavelength of 689 nm. Visudyne is administered at a dose of 6 mg/m^2 body surface area (BSA). The light dose corresponds to the absorbance peak of the drug. 50 J/cm^2 are administered at an intensity of 600 mW/cm^2 with the treatment time of 83 seconds. The maximum lesion size in the trials was 5400 µm in diameter in predominantly classic CNV. However, the treatment should not be restricted by the size of the lesion if all other criteria for treatment are met (19). The lesion area includes the entire CNV (classic or occult), features that obscure the boundaries like blood that is thick enough to obscure hyperfluorescence from CNV

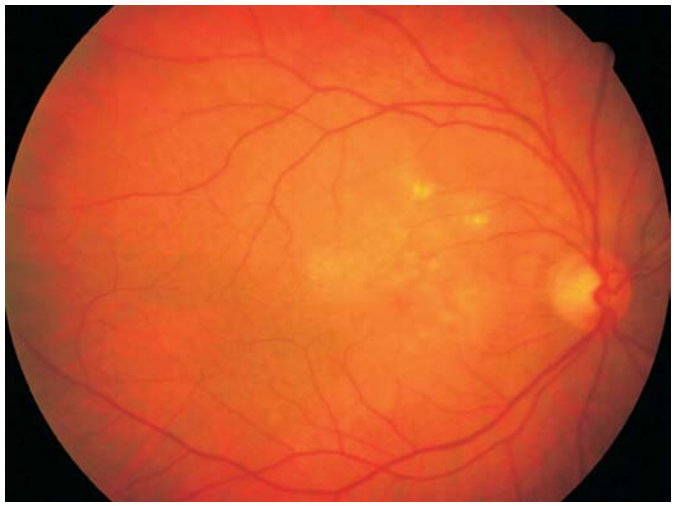

Figure 3a. *Neovascular AMD with subretinal fluid overlying the CNV (VA 20/200).*

Sl. 3a. *Neovaskularna SDM s subretinalno tekočino, ki prekriva CNV (VA 20/200).*

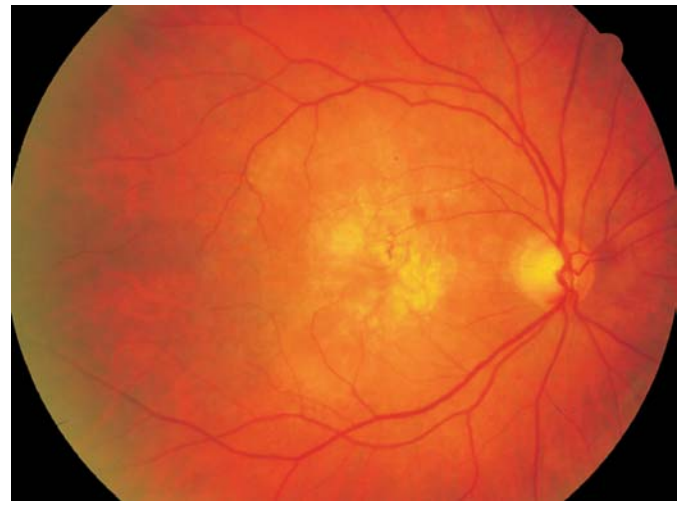

Figure 3b. *The colour photograph 3 months after the second PDT shows no evidence of subretinal fluid (VA 20/100).*

Sl. 3b. *Barvna slika 3 mesece po drugi PDT ne kaže znakov za subretinalno tekočino (VA 20/100).*

