

CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION TREATED WITH PHOTODYNAMIC THERAPY AND INTRAVITREAL TRIAMCINOLONE ACETONIDE

Romano Vrabec, Zoran Vatauvuk, Goran Benčić, Ivan Čima, Ognjen Zrinščak and Zdravko Mandić

University Department of Ophthalmology, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – The aim of the study was to show the effect of combined photodynamic therapy and intravitreal injection of triamcinolone acetonide in the treatment of choroidal neovascularization due to age-related macular degeneration. This retrospective, nonrandomized study included 20 patients with predominantly classic choroidal neovascularization due to age-related macular degeneration with no prior treatment. At baseline, all patients underwent ophthalmologic examination. Fluorescein angiography and optical coherent tomography were performed and analyzed. Triamcinolone acetonide, 4 mg, was intravitreally applied at 24-48 hours after standard photodynamic therapy. Follow up was scheduled at 3, 6 and 9 months. After 9 months, visual acuity improved in four, remained unchanged in 14 and decreased in two patients. In all patients, complete closure of choroidal neovascularization occurred after 9 months. At that time, a decrease in the central foveal thickness was also recorded in all patients. Combined photodynamic therapy and intravitreal injection of triamcinolone acetonide is a safe method in the treatment of choroidal neovascularization due to age-related macular degeneration, and leads to complete closure of choroidal neovascularization. To prove these promising results, a carefully designed, randomized, controlled study in a larger group of patients is needed.

Key words: *Macular degeneration – complications; Macular degeneration – therapy; Choroidal neovascularization – etiology; Choroidal neovascularization – drug therapy; Photochemotherapy*

Introduction

Choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD) is the leading cause of blindness in patients older than 65 in industrialized countries. Approximately 6% of patients aged 65-74 and 19% of patients older than 75 have signs of AMD. Two patterns of AMD have been identified. Non-exudative or dry AMD is present in 90% of patients with AMD. It is slowly progressive and characterized by drusen and geographic atrophy of retinal pigment epithelium (RPE). Visual acuity remains unchanged for a

long period. Exudative or wet AMD, which is present in 10% of patients with AMD, is associated with exudation, CNV, progressive course and significant decrease in visual acuity. The pathogenesis of AMD is not fully understood. Main changes are confined to the level of RPE cells and Bruchs membrane, and include a number of pathogenic effects like angiogenesis, cell-mediated inflammation, leukocyte adhesion and extravasation, and matrix remodeling. It seems that an increased activity of angiogenic factors, especially vascular endothelial growth factor (VEGF), is the most important pathway in the development of neovascularization¹⁻⁵.

Until several years ago, neovascular lesions due to AMD could only be treated with argon laser photocoagulation, which was associated with some limitations in the foveal region due to the high energy absorption⁶⁻⁸. Only extra- or juxtafoveal lesions could be treated. At

Correspondence to: *Romano Vrabec, MD*, University Department of Ophthalmology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: romanovrabec@yahoo.com

Received February 2, 2007, accepted in revised form April 19, 2007

the beginning of this millennium, with the advent of photoactivated drugs and diode laser, we are able also to treat subfoveal neovascular lesions and keep the foveal area intact. Verteporfin is a photoreactive drug which, when activated with low energy diode laser, produces photochemical reaction with consequent thrombosis of the newly formed blood vessels. Photodynamic therapy (PDT) has soon become a well established and approved therapeutic approach for certain types of neovascular lesions⁹⁻¹⁴. Despite its selective therapeutic effect, PDT also releases free oxygen radicals causing damage to endothelial cells, thus inducing inflammatory reaction with a new subsequent release of angiogenic factors and recurrence of neovascularization^{15,16}. Since intravitreal application of steroids, especially triamcinolone acetonide, is known to have significant anti-inflammatory, antiangiogenic and antifibrotic effects, as demonstrated in patients with diabetic macular edema, combining PDT and triamcinolone acetonide could provide better treatment for CNV due to AMD through the expected synergistic effect of both procedures. In this retrospective pilot study we reviewed outcomes of such a combined procedure.

Patients and Methods

In this nonrandomized, retrospective study we included 20 patients (14 female and 6 male) with predominantly classic CNV due to AMD and without any prior treatment, median age 69 (range 64-81). All patients were evaluated at our department including visual acuity testing on Snellen chart, intraocular pressure measurement with Goldmann applanation tonometer, slit lamp examination, and 78 and 90 D lens fundus examination. The size and type of CNV were determined by fluorescein angiography. Central foveal thickness was analyzed by optical coherent tomography (Stratus, Zeiss). The standard protocol for PDT was used, as follows: 30 mL of Visudyne® (6 mg/m²) was injected intravenously into the cubital vein over 10 minutes. Laser application followed 15 minutes after the injection, at a wavelength of 689 nm, duration of 83 seconds and intensity of 600 mW/cm², which is equivalent to the light dose of 50 J/cm².

