·Clinical Research·

Low-fluence photodynamic therapy combinations in the treatment of exudative age-related macular degeneration

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Abstract

• AIM: To compare the efficacy of low-fluence photodynamic therapy (PDT) combinations in the treatment of age-related macular degeneration (AMD).

• METHODS: Forty-five previously untreated eyes of 45 patients with exudative AMD whose best-corrected visual acuity (BCVA) was ≥ 0.3 (Snellen) were enrolled. 15 patients in Group I underwent low-fluence PDT (25J/cm^2-300mW/cm^2-83sec) and intravitreal pegaptanib combination, 15 patients in Group II underwent PDT (50J/cm^2-600mW/cm^2-83sec) and intravitreal pegaptanib combination while, 15 patients in Group III underwent intravitreal pegaptanib monotherapy. Complete ophthalmologic examinations were performed in pre and post treatment visits, and the results were statistically analised. A clinical activity score (CAS) was calculated by using changes in lesion size, amount of hemorrhage, staining pattern in FA and OCT measurement of intra/subretinal fluid. ≤ 3 logMAR lines of decrease in BCVA and decrease in CAS were considered as successful treatment.

• RESULTS: The mean age of 19 female (42.2%) and 26 male (57.8%) patients was (72.82 ± 8.02) years. Mean follow-up was (13.93± 5.87) months. Lesion type was occult in 28 eyes (62.2%). Treatment success rates according to BCVA assessments were 86.7%, 80%, 60% and mean BCVA decrease were 0.3, 1.0, 2.2 logMAR lines in Group I, II and III, respectively (P>0.05). According to the changes in central macular thickness and CAS, no difference was found among the study groups(P=0.850 and P=0.811, respectively). Patients treated with combination regimens had lower intravitreal injection frequencies (P=0.015).

• CONCLUSION: Combination regimen with intravitreal pegaptanib and low-fluence PDT seems to be safe and effective in stabilizing the clinical activity and BCVA in exudative AMD.

• KEYWORDS:age-related macular degeneration; photodynamic therapy; low-fluence photodynamic therapy; anti-VEGF
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INTRODUCTION

Age related macular degeneration (AMD) is the most common cause of central vision loss and legal blindness in developed countries over 50 years of age. The prevalence of legal blindness due to late AMD is approximately 1.7% after the age of 50 and 18%-30% after the age of 85[1-4]. However no complete therapy is proven for exudative AMD, argon laser photocoagulation is commonly used in the treatment of extrafoveal choroidal neovascularization (CNV) [5,6]. Oral supplementation with antioxidant vitamin and minerals are also tried in AMD due to the evidence that nutrition plays crucial role in the pathogenesis of the disease. New treatment procedures such as photodynamic therapy for juxtafoveal and subfoveal CNV, intravitreal and periocular steroid injections, vascular endothelial growth factor (VEGF) inhibitors that supress angiogenesis may be used already.

Rather than the increase in visual acuity, reduced risk of vision loss could be demonstrated in both PDT studies and monotherapy studies[7, 8]. Also increased retinal inflammation and VEGF secretion after PDT may trigger intraretinal edema, novel CNV development and disease recurrence [9]. Due to the multifactorial pathogenesis of CNV development, AMD treatment should contain three main factors which were suppression of inflammation, regression of present CNV and prevention of novel CNV development by inhibition of angiogenic stimulus[10]. But there is no effective and safe monotherapy agent that affects all of these three mechanisms. So new sinergistic combination treatment protocols which activate all of these pathways and require

less application have been commonly used [10-23]. Final visual acuity may improve and the intravitreal injection rates may reduce by the sinergistic effect of verteporfin PDT with intravitreal anti-VEGF injection. Addition of intravitreal steroid injections into such combinations for the reduction of retinal edema and hemorrhage and inhibition of VEGF production by supressing inflammation may also be beneficial. Anti-VEGF treatment reduces retinal and vitreal basal VEGF, as well as inhibits intensive VEGF production after PDT, hence it is very important for prevention of novel CNV development [10-23]. Because of the recent studies demonstrate similar results with the reduction of light dose in PDT, new treatment parameters called as low fluence PDT are being tested in order to avoid the possible side effects of laser beam on retinal pigment epithelium [10,20-27]. In the present study, comparison of the efficacy of intravitreal pegaptanib sodium monotherapy with conventional dose and low fluence PDT combinations in the treatment of AMD was aimed.

