

Predictors of 1-year visual outcome in OCT analysis comparing ranibizumab monotherapy versus combination therapy with PDT in exsudative age-related macular degeneration

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Summary

Aim The aim of this study was to find predictive factors of 1-year visual outcome, analyzing novel optical coherence tomography (OCT) biomarkers in exsudative age-related macular degeneration (choroidal neovascularization (CNV)) in two groups of different treatment modalities.

Methods In all, 34 consecutive patients with new-onset CNV were randomized 1:1 to receive either ranibizumab monotherapy or ranibizumab combined with photodynamic therapy (PDT) with verteporfin. After three initial injections with ranibizumab, re-treatment was performed according to an as-needed scheme; PDT was performed once at baseline. Best-corrected visual acuity (BCVA) and OCT parameters like central macular volume (CMV), central macular thickness (or central retinal thickness (CRT)), subretinal and intraretinal fluid, fibrovascular lesion thickness, or inner segment/outer segment (IS/OS) junction were analyzed.

Results After 12 months, a visual gain of 6.1 letters was found in the monotherapy group, whereas patients in the combination therapy group lost –4.8 letters from baseline to the 12-month visit. CMV and CRT decreased considerably between baseline and month 2–3 in both groups, with a following slight increase until month 12. Additional application of PDT had negative effect to

12-month BCVA, whereas higher baseline BCVA and integrity of the IS/OS junction at month 12 had positive effect to 12-month BCVA.

Conclusions Better baseline BCVA and the integrity of IS/OS junction at 12-month visit were the most important predictive factors for final BCVA. Combination therapy caused worse final BCVA and a higher degree of IS/OS disruption.

Keywords Ranibizumab · OCT · PDT · Visual outcome · Combination therapy · Age-related macular degeneration

Introduction

Age-related macular degeneration (AMD) is the prevalent cause of moderate and severe vision loss in developed countries and the third major cause of blindness worldwide [1–3].

There are two known forms of AMD. Nearly 90% of patients have the non-neovascular form, characterized by drusen and atrophic changes [1–4]. However, 80–90% of the severe vision loss is caused by the neovascular form characterized by choroidal neovascularization (CNV), which has been shown to occur in 18% of patients within 5 years [5, 6].

For the treatment of neovascular AMD, photodynamic therapy with Visudyne[®], a photosensitizer, is available for more than 10 years [7, 8]. Verteporfin monotherapy reduces the risk of moderate and severe vision loss, but rarely results in recovery of vision [7–10]. Antivascular endothelial growth factor (anti-VEGF) drugs like ranibizumab improve vision in 25–40% of patients as shown in many studies [11, 12], but constant treatment seems to be necessary [12, 13]. The need for frequent injection represents a significant burden for patients and health care systems. Verteporfin and anti-VEGF drugs have different mechanisms of action, so it is hypothesized that combi-

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nation therapy could lead to better results and reduce the number of re-treatments [7, 8, 13–22].

In the past years, re-treatment criteria were usually based on increasing fluid or retinal thickness evaluated with optical coherence tomography (OCT), signs of activity like bleeding in funduscopy, and visual acuity. With the introduction of spectral-domain OCT (SD-OCT) objective, quantitative assessment of morphologic parameters plays an increasingly important role; the focus of many recent articles has been on the identification of novel OCT-derived anatomic biomarkers [23–30].

The aim of our study was to compare novel biomarkers like subretinal (SRF) and intraretinal fluid (IRF) or fibrovascular lesion thickness (FVL) in a ranibizumab monotherapy group with a combination group treated with ranibizumab and photodynamic therapy (PDT).

Material and methods

In all, 34 individuals diagnosed with new-onset CNV were prospectively included at the department of ophthalmology of Hietzing Hospital, Vienna, Austria.

Patients with a subfoveal CNV showing activity, for instance, presence of retinal hemorrhage, intraretinal edema, subretinal fluid, or fibrovascular pigment epithelial detachment (PED), were consecutively included. Diagnosis of CNV was based on fluorescein angiography (FA) criteria.

Eligible patients were randomized 1:1 to receive either ranibizumab monotherapy or ranibizumab combined with PDT with verteporfin. Randomization envelopes were prepared by a member of the Department of Medical Statistics in Vienna not involved in the study.

Additional inclusion criteria were as follows: BCVA letter score of 73–24 letters, lesion size of $\leq 5400 \mu\text{m}$, and willingness to return for scheduled visits for a 12-month period.