At 24-48 hours after PDT, we applied 4 mg of triamcinolone acetonide intravitreally *via* pars plana (3.5-4.0 mm from limbus). The procedure was done in operating theater under sterile conditions. We used tetracaine eye drops for topical anesthesia.

Eyes were evaluated at baseline, and at 3, 6 and 9 months after treatment. Intravitreal triamcinolone acetonide and PDT retreatment rates were recorded.

Contraindications were related to known hypersensitivity to any component of Visudyne® (verteporfin) and porphyria.

Statistical analysis was done using Mann-Whitney U test.

Results

In all patients, the size of CNV lesion was less than 2 disc diameter (DD), mean lesion size 1.5 DD. The mean Snellen chart visual acuity was 0.2 at baseline, 0.3 (p=0.23) at 3 months, 0.2 (p=0.24) at 6 months, and 0.3 (p=0.23) at 9 months. At 3 months, complete closure of CNV occurred in 13, CNV remained unchanged in five, and increased in two patients. At 6 months, complete closure of CNV occurred in 15 and remained unchanged in five patients. At 9 months, complete closure of CNV occurred in all patients treated with combined therapy (Table 1). The mean number of treatments was 1.3 (Table 2).

Table 1. Results obtained by photodynamic therapy (PDT) combined with intravitreal injection of triamcinolone acetonide (IVTA)

	PDT and IVTA
Number of patients	20
Female/Male (n)	14/6
Median age (range) (yrs)	69 (64-81)
Mean visual acuity at baseline	0.2
Mean visual acuity after 9 months	0.3
Mean lesion size at baseline	1.5 DD
Mean lesion size at 9 months	Complete closure

The median central foveal thickness (CFT) was 340 μ m (270-588 μ m) at baseline, 232 μ m (191-510 μ m) at 3 months, 270 μ m (195-530 μ m) at 6 months and 256 μ m (186-507 μ m) at 9 months.

Table 2. Number of treatments with photodynamic therapy (PDT) combined with intravitreal injection of triamcinolone acetonide (IVTA)

Number of treatments	PDT + IVTA
1	13
2	6
3	1

The mean intraocular pressure was 14 mm Hg before and 15 mm Hg after treatment. During the follow up period, there was no significant intraocular pressure elevation or cataract progression, and no procedure related complications such as endophthalmitis or RPE tear were recorded.

Discussion

In this small, retrospective study including patients with predominantly classic CNV due to AMD, PDT and intravitreal triamcinolone acetonide showed some benefits in visual acuity over the 9-month follow up. The increase in visual acuity was not statistically significant, however, 78% of patients showed stabilization of visual acuity compared with baseline. At 9 months, complete closure of CNV without any visible activity on fluorescein angiography occurred in all patients. Also, a decrease in the mean CFT was recorded on optical coherent tomography during the follow up period.

Photodynamic therapy was the first therapy approved for subfoveal CNV because it causes targeted destruction of endothelial cell and occlusion of newly formed blood vessels without damaging the overlying retinal structures. Over the past few years, it has also been demonstrated that PDT treatment causes release of free oxygen radicals from damaged cells, which can lead to up-regulation of angiogenic factors. It is now believed that inflammatory components play an important role in the pathogenesis of CNV, especially polymorphism of complement factor H¹⁷. PDT can promote inflammation as well as release of VEGF, which then leads to CNV recurrence.

Intravitreal use of steroids has been demonstrated to exert antiangiogenic effects such as down-regulation of extracellular matrix metalloproteinases (MMPs), reduction in VEGF expression, down-regulation of intercellular adhesion molecule (ICAM)-1 expression, inhibition of migration, and activation of inflammatory cells. Steroids also have important anti-inflammatory effects like inhibition of synthesis and release of various inflammatory mediators, and antifibrotic effect by inhibition of the basic fibroblast growth factor (bFGF)¹⁸⁻²¹. Because of numerous beneficial effects and relatively safe procedure for intravitreal application, steroids, triamcinolone acetonide in particular, are nowadays widely in use. Monotherapy with intravitreal triamcinolone acetonide showed good short-term results, however, retreatment would be necessary after some time²².