MATERIALS AND METHODS

Subjects Fourty-five previously untreated eyes of 45 patients with exudative AMD whose best-corrected visual acuity (BCVA) was equal or over 0.3 (Snellen), were enrolled in the study. All subjects signed their informed consent form prior to enrollment in accordance with the Declarations of Helsinki guidelines, and the study was approved by the local ethics committee. In case of bilateral exudative AMD, only one eye of the participants with the worse BCVA which was also equal or over 0.3 (Snellen), was enrolled. Patients with CNV owing to conditions other than AMD were excluded. Participants were assigned randomly in 1:1:1 order to the one of the three study treatment procedures. 15 patients in Group I underwent low-fluence PDT ($25J/cm^2$; $300mW/cm^2$; 83 sec) and intravitreal pegaptanib sodium combination. 15 patients in Group II underwent PDT according to standart protocol ($50J/cm^2$; $600mW/cm^2$; 83 sec) and intravitreal pegaptanib sodium combination while, 15 patients in Group III underwent intravitreal pegaptanib sodium alone for the treatment of exudative AMD. After the first injections, at least two additional doses of 0.3mg intravitreal pegaptanib sodium (Macugen, Pfizer) with six-week intervals were applied to the entire study population. All injections were performed under standard sterile conditions and topical antibiotherapy were administered for a week after the injection. After the first intravitreal pegaptanib application, PDT with Verteporfin (Visudyne, Novartis) was performed within 48 hours in the first and second study groups. Non-thermal diode laser with wavelength of 689nm (Carl Zeiss meditec AG, Jena, Germany) with the spot size that is set to be 1000μm larger than the maximum diameter of the exudative AMD lesion was applicated.

Table 1 Clinical activity score

Parameter	Grade	Score
Subretinal hemorrhage	No hemorrhage	0
	< 1 MPS Disk area	1
	1 – 3 MPS Disk area	2
	> 3 MPS Disk area	3
OCT measurement of intra/subretinal fluid (onset: 2 points)	No	0
	Regression	1
	Stability	2
	Progression	3
Staining pattern in FA	No	0
	Staining of the scar tissue	1
	Lesional shiny staining	2
	Late leakage	3
Lesion size (onset: 2 points)	Disappearance	0
	Regression	1
	Stability	2
	Progression	3

Methods Detailed ophthalmologic examination including Snellen BCVA, slit-lamp examination, ocular tonometry and dilated fundoscopy, as well as OCT (Stratus OCT with Stratus 4.0 software, Carl Zeiss Meditec and Heidelbelg HRA-OCT Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) and FA (Carl Zeiss Meditec AG, Jena, Germany and Heidelbelg HRA-OCT Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) were performed at baseline. Detailed examination and OCT were also performed at each postoperative visits which were planned at every sixth week, however FA was carried out at three-month intervals. The results of examinations were used in statistical analysis.

Retreatment with the anti-VEGF agent after the third intravitreal pegaptanib sodium injection was applied in case of one or more Snellen line decrease in BCVA, 100μm or more increase in central macular thickness (CMT) on OCT, less than 50% improvement in leakage or appearance of a new spot on FA, detection of a new hemorrhage focus or increase in the size of the lesion at the control visits. Also comparison of total number of intravitreal injections among the three study group was verified.

Before the treatment and at the final follow-up visit, a clinical activity score (CAS) was calculated for each lesion by using changes in the lesion size (onset: 2 points), amount of hemorrhage, staining pattern in FA and OCT measurement of intra/subretinal fluid (onset: 2 points) as Aktas *et al* [28] described in cases with occult CNV in AMD (Table 1). Snellen acuities were converted into the logarithm of the mean angle of resolution (logMAR) for statistical analysis. ≤3 logMAR lines of decrease in BCVA and decrease in CAS were considered as successful treatment. CMT and leakage fault detection as well as total number of intravitreal injections were also studied among the study groups.