Patients were excluded from the study if the CNV was not subfoveal or not related to AMD or if they had received any prior treatment for AMD.

The following parameters were obtained at baseline and monthly after treatment initiation: best-corrected visual acuity (BCVA) using early treatment diabetic retinopathy study (ETDRS) charts, intraocular pressure (IOP) as measured by applanation tonometry, findings documented by indirect dilated fundus examination, and central retinal thickness (CRT) as measured by OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany).

FAs (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) were performed at baseline and 1, 3, 6, and 12 months after the baseline treatment. ICG angiography was performed at baseline to rule out other pathologies like polypoidal choroidal vasculopathy. Additional FA examinations were possible at discretion of the investigator.

Intravitreal injections were performed under aseptic conditions, according to the directions of several studies

regarding the efficacy and safety of intravitreal injections [11, 31, 32]. Using a 30-gauge needle, 0.5 mg (0.05 ml) of ranibizumab was injected via pars plana at month 0, 1, and 2.

From month 3 to 12, re-treatment with ranibizumab was performed if one of the following changes was observed between visits: new intra- or subretinal fluid, visual loss of at least 5 letters in conjunction with fluid in the macula as detected by OCT, an increase in OCT central retinal thickness of at least $100 \mu\text{m}$, or new macular hemorrhage.

Patients in the combination group received verteporfin PDT 1 day after the intravitreal injection of 0.5 mg of ranibizumab at baseline. PDT was administered using a light dose of $50 \text{ J}/\text{cm}^2$ at $600 \text{ mW}/\text{cm}^2$ of lesion. At month 1 and 2, ranibizumab was injected without PDT; from month 3 to 12, the same re-treatment criteria for ranibizumab were used as in the monotherapy group.

For statistical analyses, OCT parameters from baseline and month 3, 6, and 12 were evaluated. Interpretation of OCT images was performed by trained personnel being unaware of BCVA or randomization. Every evaluation was performed twice by the same personnel. The central retinal thickness (CRT) and central macular volume (CMV) measurements were obtained from the macular thickness maps after alignment control. The center point of the scan always corresponded to the fovea. If the fovea was not centered in the middle, the template was adjusted to the actual location. SRF was defined as the area lying between the outer border of the photoreceptors and the inner surface of the retinal pigment epithelium (RPE). FVL was the moderately to highly reflective lesion that could be separated from the RPE and retina. The scan showing the most extensive involvement of the macula was used for boundary delineation and calculation. IRF was described to be present (+) or absent (–).

For evaluation of the inner segment/outer segment (IS/OS) junction, the photoreceptor IS/OS layer was evaluated within $350 \mu\text{m}$ from foveola. Two well-trained examiners measured the disrupted IS/OS line using the software callipers. The percentage of disruption along the IS/OS layer was recorded and averaged to generate a number between 0% (total loss of the IS/OS layer) and 100% (no IS/OS disruption) at baseline and month 12.

Data were analyzed using PASW Statistics 19.0 (SPSS Inc., Chicago, IL, USA). Nonparametric correlations were calculated using the Spearman rho test. Comparing differences in mean value and standard deviation of variables, a two-tailed paired *t*-test was performed. To determine predictors of 12-month visit visual acuity, multiple regression analysis was performed. Among all tested models, the best-fitting model was used, and model fit was assessed by r^2 as goodness-of-fit statistics. Statistical significance was considered to be present at 5%.

This study was approved by the Ethics Committee of the City of Vienna. Written informed consent was obtained from all participants, and the study was in adherence to the tenets of the Declaration of Helsinki.

Table 1 Age, gender distribution, and baseline characteristics of eyes in the two study groups

	Monotherapy (n=16)	Combined therapy (n=14)	P
Age (years)	81.1±7.9	83.3±6.1	0.424
Gender (male:female)	4:12	4:10	0.741
BCVA (ETDRS letters)	53.8±11.4	61.3±12.0	0.097
CRT (µm)	420.7±89.3	468.3±148.4	0.294
CMV (µm ³)	0.34±0.07	0.35±0.11	0.692
6 mm CMV (µm ³)	10.06±1.5	9.0±1.6	0.105
SRF (µm)	140.8±133.1	173.7±147.6	0.555
IRF (+:–)	9:7	5:9	0.125
FVL (µm)	156.7±153.5	150.2±144.2	0.913
IS/OS (%)	27.8±35.5	25.8±38.9	0.184

Data are presented as mean ± standard deviation
P: difference between the two groups using unpaired *t*-test
 IS/OS line disruption—within 350 µm from foveola
BCVA best spectacle-corrected distance visual acuity, *CRT* central retinal thickness, *CMV* central macular volume, *SRF* subretinal fluid thickness, *IRF* presence of intraretinal fluid, *FVL* fibrovascular lesion thickness, *IS/OS* inner segment/outer segment

Results

A total of 30 patients completed the 12-month visit: 16 in the monotherapy and 14 in the combination therapy group.

