# Effect of Photodynamic Therapy with Posterior Sub-Tenon Triamcinolone Acetonide on Predominantly Classic Choroidal Neovascularization: One-Year Results

## *Posterior Subtenon Triamsinolon Asetonid ile Kombine Fotodinamik Tedavinin Predominant Klasik Koroidal Neovaskülarizasyon Üzerine Etkisi: Bir Yıllık Sonuçlarımız*

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## Abstract

**Objective:** The aim of this study was to compare the results of monotherapy (photodynamic therapy) and combined therapy (photodynamic therapy with posterior sub-Tenon triamcinolone acetonide) in age-related macular degeneration (AMD).

**Materials and Methods:** Forty eyes from forty patients with diagnosed neovascular AMD were enrolled in this study during March-2005 – October-2008. All patients were grouped in either the study or the control group. Both the study and control groups consisted of 20 eyes from 20 patients. The study group was treated with posterior sub-Tenon triamcinolone acetonide (PSTA) along with their initial photodynamic therapy (PDT) treatment. The control group members were treated with PDT alone. All patients were examined at 1, 3, 6 and 12 months. Visual acuity (VA), lesion size and number of treatment sessions were recorded during each examination.

**Results:** The mean difference between pre- and post-treatment VA using the Snellen chart was +0.6 ± 1.7 in study group and -1.4 ± 1.7 in control. The difference for VA was significant in the study group as compared to control ($p<0.05$). The decrease in lesion size in the study group was 680±1195.2 µm, and the decrease was 32.75 ± 809.9 µm in the control. The difference with regard to the decrease in lesion sizes was significant in the study group as compared to the control ($p<0.05$). Total PDT treatment sessions were applied 1.2 times per patient in the study group and 1.9 times per patient in the control group. The difference was not significant ($p>0.05$).

**Conclusion:** Our study showed that PSTA with PDT significantly reduces CNV growth, and improves VA at the 12-month follow-up in patients with AMD.

**Keywords:** Age-related macular degeneration, Photodynamic therapy, Posterior sub-tenon triamcinolone acetonide

## Özet

***Amaç:*** *Yaşa bağlı makula dejenerasyonu (YMD) ile ilişkili koroid neovaskülarizasyon tanılı olgularda posterior subtenon triamsinolon asetonid (PSTA) ile kombine edilmiş fotodinamik tedavi (FDT)'nin etkinliğini değerlendirmektir.*

***Gereç ve Yöntem:*** *Çalışmaya Mart - 2005 ile Ekim - 2008 tarihleri arasında YMD'ye ikincil koroid neovaskülarizasyonu (KNV) olan 40 hastanın 40 gözü alındı. Hastalar çalışma ve kontrol grubu olarak ikiye ayrıldı. Çalışma grubuna 20 hastanın 20 gözü, kontrol grubuna 20 hastanın 20 gözü dahil edildi. Çalışma grubuna PSTA ile kombine FDT uygulandı. Kontrol grubuna sadece FDT uygulandı. Tüm hastalar tedavinin 1, 3, 6 ve 12. aylarında tekrar değerlendirildi. Kontrollerde olguların görme keskinliği (GK), lezyon büyüklükleri ve tedavi sayıları kaydedildi.*

***Bulgular:*** *Tedavi öncesi ve sonrası snellen eşeli ile değerlendirilen GK'daki ortalama değişiklik, çalışma grubunda ortalama +0.6 ± 1.7 ve kontrol grubunda -1.4 ± 1.7 idi. GK seviyeleri değişiklik kontrol grubuna oranla, çalışma grubunda istatiksel olarak anlamlı farklılık gösterdi. İki grubun tedavi öncesi ve sonrası lezyon büyüklüğündeki azalma çalışma grubunda ortalama 680 ± 1195.2 µm azalma, kontrol grubunda ise 32.75 ± 809.9 µm saptandı. Lezyon büyüklüğündeki azalma çalışma grubunda kontrol grubuna oranla istatistiksel olarak anlamlı idi. FDT tedavi sayısı çalışma grubunda ortalama 1.2, kontrol grubunda ise 1.9 idi. Aralarında istatistiksel olarak anlamlı fark yoktu.*

***Sonuç:*** *On iki aylık takip sonucunda, AMD'li hastalarda PSTA ile kombine FDT uygulamalarının KNV gelişimini durdurduğu ve GK'yı düzelttiği saptandı.*

