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**SHORT COMMUNICATION**

# Single-session photodynamic therapy combined with intravitreal bevacizumab for neovascular age-related macular degeneration

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PURPOSE. *To evaluate the efficacy of combined single-session photodynamic therapy (PDT) and intravitreal bevacizumab (IVB) for treatment of neovascular age-related macular degeneration (AMD).*
METHODS. *In a prospective interventional case series, patients with subfoveal choroidal neovascularization (CNV) underwent PDT followed by 1.25 mg IVB injection. Best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) measurements were repeated at 6-week intervals and fluorescein angiography was performed after 12 weeks and when considered necessary thereafter. Repeat injections of IVB were performed based on fluorescein angiographic evidence of CNV leakage.*
RESULTS. *Fourteen eyes were included in this study. Mean follow-up was 52.4±15.2 weeks (range: 26–74 weeks). Initially, mean BCVA was 0.80±0.42 logMAR and mean central macular thickness (CMT) was 308±88 μm. At week 12, BCVA improved to 0.62±0.47 logMAR (p=0.006) and CMT reduced to 186±53 μm (p=0.003). Corresponding results were 0.53±0.52 logMAR (p=0.02) and 193±78 μm (p=0.002) after 24 weeks. A second IVB injection was performed in 13 eyes with a mean interval of 16.3±5.9 weeks.*
CONCLUSIONS. *Combination therapy with single-session PDT and IVB can improve vision and reduce CMT in neovascular AMD. Repeat IVB injections may maintain the visual gain from the initial combination therapy. (Eur J Ophthalmol 2008; 18: 297-300)*

KEY WORDS. *Age-related macular degeneration, Bevacizumab, Combination therapy, Macular disease, Photodynamic therapy*

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## INTRODUCTION

Photodynamic therapy (PDT) is a US Food and Drug Administration–approved treatment for neovascular age-related macular degeneration (AMD). Visual improvement, however, seldom occurs after PDT (1, 2). Other drawbacks of this treatment modality include the need for retreatments with possible adverse effects on the choroidal vasculature (3-5) and cost. Bevacizumab is a full-length humanized anti-VEGF antibody, which has recently gained popularity for treatment of neovascular AMD. Intravitreal injection of bevacizumab may improve visual acuity, decrease retinal thickness, and reduce angiographic leakage in AMD (6). Monotherapy with bevacizumab, however, necessitates multiple intravitreal injections within 4- to 6-week intervals and each injection carries the risk of serious complications. It has been suggested that antiangiogenic drugs may be combined with PDT as an effective treatment for neovascular AMD (7, 8). We performed a prospective study to evaluate the results of a new treatment approach consisting of single-session PDT and intravitreal bevacizumab (IVB) as initial pulse treatment and repeated IVB injections as maintenance therapy for neovascular AMD.

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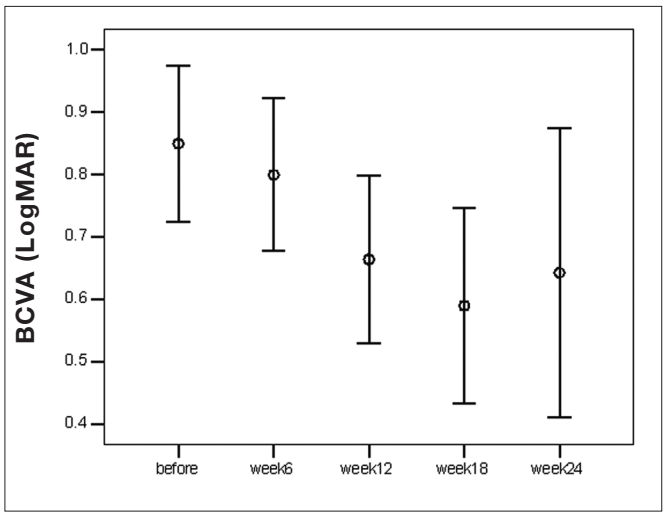


**Fig. 1 -** *Significant visual improvement occurred after 12 weeks and persisted during the follow-up period.*

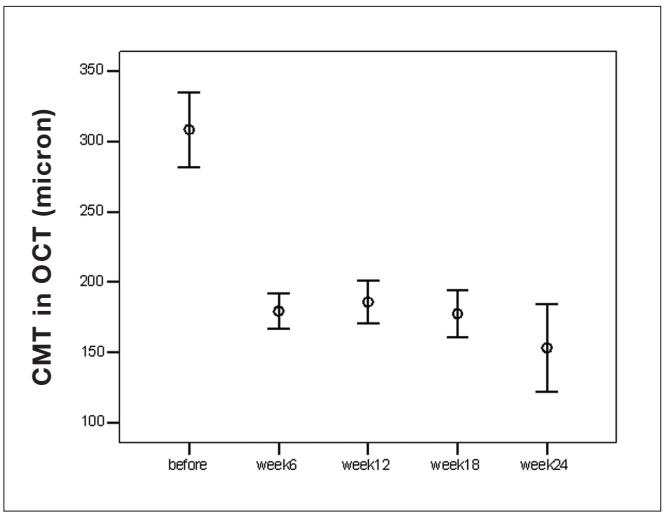


**Fig. 2 -** *Significant reduction of central macular thickness was observed at week 6 and continued during the follow-up.*

