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Comparative study of photodynamic therapy monotherapy versus triple management in age-related macular degeneration*

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Aim: To compare the effectiveness of photodynamic therapy (PDT) and PDT combined with intravitreal triamcinolone (IVTA) and vascular endothelial growth factor inhibition (anti-VEGF) in age-related macular degeneration (AMD).

Materials and methods: Eighty eyes of 80 patients diagnosed with choroidal neovascularization (CNV) caused by AMD were included in the study. PDT was carried out on 40 eyes in group I, and PDT combined with 4 mg IVTA and anti-VEGF (1.25 mg bevacizumab in 20 eyes, 0.3 mg pegaptanib sodium in 20 eyes) was carried out in group II. The primary efficacy endpoint was the mean change from baseline visual acuity at month 12.

Results: Mean follow-up was 14.2 ± 2.18 months in group I and 12.45 ± 2.82 months in group II. In group I there was a 2.88 logMAR line decrease and 1.95 logMAR line increase in group II in vision between pretreatment and 12th month measurements ($P < 0.05$). Mean PDT session was 2.00 in group I and the mean combined treatment session was 1.15 in group II in the 12th month.

Conclusion: Combination of IVTA and anti-VEGF with PDT is more effective and safer than PDT monotherapy in the treatment of CNV secondary to AMD. Combination treatment decreases the frequency and number of treatment sessions for an improved visual prognosis.

Key words: Age-related macular degeneration, bevacizumab, choroidal neovascularization, pegaptanib sodium, photodynamic therapy

1. Introduction

Age-related macular degeneration (AMD) is the most common cause of central vision loss and legal blindness in developed countries for persons over 65 years of age (1,2). However, no complete therapy is proven for the cure of exudative AMD. Argon laser photocoagulation is commonly used in the treatment of extrafoveal choroidal neovascularization (CNV) (2,3). New treatment procedures such as photodynamic therapy (PDT) for juxtafoveal and subfoveal CNV, intravitreal and periocular steroid injections, and vascular endothelial growth factor (VEGF) inhibitors that suppress angiogenesis have begun to be used.

As a result of any hypoxia, VEGF is released from the retinal and retinal pigment epithelium cells in very high levels and then not only is neovascularization shown, but also inflammation, vasodilatation, leakage from the vessels, and hemorrhage might be seen in the same tissues (4,5).

Due to the multifactorial pathogenesis of CNV development, AMD treatment should contain 3 main factors, which are suppression of inflammation, regression of present CNV, and prevention of CNV development by inhibition of angiogenic stimulus (6). Due to the multifactorial pathogenesis of CNV development in AMD cases, the logic of treatment modalities should cover 3 main activities, which are suppression of inflammation and edema, regression of the neovascular membrane, and tamponade of the highly increased VEGF levels, especially after PDT. However, there is no effective and safe monotherapy that covers all 3 of these mechanisms. Thus, new synergistic combination treatment protocols that activate all of these pathways and require less application have been commonly used (6,7). Combination of PDT, intravitreal steroid, and vascular endothelial growth factor inhibition (anti-VEGF) injections were used together for this purpose. In these combination regimens, an intravitreal steroid injection was used in order to reduce retinal edema and hemorrhage as well as inhibit VEGF production by suppressing inflammation (8,9). Decreased retinal edema and hemorrhage should improve the effectiveness of PDT. Anti-VEGF treatment is also important for the prevention of new CNV development

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by inhibiting retinal and intravitreal basal VEGF as well as intensive production of these growth factors after PDT (6,10–12).

In this study, comparison of the effectiveness of PDT monotherapy and PDT combined with intravitreal triamcinolone acetonide (IVTA) and anti-VEGF in neovascular AMD was the aim because treatment modalities in wet AMD cases could not be agreed upon and the finalization of treatment series is still controversial. Therefore, we aimed to advance a different combination of the known treatment modalities for a cheaper and easier application series that has fewer intravitreal sessions and better final visual acuity with some specific efficacy aimed toward each elementary lesion of the disease.

