

# Combined Intravitreal Pharmacosurgery in Patients with Occult Choroidal Neovascularization Secondary to Wet Age-Related Macular Degeneration

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## Key Words

Age-related macular degeneration · Bevacizumab · Occult choroidal neovascularization · Triamcinolone · Limited vitrectomy

## Abstract

**Aim:** The aim was to investigate the efficacy and safety of combined intravitreal therapy in patients with occult choroidal neovascularization (CNV) secondary to wet age-related macular degeneration (AMD) over 6 months. **Methods:** In this prospective pilot study of a case series, 106 patients (mean age 75.4 years) with predominantly occult CNVs were treated with a 1.5-ml core pars plana vitrectomy with intravitreal injections of triamcinolone (8 mg), bevacizumab (1.25 mg) and balanced salt solution. The best-corrected visual acuity (BCVA; logMar), central macular thickness (optical coherence tomography), and intraocular pressure (IOP; Goldmann tonometry) were assessed at baseline and follow-up visits. **Results:** Statistically significant increases in BCVA (vs. baseline) were observed at 2 months (mean +0.9; standard deviation  $\pm 0.6$  lines), 4 months (+1.3;  $\pm 0.7$ ), and 6 months (+1.2;  $\pm 0.7$ ) after the initial combined intravitreal therapy in 96/106 patients. At 6 months, BCVA had deteriorated in 20 of 96 (20.8%) patients by  $< 2.5$  lines, remained stable in 38 of 96 (39.6%) and improved in 31 (32.3%) patients by 1–3 lines, and in 7 (7.3%) patients by  $> 3$  lines. The mean central retinal thickness decreased by  $-41.2\%$  ( $-195$ ;  $\pm 46$   $\mu\text{m}$ ) over 6 months. 55% demanded intravitreal anti-vascular endothe-

lial growth factor (VEGF) treatment after initial therapy. Increases in IOP were managed by eye drops in 11 (10%) patients with no other adverse event occurring. **Conclusion:** After the combined intravitreal therapy, including two drugs and a limited core vitrectomy, a significant and sustained improvement in vision of patients with occult CNVs was observed over 6 months. In 45% of the initially treated patients, anti-VEGF therapy did not have to be continued, which might be attributed to both the pharmacological effects of the drugs and the physiological changes induced by the vitrectomy (posterior vitreous detachment, liquefaction, and oxygen redistribution).

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## Introduction

In patients with age-related macular degeneration (AMD), choroidal neovascularization (CNV) occurs as a result of highly diverse pathophysiological processes, and the underlying pathogenesis is still unclear. Accordingly, current therapeutic approaches target various etiological mechanisms. Recombinant monoclonal antibodies inhibiting the vascular endothelial growth factor (VEGF), i.e., a potent pro-angiogenic and edematous growth factor, have been successfully applied in the treatment of exudative AMD. If the therapy with VEGF inhibitors is discontinued temporarily or permanently, however, visual acuity may deteriorate again and CNV may recur [1, 2]. While

long-term therapy with VEGF inhibitors may prove financially prohibitive for some patient groups, an increased risk of endophthalmitis was also noted [3]. Since there is also the possibility that the efficacy in terms of preventing CNV appears to decrease over time, monotherapy with anti-VEGF drugs may ultimately not represent the optimum choice for the long-term treatment of CNV [4].

The use of a combination of multiple synergistic pharmacological agents offers an alternative therapeutic approach not only for preventing angiogenesis but also for treating existing CNV [5]. A combination therapy including photodynamic therapy with verteporfin and intravitreal treatment with bevacizumab and dexamethasone was recently evaluated in patients with CNV secondary to AMD [6].

While a limited core pars plana vitrectomy was performed as part of the combination therapy, the authors did not attribute any importance at the beginning of the study to the role of the vitrectomy in treating CNV.

