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Combination treatment of photodynamic therapy with verteporfin and intravitreal ranibizumab in patients with retinal angiomatous proliferation

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ABSTRACT.

Purpose: **To investigate the efficacy and safety of initial photodynamic therapy (PDT) with a ranibizumab loading dose of three monthly intravitreal injections and a subsequent PRN ranibizumab regimen in the treatment of retinal angiomatous proliferation (RAP).**

Methods: **In this 12-month prospective case series, 15 patients underwent PDT followed by 3 intravitreal ranibizumab injections at monthly intervals. At monthly follow-up examinations, further single ranibizumab injections were given in case of any intra- or subretinal fluid on optical coherence tomography (OCT), visual loss ≥5 letters or signs of activity on fluorescein or indocyanine green angiography.**

Results: **Best-corrected visual acuity (BCVA) improved from 58.1 ± 13.2 at baseline by 9.2 letters (SD ± 8.5; p = 0.004) at 6 months and by 8.7 letters (SD ± 11.4; p = 0.017) at 12 months. Neither at 6 nor at 12 months, any patient had lost ≥15 letters. The mean number of injections per patient was 4.8 (SD ± 1.4) in the first year of therapy after PDT. The average time to first retreatment was 3.7 months (range 1–7 months). No serious adverse events, such as endophthalmitis or retinal detachment, were noted.**

Conclusion: **PDT with 3 ranibizumab loading injections and subsequent ranibizumab as needed resulted in a significant gain of 8.7 ± 11.4 letters at month 12. This regimen is safe and efficacious, but even in a population of mostly early stages of RAP, retreatment rates remained high.**

Key words: Age-related macular degeneration – Anti-VEGF therapy – Photodynamic therapy – Ranibizumab – Retinal angiomatous proliferation

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Introduction

Retinal angiomatous proliferation (RAP) is a subtype of neovascular age-related macular degeneration (AMD), accounting for up to 15% of AMD cases. Yanuzzi and coworkers referred to it as type 3 neovascularization and defined three stages: 'stage I' consisting of intraretinal neovascularization bordered by telangiectatic vessels, 'stage II' presenting with progression extending beneath the neurosensory retina and subdivided into stage IIa and IIb according to presence or absence of a pigment epithelial detachment (PED), respectively, and 'stage III' characterized by establishment of a retinal–choroidal anastomosis. (Yannuzzi et al. 2001, 2008; Freund et al. 2008, 2010) If left untreated, RAP leads to rapid visual loss, and one-third of fellow eyes is affected within 3 years after diagnosis of unilateral disease. (Gross et al. 2005; Viola et al. 2009; Campa et al. 2010).

Focal laser photocoagulation, photodynamic therapy (PDT), intravitreal and periocular triamcinolone and subretinal surgery have been used to treat RAP lesions, but the emergence of anti-VEGF substances as standard treatment for exudative AMD has shifted the focus to ranibizumab and bevacizumab. (Boscia et al. 2006; Freund et al. 2006; Johnson & Glaser 2006; Krieglstein et al. 2006; Meyerle et al. 2007; Gharbiya et al. 2009; Konstantinidis et al. 2009; Lo Giudice et al. 2009; Montero et al. 2009; Rouvas et al. 2009) These substances have been shown to be effective in the treatment of RAP, but the optimal treatment regimen and whether a multimodal approach would be beneficial remain unclear.

This case series investigates the efficacy and safety of intravitreal ranibizumab (Lucentis, Novartis AG, Switzerland) used in combination with verteporfin photodynamic therapy (Visudyne, Novartis AG, Switzerland) in the treatment of sub- and juxtafoveal RAP lesions.

Methods

Patients

The present prospective study comprised 15 patients with RAP, who were included between July 2008 and July 2009 at the Department of Ophthalmology of the Medical University of Graz/Austria. Inclusion criteria for the study were the presence of treatment-naïve RAP at any stage and a best-corrected visual acuity (BCVA) in the affected eye between 24 and 73 letters with Early Treatment Diabetic Retinopathy Study (EDTRS) visual acuity chart testing. RAP lesions only less or equal to 5400 μm in greatest linear dimension and lying within 200 μm of the geometric centre of the foveal avascular zone were included. This was determined by fluorescein and indocyanine green angiography (FA/ICG). Eyes that underwent surgery within 6 months prior to baseline and eyes with other ocular pathologies currently compromising vision or likely to do so during the study were excluded.

Study design

All patients who met the study criteria and consented to participate in the study were scheduled for baseline examination. Within 7 days after examination, every patient received verteporfin photodynamic therapy according to the standard protocol as described by the TAP study group (1999). This was followed by an intravitreal injection of 0.5-mg ranibizumab the next day. The regimen included additional injections of 0.5-mg ranibizumab both 1 and 2 months after the first treatment. After that, patients received intravitreal ranibizumab injections according to a PRN regimen. To minimize the risk of RPE tears, which have been reported to occur in up to 19% after repeated PDT therapy for RAP with a PED, we performed PDT at the initiation of the study only. (Boscia et al. 2006; Introini et al. 2012).

