

# Quadruple Therapy Leads to a Sustained Improvement of Vision in Patients with Wet Age-Related Macular Degeneration

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## Key Words

Combined intravitreal therapy · Photodynamic therapy · Age-related macular degeneration, wet · Choroidal neovascularization

## Abstract

**Aim:** To investigate the efficacy of a combined intravitreal therapy with prior photodynamic therapy (PDT) in patients with wet age-related macular degeneration. **Methods:** Fifty-two patients (mean age: 72.7 years) with predominantly classic choroidal neovascularization received low-fluence PDT (42 J/cm<sup>2</sup> for 72 s), followed 24 h later by a 0.4-ml core pars plana vitrectomy with intravitreal injection of dexamethasone (0.8 mg) and bevacizumab (1.25 mg). The best-corrected visual acuity (BCVA; 6 m Snellen), central macular thickness (optical coherence tomography), intraocular pressure and the need for retreatment were assessed. **Results:** BCVA changed significantly (vs. baseline) at 3 months (+0.11), 9 months (+0.19) and 14 months (+0.16). At the end of the follow-up period, BCVA had improved by >0.1 in the majority of the patients (72.9%), and the mean central retinal thickness had decreased by –44.3% (–211 μm). The retreatment rate was 25%. No increase in intraocular pressure or other

adverse event was reported. **Conclusions:** The pharmacological effects of the drugs, the low-fluence PDT, and the physiological effects of the therapy may have contributed to the sustainability of the therapeutic benefits.

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## Introduction

The pathophysiological processes that lead to choroidal neovascularization (CNV) in patients with age-related macular degeneration (AMD) are highly diverse. Correspondingly, current therapeutic strategies aim at multiple etiological mechanisms. The inhibition of vascular endothelial growth factor (VEGF), a potent proangiogenic and edematous growth factor, using recombinant monoclonal antibodies has revolutionized the way exudative AMD is treated. The sustained application of VEGF inhibitors, however, carries a higher risk of endophthalmitis and may prove financially prohibitive for some patients [1]. Moreover, if therapy with VEGF inhibitors is stopped or interrupted, visual acuity returns to baseline levels [2], and CNV may recur [3]. The efficacy in terms of preventing CNV also appears to generally

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0030-3755/11/2262-0045\$38.00/0

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decline with longer duration of therapy [4]. Therefore, monotherapy with VEGF inhibitors may ultimately be less beneficial in the treatment of CNV.

Combination therapy aims not only at the prevention of angiogenesis but also at the regression of existing CNV by using multiple pharmacological agents, which work synergistically and typically include the VEGF inhibitor bevacizumab [5, 6]. Recently, Augustin et al. [7] evaluated a combination of photodynamic therapy (PDT) with verteporfin and intravitreal treatment with bevacizumab and dexamethasone in patients with CNV secondary to AMD. While the combination therapy included a limited core pars plana vitrectomy, the role of the vitrectomy in treating CNV was considered negligible by the authors. There is, however, reason to believe that physiological changes induced by a limited (or full) vitrectomy may exert a beneficial therapeutic effect. Vitrectomy was shown to increase intraocular oxygen tension [8, 9], which in turn affects retinal oxygenation [10]. By reducing the viscosity in the vitreous cavity, either by a full or limited vitrectomy, VEGF may diffuse away from the retina. Thus, vitrectomy may also physically remove the angiogenic growth factor from the intraocular cavity.

The presence of vitreous attachment to the macula was suggested to be a possible risk factor for neovascular AMD by perpetuating macular exposure to inflammatory cytokines or free radicals and by interfering with macular oxygenation [11–13]. It is likely that vitreous attachment, through the same mechanisms, also contributes to angiogenesis. We hypothesize that a partial core vitrectomy facilitates posterior vitreous detachment. Consequently, posterior vitreous detachment induced by vitrectomy, in combination with pharmacological agents, may promote neovascular regression.

In this study of a case series, we investigated the effects of an intravitreal combination therapy in patients with wet AMD and predominantly classic CNV. A PDT using low-fluence verteporfin was applied, and a limited core vitrectomy was performed in combination with intravitreal treatment using bevacizumab and dexamethasone.