There are several indications, however, that physiological changes brought about by a limited or full vitrectomy may have a beneficial therapeutic effect. It was shown that vitrectomy increases the intraocular oxygen tension [7, 8], which is known to affect retinal oxygenation [9]. Furthermore, a full or limited vitrectomy may also physically decrease VEGF from the intraocular cavity by reducing the viscosity in the vitreous, which facilitates the diffusion of VEGF away from the retina.

Posterior vitreomacular adhesion was proposed to be a potential risk factor for exudative AMD by maintaining macular exposure to inflammatory cytokines or free radicals and by interfering in macular oxygenation [10]. In the same way, vitreous attachment may also promote angiogenesis. We assume that a partial 1.5-ml core vitrectomy facilitates posterior vitreous detachment, changes the viscosity of the vitreous which, in turn, may promote neovascular regression [11]. In this study, in patients with occult CNV secondary to wet AMD, we examined the efficacy of an intravitreal combination therapy using a limited core vitrectomy and intravitreal treatment with bevacizumab and triamcinolone.

## Patients and Methods

### Study Design and Patients

This pilot study of a case series was prospectively followed in accordance with the European Guidelines for Good Clinical Practice and the Declaration of Helsinki and registered with www.clinicaltrials.gov (NCT00805649). Informed consent was obtained from each patient before the start of therapy.

**Table 1.** Demographics and baseline characteristics of patients with AMD and occult CNVs

Demographics and baseline characteristics		
Patients	n	106
Age, years	median (range)	77 (47–93)
	mean $\pm$ SD	75.4 $\pm$ 9.5
Sex	male/female	40/66
Lesion size, $\mu$ m	median (range)	2,500 (1,000–6,000)
	mean $\pm$ SD	2,740 $\pm$ 1,071
Lens status	intraocular lens	26 (24.5%)
	incipient cataract	80 (75.5%)

Patients with wet AMD were included in the study if they were older than 45 years, and if they had an occult CNV between 1 and 6 mm in size at the greatest extension underneath the geometric center of the fovea with a visual acuity of 0.3–1.8 logMAR. Exclusion criteria were a history of prior vitreoretinal surgery, neovascular retinopathy, optic neuropathy, glaucoma, or ocular hypertension, or an intravitreal injection (anti-VEGF, steroids) 5 months prior to study inclusion.

### Pharmacosurgery

A limited core pars plana vitrectomy was performed using a vitrector (Intrector<sup>®</sup>, InSight Instruments, Stuart, Fla., USA) which has two separate channels for aspiration and infusion. After conjunctival displacement, an oblique sclerotomy was performed to illuminate the tip of the vitrector with a headset and a magnifying 38-dpt lens. An assistant then aspirated a total of 1.5 ml by cutting mid- and posterior vitreous as instructed by the surgeon with isovolumic substitution of 1.2 ml balanced salt solution (Alcon, Freiburg, Germany) to avoid relevant perioperative hypotonia. At the end of the limited posterior core vitrectomy, 1.25 mg (0.1 ml) bevacizumab (Avastin<sup>®</sup>, Genentech, San Francisco, Calif., USA) and 8 mg (0.2 ml) triamcinolone (TriamHEXAL<sup>®</sup> 40 mg/1 ml, HEXAL AG, Holzkirchen, Germany) were injected. In the following, the term ‘triple therapy’ is used for this therapy, which comprises the three treatments core vitrectomy and injection of triamcinolone and bevacizumab.

### Measurements

At baseline (T0) and all follow-up examinations, i.e., at 2 (T1), 4 (T2) and 6 (T3) months after initial pharmacosurgery, an ophthalmic examination including slitlamp biomicroscopy and funduscopy was performed and the best-corrected (EDTRS standardized refraction) visual acuity (BCVA) was assessed using 6m Snellen charts with the forced-choice technique. One line was credited if four out of five optotypes were recognized. The central foveal thickness was measured using optical coherence tomography (Stratus<sup>®</sup> OCT, Carl Zeiss Meditec, Santa Ana, Calif., USA), and the intraocular pressure (IOP) was assessed using Goldmann applanation tonometry. Fluorescein angiography was carried out to identify the lesion type, the location, and the absence or degree of active CNV leakage. Fluorescein angiograms were evaluated by experienced vitreoretinal specialists (F.H.K., M.J.K., S.S.) and