***Anahtar Kelimeler:*** *Yaşa bağlı makula dejenerasyonu, Fotodinamik tedavi, Posterior subtenon triamsinolon asetonit*

## Introduction

Age-related macular degeneration (AMD) is a degenerative disorder of the central area of the retina. It is the most common irreversible cause of severe loss of vision in the elderly population and the most frequent cause of blindness in the developed world. It usually occurs bilaterally and is often associated with visual impairment [1-3]. Clinically and histopathologically, it has two forms: nonexudative and exudative. Visual loss is usually more severe in the exudative form. The exudative stage of AMD can be further subdivided according to the level of subfoveal neovascularization. Ocular photodynamic therapy (PDT) with verteporfin has been demonstrated to reduce vision loss in patients with the classic or predominantly classic type of exudative AMD [4-6]. Verteporfin therapy has also been shown to reduce the risk of moderate and severe visual acuity loss in occult cases with no classic choroidal neovascularization (CNV), particularly in patients presenting with either smaller lesions regardless of initial visual acuity, or lower levels of visual acuity regardless of initial lesion size [7]. Accordingly, adjunctive antiangiogenic therapy in combination with PDT may prove beneficial to enhance its therapeutic effect. Corticosteroids are potent anti-inflammatory drugs that have been shown to inhibit angiogenesis and resolve CNV in animal models [8, 9]. It has been suggested that oral, periocular or intraocular corticosteroids reduce the growth of CNV associated with the posterior uveitides [10-11].

In recent studies, intravitreal steroid used as an adjunct to PDT has been found to reduce the growth of CNV and the need for retreatment [12-14]. However, its risks include raised intraocular pressure (IOP), cataract, endophthalmitis, and retinal detachment [14-15]. Sub-Tenon's capsule of steroid has been effective in the treatment of ocular diseases such as uveitides and postoperative cystoid macular edema [16]. Posterior sub-Tenon placement of triamcinolone acetonide (PSTA) is believed to have a more concentrated effect on the macular region [17]. The risk of endophthalmitis and retinal detachment is also expected to be reduced [17].

The goal of this study was to show and discuss the results of combined treatment with an injection of sub-Tenon's capsule triamcinolone acetonide (TA) followed by PDT in AMD patients.

## Materials and Methods

Patients were recruited at Ataturk University Hospital between September 2005 and March 2008. Patient selection and treatment methods were essentially the same as those described for the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) study for all patients, with the exception of the addition of TA to the treatment regimen used with the second series of patients [5, 6]. At baseline, all the patients met the criteria of 100% classic CNV with visual acuity (VA) of 20/200 or better. The study protocol was approved by the research and development committee of our hospital. Informed consent was obtained from all the participants.

All the patients were treated using the same equipment at the same treatment center by the same ophthalmologists. The outcome measures were the change in VA, total lesion size and the need for retreatment. Exclusion criteria were CNV lesions that were not due to AMD, any history of glaucoma or ocular hypertension, cataract, concomitant ophthalmic disease due to other causes, and any medical history that would exclude the use of verteporfin, corticosteroids, or both. Furthermore, patients who were found to have extrafoveal or juxtafoveal CNV associated with AMD and those with minimal classic and occult types of CNV on fluorescein angiography (FA) were excluded from the study. Each subject's VA was evaluated upon first presentation. Using a Goldmann applanation tonometer, intraocular pressure (IOP) was measured. The anterior segment was evaluated by biomicroscopic examination, as well as fundus biomicroscopy with a contact lens. All the cases were evaluated with FA. In this evaluation, the total lesion size was measured after 5 minutes of the FA sequence to allow visualization of occult components if present. The greatest linear dimension of the total lesion had to be smaller than 5,400 µm, in line with the TAP study [5].

Baseline FA was recorded for all the patients within one week of PDT treatment. All the FAs were graded by two of the authors. A consecutive series of patients given posterior sub-Tenon TA (40 mg/ml) immediately after the first verteporfin treatment (PDT + TA, study group) was compared with a consecutive series of patients treated with PDT alone (control group) for CNV secondary to AMD. The two series were collected for two consecutive time periods.

The cases in the study and the control group were compared for differences in VA, lesion size on FA, and mean number of retreatment sessions per patient.