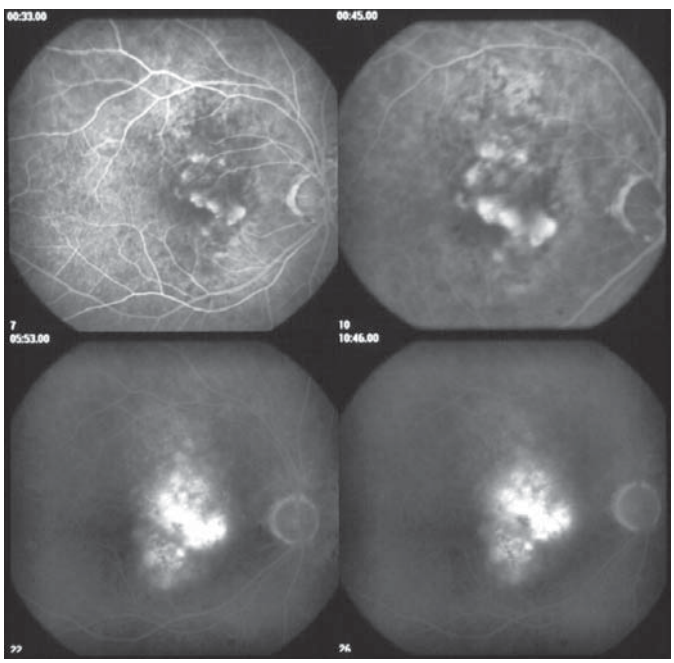

Figure 3c. *The angiogram reveals a predominantly classic subfoveal CNV before PDT.*

Sl. 3c. *Angiogram prikaže predominantno klasično subfovealno CNV pred PDT.*

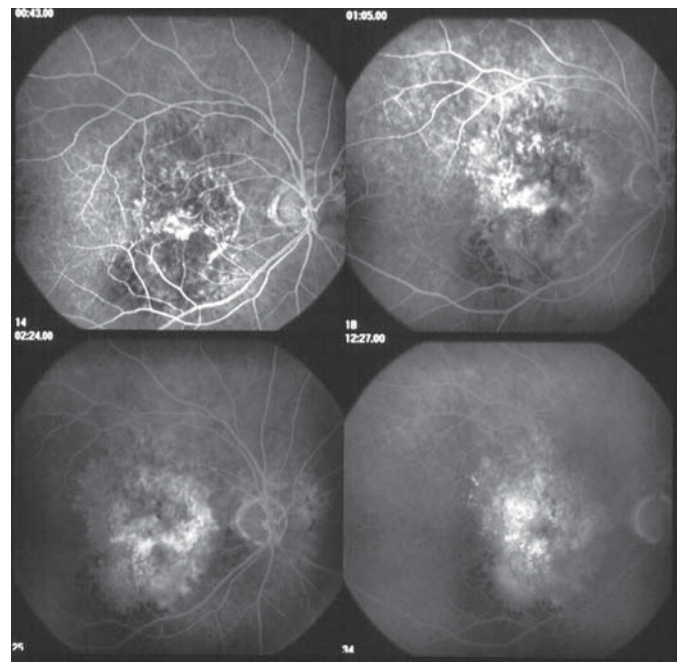

Figure 3d. *Three months after the second PDT there is staining of the CNV but no dye leakage.*

Sl. 3d. *3 mesece po drugi PDT se CNV barva, a ni propuščanja kontrasta.*

potentially underlying the blood, blocked fluorescence due to pigment or scar, and serous detachment of the RPE. The treatment spot is chosen 1000 µm larger than the greatest linear dimension of the lesion (GLD) on the retina. This has been obtained by dividing the length of the greatest distance between two points on the boundary of the entire lesion by the magnification of that image relative to the true size of the retina. The treatment spot should not overlie the optic nerve and should be placed at least 200 µm away from the edge of the optic disc. Optimal selectivity and efficacy is achieved by activating verteporfin 15 minutes after the start of a 10-minute intravenous infusion. The treatment should ideally be applied within one week of the angiogram, on which the treatment decision is based.

The resulting photochemical reaction generates reactive oxygen species that cause local cellular and tissue damage with specific choroidal neovascular vessel occlusion. Unlike laser photocoagulation, PDT may not cause irreversible functional damage to the normal retinal tissue (14).