## Methods

### *Study Design and Patients*

This retrospective study of a case series was conducted in accordance with the European Guidelines for Good Clinical Practice and the Declaration of Helsinki approved by the local Institutional Review Board and officially registered with www.clinicaltrials.gov (NCT00805649) during April 2007 and March

2010. Informed consent was obtained from all patients before the start of therapy. Patients with wet AMD who were more than 45 years old were included if they had a CNV between 1 and 6 mm in size (at the greatest extension) underneath the geometric center of the fovea and if they had a baseline visual acuity of 0.5–0.02. Patients were excluded from the study if they had a history of prior vitreoretinal surgery, neovascular retinopathy, glaucoma, ocular hypertension or optic neuropathy.

### *Pharmacosurgery*

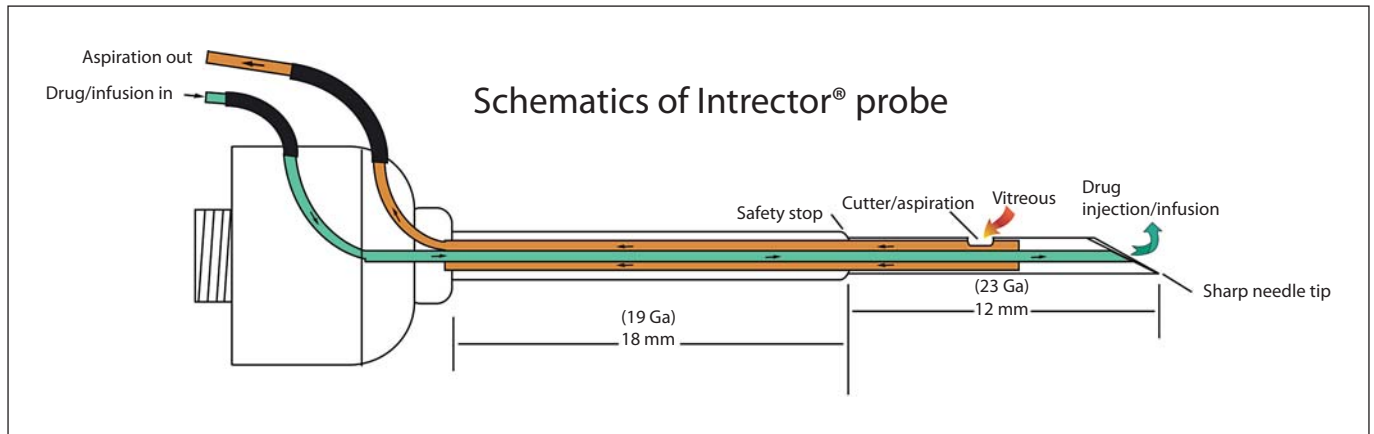
A PDT with verteporfin (Visudyne, Novartis, Basel, Switzerland) was performed in accordance with the recommendations of the manufacturer, except for the duration of light exposure, which was shortened to 70 s, thus yielding a total dose of 42 J/cm<sup>2</sup> (low-fluence PDT regimen). The low-fluence PDT regimen was used in a theoretical attempt to increase the selectivity of the PDT treatment effect and to minimize the inflammatory component of the PDT treatment reaction, as suggested by recent publications [7, 14]. The potential benefits of the low-fluence PDT are based on the hypothesis that, with the standard light fluence rate, the tissue oxygen concentration determines the rate of the photochemical reaction within the area of light application. If oxygen is at similar concentrations in the CNV, choriocapillaris and adjacent tissues, application of light would not result in selectivity of treatment. With reduced-fluence PDT, the delivery of light photons becomes the rate-determining step in the photochemical reaction, and so selective accumulation of verteporfin in the CNV would result in selective treatment in the CNV and lessen effects in the choriocapillaris and pigment epithelial cells.