Criteria for retreatment were worsening of BCVA ≥5 letters, activity on FA/ICG angiography, which was defined as late leakage, or any evidence of new or persistent sub- or intraretinal fluid based on optical coherence tomography (OCT) imaging. This was determined during monthly examinations featuring BCVA measurement, applanation tonometry, biomicroscopic examination, OCT, fundus photography and medical history. Additionally, FA/ICG angiography was performed at baseline, day 90, day 180 and day 360. A general ophthalmologist assessed possible adverse events three days after every intravitreal injection. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. All patients provided written consent.

End-points

The primary end-point was the change in BCVA between baseline and month 12. Secondary end-points included the mean change in BCVA between baseline and month 6, the proportion of patients with a gain of ≥5, 10 or 15 letters and of patients with a loss of ≥15 letters, the total number of treatments, the mean time to first retreatment following the initial loading dose and the mean change in foveal thickness on OCT.

Table 1. Baseline characteristics*.

Age – year	79.7 ± 4.7
Female sex – No./ total no. (%)	10/15 (66.7)
BCVA – ETDRS letters	58.1 ± 13.2
RAP classification – No./total no. (%)	
Stage I	7/15 (46.7)
Stage IIa	4/15 (26.7)
Stage IIb	4/15 (26.7)
Stage III	0/15 (0)
Foveal thickness – μm	355.9 ± 83

* Plus-minus values are means ± SD.

Statistical analysis

The changes in BCVA and retinal thickness were analysed using Wilcoxon rank sum test with a 95% confidence interval and two-tailed p-values. Results are presented as means ± standard deviation (SD), except as otherwise noted. A p-value < 0.05 was considered statistically significant. SPSS version 19 for windows, SPSS, Inc., was used for statistical analysis.

Results

Patients

All 15 patients completed the loading regimen according to the study protocol. The baseline characteristics of these patients are shown in Table 1. All but one patient completed follow-up on time. In that patient, there was a delay of 10 weeks for follow-up visit 7 due to depression, which had been known already before the start of the study, and was therefore not considered an adverse event.

Adverse events

No serious adverse events, such as endophthalmitis or retinal detachment, were observed.

BCVA

The mean BCVA improved significantly by 9.2 ± 8.5 letters at month 6 ($p < 0.004$) and by 8.7 ± 11.4 letters at month 12 ($p < 0.017$) from baseline. Table 2 shows the clinical outcomes at month 6 and 12 from baseline. After an initial 4 month's

Table 2. Clinical outcomes at 6 months and 12 months*.

Outcome	6 months	12 months
Change in BCVA – letters	+9.2 ± 8.5	+8.7 ± 11.4
Mean injections – No.(min/max)	3.3 (3/4)	4.8 (3/8)
Letters gained	No. of patients (%)	No. of patients (%)
≥5	12 (80)	9 (60)
≥10	9 (60)	7 (46.7)
≥15	4 (26.7)	4 (26.7)
Foveal thickness – μm	201.6 ± 53.0	211.3 ± 82.2

* Plus-minus values are means ± SD.

improvement, the BCVA remained stable. Neither at 6 nor at 12 months, any patient had lost ≥15 letters.

Morphologic changes

Mean foveal thickness decreased by 157.3 ± 82 μm 2 months from baseline and remained stable thereafter throughout the observation period. This reduction was highly statistically significant ($p < 0.001$). Figure 1 illustrates the changes in retinal thickness and BCVA over time. In FA/ICG, all lesions were inactive at month 3, but at month 12, 33% ($n = 5$) of the patients showed angiographic activity. PED resolved in all patients after the initial loading regimen and did not recur in any patient.

Retreatment

After initial PDT followed by 3 monthly injections of ranibizumab, 11 patients (73.3%) needed retreatment at least once during the 9-month follow-up. The mean interval between completion of the loading dose and the first retreatment with intravitreal ranibizumab in these patients was 3.7 months (range 3–7 months). The overall annual injection rate was 4.8 (range 3–8).

Discussion

This study's regimen of PDT with 3 ranibizumab loading injections and subsequent monthly ranibizumab in case of any retinal fluid on OCT resulted in a significant gain of 8.7 ± 11.4 letters at month 12.

When interpreting our data, it is important, however, to keep in mind that 11 of 15 eyes showed stage I or IIa lesions. It is well known that these lesions respond better to treatment than more advanced stages. (Reche-Frutos et al. 2011) None of the study patients had a stage III RAP, where visual recovery after any form of therapy might be limited, because of the destruction of retinal pigment epithelium and retinal architecture. Additionally, the established retino-choroidal anastomosis in stage III lesions might react particularly poor to PDT. Success rates in occluding vessels permanently with this treatment are heavily impacted by the vessel's haemodynamic conditions, as PDT induces the formation of rather small fibrin poor clots. These clots might dissolve or be swept away by high perfusion pressures present in established anastomoses. This makes stage III RAP prone to reperfusion after PDT. Thus, it has been proposed that PDT mainly targets the choroidal component of RAP, where perfusion pressures are considerably lower than in the retinal component. (Ghazi et al. 2001; Boscia et al. 2006) In contrast to initial studies (Yannuzzi et al. 2001), more recent findings of Freund et al. suggest that early choroidal involvement in RAP does occur (Freund et al. 2008), setting a theoretical basis for potential efficacy of PDT in these lesions.