2. Materials and methods

Eighty eyes of 80 patients diagnosed with CNV secondary to AMD between January 2005 and July 2008 were included in the study. The study was prospective. The treatment protocol was approved by the local ethics committee, and the study was conducted according to the Declaration of Helsinki. Patients gave written informed consent after a detailed discussion of the study procedures, risks, and benefits before entering the study. For inclusion in the study, the patient had to be 50 years or older, have eyes with any type of active subfoveal CNV secondary to neovascular AMD, and have a best-corrected visual acuity (BCVA) of 20/400 or better (Snellen equivalent) assessed with the use of the Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Exclusion criteria were glaucoma, diabetic retinopathy, macular disorders other than AMD, and previous treatment for CNV. Patients were randomly divided into 2 groups in terms of treatment regimen. PDT was carried out on 40 eyes in group I, while PDT combined with 4 mg/0.1 cc IVTA (Kenacort-A® 40 mg, Bristol-Meyers Squibb) and anti-VEGF (1.25 mg bevacizumab, Altuzan®, Roche in 20 eyes; 0.3 mg pegaptanib sodium, Macugen®, Pfizer in 20 eyes) was used in group II. At baseline, all patients underwent an ophthalmological examination, including BCVA measurement using the ETDRS logMAR chart at 4 m, slit-lamp and fundus examination, and intraocular pressure (IOP) measurement by Goldman applanation tonometry. Optical coherence tomography (OCT) was performed to assess retinal thickness. Baseline 1-mm central retinal thickness was measured by OCT (Stratus OCT with Stratus 4.0 software, Carl Zeiss Meditec AG) using 6-diagonal fast scans. Standard fluorescein angiography (FA) using the Heidelberg Retina Angiograph II (Heidelberg Engineering) was performed on all patients before treatment. Standard parameters were used for PDT (Carl Zeiss Meditec AG) with verteporfin (Visudyne®, Novartis) according to TAP and VIP trial recommendations (13,14). On every visit, both ophthalmic examination and OCT were performed; FA was performed within 3-month intervals.

Patients were scheduled for follow-up visits at 1-month intervals and underwent identical examination procedures, including BCVA measurement, IOP documentation, slit-lamp and dilated fundus examination, and OCT measurement. FA was performed every 3 months or earlier if OCT showed significant edema. Retreatment was performed if one of the following changes was observed between visits: a loss of 5 letters in conjunction with fluid in the macula as detected by OCT, an increase in OCT central retinal thickness of at least 100 μm, new-onset classic CNV, new macular hemorrhage, or persistent macular fluid detected by OCT.

In group II, intravitreal injections were performed under sterile conditions in the operating room. Four days after the 4 mg IVTA injection, PDT was performed. Anti-VEGF was injected 45 min after PDT. A topical antibiotic, every 6 h for 1 week, was prescribed and patients were instructed to return in case of ocular pain or redness or any deterioration of vision. Patients were examined 1 day and 1 week after injection. Topical antiglaucoma medication was prescribed if IOP was greater than 21 mmHg.

The primary outcome measure was the proportion of eyes that maintained stable vision (<3 logMAR lines of visual loss). Other outcome measures included changes in BCVA logMAR, changes in the number of lines, area of leakage from CNV, and the mean number of treatments required during the 1-year study period. While the change in the mean BCVA was evaluated, visual acuity that was a loss of less than 3 logMAR lines was considered as a success, but the loss of 3 logMAR lines and above was considered as failure.

2.1. Statistical analysis

The data of the 2 groups were compared. Both parametric and nonparametric tests were used according to the data, including t-test, Mann–Whitney U test, chi-square test, Fisher exact test, and Wilcoxon signed-rank for statistical analysis.

3. Results

The study group comprised 80 patients, with 40 patients for each group. Mean follow-up was 14.2 ± 2.18 months (range: 12–19 months) in group I (PDT monotherapy) and 12.45 ± 2.82 (range: 6–16) months in group II (PDT, IVTA, and anti-VEGF combined treatment). All of the patients completed 6 months of follow-up in both groups. In group I, 40 patients completed 12 months of follow-up. In group II, 5 patients were not able to complete 12 months of follow-up. Three out of 5 patients died due to geriatric problems and 2 missed their visits because of living outside of the city during the follow-up period. There were no statistical differences between the baseline demographics of the groups (Table) ($P \leq 0.05$).

Table. Baseline demographics of the patients.

