Original Article

One-Year Outcomes Comparison of Anti-VEGF Monotherapy and Combined Anti-VEGF+Photodynamic Therapy for Retinal Angiomatous Proliferation

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Abstract

Objectives: This study was a comparison of the results achieved in patients with age-related macular degeneration and retinal angiomatous proliferation (RAP) diagnosis receiving intravitreal anti-vascular endothelial growth factor (anti-VEGF) monotherapy and receiving photodynamic treatment (PDT) combined with anti-VEGF treatment.

Methods: A retrospective chart review of patients with RAP who were treated in the retina clinic of Beyoglu Eye Training and Research Hospital was conducted. Patients were divided into 2 groups: patients who received anti-VEGF monotherapy formed Group I, and Group II comprised those who underwent combined therapy with PDT. Best corrected visual acuity (BCVA) and central macular thickness values at baseline and at months 6 and 12, and the number of anti-VEGF injections and PDT sessions were recorded.

Results: Fifteen eyes of 14 patients were included. Six of the patients were female and 8 were male; the mean age was 73.2±9.7 years. The mean baseline BCVA was 0.70±0.52 log of the minimum angle of resolution. Visual acuity increased in 1 of 15 eyes (6.6%), remained stable in 10 eyes (66.6%), and decreased in 4 eyes (26.6%). A total of 7 eyes received anti-VEGF monotherapy, and 8 eyes received combined PDT and anti-VEGF treatment. The mean number of injections was 10.7±7.8. Five eyes received 1 PDT session and 3 eyes received 2 sessions.

Conclusion: In this study, visual acuity was preserved in the majority of patients receiving anti-VEGF monotherapy and combined PDT and anti-VEGF treatment for RAP lesions.

Keywords: Anti-vascular endothelial growth factor, photodynamic treatment, retinal angiomatous proliferation.

Introduction

Age-related macular degeneration (AMD) is the most common disease causing irreversible blindness in developed countries (1). Choroidal neovascularization (CNV) is the main lesion type for classifying exudative AMD. CNV types 1 and 2 indicate anatomically sub-retinal pigment epithelium (RPE) and subretinal lesions, respectively. In addition to these 2 types, intraretinal neovascular lesions are now accepted as a subdivision of exudative AMD and are referred to as type 3 CNV, which results in retinochoroidal anastomosis, and the condition is known as retinal angiomatous proliferation (RAP) (2-4).

RAP lesions are subdivided into 3 groups: In type 1, the lesions are located intraretinally, type 2 lesions reach the subretinal space, and with further progression, type 3 lesions reach the sub-RPE spaces, forming retinochoroidal anastomosis. Indocyanine green angiography (ICG) can be used to distinguish RAP lesions from lesions described as occult CNV with fundus fluorescein angiography (FFA) (2, 5).

Exudative AMD treatment includes argon laser photocoagulation, (6) photodynamic treatment (PDT), (7-9) and in-

travitreal antiangiogenic factor (anti-VEGF), which has been the principal method used for the last decade (10-12). Anti-VEGF monotherapy can provide the necessary decrease in subretinal fluid, an active disease marker in clinical examination and optical coherence tomography (OCT), and also increase visual acuity (13). RAP lesions, however, might require more aggressive treatment protocols with PDT in clinical practice (14). RAP lesions may be detected when anti-VEGF-resistant cases primarily diagnosed as exudative AMD are re-evaluated (15).

The main purpose of this study was to evaluate the results of anti-VEGF monotherapy versus anti-VEGF therapy combined with PDT in primarily diagnosed RAP cases as well as secondarily diagnosed RAP cases refractory to anti-VEGF treatment.

Methods

Fifteen eyes of 14 patients from the Beyoglu Eye Training and Research Hospital retina clinic were included in this single-center retrospective study. Written informed consent was obtained from each patient before anti-VEGF injections and PDT were performed. All patients underwent a complete ophthalmic examination, including past medical history, visual acuity measurement with ETDRS chart, anterior chamber slit-lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, and dilated fundus examination with a 90 D lens. Fundus fluorescein and indocyanine green angiographies (Spectralis HRA-2; Heidelberg Engineering GmbH, Heidelberg, Germany) and OCT (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany) were also performed.

Associated systemic diseases, the length of the interval between presentation and RAP diagnosis, the presence of pigment epithelial detachment (PED) in the same eye, the presence of exudative AMD (drusen, PED, CNV) in the fellow eye, preoperative and postoperative best corrected visual acuity (BCVA) and central macular thickness (CMT) values, the number of anti-VEGF injections and PDT sessions before and for the first year after RAP diagnosis, disease activity status on last examination, and length of follow-up were noted.