Table 2 Demographics *n* (%)

Demographics	Group I	Group II	Group III	Overall	*P*
Gender					0.695
Female	5 (33.3)	7 (46.7%)	7 (46.7)	19 (42.2)	
Male	10 (66.7)	8 (53.3%)	8 (53.3)	26 (57.8)	
Age (a)	73.07±8.08	71.20±8.23	74.20±8.02	72.82±8.02	0.596
Diabetes mellitus	3 (20)	0 (0%)	3 (20)	6 (13.3)	0.177
Hypertension	8 (53.3)	5 (33.3%)	11 (73.3)	24 (53.3)	0.090
BCVA (Snellen)	0.34±0.06	0.39±0.14	0.33±0.08	0.35±0.10	0.239
BCVA (logMAR)	0.46±0.06	0.42±0.13	0.47±0.08	0.45±0.09	0.280
IOP (mmHg)	15.40±1.35	15.40±1.35	15.40±1.35	15.40±1.35	0.216
Biomicroscopy					0.054
Phakic	10 (66.7)	11 (73.3)	15 (100)	36 (80)	
Pseudophakic	5 (33.3)	4 (26.7)	0 (0)	9 (20)	
Lesion type					0.198
Classic	4 (26.7)	2 (13.3)	0 (0)	6 (13.3)	
Predominantly classic	0 (0)	1 (6.7)	1 (6.7)	2 (4.4)	
Minimally classic	1 (6.7)	5 (33.3)	3 (20)	9 (20)	
Occult	10 (66.7)	7 (46.7)	11 (73.3)	28 (62.2)	
Lesion size (μm)	3586.7±1364.4	4373.3±1239.5	4266.7±1172.7	4075.6±1281.8	0.192
CMT (μm)	396.1±120.0	450.4±230.5	422.1±83.6	422.9±155.6	0.644
CAS	7.27±1.10	7.40±0.74	7.67±1.05	7.44±0.97	0.524

According to type of lesion, study population was grouped as classic, predominantly classic, minimally classic and occult. Statistical analysis of the changes in BCVA, CAS, CMT and leakage fault detections, total number of intravitreal injections were also evaluated depending on the treatment modality in patients with occult AMD lesion. Depending on the treatment modalities, similar comparisons were planned in the study eyes after grouping them according to the widest diameter of the AMD lesion as 3600μm or less and over than 3600μm.

Statistical Analysis The data were stored on a computerized database and analyzed using SPSS 15.0 for Windows (Statistical Package for Scientific Studies for Windows, SPSS Inc., Chicago, IL). Oneway ANOVA, Kolmogorov-Smirnov, chi square, Fisher's exact and Student's t tests as well as Kruskal-Wallis, Mann Whitney U and Wilcoxon tests were used in the statistical analysis and $P<0.05$ was considered statistically significant.

RESULTS

Nineteen female (42.2%) and 26 male (57.8%) patients with the mean age of (72.8 ±8.0) years (50-87 years) were enrolled and assigned to one of the three treatment groups, randomly. No statistically significant difference was detected among these treatment groups with respect to baseline clinical and demographic characteristics (Table 2). Treatment was started avaragely (9.07±9.75) months after the initial symptoms of exudative AMD in each patient and mean follow-up time was (13.93 ±5.87) months (6-24 months). Occult subfoveal CNV was diagnosed in 28 patients (62.2%). No statistically significant difference was found between study subgroups according to initial lesion diameter, CMT and CAS results (Table 2).

Table 3 Changes in the central macular thickness (CMT) and clinical activity score (CAS)

Treatment protocol	Pretreatment	Posttreatment	*P*
Group I			
CMT (μm)	396.13±119.93	345.67±74.61	0.047
CAS	7.27±1.10	5.47±1.69	0.002
Group II			
CMT (μm)	450.40±230.47	339.07±129.94	0.009
CAS	7.40±0.74	5.33±2.06	0.004
Group III			
CMT (μm)	422.13±155.58	348.53±88.95	0.020
CAS	7.67±1.05	5.60±1.84	0.003

Patients in group I and II received significantly fewer intravitreal injection application (mean 3.33±0.61 and 3.40± 0.91) compared to injection frequency (mean 4.20±1.01) in group III patients ($P=0.015$).