In a preliminary report of their 3-year study, Rouvas et al. described a reduction in ranibizumab injections after complementary PDT compared to ranibizumab alone, but their two groups are difficult to compare when taking into account that considerable differences in follow-up and RAP stage exist (8.4 versus 14 months; 76.9% II + 23.1% III versus 100% II). (Rouvas et al. 2009) In addition, naïve as well as pretreated RAP were included. This reduction remained significant after 3 years. (Rouvas et al. 2012).

In the literature on the treatment of RAP with ranibizumab, low patient numbers compared to overall AMD and different study designs especially concerning follow-up and RAP stage make a comparison of treatment rates and visual outcome difficult. Visual outcome is subject to remarkable variation and ranges from stabilization to gains of more than 2 lines. (Konstantinidis et al. 2009; Rouvas et al. 2009; Kramann et al. 2010) Treatment rates range from 3.9 injections in 12 months to 5.9 injections in only 8.4 months. (Konstantinidis et al. 2009; Rouvas et al. 2009; Parodi et al. 2011) Interestingly, most of these data were obtained from stage II and III RAP.

Despite the high proportion of early-stage RAP and the complementary use of PDT in our study, we observed similarly high retreatment rates as other studies on ranibizumab for treatment-naïve RAP. This might be due to our strict retreatment criteria, which subsequently led to high injection rates. Using similar criteria, Reche-Frutos et al. reported an even higher annual retreatment rate of 5.6, but in their study, 70% of stage III, 44.4% of stage IIb and 20% of stage IIa were pretreated. (Reche-Frutos

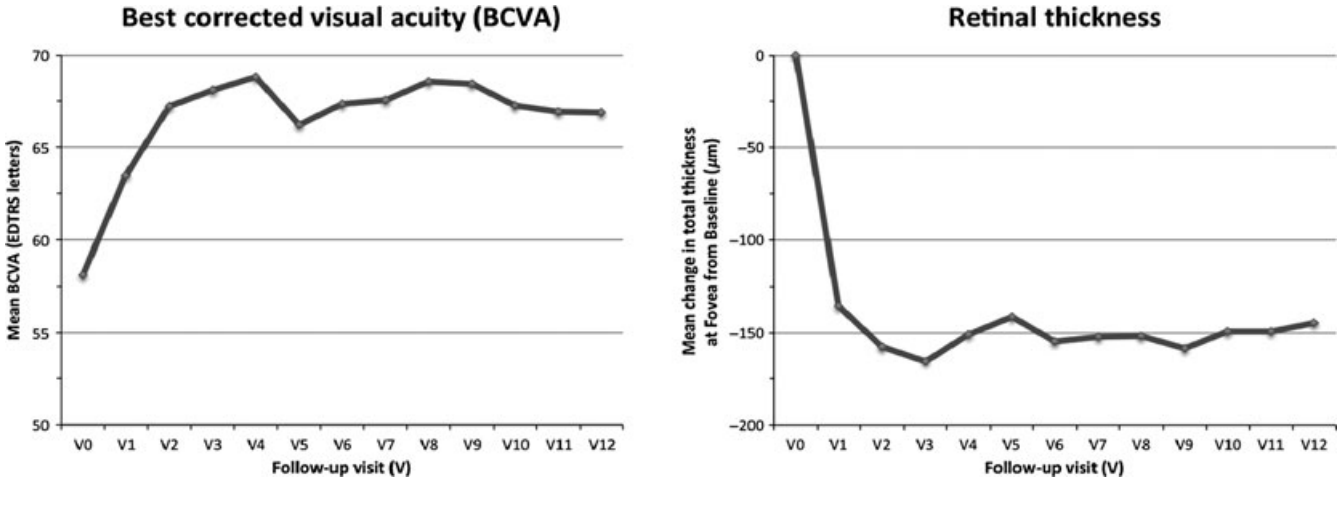

Fig. 1. Mean change from baseline (V0) in BCVA and in retinal thickness at the fovea during the 12 months of follow-up.

et al. 2011) The inclusion of pretreated lesions and the different profile of RAP stages could explain their higher retreatment rates. However, due to the lack of a control group in our study, we are, unfortunately, unable to draw definite conclusions concerning the extent of the effect by additional PDT to intravitreal ranibizumab. To shed light on this matter, we require further studies on a larger scale.

Whereas previous large-scale studies on exudative AMD often excluded RAP, the CATT study included type 1 and type 2 neovascularization as well as RAP. However, their 123 RAP patients were not analysed separately. (Martin et al. 2011) Future research focusing on anatomical features of AMD might provide better understanding of varying responsiveness to treatment.

In summary, our data suggest that the combination of PDT and ranibizumab is efficacious and save for patients with RAP, but even in a population of mostly early stages, retreatment rates remained high.

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