Patients were administered 0.5 mg ranibizumab (Lucentis; Novartis, Basel, Switzerland) or 2 mg aflibercept (Eylea; Bayer Pharma AG, Berlin, Germany) for anti-VEGF monotherapy, and PDT was performed with verteporfin on day 3 (Visudyne; Novartis, Basel, Switzerland) for combined therapy. Patients in both groups received retreatment in the event of leakage detected on FFA or ICGA, loss of over 5 letters in BCVA, or a mean increase in CMT of ≥100 µm as measured by OCT.

Primary outcome measures were defined as BCVA log of the minimum angle of resolution (logMAR) and CMT chang-

es between baseline and 12 months. A secondary outcome measure was the percentage of patients showing improvement or deterioration in BCVA of more than 5 letters. Statistics were analyzed with IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA) with a level of significance of p<0.05. The categorical variables were described as absolute and relative frequencies, while the continuous variables were reported as mean, median, SD, and range. A chi-square test was used to compare the categorical variables. Comparison of continuous variables was performed with a parametric (independent samples t-test) or nonparametric test (Mann-Whitney U test), depending on the characteristics of the variables.

Results

Fifteen eyes of 14 patients were included and divided into 2 groups for the study. Group I included 7 of 15 eyes treated with anti-VEGF monotherapy, and Group II included 8 of 15 eyes that received combined anti-VEGF and PDT. In Group I, 4 patients were female, and 3 patients were male; in Group II, 3 were female, and 5 were male. Table 1 shows the demographic and clinical characteristics at baseline according to groups (age, sex, phakic status, baseline BCVA, RAP stage). Mean baseline BCVA and CMT differences between the 2 treatments were found to be statistically insignificant (p=0.06 and p=0.58, respectively). One patient in the study was treated with anti-VEGF monotherapy in 1 eye and combined therapy in the other eye. The most frequent RAP type was type III (57% in Group I, 71% in Group II). The mean length of time from the first AMD treatment to RAP diagnosis was 9.8±12.6 months in Group I and 10.1±11.9 months in Group II. Primary diagnosis was RAP for 3 patients in Group I and for 4 patients in Group II. PDT was added to therapy when the lesion showed no or poor response to anti-VEGF therapy at the time of RAP diagnosis. Patients in both groups had not received PDT before RAP diagnosis. Two eyes were reported to be resistant to previous intravitreal ranibizumab injection in Group I, whereas 5 eyes were found to be resistant to the same treatment in Group II.

The mean baseline BCVA changed from 0.49±0.32 logMAR (range: 0.15-1.0 logMAR) to 0.61±0.51 logMAR (range: 0.1-1.52 logMAR) at 12 months in Group I (p=0.06), and from 1.0±0.59 logMAR (range: 0.3-2.0 logMAR) to 1.07±0.31 (range: 0.7-1.52 logMAR) at 12 months in Group II (p=0.22). Both groups had statistically insignificant visual deterioration. The mean change in BCVA from baseline to 12-month follow-up was 0.11±0.23 logMAR in Group I and 0.21±0.26 logMAR in Group II (p=0.38). No statistically significant difference was found between the groups in terms of mean BCVA change.

BCVA increased in 1 eye (14.3%), decreased in 3 eyes (42.9%), and remained stable in 3 eyes (42.9%) in Group I.

Table 1. Demographic and clinical characteristics at baseline according to groups

Parameter	Eyes studied	Treatment group I	Treatment group II
Age (years)	73.2±9.3	71±7.6	75.13±10.7
	(range 55-91)	(range 55-79)	(range 62-91)
Sex (male/female)	8/7	3/4	5/3
Phakic status	8/7	5/2	3/5
(phakic/pseudophakic)			
Baseline BCVA	0.76±0.54	0.49±0.32	1.0±0.59
(logMAR)	(range 0.15-2.0)	(range 0.15-1.0)	(range 0.3-2.0)
RAP type: I/II/III	1/5/9	1/2/4	0/3/5

BCVA: best corrected visual acuity; LogMAR: log of the minimum angle of resolution; RAP: retinal angiomatous proliferation.

Similarly, BCVA increased in 1 eye (12.5%), decreased in 4 eyes (50%) and remained stable in 3 eyes (37.5%) in Group II. No statistically significant difference was found between groups (p=0.96).

