# The Triple Therapy in Choroidal Neovascularization Due to Age Related Macular Degeneration

## Yaşa Bağlı Makula Dejenerasyonu Kaynaklı Koroid Neovaskülarizasyonunda Üçlü Tedavi

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### ABSTRACT

**Purpose:** To evaluate the effectiveness of triple therapy in patients with subfoveal choroidal neovascular membrane (SCNM) due to age-related macular degeneration (AMD) as a primary treatment or as a secondary treatment in patients that were unresponsive to prior photodynamic therapy (PDT).

**Materials and Methods:** Twenty-nine eyes of 26 patients (10 male, 16 female, mean age: 71.2 years) with SCNM related to AMD were evaluated retrospectively. Patients that had no previous PDT constituted Group 1 (17 eyes), and patients that underwent previous PDT constituted Group 2 (12 eyes). Intravitreal injection of 2 mg triamcinolone acetonide combined with 1.25 mg bevacizumab was performed within 10 days period before or after PDT.

**Results:** The mean follow-up was 7.6 months (range, 3-18 months).The average Snellen visual acuity was 0.13±0.02 (± standard error of mean) at the baseline and 0.21±0.03 at the final visit (p=0.02). In Group 1 the mean baseline Snellen visual acuity improved from 0.11±0.03 to 0.26±0.05 at the last visit (p=0.004), whereas in Group 2 the mean visual acuity remained the same (0.16±0.02 versus 0.14±0.02, p=0.46). At the last follow-up, hyperfluorescence on angiography representing the activity of the membrane was evident in 8 eyes (47%) in Group 1, and in 10 eyes (83%) in Group 2. At the final visit, 11 eyes (38%) were leakage-free on fluorescein angiography.

**Conclusion:** Triple therapy for SCNM improves visual acuity when used as a primary treatment and stabilizes visual acuity in eyes refractory to prior PDT.


**Key Words:** Choroidal neovascular membrane, intravitreal triamcinolone, intravitreal bevacizumab, photodynamic therapy.


### ÖZ

**Amaç:** Yaşa bağlı maküla dejenerasyonu sonucu gelişen subfoveal koroid neovasküler membranlı hastalarda üçlü tedavinin primer tedavi veya fotodinamik tedaviye dirençli vakalarda sekonder tedavi modalitesi olarak etkinliğini değerlendirmek.

**Gereç ve Yöntemler:** Yaşa bağlı maküla dejenerasyonu sonucu subfoveal koroid neovasküler membranı gelişen 26 hastanın 29 gözü (10 erkek ve 16 kadın, ortalama yaş 71.2 yıl) geriye dönük olarak incelendi. Daha önce hiç fotodinamik tedavi yapılmamış hastalar Grup 1 (17 göz) ve daha önce fotodinamik tedavi yapılmış hastalar Grup 2 (12 göz) olarak değerlendirildi. Hastalara fotodinamik tedaviden önce ya da sonra 10 günlük süre içinde intravitreal olarak 2 mg triamsinolon asetonit ile kombine 1.25 mg bevacizumab enjeksiyonu uygulandı.

**Sonuç:** Ortalama takip süresi 7.6 aydı (3-18 arası). Tedavi öncesi ortalama 0.13±0.02 (± SEM) olan Snellen görme keskinliği tedavi sonrası 0.21±0.03' e yükseldi (p=0.02). Grup 1' de tedavi öncesi görme keskinliği 0.11±0.03 iken son kontrolde 0.26±0.05 bulundu (p=0.004). Grup 2'de başlangıç (0.16±0.02) ve son görme keskinlikleri (0.14±0.02) fark göstermedi (p=0.46). Grup 1'de 8 gözde (%47), Grup 2'de 10 gözde (%83) tedavi sonrası anjiografide aktif membrana bağlı hiperflorasans izlendi. Son kontrolde toplam 11 (%38) gözde flöresan sızıntısı görülmedi.