	Group I n = 40	Group II n = 40
Male	14 (35%)	20 (50%)
Female	26 (65%)	20 (50%)
Mean age (years, mean ± SD)	71.0 ± 8.93	71.8 ± 8.32
Phakic	28 (70%)	31 (77.5%)
Pseudophakic	12 (30%)	9 (22.5%)
Mean follow-up time (months)	14.2 ± 2.18	12.45 ± 2.82
Membrane type		
Predominantly classic	22 (55%)	25 (62.5%)
Occult	13 (32.5%)	11 (27.5%)
Minimally classic	5 (12.5%)	4 (10%)
Mean baseline CNV	3751 ± 1259	3846 ± 1351
Greatest linear dimension (μm)		
Mean baseline		
BCVA (logMAR)	0.95 ± 0.34	0.90 ± 0.43

Change in BCVA from baseline to the time of the last follow-up visit in groups I and II patients are shown in Figure 1. When the mean BCVA was measured in group I patients, it was seen that when the follow-up period lasted longer there was a decrease in the mean BCVA. Among the patients in group II, the mean BCVA was significantly improved at the first month and the improvement was maintained throughout the 12 months of follow-up. Of the patients who were treated with combined therapy in group II, there were, on average, 1.50 and 1.95 logMAR lines of gain in vision at 6 and 12 months, respectively, as compared with an average decrease of 1.57 and 2.88 logMAR lines in group I patients (PDT monotherapy group) at 6 and 12 months, respectively ($P \leq 0.05$).

The proportion of patients whose treatment was successful (<3 logMAR lines of visual loss) in group I and II is shown in Figure 2. Although the success rate in group II was higher than that of group I in all of the months, it was not statistically significant in any of the months ($P \geq 0.05$). The proportion of the patients for whom the mean BCVA increased by at least 3 logMAR lines in group I and group II is shown in Figure 3. The difference between groups was statistically significant at 6 and 12 months ($P \leq 0.05$). During the follow-up period, when the mean BCVA at the rate of loss of 6 logMAR lines and above was compared between the groups, the difference was not significant ($P \geq 0.05$).

The patients were categorized into 4 groups according to the findings of FA at 3, 6, and 12 months as no leakage, minimal leakage (less than 50% of baseline leakage),

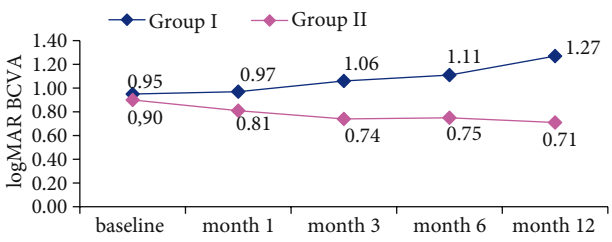

Figure 1. Change in mean BCVA from baseline to the time of the last follow-up visit.

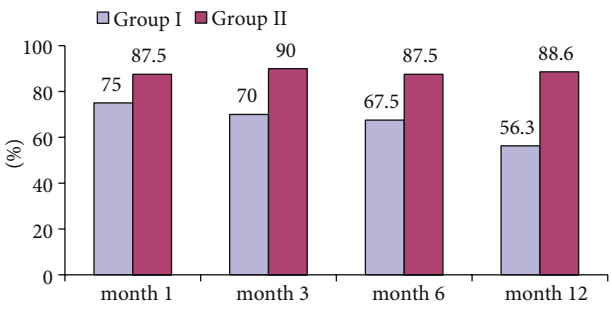

Figure 2. The proportion of the patients whose treatment was successful.

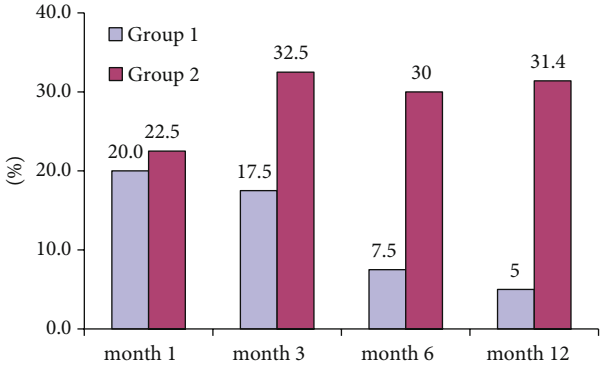

Figure 3. The proportion of the patients for whom the mean BCVA increased by at least 3 logMAR lines.

