

Photodynamic Therapy Combined with Intravitreal Bevacizumab (Avastin) in Treatment of Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

Ratimir Lazić, Nikica Gabrić, Iva Dekaris, Morena Gavrić and Damir Bosnar

Eye Clinic »Svjetlost«, Zagreb, Croatia

ABSTRACT

To evaluate photodynamic therapy with verteporfin combined with intravitreal bevacizumab in minimally classic and occult choroidal neovascularization secondary to age-related macular degeneration. 46 eyes of 46 patients (mean age 74.5) included in this prospective, noncomparative, interventional case series. Median follow-up was 24 weeks (12–36). Verteporfin photodynamic therapy (PDT) was followed by 0.05 mL (1.25 mg) of bevacizumab injected intravitreally within 24 hours and again after 6 weeks. Whole procedure was repeated in 3-month intervals in case of leakage. Visual acuity (VA) improved in majority of patients (baseline VA 1.041 log MAR) by mean increase of 1.45 lines (last follow-up) ($p=0.001$). Central foveal thickness (CFT) and total macular volume (TMV) decreased by 53 μm ($p=0.03$) and 1.04 mm^3 ($p<0.001$) respectively. No serious complications were observed. Combined treatment may improve outcome of monotherapy. Significant improvement in VA, CFT and TMA was noted in majority of patients and maintained during follow-up.

Key words: bevacizumab, photodynamic therapy, choroidal neovascularization

Introduction

Photodynamic therapy with verteporfin is very effective in patients with classic subfoveal neovascularization due to age related macular disease.^{1–3} Also it has shown positive effect in reducing the risk of visual loss in patients with occult choroidal neovascularization,⁴ and in minimally classic CNV.⁵ Since we noticed from our own clinical experience, verteporfin therapy does not produce too good results in treatment of minimally classic and occult lesions, as in treatment of classical CNV, the further investigation for novel approaches in treatment of such lesion subtypes is fully justified. The positive outcomes of antiVEGF therapy (e.g. pegaptanib) in treatment of neovascular AMD have been fully reported in several studies.^{6,7} Also, there are clinical studies going on to compare various treatment modalities for neovascular AMD: e.g. verteporfin vs. pegaptanib. New antiVEGF agent, bevacizumab, has also been used in off-label treatment of neovascular AMD and neovascularization due to patho-

logic myopia for a year now.^{6,8–10} Bevacizumab, a humanized monoclonal antibody directed against vascular endothelial growth factor, was already approved by Food and Drug Administration for the treatment of metastatic colorectal cancer.^{5,11}

Since the pathogenesis of choroidal neovascularization is multifactorial including both angiogenesis, extravasation and inflammation, it is fully justified to try to incorporate several treatment modalities for combating the diseases. There have been studies suggesting the additive effect to verteporfin therapy of anti-inflammatory and anti-angiogenic drugs in treatment of neovascular AMD.^{12,13} Since the anti-angiogenic effect of triamcinolone administered alone is quite weak,^{14,15} producing only mild transient effect, and since bevacizumab administered alone did show promising results in treatment of CNV,^{6,8–10} it is quite justified trying to combine verteporfin and intra-

vitreal bevacizumab as a possibly effective combined treatment of neovascular AMD. Also photodynamic therapy itself may contribute to additional VEGF expression,¹⁶ therefore further additive effect may be proposed.

In this study we focused on minimally classic and occult membranes, as those in clinical practice present main challenge, and according to our own clinical findings, do not respond that well to photodynamic therapy alone or when combined with intravitreal triamcinolone. So in this study we aimed at providing preliminary efficacy and safety results to help determine whether combined verteporfin and bevacizumab treatment can improve visual acuity and macular morphology parameters such as thickness and volume in patients with neovascular AMD.