**Table 2.** BCVA and central macular thickness in patients with AMD and occult CNVs (n = 106) before (T0) and after initial treatment (T1–3)

	T0 (baseline)	T1 (2 months)	T2 (4 months)	T3 (6 months)
Best corrected visual acuity				
Median, logMAR (range)	0.85 (0.30–1.70)	0.85 (0.22–1.70) T1 vs. T0: p < 0.05	0.55 (0.1–2.00) T2 vs. T0: p < 0.001 T2 vs. T1: p < 0.005	0.7 (0.1–2.00) T3 vs. T0: p < 0.001 T3 vs. T1: p < 0.05 T3 vs. T2: p > 0.45
Mean ± SD, logMAR	0.88 ± 0.26	0.72 ± 0.37	0.63 ± 0.32	0.65 ± 0.33
Central macular thickness				
Median, μm (range)	519 (379–563)	295 (200–365) T1 vs. T0: p < 0.001	270 (180–340) T2 vs. T0: p < 0.001 T2 vs. T1: p > 0.69	276 (190–355) T3 vs. T0: p < 0.001 T3 vs. T1: p > 0.92 T3 vs. T2: p > 0.62
Mean ± SD, μm	473 ± 50.2	283 ± 33.2	264 ± 30.9	278 ± 46.4

The p value was analyzed using a Wilcoxon matched pairs test (non-normally distributed data) for intravariability differences.

throughout the study, at the three follow-up visits, the need for a booster with an additional 1.25 mg bevacizumab monotherapy was evaluated. The indication for a booster injection was set if there was a pronounced activity in fluorescein angiography and/or optical coherence tomography or an increase of macular edema by 75 μm. Any therapy-associated adverse events, e.g. IOP increase or intraocular inflammation, were recorded.

#### Data Analysis

The Excel® (Microsoft, Richmond, Va., USA) and BiAS programs (Version 8.2 for Windows®, Epsilon-Verlag, Darmstadt, Germany) were applied for the statistical analysis of the primary outcome measures BCVA, central macular thickness, and re-treatment rate. The David's test was used to analyze non-normally distributed data. The Wilcoxon matched pairs test was used to evaluate the median change in BCVA and central retinal thickness (CMT) from baseline to each follow-up visit. The frequency of cataract surgeries in the two patient groups during the follow-up period was compared using the  $\chi^2$  test.