Verteporfin is cleared from the body via biliary excretion in the liver and is normally eliminated within 24 hours, minimizing the problems of systemic photosensitivity after treatment. The treatment is generally well tolerated. The patients should be provided with the information of the precautions that ne-

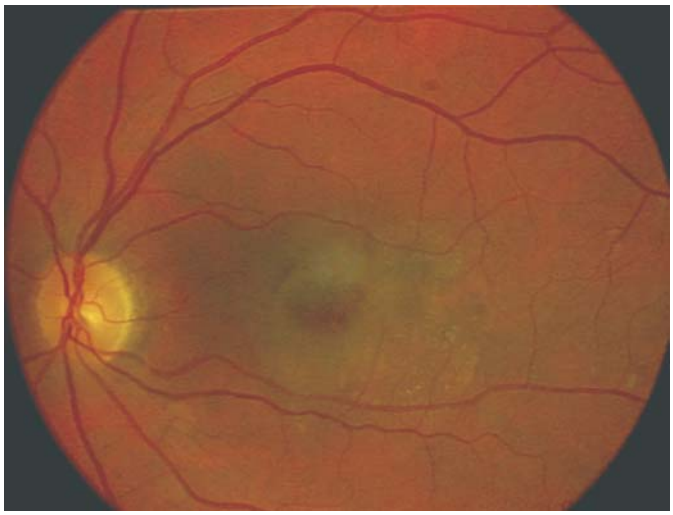

Figure 4a. *Neovascular AMD with subretinal fluid overlying the CNV.*

Sl. 4a. *Neovaskularna SDM s subretinalno tekočino, ki prekriva CNV.*

ed to be taken to avoid side effects. They have to wear sunglasses and should avoid exposure of skin and eyes to sunlight or bright indoor light for 48 hours after treatment.
Contraindications for PDT are severe hepatic impairments, porphyria, porhyrin allergy, and severe cardiovascular or kidney diseases.
Complications observed with PDT are intra- or subretinal haemorrhage, vitreous haemorrhage, decreased vision, RPE tear, and visual field defects.
Side effects in the TAP 2 (15) study were injection-site events (13.4%), infusion-related back pain (2.2%), and mild photosensitivity (3%).

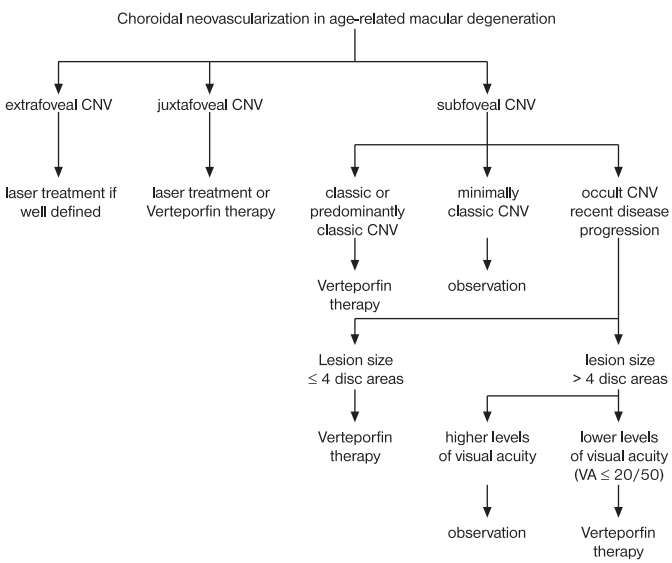

Figure 5. *Algorithm for managing patients with choroidal neovascularization secondary to AMD (CNV = choroidal neovascularization, VA = visual acuity).*

Sl. 5. *Algoritem za obravnavanje bolnikov s horoidalno neovaskularizacijo zaradi SDM (CNV = horoidalna neovaskularizacija, VA = vidna ostrina).*