Successful treatment evaluated with the decrease in CAS was achieved in 86.7%, 86.7% and 73.3% of the cases in group I, II and III, respectively. However, retinal thickness and clinical activity were significantly decreased in each of all study groups, neither the change in mean CMT nor the difference in mean CAS showed statistically significance among study subgroups (Table 3). Although macular thickness and CAS were significantly decreased at the end of the follow-up period, visual acuity did not improve as expected. There was no statistically significant difference in overall mean BCVA in the last follow-up visit compared with the pretreatment scores($P>0.05$). In treatment subgroup analysis, 0.3 logMAR, 1.0 logMAR and 2.2 logMAR lines of decrease were found, respectively (Figure 1). Successful

Table 4 Treatment success rates owing to the changes in BCVA *n* (%)

Study groups	Follow-up	⩾ 3 line of decrease	< 3 line of decrease	Stability	< 3 line of gain	⩾ 3 line of gain	Treatment success
I	1st month	2 (13.3)	7 (46.7)	2 (13.3)	3 (20)	1 (6.7)	86.7%
	3rd month	2 (13.3)	5 (33.3)	1 (6.7)	7 (46.7)	-	86.7%
	6th month	3 (20)	2 (13.3)	3 (20)	6 (40)	1 (6.7)	80%
	Last visit	2 (13.3)	3 (20)	2 (13.3)	7 (46.7)	1 (6.7)	86.7%
II	1st month	4 (26.7)	5 (33.3)	4 (26.7)	2 (13.3)	-	73.3%
	3rd month	4 (26.7)	3 (20)	4 (26.7)	4 (26.7)	-	73.3%
	6th month	3 (20)	4 (26.7)	2 (13.3)	5 (33.3)	1 (6.7)	80%
	Last visit	3 (20)	5 (33.3)	4 (26.7)	2 (13.3)	1 (6.7)	80%
III	1st month	5 (33.3)	1 (6.7)	6 (40)	3 (20)	-	66.7%
	3rd month	6 (40)	1 (6.7)	3 (20)	3 (20)	2 (13.3)	60%
	6th month	5 (33.3)	4 (26.7)	2 (13.3)	3 (20)	1 (6.7)	66.7%
	Last visit	6 (40)	4 (26.7)	-	4 (26.7)	1 (6.7)	60%

Table 5 Treatment success rates owing to the changes in BCVA in cases with occult AMD *n* (%)

Study groups	Follow-up	⩾3 line of decrease	< 3 line of decrease	Stability	< 3 line of gain	⩾3 line of gain	Treatment success
I(*n*=10)	1st month	1 (10)	7 (70)	-	1 (10)	1 (10)	90%
	3rd month	1 (10)	5 (50)	-	4 (40)	-	90%
	6th month	2 (20)	2 (20)	1 (10)	4 (40)	1 (10)	80%
	Last visit	2 (20)	2 (20)	1 (10)	4 (40)	1 (10)	80%
II(*n*=7)	1st month	2 (28.6)	1 (14.3)	3 (42.9)	1 (14.3)	-	71.4%
	3rd month	2 (28.6)	1 (14.3)	3 (42.9)	1 (14.3)	-	71.4%
	6th month	2 (28.6)	1 (14.3)	1 (14.3)	2 (28.6)	1 (14.3)	71.4%
	Last visit	2 (28.6)	1 (14.3)	2 (28.6)	1 (14.3)	1 (14.3)	71.4%
III(*n*=11)	1st month	4 (36.4)	1 (9.1)	4 (36.4)	2 (18.2)	-	63.6%
	3rd month	4 (36.4)	2 (18.2)	1 (9.1)	2 (18.2)	2 (18.2)	63.6%
	6th month	4 (36.4)	3 (27.3)	1 (9.1)	2 (18.2)	1 (9.1)	63.6%
	Last visit	4 (36.4)	4 (36.4)	-	2 (18.2)	1 (9.1)	63.6%

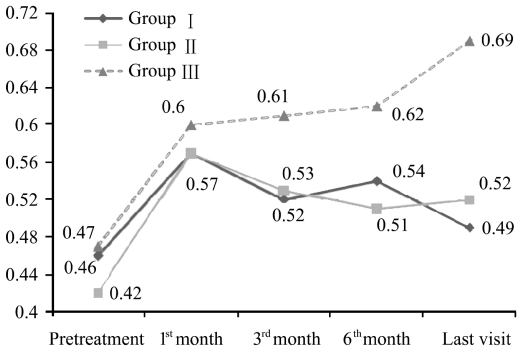

Figure 1 Mean logMAR changes in BCVA among subgroups.

treatment evaluated with ⩽3 logMAR lines of decrease in BCVA was achieved in 86.7%, 73.3% and 66.7% of the patients in group I, II and III respectively (P>0.05) which was shown in Table 4. Absence of leakage of CNV lesion determined by FA was also found in 66.7%, 66.7% and 53.3% of the effected eyes in group I, II and III, respectively (P= 0.185).