moderate leakage (more than 50% of baseline leakage), and increased leakage (equal to or greater than baseline leakage). According to FA leakage, no leakage or minimal leakage was considered as treatment success and moderate leakage was considered as treatment failure. The group that was found to be unsuccessful was treated again. Success rate in FA in groups I and II is shown in Figure 4. The difference between groups was statistically significant in all months ($P \leq 0.05$). Mean central foveal thickness (CFT) of the patients in groups I and II is shown in Figure 5. The decrease in the mean CFT after treatment compared

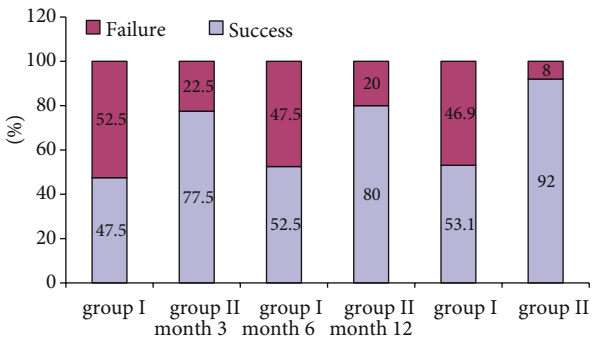

Figure 4. Success rate in FA.

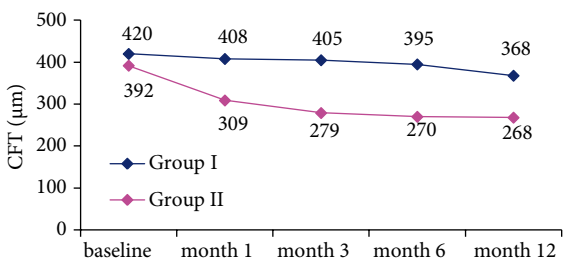

Figure 5. Change in mean central foveal thickness (CFT) from baseline to the time of the last follow-up visit.

with baseline was statistically significant only at 12 months in group I ($P \leq 0.05$), but was statistically different at all months in group II ($P \leq 0.05$).

The patients for whom PDT monotherapy was performed in group I were followed for an average of 14.2 ± 2.18 (range: 12–19) months. These patients attended a mean of 2 sessions of PDT. PDT was performed at 1 session (35%) in 14 eyes, 2 sessions (40%) in 16 eyes, 3 sessions (17.5%) in 7 eyes, 4 sessions (5%) in 2 eyes, and 5 sessions (2.5%) in 1 eye. The patients who were treated with combined therapy in group II were followed for an average of 12.45 ± 2.82 (range: 6–16) months. These patients attended an average of 1.15 sessions of combined treatment. Thirty-four eyes (85%) were treated with only a single combination therapy and 6 eyes (15%) with activation of CNV were treated with combined therapy a second time. Thirteen eyes that had been treated with a single combination therapy were injected intravitreally with anti-VEGF or intravitreal anti-VEGF + IVTA (anti-VEGF into 4 eyes once, anti-VEGF 2 times into 4 eyes, and anti-VEGF + IVTA into 5 eyes) due to decreased visual acuity and increased intraretinal or subretinal fluid accumulation. There was no need for additional PDT or intravitreal injections for 60% of the patients after the initial combined treatment.

Generally, the treatments were well tolerated in both groups. Infusion-related back pain was noted in 2 out of 40 (5%) patients and subretinal hemorrhage developed 2 weeks after the treatment in 1 (2.5%) patient in group I. In group II, infusion-related back pain was noted in 3 out of 40 (7.5%) patients, cataracts progressed in 5 out of 31 (16.1%) phakic patients, and a transient IOP increase was observed in 4 (10%) patients, which was controlled by topical monotherapy during the follow-up period. One (2.5%) patient with high IOP and cataract progression underwent combined glaucoma and cataract surgery 6 months after the treatment. Complications attributable to the injection procedure, such as pseudoendophthalmitis, retinal detachment, retinal tears, or vitreous hemorrhage, were not observed.