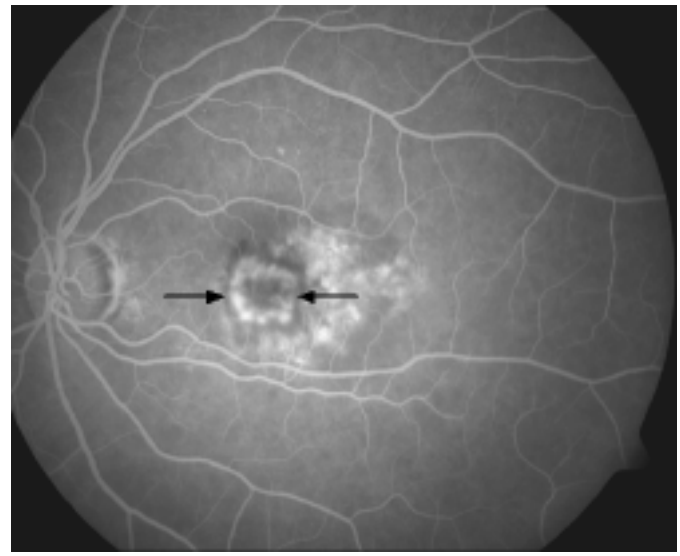

Figure 4b. *Fluorescein angiogram shows minimally classic CNV (arrows) occupying less than 50% of the entire lesion.*

Sl. 4b. *Fluoresceinski angiogram kaže minimalno klasično CNV (puščice), zavzema manj kot 50% celotne lezije.*

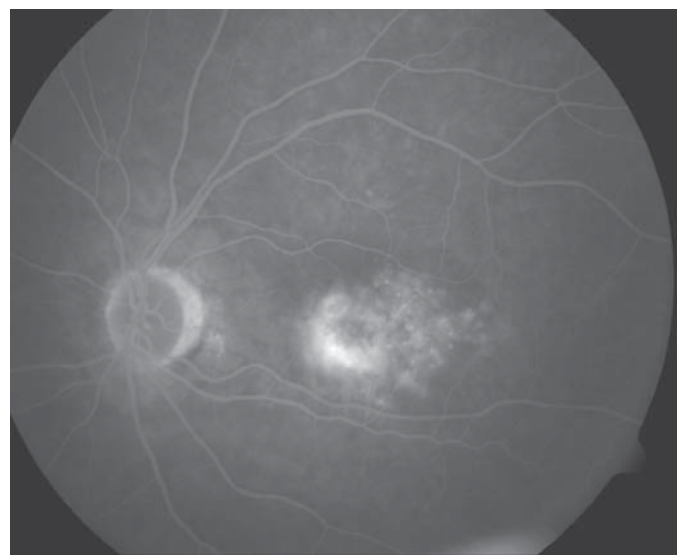

Figure 4c. *The late frame shows dye leakage from the classic part of the CNV, and staining corresponding to the occult part of the CNV.*

Sl. 4c. *Pozna zgradba pokaže puščanje iz klasičnega dela CNV in obarvanje pripadajočega okultnega dela CNV.*

Follow-up visits

The patients should return for follow-up at least every three months after initial or subsequent treatment to determine if there still is fluorescein leakage from CNV. If the fluorescein angiogram at that time shows any dye leakage from CNV, PDT re-treatment is required. On average, verteporfin-treated patients received five to six treatments over a 24 months follow-up (15, 18).
After successful Verteporfin treatment, the patient should return for follow-up visits every 3 months for at least 6 months, then follow-up might be scheduled at 6-month intervals.
Low vision aids may help maximizing the remaining vision and maintaining the patient's independence.

Conclusions

The increasing life expectancy in the western world puts a growing number of people at risk of vision impairment due to AMD. The challenge for ophthalmologists is the preservation of adequate visual function in those people as long as possible.

The availability of photodynamic therapy has expanded the range of evidence-based treatment options for CNV secondary to AMD. Verteporfin has been proved to selectively occlude predominantly classic and occult subfoveal CNV, and significantly reduce the risk of vision loss in patients with neovascular AMD. Regarding the clinical use, treatment guidelines are helpful in improving the quality of management and outcome in patients with AMD.

Considering recent advances in treatment of neovascular AMD and the increasing number of people affected, it is important that the disorder is detected in an early stage and that patients are taken care by trained retina specialists. Regular eye examinations in people over 50 years of age and patient education are important in improving the prognosis.

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