CNV lesion type was revealed as occult in 28 eyes (62.2%). Statistical analysis of the changes in BCVA, CAS, CMT and total number of intravitreal injections were evaluated depending on the treatment modality in patients with occult AMD lesion. There was no statistically significant difference in mean BCVA of the study groups in the postoperative first, third and sixth months as well as last follow-up visit compared with the pretreatment scores (P=0.379, P=0.574, P=0.838, P =0.511 and P=0.199, respectively). However no statistically significant difference was found in mean BCVA changes among three study subgroups (P=0.500); BCVA decrease was revealed as 2.5 logMAR lines in group III while 0.7 logMAR and 0.6 logMAR lines of decrease were determined in group I and II, respectively. Successful treatment evaluated with ⩽3 logMAR lines of decrease in BCVA was achieved in 80%, 71.4% and 63.6% of the patients in group I, II and III, respectively(P>0.05) that was shown in Table 5. Although retinal thickness and clinical activity were significantly decreased in each of all study groups, the change in mean CMT and the difference in mean CAS were not statistically significant among them(P=0.354 and P=0.657, respectively). Successful treatment evaluated with the decrease in CAS was achieved in 90%, 85.7% and 81.8% of the cases in group I, II and III, respectively. Patients in group I and II received significantly fewer intravitreal injection treatment (mean 3.30±0.68 and 3.57± 1.13) compared to injection frequency (mean 4.27±1.10) of group III patients (P=0.049).

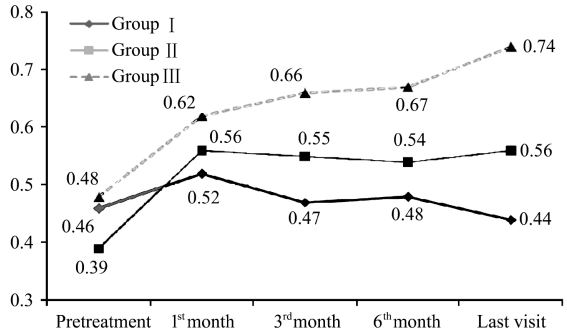

Figure 2 logMAR changes among patients whose CNV diameter was >3600μm.

The widest diameter of the AMD lesion was detected over than 3600μm in 33 cases (73.3%). However better mean BCVA values was evident in group I when compared with group II and III, no statistically significant correlation was found between final BCVA and treatment procedure (P= 0.051) which was demonstrated in Figure 2. Successful treatment evaluated with ≤3 logMAR lines of decrease in BCVA was achieved in 88.9%, 72.7% and 61.5% of the patients at the last follow-up in group I, II and III respectively (P>0.05). However, clinical activity were significantly decreased in each of all study groups, the difference in mean CAS showed no statistically significance (P=0.768).

Finally, no major ocular side effects such as endophthalmitis, retinal detachment and cataract formation were noted. Subconjunctival hemorrhage and floaters after injections were revealed in only a few cases which were resolved without treatment.

DISCUSSION

PDT is a therapy procedure that decrease the risk of severe vision loss by 50% compared to the natural course of the disease. Avaregely 3 lines of loss in visual acuity was revealed with the mean of 3.4 treatment sessions within the first year in TAP and VIP studies[7,8,29]. Transient trombosis at retina and choriocapillaris may be seen after treatment besides verteporfin PDT has a high selectivity to neovascular vessels [30]. Also early inflammatory response and stimulated VEGF expression secondary to transient trombosis at choriocapillaris after PDT may cause frequent recurrences of AMD[9].

Histopathological studies had shown the damage at environmental retinal pigment epithelium layer via photodynamic occlusion of healthy choriocapillaris tissue depending on the applied light dose [22-27]. However early results of the studies using low fluence PDT demonstrated the similar activity with conventional dose of PDT, and some authors suggested the much more efficacy of low-fluence PDT on neovascular tissue, low-fluence PDT treatment has not yet widespread in clinical practice [25-27]. Framme *et al* [26] demonstrated much more selective vascular occlusion without photoreceptor and retinal pigment epithelium damage via 100mW/cm^2 dose of PDT in an experimental neovascularization model, and suggested the greater efficacy of low-fluence PDT application over the conventional dose. VIM study group also showed less visual alteration in AMD patients who received PDT at a dose of 25mW/cm^2 when compared with the conventional dose [24]. Michels *et al* [25] published that bolus administration of vertaporfin combined with a reduced light dose lead less choroidal hypoperfusion which was demonstrated in fluorescein and ICG angiographies.