**Photodynamic Therapy:**

The greatest linear dimension of the lesion was measured from the fluorescein angiogram. Any area of hypofluorescence associated with overlying blood or a serious detachment of the retinal pigment epithelium contiguous with CNV was considered to be part of the greatest linear dimension of the lesion. Verteporfin (6 mg/m2) was infused intravenously over 10 minutes. Fifteen minutes after the start of infusion, a laser light at 689 nm delivered 50 J/cm2 at an intensity of 600 mW/cm2 for 83 seconds with a spot size with a diameter 1.000 mm larger than the

**Table 1.** Pre- and post-treatment visual acuity and total lesion size in study and control groups.

| Parameters (mean ± SD) | Pre-treatment | Post-treatment |
|---|---|---|
| Visual acuity (Snellen lines) in study group | 0.16 ± 0.11 | 0.23 ± 0.16 |
| Visual acuity (Snellen lines) in control group | 0.2 ± 0.140 | 0.08 ± 0.08 |
| Total lesion size in study group (µm) | 2493 ± 842.5 | 1812 ± 692.4 |
| Total lesion size in control group (µm) | 2827 ± 1045.8 | 2794 ± 1006.9 |

greatest linear dimension of the lesion. Patients were instructed to wear protective sunglasses and not to expose their eyes to sunlight for the next 2 days [18].

**Posterior Juxtascleral Sub-Tenon's Capsule:**

In total, 40 mg/ml of the PSTA (Kenalog, Squibb, United Kingdom) was administered with a sub-Tenon's capsule cannula (20 G; 0.9 X 25 mm) in the superior temporal quadrant (administered by RK, who was accredited for this procedure in randomized clinical control trials, with an assistant using two cotton buds pressed on either side of the injection site to prevent reflux). The TA was given immediately after PDT in an artificially lit aseptic environment. Amethocaine (as a topical anesthetic) and 5% povidone were instilled 5 minutes before administration. A Clarke's speculum was then inserted; with the patient facing inferonasally, the superotemporal conjunctiva and Tenon's capsule were incised 8 mm from the limbus, and a subtenon cannula was inserted. A single milliliter of 40 mg/ml TA was infused, and the cannula was removed followed by a further instillation of 5% povidone. If repeated PDT was necessary at 3-month intervals, TA was not re-administered.

All the cases were invited for follow-up visits after PDT in the first week, first month, third month, and afterwards at three-month intervals if no problems were encountered. At the screening visit, a comprehensive ophthalmic evaluation was performed, including a medical history, blood pressure measurement, VA, stereoscopic digital color fundus photography, FA, and IOP measurements. The presence of leakage in more than 50% of the area treated by FA or exceeding the margins of the same area was considered a criterion for re-treatment. In the patients with such problems, PDT was repeated. The area of the total lesion and the area of leakage were measured at each visit (by AVM, who was blinded to the treatment group). Interobserver and intraobserver variability in measuring lesion size was determined for a subgroup of the PDT + TA group. Comparisons were made by the Mann-Whitney U-test. P<0.05 was considered statistically significant.

## Results

Eleven patients in the study group (55%) and twelve (60%) in the control group were male. The mean age was 70.5 ± 3.8 years (61 - 82 years) in the study group and 71.7 ± 5.4 years (63 - 78 years) in the control group. There were no significant differences between groups with regard to gender or age. All the patients were followed up for one year. Based on evaluation with the Snellen table, the VA values of study and control groups from the first examination and the last control visit after the treatment results are shown in Table 1. The mean change in the pre- and post-treatment VA values for study group was +0.6 ± 1.7 Snellen lines, and for control group, it was -1.4 ± 1.7 Snellen lines (Table 2). The difference in VA was statistically significant (p<0.05) (Table 2). The mean results for pre- and post-treatment lesion size in the study and control groups are shown in Table 1. The mean decreases in the lesion sizes of the two groups were 680 ± 1195.2 µm for the study group and 32.75 ± 809.9 µm for the control group (Table 2). The difference between the two groups was statistically significant (p<0.05) (Table 2). PDT was performed twice in 10 patients (50%) and three times in 10 patients (50%) from the control group; it was performed once in 10 patients (50%), twice in 7 patients (35%), and three times in 3 patients (15%) from the study group during a period of one year. Thus, the treatment was applied 1.2 times per patient in the study group and 1.9 times per patient in the control group. However, the difference was not statistically significant (p>0.05).

**Table 2.** The mean change in pre- and post-treatment visual acuity and lesion sizes in study and control groups

| Parameters (mean ± SD) | Study group (n=20) | Control group (n=20) |
|---|---|---|
| The mean change in pre- and post-treatment visual acuity (Snellen lines) * | +0.6 ± 1.7 | -1.4 ± 1.7 |
| The mean change in pre- and post-treatment lesion size (µm)* | 680±1195.2 | 32.75 ± 809.9 |

*p<0.05

On FA performed at 3-month intervals, the leakage characteristics of the lesions were evaluated. The leakage classification used in the TAP study was taken as the basis. Presence of leakage that exceeded the lesion margins on the first examination or a leakage in more than 50% of the initial lesion area was considered an unsuccessful treatment. Thus, PDT was repeated in these patients [5, 6]. Mild leakage and no leakage were considered successful treatments.