**Tartışma:** Subfoveal koroid neovasküler membranlı gözlerde üçlü tedavinin primer uygulaması görme keskinliğini arttırırken, fotodinamik tedaviye dirençli gözlerdeki sekonder uygulaması görme keskinliği stabilizasyonu sağlamaktadır.


**Anahtar Kelimeler:** Koroid neovasküler membran, intravitreal triamsinolon, intravitreal bevacizumab, fotodinamik tedavi.

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## INTRODUCTION

Subfoveal choroidal neovascular membrane (SCNM) is a neovascular tissue originating from the choriocapillaris layer. The newly formed vessels gain access to the sub- retinal pigment epithelial (RPE) space and further to intraretinal structures through a break in Bruch membrane. Together with the exudation and hemorrhages from the new vessels the lesion ultimately leads to fibrosis and irreversible vision loss. It is most commonly observed in exudative type age-related macular degeneration (AMD), and also in pathological myopia, angioid streaks, travmatic choroidal rupture, ocular histoplasmosis syndrome, as a complication to inappropriate argon laser photocoagulation, and finally can occur solely as an idiopathic case. SCNM is classified according to flourescein angiography into two major types named classic and occult.[1,2]

In the standard management of the SCNM, photodynamic therapy (PDT) constitutes the mainstay treatment.[1,2] However, because PDT alone does not have satisfactory results in the eradication of the disease new adjunctive methods have been investigated: Combination of PDT with intravitreal steroids or with anti-vascular endothelial growth factor (VEGF) agents has been shown to have better results.[3-9] More recently, a more promising method by combining all of the three has been gaining popularity. With the triple therapy not only stabilization but also improvement in visual acuity with decreased number of PDT is expected. Decreasing the number of repeat PDT will decrease the cost of the total treatment and limit the excess damage to ocular tissue. We designed our study to evaluate the effectiveness of the triple therapy, that is PDT in combination with intravitreal triamcinolone acetonide and bevacizumab as a primary treatment modality as a primary treatment and as a secondary treatment modality in cases unresponsive to prior PDT.

## MATERIALS AND METHODS

The study was conducted retrospectively from the patient charts. Patients with SCNM associated with AMD were included in this study. The patients were grouped

**Table1:** Patients' demographics, baseline and final visit findings.

| Case No | Age (y) | Type of lesion | Prior PDT | Treatment | Follow-up (mo) | Initial VA | Final VA | Final FFA Activity | Clinical details during the study period |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 86 | C | 0 | 1 | 3 | 0.10 | 0.30 | + | |
| 2 | 67 | O | 0 | 1 | 3 | 0.05 | 0.03 | - | CE |
| 3 | 86 | O | 0 | 1 | 5 | 0.20 | 0.40 | - | |
| 4 | 76 | C | 0 | 1 | 3 | 0.10 | 0.40 | - | |
| 5 | 73 | C | 0 | 1 | 12 | 0.01 | 0.05 | + | |
| 6 | 73 | C | 0 | 1 | 12 | 0.30 | 0.60 | - | |
| 7 | 75 | C | 0 | 1 | 3 | 0.01 | 0.01 | + | |
| 8 | 53 | C | 0 | 2 | 18 | 0.10 | 0.05 | + | |
| 9 | 61 | C | 0 | 2 | 5 | 0.05 | 0.10 | + | |
| 10 | 66 | O | 0 | 2 | 3 | 0.10 | 0.30 | - | |
| 11 | 79 | C | 0 | 1 | 7 | 0.04 | 0.80 | - | 2 IVB-IVTA, 1 IVTA |
| 12 | 73 | C | 0 | 1 | 12 | 0.03 | 0.10 | - | $C_3F_8$-tPA |
| 13 | 75 | O | 0 | 4 | 12 | 0.02 | 0.05 | - | $C_3F_8$-tPA, IVTA |
| 14 | 66 | O | 0 | 2 | 12 | 0.10 | 0.20 | + | 2 IVB-IVTA, 1 IVTA |
| 15 | 70 | O | 0 | 3 | 12 | 0.20 | 0.10 | + | CE, IOP rise, 2 IVB-IVTA, 1 IVTA |
| 16 | 80 | C | 0 | 2 | 12 | 0.10 | 0.30 | - | |
| 17 | 72 | O | 0 | 1 | 3 | 0.50 | 0.70 | + | 1 IVTA |
| 18 | 77 | O | 1 | 1 | 3 | 0.10 | 0.10 | - | |
| 19 | 67 | O | 2 | 1 | 3 | 0.10 | 0.10 | + | |
| 20 | 67 | O | 2 | 1 | 3 | 0.10 | 0.10 | + | |
| 21 | 76 | C | 1 | 1 | 3 | 0.40 | 0.30 | + | 1 IVB-IVTA |
| 22 | 54 | C | 1 | 2 | 13 | 0.16 | 0.16 | - | |
| 23 | 66 | O | 3 | 3 | 13 | 0.30 | 0.10 | + | |
| 24 | 66 | C | 1 | 3 | 12 | 0.20 | 0.05 | + | |
| 25 | 76 | O | 4 | 2 | 5 | 0.05 | 0.05 | + | CE, IOP rise |
| 26 | 76 | O | 4 | 2 | 5 | 0.20 | 0.30 | + | |
| 27 | 70 | O | 2 | 4 | 13 | 0.15 | 0.30 | + | RPE tear |
| 28 | 78 | O | 2 | 1 | 3 | 0.10 | 0.10 | + | |
| 29 | 60 | O | 1 | 2 | 7 | 0.10 | 0.05 | + | |