Methods

There were 46 eyes of 46 patients included in this prospective, interventional, noncomparative case series. Patients were recruited by our retinal subdivision and were required to meet inclusion criteria. At baseline, all patients underwent VA measurement using EDTRS chart, slit lamp and fundus examination and IOP measurements. Fluorescein angiography was performed to identify lesion subtype and location and to verify active choroidal neovascular leakage. Also OCT scan was performed to verify exudation, and to measure foveal thickness and macular volume. Inclusion criteria were as follows: patient age 50, VA better or equal to 20/400, active leakage at FA and OCT scan, subfoveal lesion location, GDL of 7500 μm , no previous treatment. This study complied with the and has been approved by the Ethics Committee of the Eye Clinic, and written informed consent was obtained from the patients in the study describing the experimental nature of the bevacizumab off-label use and potential risks.

Photodynamic therapy with verteporfin (Visudyne, Novartis Ophthalmics, Basel, Switzerland) was performed according to the recommended standard procedure.^{1,2} Following PDT, within a mean of 24 hours (20–28 h), patients received topical and subconjunctival anesthesia. 1.25 mg of bevacizumab (Avastin 100 mg / 4 mL vial, Genentech Inc, San Francisco, USA) in a volume of 0.05 mL solution, was administered intravitreally through pars plana by 27-gauge needle. The injection was given in the operating room under the operating microscope, after the povidone-iodine eye cleansing. No paracentesis was required due to small volume injected. An additional intravitreal application of bevacizumab was performed in a 6 weeks interval using the protocol already described.

Patients were asked to come back for follow-up visits in 12-week (post-PDT) intervals, when similar ophthalmologic examination was performed including VA measurement, IOP measurement, angiography and OCT scan. In case of active leakage presence at the 12-week follow-up visits, the already described combined regimen of verteporfin PDT and 2 bevacizumab intravitreal applications was carried out.

The main outcome measures were a mean change in VA between baseline and last follow-up, measured using EDTRS chart, a mean change in central foveal thickness (CFT) and total macular volume (TMV) (within 3000 μm radius from center of fovea) at baseline and last follow-up, measured by OCT. The mean VA, foveal thickness and macular volume at the final follow-up were then compared with the baseline values, and statistically analyzed using paired t test to determining statistical significance between two corresponding groups.

Results

A total of 46 eyes of 46 patients with choroidal neovascularization due to AMD were included in the study, meeting the inclusion criteria described previously. There were 29 females and 17 males, with a mean age of 74.5 years (range 60–84). The mean lesion size was 3889 μm (range 700–7700). There were 36 minimally classic CNV subtypes and 10 occult CNV subtypes as documented angiographically and by OCT scan. Both lesion subtypes responded with a reduction in leakage, as evaluated by an experienced retinologist. Median follow-up was 24 weeks (12–36). The mean VA at baseline was 20/200⁻² (1.041 logMAR), the mean central foveal thickness (CFT) was 384 μm , while the mean total macular volume (TMV) was 9.39 mm³. There was a significant mean increase in VA from baseline to the time of last follow-up visit of 1.45 lines ($p=0.001$) (Fig. 1). The patients with minimally classic subtype had a mean increase of 1.53 ($p<0.001$) while patients with occult CNV had a mean increase in VA of 1.37 lines ($p=0.01$).

Furthermore there was a significant mean decrease in CFT from baseline (384 μm) to the time of last follow-up visit of 53 μm ($p=0.03$). Patients with minimally classic membranes responded with even greater foveal thickness reduction than patients with occult membranes, 67 μm ($p=0.01$), 49 μm ($p=0.04$) respectively (Fig. 2). The mean macular volume at last follow-up decreased significantly for 1.04 mm³ ($p<0.001$) compared to baseline (9.39 mm³) (Fig. 3).

Thirty nine patients (84.8 %) required only one combined treatment to achieve resolution of leakage, while 6 (13%) patients needed an additional combined treatment to resolve the leakage. Only 1 patient (2.1%) needed a third treatment regimen, but only a reduction of leakage was achieved in this case. So the mean number of combined regimen treatments was 1.15 for the eye. In minimally classic subtype 6 patients needed an additional treatment, compared to 1 patient in occult subtype group.

When treatment results were analyzed with respect to lesion size, lesions larger than 5000 μm maintained stable vision, but improvement in VA was not statistically significant. On the other hand, those lesions showed significant macular volume decrease, which effect was maintained to the last follow-up visit.