Combined treatment with PDT and intravitreal triamcinolone acetonide seems to be reasonable because we can treat neovascular lesion and decrease inflammatory reaction, VEGF release, vascular permeability and expression of adhesion molecules²³⁻²⁵. Both procedures have been shown to be relatively safe. PDT is a safe procedure without any complications, while the well known adverse effect of triamcinolone acetonide is the intraocular pressure increase. In our study, we did not record any case of significant intraocular pressure elevation, or of development or progression of cataract or endophthalmitis.

The mean number of treatments *per* patient was 1.3, which is consistent with literature reports²⁵ (Table 2). The number of combined PDT and intravitreal triamcinolone acetonide retreatments was lower than of PDT retreatments alone.

In recent time, some new medications for neovascular lesions due to AMD have been developed, such as anti-VEGF specific drugs acting at the level of production of angiogenic factors. Currently, many randomized, multicenter and controlled studies evaluating intravitreal application of various anti-VEGF drugs are under way. Although our study was non-randomized, non-masked and with a small number of patients, the results are promising. Further evaluation of the beneficial effects of this treatment method requires a randomized and controlled study with more patients. It is also necessary to compare the results of combined PDT and intravitreal triamcinolone acetonide treatment with anti-VEGF treatment as well as with combined PDT and anti-VEGF treatment.

Conclusion

Combined PDT and intravitreal injection of triamcinolone acetonide treatment for CNV due to AMD is a safe method that leads to complete closure of CNV. To confirm these promising results, carefully designed, randomized and controlled study in a larger group of patients is needed.

References

1. PENFOLD PL, KILLINGSWORTH M, SARKS SH. An ultrastructural study of the role of leukocytes and fibroblasts in the breakdown of Bruch's membrane. *Aust J Ophthalmol* 1984; 12:23-31.
2. PENFOLD PL, PROVVIS JM, BILLSON FA. Age-related macular degeneration: ultrastructural studies of the relationship

- of leukocytes to angiogenesis. *Graefes Arch Clin Exp Ophthalmol* 1987;225:70-6.
3. KILLINGSWORTH MC, SARCS JP, SARCS JH. Macrophages related to Bruch's membrane in age-related macular degeneration. *Eye* 1990;4:613-21.
 4. OH H, TAKAGI H, TAKAGI C, SUZUMA K, OTANI A, ISHIDA K *et al.* The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1990;40:1891-8.
 5. GEHRM KM, ANDERSON DH, JOHNSON LV, HAGEMAN GS. Age-related macular degeneration: emerging pathogenetic and therapeutic concepts. *Ann Med* 2006;38:450-71.
 6. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS Report No. 1. *Arch Ophthalmol* 1985;103:1796-806.
 7. Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy. Five year results from randomized trials. *Arch Ophthalmol* 1991;109:1109-14.
 8. Macular Photocoagulation Study Group. Subfoveal neovascular lesions in age-related macular degeneration: guidelines for evaluation and treatment in the Macular Photocoagulation Study. *Arch Ophthalmol* 1991;109:1242-57.
 9. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials – TAP Report 1. *Arch Ophthalmol* 1999;117:1329-45.
 10. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials – TAP Report 2. *Arch Ophthalmol* 2001;119:198-207.
 11. Verteporfin In Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1- year results of a randomized clinical trial – VIP Report No. 1. *Ophthalmology* 2001;108: 841-52.
 12. Verteporfin In Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization – Verteporfin in Photodynamic Therapy Report 2. *Am J Ophthalmol* 2001;131:541-60.
 13. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy and Verteporfin in Photodynamic Therapy Study Group. Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP Report No. 1. *Am J Ophthalmol* 2003;136:407-18.
 14. SCHMIDT-ERFURTH U, MILLER J, SICKENBERG M, BUNSE A, LAQUA H, GRAGOUDAS E *et al.* Photodynamic therapy of subfoveal choroidal neovascularization: clinical and angiographic examples. *Graefes Arch Clin Exp Ophthalmol* 1998;236:365-74.
 15. SCHMIDT-ERFURTH U, MICHELS A, BARBAZETTO I, LAQUA H. The photodynamic effects of choroidal neovascularization and physiological choroids. *Invest Ophthalmol Vis Sci* 2002;43:830-41.
 16. RUDOLF M, MICHELS S, SCHLÖTZER-SCHREHARDT U, SCHMIDT-ERFURTH U. Expression of angiogenic factors by photodynamic therapy. *Klin Monatsbl Augenheilkd* 2004;221:1026-32.
 17. HAINES JL, HAUSER MA, SCHMIDT S, SCOTT WK, OLSON LM, GALLINS P *et al.* Complement factor H variant increases the risk of age-related macular degeneration. *Science* 2005;308:419-21.
 18. ISHIBASHI T, MIKI K, SORGENTE N, PATTERSON R, RYAN SJ. Effects of intravitreal administration of steroids on experimental subretinal neovascularization in the subhuman primate. *Arch Ophthalmol* 1985;103:708-11.
 19. WILSON CA, BERKOWITZ BA, SATO Y, ANDO N, HANDA JT, de JUAN E Jr. Treatment with intravitreal steroids reduces blood-retinal barrier breakdown due to retinal photocoagulation. *Arch Ophthalmol* 1992;110:1155-9.
 20. PENFOLD PL, GYORY JF, HUNYOR AB, BILLSON FA. Exudative macular generation and intravitreal triamcinolone. A pilot study. *Aust N Z J Ophthalmol* 1995;23:293-9.
 21. EBRAHEM Q, MINAMOTO A, HOPPE G, ANAND-APTE B, SEARS JE. Triamcinolone acetonide inhibits IL-6- and VEGF-induced angiogenesis downstream of the IL-6 and VEGF receptors. *Invest Ophthalmol Vis Sci* 2006;47:4935-41.
 22. JONAS JB, SPANAU UH, KAMPPETER BA, VOSSMER-BAEUMER U, HARDER B. Repeated intravitreal injection of triamcinolone for exudative age-related macular degeneration. *Ophthalmic Res* 2006;38:324-8. Epub 2006 Oct 13.
 23. RUIZ-MORENO JM, MONTERO JA, BARILE S, ZARBIN MA. Photodynamic therapy and high-dose intravitreal triamcinolone to treat exudative age-related macular degeneration: 1-year outcome. *Retina* 2006;26:602-12.
 24. FACKLER TK, REDDY S, BEARELLY S, STINNETT S, FEKRAT S, COONEY MJ. Retrospective review of eyes with neovascular age-related macular degeneration treated with photodynamic therapy with verteporfin and intravitreal triamcinolone. *Ann Acad Med Singapore* 2006;35:701-5.
 25. AUGUSTIN AJ, SCHMIDT-ERFURTH U. Verteporfin therapy and triamcinolone acetonide: convergent modes of action for treatment of neovascular age-related macular degeneration. *Eur J Ophthalmol* 2006;16:824-34.