PDT: photodynamic therapy, VA: visual activity, FFA: fundus fluorescein angiography, Type of lesion: C: classic or predominantly classic, O: occult. Initial and final VA: Snellen visual acuity. Activity: (-): lesion stable on OCT and/or FFA, (+): activity on OCT and/or FA. CE: cataract extraction, $C_3F_8$-tPA: application of pneumatic retinopexy for subretinal hemorrhage with intravitreal $C_3F_8$ and tissue plasminogen activator, IVTA: intravitreal triamcinolone acetonide, IVB: intravitreal bevacizumab, IOP: intraocular pressure, RPE tear: retinal pigment epithelial tear.

**Table 2:** Detailed findings in each group that received triple treatment (data are mean±SEM).

| | Age (y) | Number of treatment | Extra injections | Follow-up (mo) | Activity presence at the last visit | Baseline VA | Final VA | P value* |
|---|---|---|---|---|---|---|---|---|
| ***Group 1 (n=17)*** | 72.4 | 1.6±0.2 | 5 | 8.1 | 47% | 0.11±0.03 | 0.26±0.05 | 0.004 |
| ***Group 2 (n=12)*** | 69.4 | 1.9±0.3 | 1 | 6.9 | 83.3% | 0.16±0.02 | 0.14±0.02 | 0.46 |

VA: Snellen visual acuity, * Wilcoxon test raphy as well as on optical coherence tomography is evident.

according to the prior PDT history: Patients that had no previous PDT constituted Group 1, and patients that underwent previous PDT constituted Group 2.

The type of the SCNM was determined according to the fundus florescein angiography and the size of the laser spot was calculated to be 1000 $\mu$m larger than the greatest lesion diameter measured on the fluorescein angiography.

The leakage on angiography and intra- or subretinal fluid accumulation on optical coherence tomography (OCT) was used as a sign for the membrane activity, and were repeated every 3 months after the treatment. In eyes that showed huge volume of sub- or intraretinal serous fluid accumulation, and cystoid macular edema development despite of triple therapy, additional intravitreal triamcinolone acetonide and/or bevacizumab injections were conducted (Table 1).

PDT with verteporfin (visudyne, Novartis) was performed according to the recommended standard procedure. The duration of laser was 83 seconds and dose was 50 J/cm$^2$. Verteporfin dosage was calculated according to the body surface area with a ratio of 2 mg/m$^2$ and the solution was infused from the antecubital vein 15 minutes before the PDT procedure.