Inflammation, angiogenesis and fibrosis are the main factors in the pathogenesis of AMD. After understanding the relation between VEGF and angiogenesis triggered by inflammation, AMD treatment started to improve faster in the last decade. Retinal inflammation and neovascularization may be triggered by PDT due to the hypoxia and mediators related with the atrophy of CNV lesion. As a result of the low efficiency of PDT, anti-VEGF agents which may improve visual prognosis has been the leading actor in the AMD treatment. Combinations of visudyne PDT and anti-VEGF agents have sinergistic effect on disease treatment as well as lower the injection frequency[1-3, 10-23,36].

VISION study demonstrated the efficacy of pegaptanib sodium in AMD treatment, and after the 54 weeks follow-up, decrease in visual acuity less than 3 logMAR lines were found statistically significantly higher in patients who received intravitreal pegaptanib injections when compared to the controls [11-14]. Continuing visual benefit was also observed in patients who received intravitreal pegaptanib therapy in year 2 of the VISION trial when compared with cessation of therapy at year 1[11, 12]. Successful treatment evaluated with ≤3 logMAR lines of decrease in BCVA was achieved in 60% of our monotherapy group with the mean of 4.20 ±1.01 treatment sessions which is in accordance with the previous studies [11,13], but successful treatment rates of our monotherapy group was found to be significantly less than the results of clinical studies with ranibizumab [31,33]. Mean intravitreal anti-VEGF injection frequency of our monotherapy group was also found to be less than the reported data of Gragoudas *et al* [13] which could be explained by the favorable initial visual acuity of our study population.

MARINA[31] and ANCHOR[32] studies with intravitreal 0.5mg ranibizumab showed 90% or more visual stabilization. Three or more lines of gain in visual acuity was also determined approximately 35% -40% of these patients. Visual gain provided at the first three months could not be preserved at twelfth month of PIER study which investigated the effect of decreased injection frequency in the follow-up [33]. The efficacy of ranibizumab monotherapy and treatment with PDT-ranibizumab combination were compared in FOCUS

study and averagely one line of gain in vision was seen in combination group while avaregely 1.6 lines of loss in visual acuity was revealed in PDT monotherapy group within the first year of the study[17, 18].

Singh *et al* [20] noticed a dose-response trend toward better visual outcomes, as well as fewer treatment frequency in the group treated with the combination of intravitreal triamcinolone acetonide injection with low-fluence PDT. ≥0 line of gain in Snellen visual acuity were found as 33%, 50%, and 56% in study subgroups treated with 50 J/cm^2, 40 J/cm^2, and 25 J/cm^2, respectively. In our study, the successful treatment rate of the combination therapy with low-fluence PDT was found to be consistent with the results of VIM study group [24], Michels *et al* [25], Singh *et al* [20], and Costagliola *et al* [22] These data are well-correlated with recent evidence of significantly less collateral damage on the physiologic choroidal tissue with PDT at a fluence of 25J/cm^2 compared with 50J/cm^2 [20, 24]. In VIP study [8], it was especially mentioned that greater lesion diameter that measured in the initial examination provided worse visual prognosis and decreased treatment success. In the present study, the rate of ≥3 logMAR lines of visual gain (6.7%) was lesser than the rates of Augustin *et al* [15], Singh *et al* [20], FOCUS [17,18], and PIER [33] study groups, which might be related with the wideness of mean initial CNV diameter of our study population. The mean OCT macular thickness was significantly decreased in each of all study groups which was consistent with the literature[10, 34, 35].

Most appropriate treatment combination is still obvious. PDT and IVTA, PDT and anti-VEGF agent or triple combinations may be preferred [10-23,31-36]. VEGF and the inflammatory mediators tend to rise soon after PDT, hence we performed PDT in order to occlusion of neovascularization approximately 2 days after the injection of anti-VEGF agent, so inflammation and excessive VEGF proliferation were inhibited by the ongoing effect of intravitreally injected anti-VEGF agent. Suppression of inflammation and VEGF production, vasoocclusion in present CNV and inhibition of atrophic scar development in late stages were expected from this combination treatment regimen. Although no ocular side effects except subconjunctival hemorrhage and floaters that resolved without treatment were noted in our study population, serious complications such as glaucoma, cataract, uveitis, retinal detachment, foveal atrophy, macular hole formation and endophthalmitis were reported due to intravitreal injections in the literature[10-20, 35-37].