There were no adverse reactions to the combined treatment regimen. Neither inflammation nor infection was observed. No patients required topical anti-glauco-

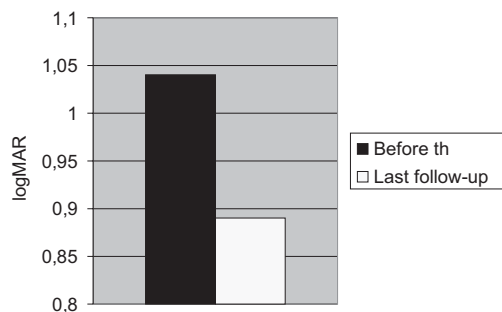


Figure 1. There was a significant mean increase in best corrected visual acuity from baseline to the time of last follow-up visit of 1.45 lines ($p=0.001$). LogMAR=logarithm of minimum angle of resolution.

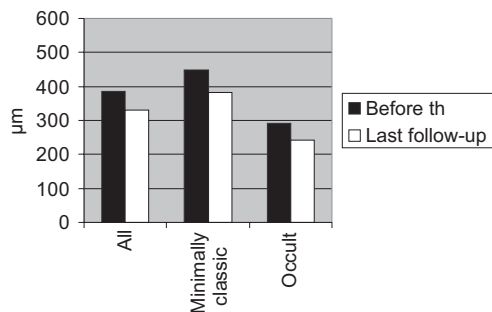


Figure 2. There was a significant mean decrease in central foveal thickness from baseline to the time of last follow-up visit of 53 µm ($p=0.03$). Patients with minimally classic membranes responded with even greater foveal thickness reduction than patients with occult membranes, 67 µm ($p=0.01$), 49 µm ($p=0.04$) respectively.

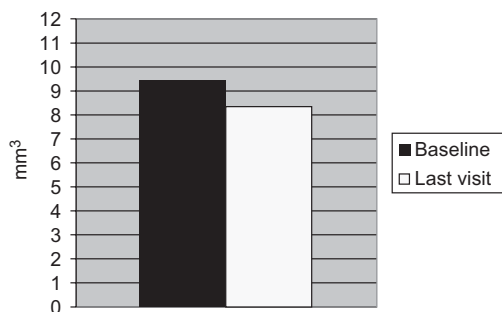


Figure 3. The mean macular volume at last follow-up decreased significantly for 1.04 mm³ ($p<0.001$) compared to baseline (9.39 mm³).

matous therapy, other than what they used previously for their preexisting glaucoma. No patient complained of significant vision blurring after bevacizumab injection and blurring resolved usually within few days. No major cataract progression was noted and only 2 patients underwent cataract extraction.

Discussion

We are not aware of any study combining intravitreal bevacizumab with verteporfin PDT in treatment of minimally classic and occult choroidal neovascularization secondary to AMD. As a matter of fact, there are only few studies evaluating efficiency of intravitreal bevacizumab given as monotherapy in treatment of exudative AMD.^{6,8,10} Since those studies clearly show significant improvement in visual acuity outcome, and since our own clinical experience confirms those finding, we tried to combine a regimen that would address our biggest clinical concern: minimally classic and occult subtype of the lesion. Even verteporfin studies¹⁻⁴ suggest that in the majority of patients with such subtypes of lesions, stabilization of visual acuity, rather than improvement can be expected. The probable reason for such an outcome can be explained by more difficult light activation of the drug absorbed by target tissue. Minimally classic and occult membranes are located more deeply than classical membranes and their exposure to the light is somewhat

blocked by blood, exudates and partially intact retinal pigment epithelium above them. In such lesions anti-VEGF substance may have better access to target structure by diffusion. It has been recently shown that although having a full length antibody structure, bevacizumab can penetrate full thickness retina.¹⁷ On the other hand, the classical component of the minimally classic lesion may already be fully established and hard to respond completely to the pharmacological treatment alone. Therefore, the rationale of combining two treatments is evident as they may be acting more synergistically in resolving the activity of the lesions. Since the half-life of bevacizumab is quite long,¹⁸ we though it would be appropriate to give bevacizumab in 6 weeks intervals as we do in monotherapy and reevaluate the treatment effect after 3 months following verteporfin PDT administration since repeated PDT treatment could be given every 3 months.