Intravitreal injection of 2 mg triamcinolone acetonide combined with 1.25 mg bevacizumab was performed within 10 days period before or following the PDT. Under topical anesthesia the eye was disinfected with povidone iodine solution and the intravitreal injection was performed at the 3-3.5 mm distance from the limbus. Following the injection, an antibiotic ointment was applied to the eye, and the eye was closed with a sterile sponge for the next 24 hours. The patient was ordered to use an antibiotic solution five times daily. Patients were scheduled for follow-up visits at day 1, week 1, month 1 and every

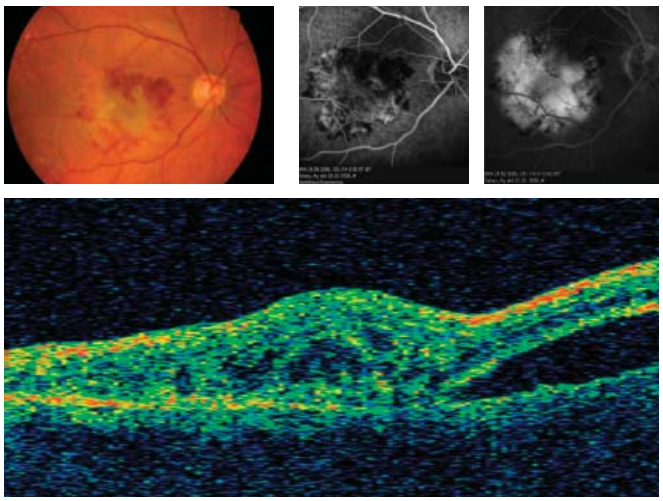

**Figure 1a:** Color fundus picture, fluorescein angiographies and optical coherence tomography of an 80-year-old male patient (Case no: 16) with a classical subfoveal choroidal membrane at baseline. Snellen visual acuity was 0.1 at the presentation. In the color fundus picture (top, left) localized subretinal hemorrhage around subretinal membrane can be appreciated. In the early (top, middle) and late (top, right) phases of angiography, hyperfluorescence due to classical subfoveal membrane is seen. Optical coherence tomography (bottom) shows intra- and subretinal fluid accumulation.

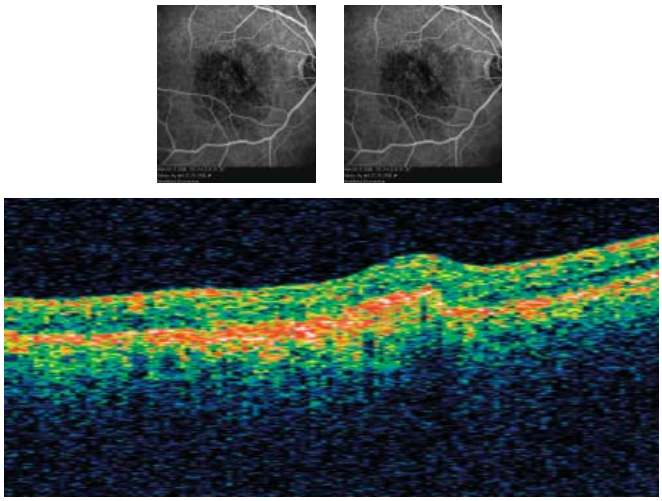

**Figure 1b:** Early (top left) and late phases (top right) of fundus fluorescein angiography, and optical coherence tomography (bottom) of the patient six months following the triple therapy improved Snellen visual acuity to 0.3. In early and late phases of angiography a prominent regression in the neovascular membrane and hyperflourescein due to scarring is evident. The intra- and subretinal fluid accumulation also improved on optical coherence tomography. Fusiform thickening on the retina pigment epithelium due to the scarring is present.