Baseline characteristics are shown in Table 1; visual acuity and details of OCT characteristics of month 3, 6, and 12 are shown in Table 2. Concerning lesion type, the ratio of occult lesion to predominantly classic/classic lesion was 11:5 in the monotherapy group and 10:4 in the combination therapy group. There were no RAP lesions in either groups.

Baseline BCVA in the monotherapy group was 53.8±11.4 and 61.3±12.0 in the combination group. After 12 months, a visual gain of 6.1 letters (58.7±17.6) was found in the monotherapy group, whereas patients in the combination therapy group lost –4.8 letters from baseline to the 12-month visit (57.2±21.4; Fig. 1). There was a significant change of visual acuity comparing the two groups (*P*=0.02).

CMV and CRT decreased considerably between baseline and month 2–3 in both groups, with a following slight increase until month 12 (Figs. 2 and 3). Stronger reduction was seen in the combination group despite higher CRT and CMV at baseline.

CRT reduced from baseline to month 12 in both groups: –92.8±77.9 µm in the monotherapy group and –131.5±125.2 µm in the combination group (Fig. 2). The difference between the groups was not significant (*P*>0.05).

A reduction in CMV from baseline to month 12 was found in both groups: –0.07±0.08 µm³ in the monotherapy and –0.11±0.08 µm³ in the combination group (Fig. 3). The difference between both groups was not significant (*P*>0.05). A significant difference between the

Table 2 Visual acuity and optical coherence tomography characteristics of eyes in the two study groups through month 3, 6, and 12

	Monotherapy (n=16)	Combined therapy (n=14)	P
3-month BCVA (ETDRS letters)	57.3±17.6	62.6±19.2	0.352
3-month CRT (µm)	323.5±102.9	290.3±47.9	0.343
3-month CMV (µm ³)	0.25±0.1	0.33±0.4	0.383
<i>3-month 6-mm CMV (µm³)</i>	<i>8.9±1.2</i>	<i>8.0±0.4</i>	<i>0.027</i>
3-month SRF (µm)	63.6±137.2	17.7±42.2	0.278
3-month IRF (+:–)	6:10	3:11	0.573
3-month FVL (µm)	90.0±117.4	49.7±38.9	0.268
6-month BCVA (ETDRS letters)	57.8±18.4	62.4±19.9	0.461
6-month CRT (µm)	329.9±77.9	290.3±44.0	0.296
6-month CMV (µm ³)	0.25±0.1	0.23±0.3	0.360
6-month 6-mm CMV (µm ³)	8.9±1.2	8.0±0.4	0.631
6-month SRF (µm)	71.7±137.9	44.17±104.2	0.576
6-month IRF (+:–)	7:9	2:12	0.080
6-month FVL (µm)	84.2±80.6	77.5±53.0	0.073
12-month BCVA (ETDRS letters)	58.7±17.6	57.2±24.4	0.565
12-month CRT (µm)	344.6±76.01	319.2±99.6	0.297
12-month CMV (µm ³)	0.26±0.06	0.24±0.05	0.416
<i>12-month 6-mm CMV (µm³)</i>	<i>8.8±0.92</i>	<i>7.6±1.8</i>	<i>0.048</i>
12-month SRF (µm)	69.4±86.4	26.6±64.2	0.175
<i>12-month IRF (+:–)</i>	<i>8:8</i>	<i>2:12</i>	<i>0.007</i>
12-month FVL (µm)	94.6±75.5	65.3±34.3	0.229
12-month IS/OS (%)	24.3±28.7	20.8±37.5	0.068

Data are presented as mean ± standard deviation
P: difference between the two groups using unpaired *t*-test, significant values are given in italic
 IS/OS line disruption—within 350 µm from foveola
BCVA best spectacle-corrected distance visual acuity, *CRT* central retinal thickness, *CMV* central macular volume, *6-mmCMV* 6 mm macular volume, *SRF* subretinal fluid thickness, *IRF* presence of intraretinal fluid, *FVL* fibrovascular lesion thickness, *IS/OS* inner segment/outer segment

two groups was observed in the 3- and 12-month 6-mm CMV and in IRF after 12 months (Table 2).