Before and after the treatment, IOP was measured in both groups. In the study group, this parameter increased by 1-5 mmHg in 10 patients, while in the control group, it increased by 1-3 mmHg in 4 patients. The difference in the IOP increase was not statistically significant. IOP was not higher than 21 mmHg, and antiglaucomatous treatment was not initiated for any of the patients in the study group. All the patients were also followed up for cataract development and progression. No cataract development was observed during follow-up. Severe lower back pain developed during infusion in one patient from the study group. Other than these complications, no injection site reaction, extravasation, or photosensitivity was observed in the study group. No patient in the study group was observed to develop traumatic cataract, retinal detachment, or intravitreal hemorrhage.

## Discussion

In this present study, our study found obvious benefit for a single periocular corticosteroid injection as adjunctive therapy to PDT in patients with subfoveal choroidal neovascularization.

Several hypotheses have been developed for the persistence of CNV and the need for re-treatments after PDT monotherapy [18, 19]. One of the mechanisms of photodynamic action is the production of oxidative radicals, which enhances a major pathogenic process of CNV induction. Following PDT, the acute oxidative damage reflects a much more powerful reaction than

the chronic life-long photodynamic light-induced process, eventually leading to CNV [20-22]. With each PDT re-treatment, the long-lasting disease process may be enhanced and the amount of photoreceptor loss may increase. Expression of VEGF, VEGF receptor 3, and pigment epithelium-derived factor induced by oxidation or ischemia was observed in the PDT-treated areas after the acute phase of the PDT reaction [23]. This may be another subacute and longer-lasting stimulus for neovascular growth and leakage and may induce inflammatory reactions. In experimental studies, PDT was shown to induce a rapid inflammatory res-ponse including infiltration of leukocytes and increased expression of cytokines such as intracellular adhesion molecule-1 and interleukin-6 [23, 24]. After PDT application to the maculas of human eyes using standard parameters, histologic studies have identified thrombotic occlusion of the choriocapillary layer, where characteristic hypofluorescence was seen in indocyanine green angiography. This finding was clearly consistent with a thrombosis of choriocapillaries and larger individual vessels. Angiogenic stimuli responsible for CNV progression may be choroidal hypo-perfusion and resulting tissue hypoxia, which may be enhanced by PDT-induced release of VEGF [24]. With their antiproliferative, anti-inflammatory, and angiostatic effects, corticosteroids are known to decrease vascular permeability [22-25]. The rationale for the present study was to combine verteporfin PDT with an anti-inflammatory and/or antiangiogenic drug, thus antagonizing VEGF expression and inflammatory reactions in the subacute phase following PDT [21].

TA has been shown to have anti-inflammatory and antiedema effects, as well as antiproliferative and antiangiogenic effects [21]. In a few experimental studies, TA was reported to have antiangiogenic effects in inhibiting CNVs in animal models [25]. Steroids inhibit angiogenesis by direct or indirect mechanisms. By impairing the functions of vascular endothelial cells, steroid treatment results in cell death. These effects are formed by inhibition of extracellular matrix turnover. Steroids' indirect effects also prevent neovascularization by reducing the migration and activation of the cells acting in angiogenesis such as macrophages and mast cells. In addition, steroids have been reported to inhibit VEGF, fibroblast growth factor, and transforming growth factor-beta expression [25, 26]. Combined treatments (PDT+ intravitreal triamcinolone acetonide (IVTA) injection) provided stabilization in BCVA, as well as decreasing the number of PDTs required to stop CNV development [12- 15]. Several serious complications have been reported with IVTA injection in the treatment of AMD. The most common complication after IVTA injection is raised intraocular pressure in the early period and cataract progression in the late period [19, 20]. The rates of elevated intraocular pressure and cataract development vary. After IVTA injection, 25-40% of the patients exhibited elevated intraocular pressure, and 18-57% developed cataracts [25, 26]. IVTA injection is also known to lead to relatively lower rates of other serious complications such as traumatic cataract, retina decollement, intravitreal hemorrhage, and endophthalmia [27- 29]. Since posterior sub-Tenon administration as an adjunct to PDT might be a good alternative option, the effect of this method of steroid administration on lesion growth should be tested [30, 31].