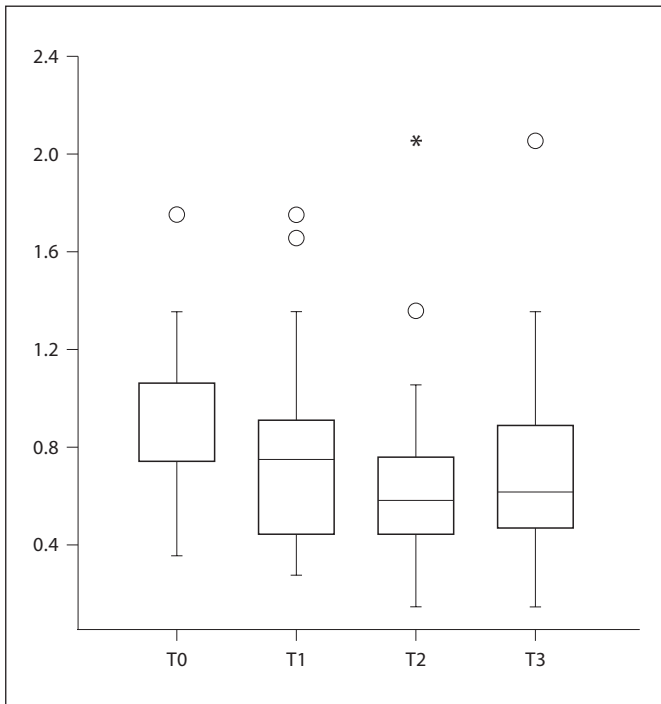
## Results

In total, 106 patients were included in the study. The majority of the patients were female (66/106; 62.3%); mean age was 75.4 years (standard deviation ± 9.9; median 77; range 47–93 years; table 1). At baseline, 26 of 106 (24.5%) eyes were pseudophakic and 80 (75.5%) were phakic. Senile minimal nuclear sclerotic cataracts were found in 26 of the 80 (32.5%) patients with phakic lens status. According to the results of the slitlamp examination, however, none of the cataracts were considered clinically relevant.

Follow-up examinations took place on average (±SD) at 1.8 months (±11 days), 3.7 months (±16 days), and 5.8 months (±15 days) after the initial pharmacosurgery. The follow-up rate was 100% (106/106) at 2 months, 94% (100/106) at 4 months, and 91% (96/106) at 6 months.

The mean lesion size was 2,740 μm (table 1) and the mean BCVA was 0.88 logMAR (±0.26; median 0.85; range 0.3–1.7) at baseline (table 2). There was a statistically significant increase in mean BCVA at 2 months (+0.9 lines; ±0.6 vs. baseline), 4 months (+1.3; ±0.7), and 6 months (+1.2; ±0.7) (fig. 1). At 6 months, i.e., at the end of the follow-up period, BCVA had deteriorated in 20 of 96 (20.8%) patients by <2.5 lines as compared with baseline. BCVA remained stable in 38 of 96 (39.6%) patients, improved in 31 (32.3%) patients by 1–3 lines, and in 7 (7.3%) patients by >3 lines (fig. 2). The decrease in mean CMT was already statistically significant at 2 months (p < 0.001) and amounted to –41.2% (–195 μm) at 6 months (table 2).

After 6 months, 53 of 96 (55.2%) patients had to receive anti-VEGF monotherapy because of an increase in CMT and leakage in fluorescein angiography. Cataract surgery was carried out uneventfully in 8 patients at 7.8 months; the effect of the cataract surgery on BCVA was overall not statistically significant (p > 0.68). The IOP increased in 11 of 106 (10.4%) patients for a mean duration (±SD) of 12 days (±3.6 days) and was successfully controlled by using topical antiglaucomatous medication.



**Fig. 1.** Change in BCVA in patients with AMD and occult CNVs before (T0) and after therapy (T1–3). A box plot based on information of 106 patients with AMD and occult CNVs is shown. Horizontal lines of the boxes represent the lower quartile, the mean, and the upper quartile. The whiskers denote the range from minimum to maximum. The circles denote and the asterisk denotes the end of range values (asterisk marked value was not calculated due to the patient's drop out).

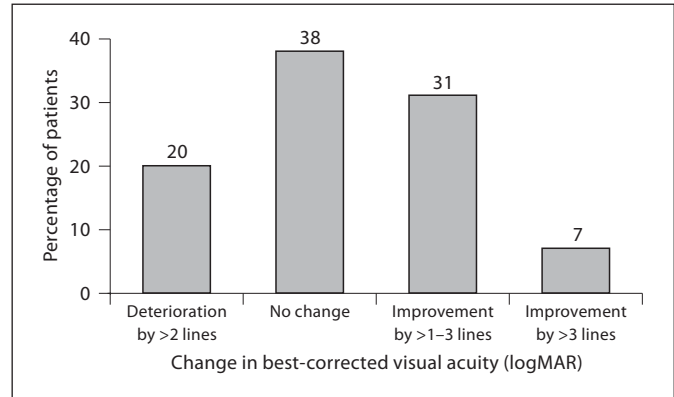
## Discussion

### *AMD – A Multifactorial Disease*

On the basis of histopathologic results, the pathogenesis of CNV cannot be diminished to angiogenesis alone. It is rather a tissue invasion of vascular cells and extravascular cells which can be described as a two-component system [12]. The first is the vascular (angiogenetic) component, where growth factors like VEGF influence the growth of endothelial cells and circulating endothelial progenitor cells. The other component is the (inflammatory) extravascular one and includes leukocytes and fibrocytes as well as retinal pigment epithelial cells and glial cells [13, 14].