## METHODS

The study was a prospective interventional case series. The IRB approved the study protocol. Eyes with all types of active subfoveal choroidal neovascularization (CNV) due to AMD were included in this study. Exclusion criteria were glaucoma, diabetic retinopathy, any macular disorder other than AMD, and previous treatment for CNV. Photodynamic therapy with verteporfin was performed according to the standard regimen. Forty-eight hours after PDT, 1.25 mg of bevacizumab (Avastin made for F. Hoffmann-La Roche Ltd. Basel, Switzerland, by Genentech, Inc., San Francisco, CA) was injected intravitreally under sterile conditions. Patients were examined 1 day and 1 week after injection and were scheduled for follow-up visits at 6-week intervals.

Preoperative evaluations consisted of best-corrected visual acuity (BCVA) assessment using the Snellen chart, color fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT). Best-corrected visual acuity assessment was recorded in logMAR. Evaluation of BCVA and OCT was repeated every 6 weeks. Fluorescein angiography was repeated at week 12 and when considered necessary thereafter. Fluorescein angiography was considered necessary when the patient complained of increased metamorphopsia and/or decreased vision. The other reasons for performing FA were ophthalmoscopic findings such as subretinal blood and neurosensory detachment. Increased CMT thickness in OCT equal to or more than 50 μm was also an indication for repeating fluorescein angiography. CNV activity was defined as the presence of leakage from the CNV on fluorescein angiography. Eyes with active CNV underwent repeat intravitreal injection of 1.25 mg bevacizumab. Repeat PDT was not considered in the protocol. A paired *t*-test was used to compare findings before and after treatment.

## RESULTS

Fourteen eyes of 14 patients (6 male, 8 female) with a mean age of 71±8.2 years were included. Mean follow-up period was 52.4±15.2 weeks. All eyes were naïve to any form of treatment at the time of presentation. Lesion type was predominantly classic in six eyes, minimally classic in three eyes, occult in three eyes, and retinal angiomatous proliferation (RAP) in two eyes. Mean BCVA was 0.80±0.42 logMAR before treatment. BCVA improved to 0.62±0.47 logMAR at week 12 after treatment (p=0.006). Further improvement to 0.57±0.47 logMAR (p=0.009) and 0.53±0.52 logMAR (p=0.02) was observed at weeks 18 and 24, respectively. BCVA improved in 9 eyes (64.3%) and