Sažetak

KOROIDNA NEOVASKULARIZACIJA KOD MAKULARNE DEGENERACIJE POVEZANE S DOBI LIJEČENE FOTODINAMSKOM TERAPIJOM I INTRAVITREALNIM TRIAMCINOLON ACETONIDOM

R. Vrabc, Z. Vataavuk, G. Benčić, I. Čima, O. Zrinščak i Z. Mandić

Prikazuju se rezultati kombinirane intravitrealne primjene triamcinolona i fotodinamske terapije kod razvoja koroidnih neovaskularizacija koje su nastale kao posljedica senilne makularne degeneracije. U retrospektivnu nerandomiziranu studiju bilo je uključeno 20 bolesnika s pretežito klasičnom koroidnom neovaskularizacijom, koji do tada nisu bili liječeni. Kod svih bolesnika učinjen je standardni oftalmološki pregled, fluoresceinska angiografija i optička koherentna tomografija. Triamcinolon acetonid, 4 mg, apliciran je intravitrealno 24-48 sati nakon fotodinamske terapije. Praćenje bolesnika je provedeno nakon 3, 6 i 9 mjeseci. Nakon 9 mjeseci kod 4 bolesnika došlo je do poboljšanja vidne oštine, kod 14 bolesnika vidna oština je ostala stabilna, dok je kod 2 bolesnika zabilježen pad vidne oštine. Potpun nestanak koroidne neovaskularizacije kod svih je bolesnika zabilježen nakon 9 mjeseci. Kombinirana primjena triamcinolona i fotodinamske terapije sigurna je metoda u liječenju pretežito klasičnih koroidnih neovaskularizacija, koja dovodi do njihovog potpunog zatvaranja i nestajanja, no za potvrdu ovih rezultata potrebna je randomizirana analiza na većem broju bolesnika.

Ključne riječi: Makularna degeneracija – komplikacije; Makularna degeneracija – terapija; Koroidna neovaskularizacija – etiologija; Koroidna neovaskularizacija – terapija