### *Monotherapy*

There have been various approaches to monotherapeutic treatment (PDT, laser photocoagulation, steroids,



**Fig. 2.** Proportion of patients with an improvement or deterioration of the BCVA at 6 months after therapy. Patients with AMD and occult CNVs (n = 96) were treated using combined intravitreal therapy (core vitrectomy, bevacizumab, and triamcinolone).

VEGF inhibitors) of CNVs in recent years, but today the injection of anti-VEGF agents is the best choice as the visual acuity can now be stabilized in the majority of patients [15–18]. As controlled studies revealed, stabilization in or improvement of visual acuity could only be achieved after continuous injections every 4 (pegaptanib, ranibizumab) to 6 weeks (bevacizumab). This hints to the fact that anti-VEGF inhibits the continued neovascularization, might provoke an upregulation of VEGF receptors and would have an undesired rebound effect when the treatment is interrupted. Principally, we know from oncology that inhibition of one pathway for angiogenesis might upregulate alternate pathways and may not be enough to satisfactorily inhibit vascular development [19]. The rationale for treating CNV might thus be to target the vascular and the extravascular components [5].

### *Combined Pharmacosurgery Leads to Longer Re-Treatment Intervals*

We therefore designed this prospective pilot case series to investigate the efficacy and safety of a combined intravitreal therapy over 6 months. In patients with occult CNV lesions secondary to AMD, combination therapy using vitrectomy and intravitreal treatment with triamcinolone and bevacizumab led to a statistically significant increase in BCVA from baseline up to 6 months after initial treatment. BCVA at 6 months had deteriorated in about 20% of the patients, remained stable in nearly 40% of the patients and improved by >1 line in another 40% of the patients. Central macular thickness significantly decreased from baseline to 4 months and then

slightly increased but, in essence, remained at a significantly lower level as compared with baseline.

It is likely that the plateau effect beginning at about 4 months after the initial pharmacosurgery is due to the pharmacokinetic characteristics of the intravitreal medications. The intraocular pharmacological half-life of triamcinolone, for example, is approximately 30 days. Since the concentrations of the corticosteroid and the VEGF inhibitor decrease, the overall therapeutic effects diminish while the oxidative stress, age-related microstructural changes and the resulting inflammatory process in AMD continue [20].

The improvements in BCVA observed in our study are overall similar to the results of recent monotherapy clinical studies using intravitreal ranibizumab or bevacizumab in patients with CNV [15–17], or to results of combination regimens like visudyne and triamcinolone [21–23], or visudyne and anti-VEGF and dexamethasone [24, 25]. To our knowledge, though, this study is the first to report about a combined intravitreal triamcinolone and bevacizumab injection, despite the 1.5-ml core vitrectomy. Thus, any comparison from the underlying results to the results of the monotherapy studies or studies of combination regimens is hard to draw. The main benefit in our opinion are the significantly fewer intravitreal injections during the follow-up monitoring. At the end of the follow-up period, i.e., at 6 months, combination therapy had been repeated, due to persistent or recurrent CNV, in about half of the patients.

#### *AMD and Ischemia*

The thickening of the Bruch's membrane, a characteristic feature of AMD, reduces the diffusion of oxygen from the choriocapillaris to the retinal pigment epithelium [26, 27]. While the hypoxia resulting from changes in the choriocapillaris and the Bruch's membrane has not been shown to contribute to CNV formation, it was suggested that outer retinal hypoxia in AMD may indirectly stimulate angiogenesis [28]. In the retinal pigment epithelium and in CNV, specific isoforms of VEGF were shown to be upregulated under hypoxic conditions [29]. It is known that intraocular oxygen tension significantly increases after vitrectomy [30]. It has also been shown that the retina can be oxygenated from the vitreous cavity [28, 31], and that increased oxygenation decreases VEGF production in ischemic retina [32].