One day after PDT, a limited core pars plana vitrectomy was carried out using the Intretractor® (Insight Instruments, Stuart, Fla., USA), which has 2 separate channels for aspiration and infusion (fig. 1). After displacement of the conjunctiva via an oblique sclerotomy (fig. 2), 0.4 ml of vitreous was aspirated. The solution used for infusion contained 0.8 mg (0.3 ml) dexamethasone (Dexa-ratiopharm®, Ulm, Germany), and 1.25 mg (0.1 ml) bevacizumab (Avastin®, Genentech, San Francisco, Calif., USA). This therapeutic approach, which combines the treatments PDT, core vitrectomy and injection of dexamethasone and bevacizumab, is referred to as ‘quadruple therapy’ in the following.

Patients were considered for retreatment using the combined intravitreal therapy if there was angiographic evidence of macular edema or leakage from CNV lesions.

### *Measurements*

At baseline (T0) and at all scheduled follow-up visits, i.e. at 3 (T1), 9 (T2) and 14 (T3) months after initial pharmacosurgery, an ophthalmic examination including slit lamp biomicroscopy and funduscopy was performed, the best-corrected visual acuity (BCVA) was assessed using 6-meter Snellen charts, the intraocular pressure was measured using Goldmann applanation tonometry, and the central foveal thickness was determined by optical coherence tomography (Stratus OCT, Carl Zeiss Meditec, Santa Ana, Calif., USA). Fluorescein angiography was used to determine the lesion type, the location, and the presence or absence of active CNV leakage. Fluorescein angiograms were interpreted by 1 of 2 experienced vitreoretinal specialists (F.H.K.). In addition, the need for retreatment was assessed, and adverse events were monitored.



**Fig. 1.** Representation of the 23-gauge Intrektor.

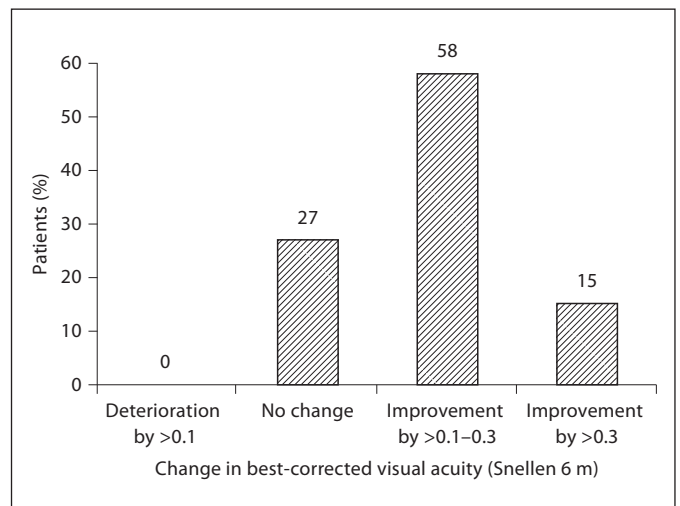
#### Data Analysis

The primary outcome measures were BCVA, central macular thickness and retreatment rate. For statistical analysis, the Excel F (Microsoft, Richmond, Va., USA) and BiAS software (version 8.2 for Windows, Epsilon-Verlag, Darmstadt, Germany) were used. Nonnormally distributed data were analyzed using David's test. The median change in BCVA and central retinal thickness from baseline to each follow-up visit was analyzed using the Wilcoxon matched-pairs test.

#### Results

A total of 52 patients were included in the study. The mean age of the patients was 72.7 years, and 30.8% (16/52) of the patients were male. Three patients had previously undergone a course of PDT. At baseline, 30 of 52 (57.7%) eyes were pseudophakic, and 22 (42.3%) were phakic. Seven patients with phakic lens status had senile minimal nuclear sclerotic cataracts. None of the cataracts, however, was felt to be clinically significant as per the results of the slit lamp examination. Follow-up examinations were performed on average ( $\pm$ SD) at 3.1 months ( $\pm$ 12 days), 9.3 months ( $\pm$ 14 days) and 13.8 months ( $\pm$ 23 days) after the initial pharmacotherapy. The follow-up rate was 100% (52/52) at 3 months, 98% (51/52) at 9 months and 92.3% (48/52) at 14 months.