The mean CMT was 417±206 μm (range: 225-713 μm) at baseline and was 288±95 μm (range: 214-486 μm) at 12 months in Group I (p=0.02), which was a significant decrease compared with that seen in Group II, which had a mean CMT of 480±229 μm (range: 265-716 μm) at baseline and changed to 406±171 μm (range 200-695 μm) at 12 months (p=0.88). However, between groups, the difference in the mean change in CMT of -129 μm in Group I and -32 μm in Group II was not statistically significant (p=0.06). The mean number of injections was 4.7±2.6 in Group I, and 6.7± in Group II. The mean number of injections was not significantly different between groups (p=0.12). In Group II, 5 patients received a single dose of PDT, and 3 patients received it 2 times.

Discussion

Regarded as a subtype of AMD, 2 RAP had been kept separate from classic AMD initially as an intraretinal lesion that responded poorly to treatment. Due to the lack of a standardized treatment protocol, comparative studies exploring various treatment modalities are still being performed. The present study is an attempt to contribute to this research by comparing 2 treatment regimes (anti-VEGF monotherapy versus combined anti-VEGF+PDT) for RAP disease.

The results of the present study can be analyzed on the basis of visual acuity and CMT values. Though Group I had fewer resistant cases than Group II (2/7 vs. 5/8), the impact on the baseline BCVA and CMT values appears to be clinically insignificant (p=0.06 and p=0.58, respectively). An overall decrease in BCVA was observed in 2 groups with baseline values that did not present a statistically significant difference; however, the sum of cases with a stable or in-

creased BCVA scores was 14% higher than those with decreased BCVA values. Although the effect of both treatment regimens on visual acuity appears to have been similar, only Group I patients had increased BCVA. When CMT scores were analyzed, a 129 μm decrease in Group I indicated a significant change, while there was no change in Group II. There was no significant difference in anti-VEGF injection doses between groups.

In a randomized prospective study of RAP treatment conducted by Arias et al., (16) 10 patients received intravitreal ranibizumab monotherapy (Group A), and 10 patients received ranibizumab+PDT (Group B). Both groups had an increase in visual acuity and a decrease in CMT values, without a significant difference between them, though the BCVA increase in Group B and the CMT decrease in Group A were interpreted as more effective. It should be noted that 3 patients in Group A had received PDT before entering the study. The significant CMT decrease in our study correlates with the tendency in this trial.

In their randomized prospective study, Rouvas et al. (17) compared RAP patients receiving ranibizumab monotherapy (n=13), ranibizumab+PDT (n=13) and triamcinolone+PDT (n=11) for a 12-month period. There was no significant difference between visual acuities, and only a significant difference between the triamcinolone+PDT group and the other groups in CMT decrease. This result differs from the results reported by Arias et al. and the present study, but both of those studies included patients who had previously received AMD treatment, unlike the study of Rouvas et al., which enrolled treatment-naive patients. In a case report review presented by Saito et al., (18) combined anti-VEGF+PDT was applied to treatment-naive patients, the majority with type II RAP lesions, and demonstrated 3 or more lines of BCVA increase in 50% of cases at 12-month interval. For Arias et al., BCVA increase remained at 20%,16 and in our study, no

increase was reported in the combined treatment group.

Nakano et al. (19) reported similar results to Rouvas et al., indicating a better increase in BCVA and decrease in CMT for PDT combined with subtenon triamcinolone than PDT monotherapy and combined PDT+anti-VEGF. There were no patients receiving anti-VEGF monotherapy in that study.

With respect to total injection numbers, significant decreases were reported for combined treatments in the studies performed by Arias et al. and Rouvas et al. (16, 17). The lack of a significant difference in our group can be explained by the fact that the patients were already refractory to anti-VEGF treatment prior to PDT.

As demonstrated by studies in literature, anti-VEGF treatment either as a monotherapy or in combination with PDT, has proved to be an efficient method of preserving visual acuity and providing anatomical success (10-14, 16-19). Our study also presented results with preserved visual acuity and improved macular anatomy. Administered therapies appear to be more effective in treatment-naive cases 18 and cases with stage II lesions; both observed decrease in recurrences (16, 20). In addition to the anatomically successful outcomes with anti-VEGF monotherapy noted by Arias et al. (16) and in the present study, there are also findings indicating that PDT combined with anti-VEGF, triamcinolone, and other modalities were superior to anti-VEGF monotherapy (17-19).

Limitations of the present study are its retrospective design and the limited study group (n=15 eyes), but when compared to other studies in literature, sufficient data could be provided to achieve adequate results (16-20). It should also be emphasized that the uneven distribution of treatment-resistant cases may have had an effect on the results.

Conclusion

Larger study groups exploring RAP treatment are warranted, given the present results. Recent study findings suggest hope for achieving standardized treatment regimes to preserve visual acuity and anatomical improvement. To eliminate bias effects on results, separate studies based on resistant-case groups receiving suggested treatment modalities might be beneficial.

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