Also there have already been several clinical studies¹²⁻¹⁵ showing the synergistic positive effect of verteporfin and intravitreal triamcinolone when used in combination treatment of choroidal neovascularization due to AMD. Although the visual outcome after such combination treatment is significantly better when compared to baseline, it is even more of a benefit to have a reduced number of retreatments required to maintain such a result, for what effect additive role of triamcinolone has been suggested. When triamcinolone is given as monotherapy no significant and lasting improvement of visual acuity is achieved¹⁹. Since bevacizumab showed a clear effect of its own in improving visual outcome when given as monotherapy,⁶ it was our hypothesis that we could document an even greater visual acuity improvement if we would combine it with PDT. As the results of the verteporfin monotherapy¹⁻³ are so evident in classic lesion subtype, we thought it would be easier to evaluate additive effect of bevacizumab in a subgroup of lesions not so responsive to verteporfin monotherapy.⁴ It is even our impression from our own clinical experience that large minimally classic membranes respond better to intravitreal bevacizumab rather than verteporfin PDT, so we even recommend to our patients intravitreal beva-

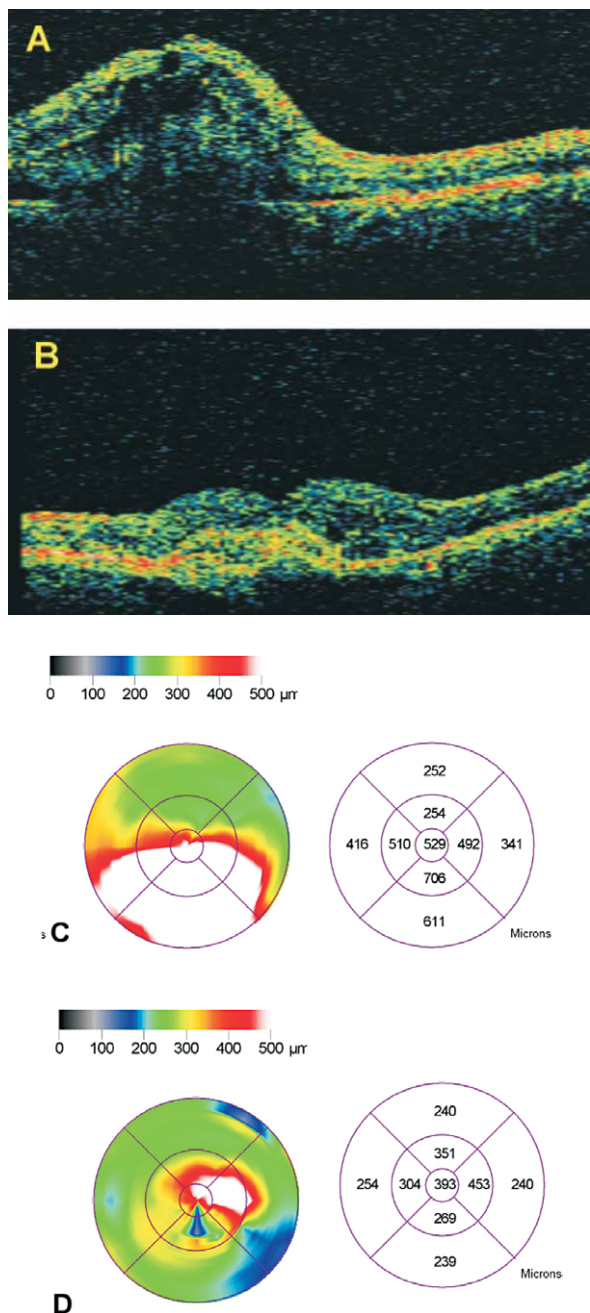


Figure 4. Before therapy a large minimally classic lesion shown on OCT scan before therapy (A), and 3 months after second treatment. Central foveal thickness decreased for 136 μm , while total macular volume decreased for 4.46 mm^3 , as is graphically shown by computer analysis (C, D). After 2 combination treatments visual acuity increased from 20/400 to 20/200 over 6 months.

cizumab over PDT in such lesions. The only difference we have noticed from our clinical practice, compared to this study, was in administration of bevacizumab when given as monotherapy. Several, (up to 6) intravitreal bevacizumab applications were usually needed to resolve the leakage if bevacizumab was given non-combined with PDT in treatment of such lesions.