Patients in the monotherapy group received an average of 7.4±1.4 intravitreal injections, whereas patients in the combination therapy group received 6.9±1.1 intravitreal injections. The difference between both groups was not significant (*P*>0.05).

A multivariable logistic regression model showed the negative effect of additional application of PDT (*P*<0.001), the positive effect of higher baseline BCVA (*P*=0.002), and the positive effect of integrity of the IS/OS junction at month 12 (*P*=0.005) to be significant predictors of 12-month BCVA (Table 3).

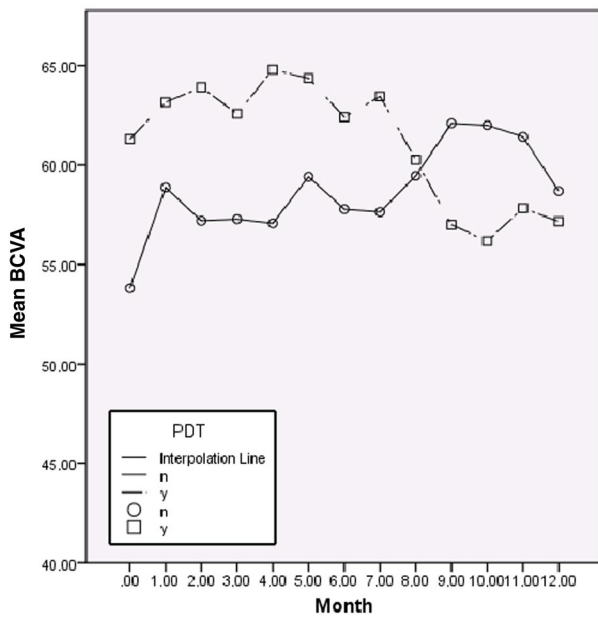


Fig. 1 Mean values of BCVA, best spectacle-corrected distance visual acuity, expressed in ETDRS letters over the 12 months (n = no PDT (monotherapy group), y = with PDT (combination therapy group); PDT photodynamic therapy)

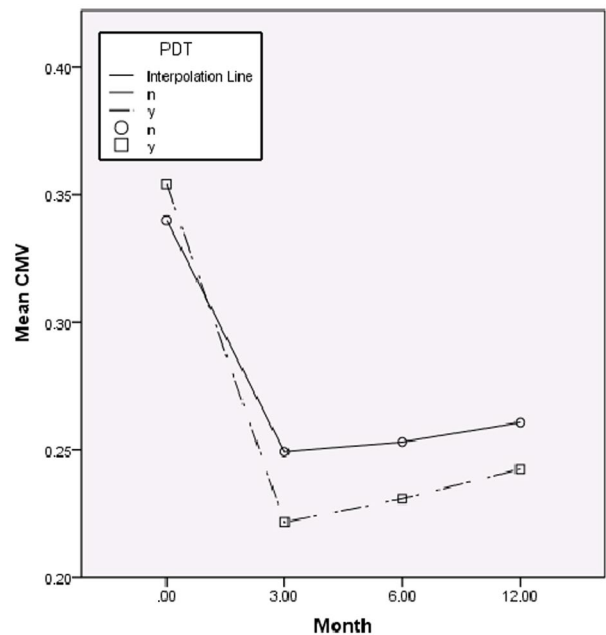


Fig. 3 Mean values of central macular volume (CMV) expressed in μm^3 over the 12 months (n = no PDT (monotherapy group), y = with PDT (combination therapy group); PDT photodynamic therapy)

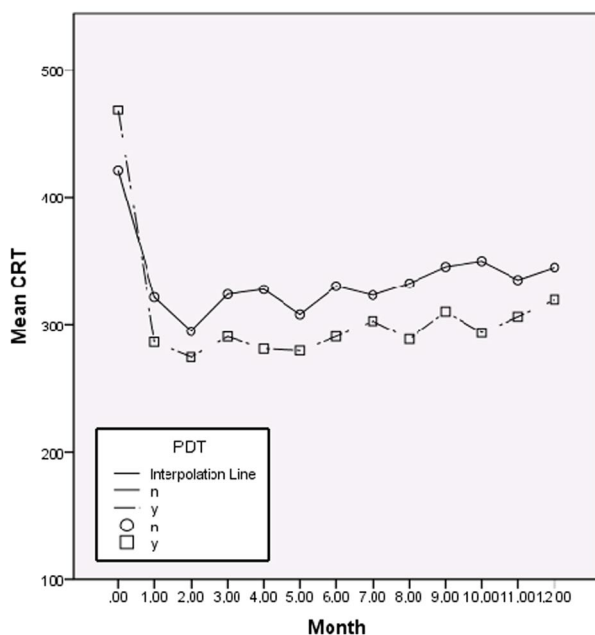


Fig. 2 Mean values of central retinal thickness (CRT) expressed in μm over the 12 months (n = no PDT (monotherapy group), y = with PDT (combination therapy group); PDT photodynamic therapy)