At baseline, the mean lesion size was 3,073  $\mu$ m, and the mean BCVA was 0.13 Snellen lines. The mean BCVA increased at 3 months by +0.11, at 9 months by +0.19 and at 14 months by +0.16 Snellen lines after initial treatment. At the end of the follow-up period, i.e. at 14 months, none of the patients had experienced a deterioration of BCVA



**Fig. 2.** Proportion of patients with an improvement or deterioration of the BCVA 14 months after therapy. Patients with AMD and predominantly classic CNV ( $n = 52$ ) were treated using PDT and combined intravitreal therapy (core vitrectomy, bevacizumab and dexamethasone).

as compared with baseline (fig. 2). While BCVA was maintained in 13 of 48 (27.1%) patients, BCVA improved in the majority of the patients by +0.1 Snellen lines (28 of 48; 58.3%) or more than 0.3 Snellen lines (7 of 48; 14.6%). The mean central retinal thickness decreased by -44.3% (-211  $\mu$ m) over 14 months.

The quadruple therapy regimen was repeated in 13 of the 52 (25%) patients at 9.5 months after the initial pharmacotherapy. Two patients underwent cataract surgery at 8.9 months; while BCVA remained stable in 1 of the 2 pa-

tients, it decreased in the other patient from 0.3 to 0.15 Snellen lines. No significant change in intraocular pressure was observed throughout the study (14.4 mm Hg at baseline vs. 14.8 mm Hg at the end of the follow-up period), and no other adverse event was reported.

There was no statistically significant change in the frequency of cataracts from baseline to 14 months. While the number of patients with an intraocular lens increased from 30 to 32, the number of patients with an incipient cataract decreased from 22 to 20.

## Discussion

The Treatment of AMD with Photodynamic Therapy study and the Verteporfin in Photodynamic Therapy study showed that PDT significantly prevents loss of vision in eyes with predominantly classic CNV [15] and in eyes with occult CNV [16]. In the present study, we applied PDT in combination with an intravitreal treatment using dexamethasone and bevacizumab. There was a sustained and statistically significant increase in BCVA from baseline up to 9 months after initial treatment. Thereafter, BCVA remained stable up to the end of the follow-up period (14 months). Despite the slight tapering off of the therapeutic efficacy, well over 50% of the patients experienced an improvement in vision by +0.1 Snellen lines, and 15% of the patients gained more than 0.3 Snellen lines at 14 months. At the same time, central macular thickness significantly decreased from baseline to 9 months and subsequently slightly increased but essentially remained at a significantly reduced level as compared with baseline.

Given the multifactorial pathophysiology of AMD, it is possible that the plateau effect beginning at about 9 months after the initial treatment is a result of the pharmacokinetic characteristics of the intravitreal medications. While oxidative stress, age-related microstructural changes and the subsequent inflammatory response in AMD continue, the concentrations of the corticosteroid and the VEGF inhibitor decrease and the therapeutic effects weaken [17]. Nevertheless, at 14 months in this study, BCVA had improved on average by 1.6 lines as compared with baseline. Overall, the improvement in vision observed compares well with the results of recent clinical studies using intravitreal ranibizumab in patients with CNV secondary to AMD [18, 19].

While this combination therapy yields results in a patient collective that represents day-to-day AMD patients without clinical trial preselection and is still comparable

with bevacizumab or ranibizumab monotherapy, this study also shows that significantly fewer intravitreal injections and follow-up monitoring are required, when compared to estimated 8.1 injections of ranibizumab monotherapy [20]. The combination therapy was repeated, due to persistent or recurrent CNV, in 25% of the patients after 9 months. Moreover, there were no intraocular pressure increases and no other adverse events, which underlines the favorable safety profile of the intravitreal combination therapy.

In terms of the primary outcome measures BCVA and macular thickness, our study also compared well with a recent study by Augustin et al. [7], which also combined PDT with a limited core pars plana vitrectomy and intravitreal injections of bevacizumab and dexamethasone. However, the average follow-up period was shorter (40 weeks; range: 22–60 weeks) than in the present study (14 months).