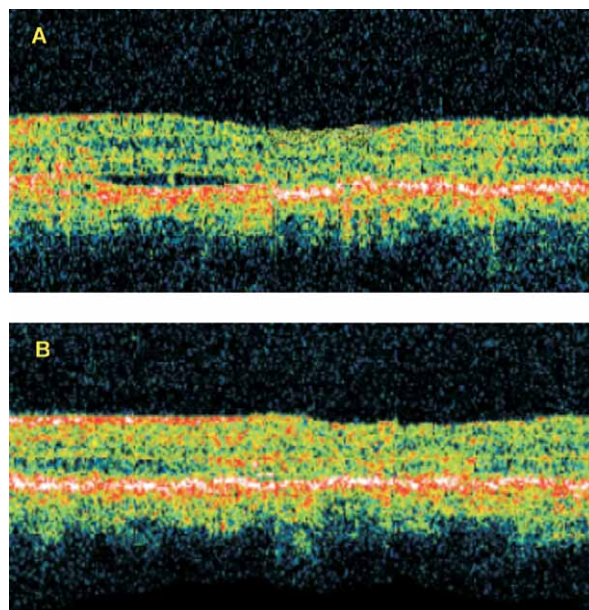


Figure 5. Before therapy a small lesion with subretinal exudation just beneath fovea as shown on OCT scan (A), and 3 months after treatment with complete resolution of subretinal fluid. Central foveal thickness decreased for 10 μm , while total macular volume decreased for 0.6 mm^3 . After combination treatment, visual acuity increased from 20/100 to 20/40 over 3 months.

The proposed dose of the intravitreal bevacizumab is very small of 1.25 mg (0.05 mL), and we have not experienced any problems with intraocular pressure raise. There is always a risk of endophthalmitis, but since no paracentesis was needed to control the eye pressure, the risk would have been even smaller. Also, the post-application time was well tolerated by patients, when compared to intravitreal triamcinolone, as bevacizumab is a clear solution, not responsible for vitreal staining.

Even in these subtypes (minimally classic and occult) of choroidal neovascularization due to AMD, we could isolate a subgroup of lesions of size smaller than 5000 μm , responding better to the treatment regimen, what reiterates the importance of early detection and early treatment initiation. This observation clearly shows the combined regimen acts as strong suppressant to choroidal neovascularization, but the damage occurring to the photoreceptor layer becomes irreversible with longer duration of the disease.

We find our study to be a pivotal study in evaluation of treatment results of combined verteporfin and bevacizumab, and further studies including more participants are needed to confirm our finding. Limitations of this study are clearly its interventional character, non-comparative nature and variability in follow-up. But the information provided could be used to design subsequent comparative prospective studies.

Regardless of whether bevacizumab survives the arrival of newer hopefully more potent antiVEGF inhibitors, some already in phase III of clinical trials, we are

sure that the main idea of this combination concept can be extrapolated to the newer antiVEGF substances, in case they prove more efficient than bevacizumab. But for now, we have a very limited pool of agents we can choose from in pharmacological treatment of exudative AMD.

As the need for more effective treatment regimen for neovascular AMD is growing, and the number of possible tools is getting wider, we may see more and more studies combining not only two therapeutic options, but rather 3 or even more. We may see maybe a combination of sev-

eral pharmacological approaches, including antiVEGF, anti-inflammatory (triamcinolone) and verteporfin PDT. The rationale is there as the complexity of pathophysiology of exudative AMD is evident.

So our results, showing improvement not only in visual acuity but also in macular morphological indices in minimally classic and occult lesions, are clearly consistent with our hypothesis that in future, the treatment modalities for exudative AMD will involve combined approaches, at least for some time.