4. Discussion

In this study, we applied combined treatment regimens including IVTA and anti-VEGF (bevacizumab or pegaptanib) injections with PDT. IVTA injection was performed initially, and PDT and intravitreal anti-VEGF injections occurred after 4 days in the combination regimen. IVTA helped to regress the macular inflammation so that the effects of inflammatory mediators and especially macular edema were inhibited. PDT was performed due to occlusion of neovascularization approximately 4 or 5 days later than IVTA. The inflammatory mediators and VEGF tend to rise after PDT. Inflammation was inhibited

by the ongoing effect of triamcinolone (TA) and VEGF proliferation was suppressed by the anti-VEGF agent that was applied within 45 min after PDT. Suppression of inflammation and VEGF production, vaso-occlusion in present CNV, and limitation of atrophic scar development in late stages were expected from this combination treatment regimen. This combination treatment can also be used in the treatment of various retinal vascular diseases. Toklu et al. (15) reported that all 6 patients with chronic central serous chorioretinopathy showed complete resolution of the exudative macular detachments and gained visual acuity for more than 6 months with the usage of combination therapy with a half-dose of verteporfin PDT and intravitreal ranibizumab injection.

PDT is a therapy procedure that decreases the risk of severe vision loss by 50% compared to the natural course of the disease (16). On average, 3 lines of loss in visual acuity were revealed with the mean of 3.4 treatment sessions within the first year in TAP and VIP studies (16). Transient thrombosis at the retina and choriocapillaris may be seen after treatment and PDT with verteporfin has a high selectivity to neovascular membranes vessels (16). Early inflammatory response and stimulated VEGF expression secondary to transient thrombosis at choriocapillaris after PDT may also cause frequent recurrences of AMD (17,18). However, stabilization in visual acuity was seen in 67.5% of the patients who received PDT monotherapy at month 6 of our study, while vision loss progressed afterwards. At the end of the 12 months of follow-up, stabilization in visual acuity was determined in 56.3% of the patients with a mean of 2 treatment sessions.

The efficacy of ranibizumab monotherapy and treatment with a PDT-ranibizumab combination were compared in the FOCUS study (19). In the first year of the study, 3 or fewer lines of loss in vision were found at 91% in the combination group and 68% in the PDT monotherapy group. Moreover, 3 or more lines of gain in vision were detected at 24% in the combination group and 5.5% in the PDT monotherapy group. On average, 1 line of gain in vision was seen in the combination group while 1.6 average lines of loss in visual acuity were revealed in the PDT monotherapy group within the first year of the study (19). Chan et al. (20) compared the efficacy of triamcinolone combination with PDT and PDT monotherapy. On average, 3.5 and 0.7 logMAR lines of loss in vision were found in the PDT monotherapy and combination groups, respectively, at the 12th month of the study. In addition, fewer than 3 lines of loss in vision were revealed at 70.8% and 33.3% in the combination and PDT monotherapy groups, respectively (20). The MONT BLANC study (21) and the DENALI study (22) compared the results of combination therapy of verteporfin PDT and intravitreal ranibizumab versus ranibizumab monotherapy in patients with AMD-related subfoveal CNV. The mean BCVA gains in the combination therapy and monotherapy group were 2.5 and 4.4 letters in the MONT BLANC study (21) and 5.3 and 8.1 letters in the DENALI study (22), respectively. The mean number of ranibizumab retreatments after month 2 in the combination therapy and monotherapy group was 1.9–2.2 in the MONT BLANC study (21) and 5.1–10.5 in the DENALI study (22). Monotherapy and combination therapy both had visual gains at month 12, but in the MONT BLANC study (21), it was not shown that there was any benefit of reduced retreatment numbers from intravitreal ranibizumab injection over 12 months. In our study, the frequency and efficacy of PDT monotherapy and IVTA and anti-VEGF (bevacizumab or pegaptanib) injections combined with PDT were reviewed for the treatment of CNV secondary to AMD. Stabilization in vision (less than 3 lines of loss) was achieved at 56.3% and 88.6% of the patients in the monotherapy group and the combination group at the 12th month of the study, respectively ($P \geq 0.05$). The success rate (less than 3 lines of loss) at the 12th month of our study mimics the results of the FOCUS study (18). However, an average of 2.88 logMAR lines of loss in vision were found in the PDT monotherapy group at the 12th month. In our study, we have reported 1.95 logMAR of visual gain in the combination group at the 12th month, which is similar to the findings of the MONT BLANC (21) and DENALI (22) studies. Additionally, 3 or more lines of gain in vision were found at 5% and 31.4% in the PDT monotherapy and combination groups at 12 months, respectively.