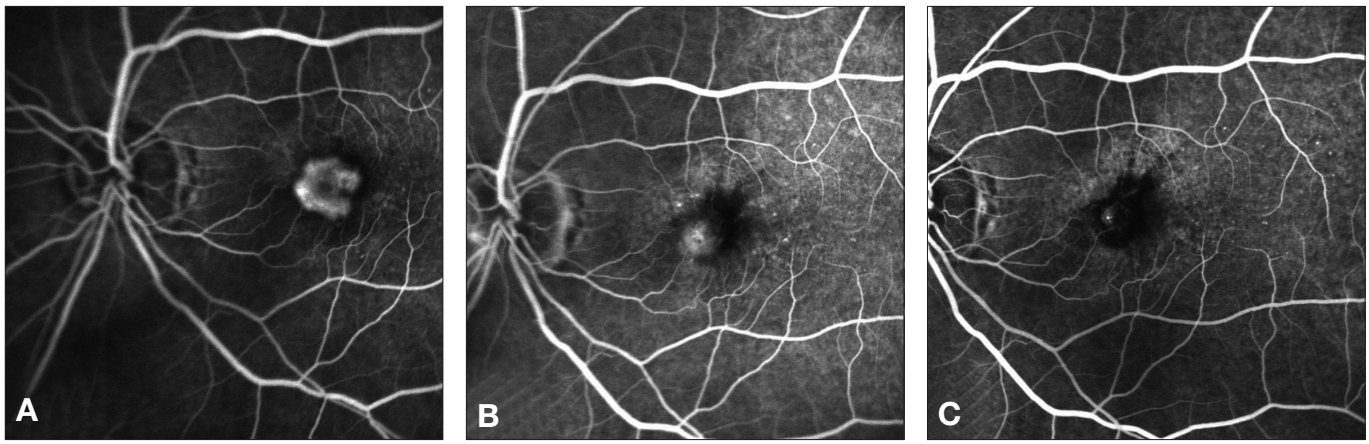


**Fig. 3 - (A)** *Fluorescein angiogram of the left eye of a 73-year-old woman revealed leakage consistent with classic subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration. Visual acuity (VA) was 20/200. Combined photodynamic therapy and intravitreal bevacizumab was performed and VA improved to 20/60 3 months later.* **(B)** *Five months later, VA decreased again and fluorescein angiography revealed recurrence of CNV leakage. Intravitreal injection of bevacizumab was repeated which resulted in visual improvement to 20/40.* **(C)** *Eighteen months after initial treatment, VA was 20/30 and no leakage was noted on fluorescein angiography.*

remained unchanged in 5 eyes (35.7%) 12 weeks after initial therapy. Corresponding figures were 11 eyes (78.6%) and 2 eyes (14.3%), respectively, 24 weeks after intervention. Decreased visual acuity was observed in 1 eye (7.1%) at week 24. Mean central macular thickness (CMT) was 308±88 µm prior to treatment. Mean CMT reduced to 179±43 µm ($p<0.001$) at week 6. Mean CMT was 186±53 µm ($p=0.003$) at week 12 and 193 ± 78 µm ($p=0.002$) at week 24. Visual improvement and CMT reduction persisted during the follow-up period (Figs. 1 and 2). A second intravitreal injection of bevacizumab was required in 13 eyes (92.8%), a third injection was performed in 6 eyes (42.8%), and a fourth injection was needed in 2 eyes (14.3%). The mean interval between the first and second injections and between the second and third injections was 16.3±5.9 weeks (range: 12 to 28 weeks) and 20.8±10.3 weeks (range: 10 to 37 weeks), respectively. The intervals between the third and fourth injections were 8 and 12 weeks. No adverse ocular or systemic events were observed during the follow-up period. Figure 3 presents the fluorescein angiograms of a representative case.

## DISCUSSION

In this case series, a combination of single-session PDT and IVB was used as pulse therapy for neovascular AMD, which resulted in visual improvement in the majority of cases and stabilization of vision in others after 24 weeks. This treatment effect was maintained with repeated injections of IVB. The average interval between the first and second treatment sessions was about 14 weeks which may reflect less need for retreatment following the initial pulse therapy.

Combination of PDT and intravitreal bevacizumab for neovascular AMD may lead to augmentation of beneficial effects of either treatment modality and reduce the risks of retreatment. Use of an antiangiogenic drug can reduce adverse effects of PDT-induced overexpression of VEGF. On the other hand, PDT may disrupt the architecture of CNV and help the antiangiogenic drug to affect the lesion more efficiently (7).

Dhalla et al reported the 7-month results of combined photodynamic therapy and IVB for CNV secondary to AMD (7). Visual acuity stabilization was observed in 83% and improvement was noticed in 67%. Retreatment was needed in 37% of their cases. Costa et al performed intravitreal injection of bevacizumab 1 week after PDT (8). The change in BCVA from baseline was significant at 12 weeks. Retreatment was required in 63.6% of cases at week 24 due to recurrent fluorescein leakage. Retreatment consisted of combined PDT and bevacizumab in these two case series. Lazic and Gabric evaluated the efficacy of PDT combined with intravitreal bevacizumab in comparison with monotherapies with a single PDT session or a single admin-

istration of IVB. In the combined group, bevacizumab was injected within 1 hour of PDT. The authors observed significant visual improvement after 1 month and its maintenance over a 3-month period following combined therapy with PDT and intravitreal bevacizumab (9).

Avoiding repeated PDT has been one of the principal goals of our treatment strategy. We limited PDT to one session for two reasons: 1) to decrease the cost of therapy and 2) to reduce potential damage to normal choroidal vasculature which is presumed to be cumulative (3-5). The rationale for single-session PDT emanates from the present knowledge regarding the possible adverse effects of repeat PDT on the physiologic choroid (3-5). In a study by Schmidt-Erfurth et al, the effects of multiple-PDT regimen were evaluated (5). Persistent hypofluorescence was documented in all patients after the second and third PDT. Quantitative analysis showed 25% enlargement in the hypofluorescent area 1 week after the second session of PDT compared to the first (4). In addition, multiple sessions of PDT may accelerate the risk of CNV recurrence due to aggravation of choroidal ischemia and subsequent overexpression of VEGF (4).

In conclusion, our preliminary results show that combined single-session PDT and intravitreal bevacizumab can lead to visual improvement or stabilization in eyes with neovascular AMD. Repeated IVB injections may maintain the visual gain. Larger studies are required to confirm the encouraging results of this study.

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