#### *Vitrectomy and Its Impact on Intraocular Physiology*

A limited or full vitrectomy may contribute to the resolution of neovascularization in AMD also through oth-

er mechanisms. Vitrectomy may induce posterior vitreous detachment, which decreases the viscosity anterior to the retina. In the same way, a full vitrectomy may enhance liquefaction in the vitreous cavity. With decreasing viscosity, the flow of molecules (flux) in the vitreous cavity increases (Fick's law for diffusion). Consequently, by removing vitreous gel, vitrectomy may promote the diffusion of angiogenic molecules such as VEGF away from the retina [11].

Therefore, the limited vitrectomy performed in our study by removing approximately 1.5 ml of the posterior and central vitreous while sparing the anterior base may have contributed to the positive clinical outcome and the sustainability of the results. The increase of intraocular oxygen levels after a comparable limited core vitrectomy could thus be demonstrated lately in an adenovirus CNV-induced albino rabbit model. In the same animal model, VEGF was undetectable after the combined treatment (limited core vitrectomy, dexamethasone and bevacizumab), whereas it was still detectable after bevacizumab monotherapy [33].

#### *Posterior Hyaloid and AMD*

Recently, the regression of macular drusen and the occurrence of pigment epithelial detachment were reported after vitrectomy in a patient with AMD [34]. The findings indicated that posterior vitreous detachment may prevent the development of exudative AMD. Likewise, another study, which examined the incidence of posterior vitreous detachment in an otherwise matched cohort of eyes with AMD, suggested that persistent attachment of the posterior vitreous cortex to the macula may be a risk factor for AMD by inducing chronic low-grade inflammation, preventing sufficient diffusion of oxygen and nutrients to macular cells, and confining angiogenic cytokines to the macular region [10]. We suppose that the posterior vitreous detachment (which was not assessed regularly in this pilot study) and the physiological changes at the macula induced by the central 1.5-ml vitrectomy may complement the effects of pharmacotherapeutics in the treatment of CNV.

#### *Safety*

The frequency of adverse events was generally low, which highlights the favorable safety profile of intravitreal combination therapy. The IOP increases, which occurred in about 10% of the patients, were most likely related to the treatment with triamcinolone but were effectively controlled with eye drops. Although there is commonly, and especially in elderly patients, a signifi-

cant risk of inducing cataracts when performing a complete vitrectomy, in this study, using a 23-gauge vitrector, the frequency of cataracts did not significantly increase from baseline to 6 months. Eight patients underwent phacoemulsification cataract extraction after 8 months, without significant effects on BCVA ( $p > 0.78$ ,  $\chi^2$  test). Since the degree of cataract was not assessed at baseline, however, cataracts may have progressed during the course of the study.

#### *Limitations of Pilot Case Series*

The aim of a pilot clinical case series is to prove if and to what extent a therapy concept is effective. Thus, a potential limitation of the present pilot study is the lack of a control group, i.e., a monotherapy arm, which is currently recruiting patients on the basis of this study. To examine this combination concept, only a relatively small number of patients could be included in this study, which did not allow evaluating correlations regarding complications such as cataract progression. In future studies, a larger number of patients should be included to evaluate the effect on cataract induction and the influence on the posterior vitreous interface.

## **Conclusion**

To conclude, in patients with occult CNV secondary to AMD, combination therapy using vitrectomy and intravitreal treatment with bevacizumab and triamcinolone resulted in a therapeutic outcome similar to that of monotherapy with bevacizumab or ranibizumab, with the added benefit of requiring significantly fewer intraocular interventions. These results can on the one hand be addressed to the drug synergism and on the other hand to the changes in the vitreous physiology induced by the limited core vitrectomy.

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