Mean visual gain scores and 3 or more lines of gain in vision in our study were found to be higher than the reported values of FOCUS (18) and the study of Chan et al. (20). Ninety-one percent of the patients in the PDT group required additional sessions of treatment in the FOCUS (19) trial, while on average 4 sessions were performed in approximately 30% of the cases. Only 27.5% of the patients in the combination treatment group required a second application. Mean treatment sessions of Chan et al. (20) were 1.50 and 1.96 in the IVTA-PDT combination treatment group and the PDT monotherapy group, respectively. When the mean treatment sessions of our study were compared with these 2 studies mentioned above, it was seen that fewer applications were needed in the combination therapy group of our study. A mean of 2 and 1.15 treatment sessions were required in the PDT monotherapy and combination therapy groups, respectively, in our study. Additional full combination therapy was performed in 6 (15%) eyes of the combination therapy subgroup that had CNV activation. Additional bevacizumab/pegaptanib injections or IVTA combined with bevacizumab/pegaptanib injections were performed on 13 eyes (32.5%) because of vision loss and intraretinal/

subretinal fluid accumulation. When intravitreal injections were taken into account, the mean of treatment sessions in the combination subgroup of our study was 1.40. There was no need for additional application with PDT or intravitreal injection in 60% of our study population.

The most appropriate treatment combination is still obvious. PDT and IVTA, PDT and anti-VEGF agent, or triple combinations may be preferred (20,23,24). There is also disagreement about the timing of the therapy. While Chan et al. (20) preferred to apply corticosteroids 5 min after PDT, Augustin et al. (6) and Ahmedieh et al. (25) applied dexamethasone and bevacizumab intravitreally 16 h and 48 h after PDT, respectively. Ranibizumab was intravitreally injected 1 week after PDT in the PIER study (16). Dallha et al. (24) applied intravitreal bevacizumab 2 weeks after PDT. We applied IVTA and anti-VEGF (bevacizumab or pegaptanib) injections with PDT. IVTA injection was performed initially with PDT and intravitreal anti-VEGF injection following in our combination regimen. Augustin et al. (6) applied 800 µg dexamethasone and 1.50 mg bevacizumab with PDT to 104 patients with CNV secondary to AMD. The mean diameter of CNV was reported as 2650 µm in this study. After 40 weeks of follow-up, fewer than 3 lines of loss in vision were achieved in 97% of the study population. Additionally, 3 lines or more of gain in vision were found at 39.4% and a mean of 1.80 logMAR lines of gain in visual acuity was reported. They applied additional combination therapy in 5 cases. Intravitreal reinjection of bevacizumab was performed in 18 cases (17.3%). In our study, we applied TA and anti-VEGF intravitreally with PDT. Our success rates were lower than those of Augustin et al. (6). However, the mean lesion diameters in their study were smaller than the mean lesion diameter of our study, which was detected as 3846 µm. The mean follow-up time of our study was longer. The treatment frequency of our study was found to be higher than that of the trial of Augustin et al. (6).

Complications such as glaucoma, cataract, uveitis, retinal detachment, and endophthalmitis may progress due to intravitreal injections. Glaucoma and cataract progression secondary to IVTA application were particularly reported in many series (6,20,24,25). Augustin et al. (26) reported glaucoma in 46 patients (25%) after treatment with 25 mg IVTA combined with PDT and antiglaucomatous medication was started in these cases. They also performed surgery on 2 patients (1.08%) because of refractory glaucoma that could not be controlled by medication. Cataract progression was detected in 48.7% of the phakic cases. Chan et al. (20) reported glaucoma in 33.3% and cataract in 26.3% of the patients who received 4 mg IVTA with PDT. When our study was compared to these series, progression of cataract and glaucoma were less frequent in our patients. Glaucoma was detected in 12.5% and cataract progression was detected in 16.1% of the cases. Cataract combined with glaucoma surgery was performed in a case that was refractory to medication. Progression of cataract and glaucoma was not reported in the study of Augustin et al. (6), which tested the efficacy of 800 µm dexamethasone and 1.25 mg bevacizumab combined with PDT, and so they recommended the application of dexamethasone instead of TA.

In light of the results of this study, safe and effective stabilization or improvement in vision was achieved by IVTA and anti-VEGF injections combined with PDT in patients with CNV secondary to AMD. Frequency of treatment was also decreased in combination regimens. Less frequent application is both cost-effective and more satisfactory for the patients with AMD.

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