In conclusion, safe and effective stabilization or improvement in vision may be achieved by anti-VEGF injections combined with PDT in patients with CNV secondary to AMD. Frequency of treatment can also be decreased in combination regimens. Less frequent application is both cost-effective and more satisfactory for the patients with AMD. Combination regimen with low-fluence PDT and intravitreal pegaptanib sodium injection seems to be a safe and effective alternative in stabilizing the clinical activity and visual acuity in exudative AMD. The intravitreal injection of pegaptanib sodium was preferred in study population, as it was the only medication that was approved by Turkish Ministery of Health in the treatment of exudative AMD while the present study was designed, but it is thought that the efficacy of low-fluence PDT could be able to studied more clearly because of the recent evidence that pegaptanib probably had less impact on study outcomes such as final visual acuity and disease activity when compared with bevacizumab and ranibizumab. Similar prospective trials will be needed to assess the effect of low-fluence PDT combinations in the treatment of exudative AMD.

REFERENCES

1 Hazin R, Freeman PD, Kahook MY. Age-related macular degeneration: a guide for the primary care physician. *J Natl Med Assoc* 2009;101(2): 134-138

2 Schmidt-Erfurth U, Pruente C. Management of neovascular age-related macular degeneration. *Prog Retin Eye Res* 2007;26:437-451

3 Martidis A, Tennant MTS. Age-related macular degeneration. In: Yanoff M, Duker JS, editors. Ophthalmology. St Louis: Mosby 2004:925-933

4 Klein R, Klein BE, Jensen SC, Meuer SM. The five year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 1997;104:7-21

5 Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy. Three year results from randomized clinical trials. *Arch Ophthalmol* 1986;104;694-701

6 Macular Photocoagulation Study Group. Laser photocoagulation for juxtafoveal choroidal neovascularization. Three year results from randomized clinical trials. Five-years results from randomized clinical trials. *Arch Ophthalmol* 1994;112:500-509

7 Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of choroidal neovascularisation in age related macular degeneration with verteporfin: One year results of two randomized clinical trials-TAP Report No.1. *Arch Ophthalmol* 1999;117:1329-1345

8 Verteporfin In Photodynamic Therapy (VIP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: Two-years results of a randomized clinical trial including lesions with ocult with no classic choroidal neovascularization-VIP Report No.2. *Am J Ophthalmol* 2001;131:541-560

9 Schmidt-Erfurth U, Schöltzer-Schrehard U, Cursiefen C, Michels S, Beckendorf A, Naumann GO. Influence of photodynamic therapy on expression of vascular endothelial growh factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. *Invest Ophthalmol Vis Sci* 2003; 44:4473-4480

10 Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration (Verteporfin PDT, Bevacizumab, and Dexamethasone). *Rctina* 2007;27:133-140

11 VEGF Inhibition Study In Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: Two-year safety results of the two prospective,

multicenter, controlled clinical trials. *Ophthalmology* 2006;113:992-1001

12 VEGF Inhibition Study In Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006;113:1508-1521

13 Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsood M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351:2805-2816

14 Forte R, Cennamo G, Finelli M, Cesarano I, D'Amico G, De Crecchio G, Cennamo G. Intravitreal triamcinolone, bevacizumab and pegaptanib for occult choroidal neovascularization. *Acta Ophthalmol* 2010;88 (8): e305-310

15 Augustin AJ, Schmidt-Erfurth U. Verteporfin therapy combined with intravitreal triamcinolone in all types of choroidal neovascularization due to age-related macular degeneration. *Ophthalmology* 2006;113:114-122

16 Spaide RF. Combination therapies for choroidal neovascularization. In: Holz FG, Spaide RF, editors. Medical Retina. Berlin Heidelberg: Springer-Verlag 2007:89-103

17 Heier JS, Boyer DS, Ciulla TA, Ferrone PJ, Jumper JM, Gentile RC, Kotlovker D, Chung CY, Kim RY; FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol* 2006;124:1532-1542