REFERENCES

1. TREATMENT OF AGE-RELATED MACULAR DEGENERATION WITH PHOTODYNAMIC THERAPY (TAP) STUDY GROUP, Arch Ophthalmol, 117(1999) 1329. — 2. TREATMENT OF AGE-RELATED MACULAR DEGENERATION WITH PHOTODYNAMIC THERAPY (TAP) STUDY GROUP, Arch Ophthalmol, 119 (2001) 198. — 3. WORMALD R, EVANS J, SMEETH L, HENSHAW K, Cochrane Database Syst Rev, CD002030 (2003). — 4. Verteporfin in Photodynamic Therapy Study Group, Am J Ophthalmol, 131 (2001) 541. — 5. AZAB M, BOYER DS, BRESSLER NM, BRESSLER SB, Arch Ophthalmol, 123 (2005) 448. — 6. AVERY RL, PIERAMICI DJ, RABENA MD, Ophthalmology, 113 (2006) 363. — 7. GRAGOUDAS ES, ADAMIS AP, CUNNINGHAM ET JR, N Engl J Med, 351 (2004) 2805. — 8. MICHELS S, ROSENFELD PJ, PULIAFITO CA, Ophthalmology, 112 (2005) 1035. — 9. NGUYEN QD, SHAH S, TATLIPINAR S, Br J Ophthalmol., 89 (2005) 1368. — 10. ROSENFELD PJ, MOSHFEGHI AA, PULIAFITO CA, Ophthalmic Surg Lasers Imaging, 36 (2005) 331. — 11. HEAR, MARSHALL J, Clin Adv Hematol Oncol., 3 (2005) 555. — 12. AUGUSTIN AJ, SCHMIDT-ERFURTH U, Ophthalmology, 113 (2006) 14. — 13. SPAIDE RF, SORENSON J, MARRANAN L. Ophthalmology, 110 (2003) 1517. — 14. JONAS JB, KREISSIG I, HUGGER P, Br J Ophthalmol, 87 (2003) 462. — 15. PENFOLD PL, GYORY J, HUNYOUR A, BILLSON FA, Aust N Z J Ophthalmol, 23 (1995) 293. — 16. SCHMIDT-ERFURTH U, SCHLOTZER-SCHREHARD U, CURSIEFEN C, Invest Ophthalmol Vis Sci, 44 (2003) 4473. — 17. SHAHAR J, AVERY RL, HEILWEIL G, Retina, 26 (2006) 262. — 18. IGNOFFO RJ, Am J Health Syst Pharm, 61 Suppl (2004) 21. — 19. GILLIES MC, SIMPSON JM, LUO W, Arch Ophthalmol, 121 (2003) 667.

R. Lazić

Eye Clinic »Sujetlost«, Bukovačka 27, 10000 Zagreb, Croatia
e-mail: ratimir.lazic@svjetlost.hr

FOTODINAMSKA TERAPIJA KOMBINIRANA SA INTRAVITREALNIM BEVACIZUMABOM U LIJEČENJU KOROIDALNE NEOVASKULARIZACIJE U SKLOPU SENILNE MAKULARNE DEGENERACIJE

SAŽETAK

Istražiti učinkovitost fotodinamske terapije verteporfinom kombinirane sa intravitrealnim bevacizumabom u liječenju minimalno klasične i okluzne koroidalne neovaskularizacije u sklopu senilne makularne degeneracije. 46 očiju 46-tero pacijenata (prosječna dob 74.5) u prospektivnoj, nekomparativnoj, intervencijskoj seriji prećenih tijekom mediana od 24 tjedna (3–32). Fotodinamska terapija verteporfinom kombinirana je sa intravitrealno primjenjenih 0.05 mL (1.25 mg) bevacizumaba unutar 24 h te ponovo nakon 6 tjedana. Cijeli kombinirani postupak ponavljan je u tromjesečnim intervalima u slučaju eksudacije. Vidna oština (VA) poboljšana je u većine pacijenata (početna VA 1.041 log MAR) za 1.45 liniju (zadnja kontrola) ($p=0.001$). Središnja fovealna debljina (CFT) i ukupni makularni volumen (TMV) smanjen je za $53\mu\text{m}$ ($p=0.03$) i 1.04 mm^3 ($p<0.001$). Značajne komplikacije nisu zabilježene. Kombinirani pristup može poboljšati ishod liječenja. Značajno poboljšanje VA, CFT i TMA je zabilježeno u većine pacijenata i održavano tijekom praćenja.