Discussion

Blockage of VEGF has become the first-line therapy in the treatment of neovascular AMD and shows good efficacy

Table 3 Parameter estimates of the significant predictors of the final multivariable logistic regression model for 12-month best-corrected visual acuity (BCVA)

Parameters	P	r ²
Group	0.001	0.762
Baseline BCVA	0.002	
12-month IS/OS (%)	0.051	
Model fit was assessed by r ² IS/OS inner segment/outer segment		

and safety data in several studies [12, 33, 34]. However, blockage effect of VEGF with ranibizumab is only temporary, and reinjections are needed. Repeated controls with periodic injections are a great burden to the aged patients and health care systems. Different strategies and combination therapies have been evaluated to reduce the number of required injections and possibly prolong the intervals of controls [7, 8, 14–17, 20, 35]. An additional PDT might lead to permanent occlusion of the neovascular vessels and so reduce the number of re-treatments.

During the past years, re-treatment criteria were primarily assessed as baseline morphologic features like CRT or BCVA. Introduction of SD-OCT allows identification of new morphologic parameters to predict visual outcomes [23–26, 28, 30].

In our study, patients with combination therapy showed a more distinct reduction in CRT, CMV, and SRF than the monotherapy group. Keane et al. [26] described a greater reduction of subretinal fluid volume in a combination group of PDT and bevacizumab compared with

a bevacizumab monotherapy group, but not of the total retinal volume.

Nevertheless, BCVA at 12-month visit was worse in the combination group. Analysis of IS/OS junction showed greater percentage of disruption in this group at 12-month visit. An apparent visual acuity difference between the two groups could be observed at month 8 and 9 (Fig. 1). Significant reduction of visual acuity was found in three patients in the combination group within this time. Additional analysis of IS/OS junction layer in these patients showed a trend towards loss of integrity within month 6–8, but the sample size was too small for reliable statistics. In literature, integrity of the IS/OS junction in neovascular AMD patients is discussed controversially. Hayashi et al. [25] found the integrity of the photoreceptor layer to be associated with the final BCVA after PDT. Gamulescu et al. [24] described the grade of continuity of outer retinal layers not to be a significant predictive value after ranibizumab injections.

Some studies suggest that the addition of standard-fluence PDT confers no benefit in terms of visual acuity or number of injections required at 12 months [15, 18, 20, 35, 36]. Other studies demonstrate reduction of re-treatments and gain of visual acuity in patients with combination therapy [7, 16, 17, 21, 34]. In a recently published study, a significant reduction of re-treatments could be achieved in the combination therapy group, but was accompanied by worse visual acuity [37]. In our study, the degree of IS/OS disruption could be an explanation for worse BCVA in the combination group despite the more distinct reduction in CRT, CMV, and SRF than the monotherapy group. A comparison of IS/OS junction in a reduced and a standard light application, PDT group would be of interest in this context.

Significant limitation of our study is the fact that for measurements of FVL, SRF, and IS/OS, only one OCT scan was used, although it was the one that showed the most extensive involvement of the fovea. Another limitation was the time necessary for manual measuring, so that we did not analyze every available OCT measurement of each study visit.

Our study has also some strength—in particular, the use of a spectral-domain OCT, which allows the identification and quantification of novel morphologic parameters. Furthermore, our study followed standardized follow-up and re-treatment protocols in conjunction with ETDRS visual acuity assessment performed by trained personnel.

In conclusion, our study shows the negative impact of additional PDT. Better baseline BCVA and the integrity of IS/OS junction at 12-month visit were the most important predictive factors for final BCVA. Combination therapy caused worse final BCVA and a higher degree of IS/OS disruption. To our knowledge, this is the first study to compare novel OCT-derived anatomic biomarkers in a monotherapy and a combination therapy group. Further studies with more patients and an additional group with reduced-fluence PDT would provide further information.

Conflict of interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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