18 Antoszyk AN, Tuomi L, Chung CY, Singh A; FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. *Am J Ophthalmol* 2008;145(5):862-874

19 Kovacs KD, Quirk MT, Kinoshita T, Gautam S, Ceron OM, Murtha TJ, Arroyo JG. A retrospective analysis of triple combination therapy with intravitreal bevacizumab, posterior sub-tenon's triamcinolone acetonide, and low-fluence verteporfin photodynamic therapy in patients with neovascular age-related macular degeneration. *Retina* 2011;31(3):446-452

20 Singh CN, Saperstein DA. Combination treatment with reduced-fluence photodynamic therapy and intravitreal injection of triamcinolone for subfoveal choroidal neovascularization in macular degeneration. *Retina* 2008; 28:789-793

21 Koss MJ, Lewicka-Chomont A, Schramm K, Rejdak R, Ohrloff C, Koch FH. Quadruple therapy leads to a sustained improvement of vision in patients with wet age-related macular degeneration. *Ophthalmologica* 2011;226(2):45-50

22 Costagliola C, Romano MR, Rinaldi M, dell'Omo R, Chiosi F, Menzione M, Semeraro F. Low fluence rate photodynamic therapy combined with intravitreal bevacizumab for neovascular age-related macular degeneration. *Br J Ophthalmol* 2010;94(2):180-184

23 Sivaprasad S, Patra S, Dacosta J, Adewoyin T, Shona O, Pearce E, Chong NV. A pilot study on the combination treatment of reduced-fluence photodynamic therapy, intravitreal ranibizumab, intravitreal dexamethasone and oral minocycline for neovascular age-related macular degeneration. *Ophthalmologica* 2011;225(4):200-206

24 Visudyne in minimally classic choroidal neovascularization study group (VIM). Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration (2 year results of a randomized clinical trial). *Arch Ophthalmol* 2005;123:448-457

25 Michels S, Hausmann F, Geitzenauer W, Schmidt-Erfurth U. Influence of treatment parameters on selectivity of verteporfin therapy. *Invest Ophthalmol Vis Sci* 2006;47:371-376

26 Framme C, Flucke B, Birngruber R. Comparision of reduced and standart light application in photodynamic therapy of the eye in two rabbit models. *Graefe's Arch Clin Exp Ophthalmol* 2006;244:773-781

27 Schlötzer-Schrehardt U, Viestenz A, Naumann GO, Lagua H, Michels S, Schmidt-Erfurth U. Dose-related structural effects of photodynamic therapy on choroidal and retinal structures of human eyes. *Graefe's Arch Clin Exp Ophthalmol* 2002;240:748-757

28 Pehlivanlı Aktaç Z, Özdek Ş, Gürelik G, Motercimzadeh G, Hasanreisoglu B. Age-related macular degeneration with reanspupillary thermotherapy in the treatment of choroidal neovasoularization due to hidden: long term results. *Ret-Vit* 2006;14:95-100

29 Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) and Verteporfin In Photodynamic Therapy (VIP) Study Groups. Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularisation secondary to age-related macular degeneration-TAP and VIP Report No.1. *Am J Ophthalmol* 2003;136:407-418

30 Schmidt-Erfurth U, Neimeyer M, Geitzenauer W, Michels S. Time course and morphology of vascular effect associated with photodynamic theraphy. *Ophthalmology* 2005;112:2061-2069

31 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419-1431

32 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355:1432-1444

33 Regillo DC, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, Shams N. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. *Am J Ophthalmol* 2008;145:239-248

34 Spaide RF, Laud K, Fine HF, Klancnik JM Jr, Meyerle CB, Yannuzzi LA, Sorenson J, Slakter J, Fisher YL, Cooney MJ. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;26:383-390

35 Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;113:363-372

36 Dhalla MS, Shah GK, Blinder KJ, Ryan EH Jr, Mittra RA, Tewari A. Combined photodynamic therapy with verteporfin and intravitreal bevacizumab for choroidal neocascularization in age- related macular degeneration. *Retina* 2006;26:988-993

37 Rishi P, Kasinathan N, Sahu C. Foveal atrophy and macular hole formation following intravitreal ranibizumab with/without photodynamic therapy for choroidal neovascularization secondary to age-related macular degeneration. *Clin Ophthalmol* 2011; 5:167-170