While Augustin et al. [7] did not consider that the vitrectomy played an important role in the combination therapy, there are multiple possible mechanisms by which a limited or full vitrectomy may indeed contribute to the resolution of neovascularization in AMD. Vitrectomy may induce a posterior vitreous detachment, which has the effect of decreasing viscosity anterior to the retina. Similarly, a full vitrectomy or our limited vitrectomy with repetition of the modality (in 25% of cases) may enhance liquefaction in the vitreous cavity [21]. The flow of molecules (flux) in the vitreous cavity is dictated by Fick's law for diffusion, i.e. the flux increases with decreasing viscosity. Therefore, the removal of vitreous gel facilitates the diffusion of angiogenic molecules away from the retina [22].

A recent case report on a patient with AMD describes the regression of macular drusen and the occurrence of pigment epithelial detachment after vitrectomy [23]. The results suggested that posterior vitreous detachment may provide prophylactic benefit against the development of exudative AMD. Similar conclusions were drawn in a study that examined the incidence of posterior vitreous detachment in an otherwise matched cohort of eyes with AMD [11–13]. The authors pointed out that persistent posterior vitreous attachment may induce chronic low-grade inflammation, may prevent sufficient diffusion of oxygen and nutrients to macular cells, and may confine angiogenic cytokines to the macular region. We suppose that posterior vitreous detachment and the subsequent mechanical and physiological changes induced at the macula may complement the effects of pharmacotherapeutics in the treatment of CNV, similar to the ongoing

clinical trial on intravitreal microplasmin in subjects with AMD with focal vitreomacular adhesion (MIVI5, NCT00913744).

Thickening of Bruch's membrane in AMD decreases the diffusion of oxygen from the choriocapillaris to the retinal pigment epithelium [24, 25]. Although the hypoxia caused by changes in the choriocapillaris and Bruch's membrane in AMD has not been shown to play a causative role in CNV formation, it was hypothesized that outer retinal hypoxia in AMD may indirectly provide a stimulus for angiogenesis [26, 27]. Under hypoxic conditions certain isoforms of VEGF were shown to be upregulated in the retinal pigment epithelium and in CNV [28]. Vitrectomy leads to a significant increase in intraocular oxygen tension [29]. It was previously shown that the retina can be oxygenated from the vitreous cavity [26, 27], and that increased oxygenation of ischemic retina reduces VEGF production [30]. We therefore hypothesize that vitrectomy may have a role in relieving the hypoxic stimulus that may contribute to the VEGF production in neovascular AMD.

In the present study, the partial vitrectomy was carried out using a hand-held, sutureless 23-gauge vitrector with 2 channels for simultaneous aspiration and infusion (Intrector). Since the instrument is portable, the limited vitrectomy can be performed using a slit lamp without the need to perform the vitrectomy in the operating room. When performing vitrectomy, particularly in elderly patients, there is commonly a significant risk of inducing cataracts. In this study, there was no statistically signifi-

cant change in the frequency of cataracts from baseline to 14 months. It should be noted, however, that, since the degree of cataract was not determined at baseline, cataracts may have progressed throughout the course of the study.

A limitation of our study was that the study design did not include a control group. Moreover, given the relatively low number of patients studied, the study was not sufficiently powered to detect significant correlations with regard to complications such as cataract progression. In future studies, a larger number of patients should be included, cataracts should be graded at baseline and subsequent visits, and vitreous attachment should be examined using optical coherence tomography.

Despite the limitations in study design, the results of the present study clearly support the conclusion that, in patients with classic CNV secondary to AMD, the combination therapy including a vitrectomy and intravitreal treatment using bevacizumab and dexamethasone yields results well comparable with those of the monotherapy with bevacizumab, while exposing patients to significantly fewer intraocular interventions.

## Disclosure Statement

F.H.K. declares a potential conflict of interest in the subject matter presented. He has received funding from Insight Instruments, Stuart, Fla., USA, for travel expenses with regard to scientific meetings and conferences. All remaining authors have no conflict of interest in the subject matter presented.

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