Sub-Tenon's capsule and orbital floor placement of steroids have been shown to be effective in the treatment of ocular diseases such as uveitis and postoperative cystoid macular edema. It has been suggested that PSTA has a more concentrated effect on the macular region than injections at sub-Tenon's capsule [30]. PSTA is safer and easier to apply than intravitreal injection. Moreover, it has a minimal risk of side effects such as endophthalmitis and retinal detachment. It is also an effective method to attain therapeutic concentration of the drug in the posterior segment of the eye. After being injected, PSTA runs into the eye by passing through the sclera. Crystals melt slowly and are in contact with the sclera for a longer period. The therapeutic response determined by improvement in macular functions may be related to the proximity of TA to the macular region. In their experimental study, Nozaki et al. [30] evaluated the TA concentration in the retina and choroid after intravitreal and sub-Tenon administration and determined the TA presence in both the retina and choroid after 4 weeks. Thomas et al [31]. administered PSTA (40 mg/ml) in 20 eyes and measured the TA concentration in the vitreous cavity after the injection. In 15 of the 20 eyes, TA levels were determined depOur study showed that there were evident differences in the proportion of patients with fluorescein leakage from CNV, distribution of the amount of leakage, lesion size, number of PDT treatments, or VA in the twelfth month after randomization to PDT with a single periocular corticosteroid injection, as compared with a treatment regimen consisting of PDT and no corticosteroids. There were no evident differences in the proportion of patients with fluorescein leakage from CNV, distribution of the amount of leakage, lesion size, number of PDT treatments, or VA in the third or sixth months in our PDT-only group as compared with the TAP study [5].

In a more recent study, Ann Van de Moere et al. [32] assessed whether posterior sub-Tenon application of 40 mg TA, given at the same time as initial PDT for predominantly classic CNV related to AMD, affected lesion growth in the third and sixth months. They determined that there was significantly less total lesion growth in the third and sixth months in patients given TA with PDT as compared with patients given PDT alone. They also found that there was a significantly smaller residual area of leak in the third month in the study group. In the sixth month, the residual area of leak in the two groups became comparable. The mean number of letters lost on the logarithm of the minimum angle of resolution chart in the sixth month was 9.1 letters in the study group, as compared with 12.4 letters in the control group. In the sixth month, 10 of 36 eyes in the study group showed >15-letter loss, whereas in the control group, 29 of 73 eyes (39.7%) showed >15-letter loss. Fewer re-treatments were required for TA in the PDT group. The authors of the study have concluded that PSTA with PDT at baseline significantly reduced CNV growth in the third and sixth months.

However, a previous study evaluated the FA and VA outcomes of patients enrolled in a trial of a single periocular corticosteroid injection immediately before PDT versus PDT alone for subfoveal CNV secondary to AMD [33]. Our results differ from this previous study, which reported that there were no evident differences in the proportion of patients with fluorescein leakage from choroidal neovascularization, distribution of the amount of leakage, lesion size, number of PDT treatments, or VA in the

third or sixth month after randomization to PDT with a single periocular corticosteroid injection, as compared to PDT with no corticosteroid. Another difference that could have contributed to the discrepant outcomes might be related to their eligibility criteria. Our study was limited to subjects with predominantly classic choroidal neovascularization and VA of 20/200 or better, whereas the study by Gilson et al. [33] included such patients in addition to those with minimally classic lesions or occult pathology with no classic lesions; baseline VA for their subjects was 20/400 or better. Their trial found little evidence for benefit from a single periocular corticosteroid injection for reducing fluorescein leakage from choroidal neovascularization 3 months after PDT for choroidal neovascularization in AMD. Despite small differences between treatment groups, the similarity of the results on all measures in corticosteroid and corticosteroid-free groups indicates that there may be little benefit for adjunctive periocular corticosteroids [33].

The use of a steroid can cause a rise in pressure as would be expected; therefore, monitoring and treatment of increased pressure is needed. However, the frequency of a rise in pressure was less than that reported with IVTA. In the study by Tanner et al. [34], 4 of 25 eyes (16%) had an intraocular pressure greater than 22 mmHg after the sub-Tenon's capsule injection of TA. Cataract progression might have also been expected, but it was not detected in this study, although the follow-up was relatively short. Conjunctivitis occurred in one patient. However, endophthalmitis was not expected to be a problem, nor was retinal detachment. Gillies et al. [35] reported an elevated IOP in 31 of 75 patients (41%) during their 1-year follow-up after an intravitreal injection of 4 mg of TA for neovascular age-related macular degeneration.

In conclusion, our study shows that posterior sub-Tenon placement of TA with PDT, the systemic and local side effects of which have been reported to be minimal, significantly reduces CNV growth in 12 months. It also reduces the need for retreatment in 12 months. Our results suggest that visual outcome may be better although this was not proven in this study. Therefore, a larger randomized trial with longer follow-up will contribute to further research.

**Conflict interest statement** The authors declare that they have no conflict of interest to the publication of this article.

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