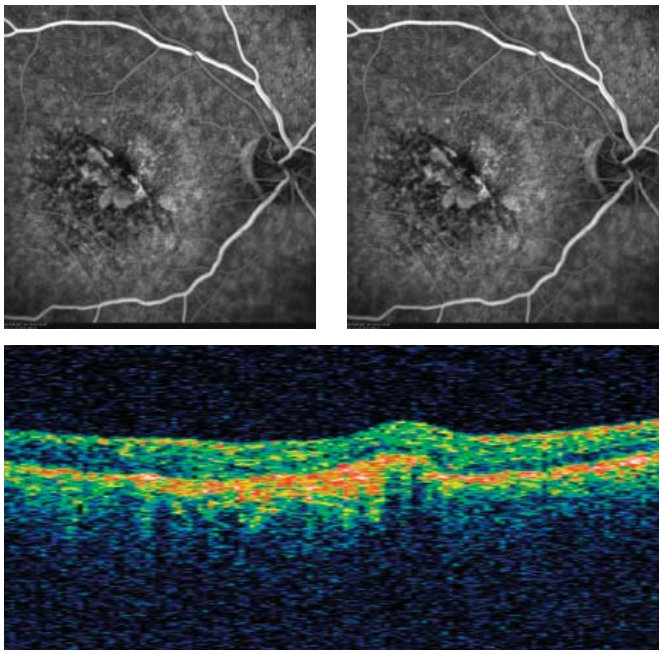

**Figure 1c:** Early (top left) and late phases (top right) of fundus fluorescein angiography, and optical coherence tomography (bottom) of the patient after the second triple therapy at 12 months from baseline. Final Snellen visual acuity was 0.3. No activation on early and late phases of fluorecein angiography as well as on optical coherence tomography is evident.

three months after the injection unless there is a sign of activation. Any intraocular pressure (IOP) exceeding 21 mmHg was treated with topical antiglaucoma agents.

The data acquired from the files were analyzed using a software programme (SPSS 11.5 version). Visual acuity demonstrating the functional success of the therapy was the main outcome measure of the study. Pre- and post-treatment visual acuity was compared by Wilcoxon two related sample test. Any *P* value of ≤0.05 was considered as statistically significant. Snellen visual acuity values were converted to logMAR values for statistical comparisons.

## RESULTS

Twenty nine eyes of 26 patients (10 male, 16 female, mean age: 71.2 years, range: 53-86 years) with SCNM due to AMD were included in this study. Table 1 demonstrates patients' demographics, baseline and final visit findings. The mean follow-up was 7.6±0.9 months ([±SEM], range, 3-18 months). The lesion type was distributed as classical or predominantly classical in 13 eyes (44.8%) and occult in 16 eyes (55.2%). In Group 1, 10 of 17 eyes (58.8%) had classical or predominantly classical SCNM while 7 of 17 eyes (41.2%) had occult SCNM. In Group 2, 3 of 12 eyes (25%) had classical or predominantly classical SCNM and 9 of 12 eyes (75%) had occult SCNM. The average Snellen visual acuity was 0.13±0.03 at the baseline and 0.21±0.03 at the final visit (p=0.02). Figure 1 shows baseline, six and twelve months angiographic and OCT characteristics of a patient. Table 2 shows detailed findings in both groups. The baseline average Snellen visual acuity was 0.11±0.03 (range, 0.01 to 0.5) in Group 1 (n=17), and 0.16±0.02 (range, 0.05 to 0.4) in Group 2 (n=12). At the last follow-up, the mean visual acuity was 0.26±0.05 (range, 0.01 to 0.8) in Group 1, and 0.14±0.02 (range, 0.05 to 0.30) in Group 2. Visual acuity improved one or more Snellen line in 13 eyes (76.5%), worsened in 3 eyes (17.6%) and remained the same in one eye (5.9%) in Group1. Visual acuity improved one or more Snellen line in 2 eyes (16.7%), worsened in 4 eyes (33.3%) and remained the same in 6 eyes (50%) in Group 2.

Overall, the mean number of PDT applied in both groups is 1.7±0.1. In Group 1 the mean PDT applied was 1.6±0.2, and in Group 2 the mean PDT was 1.9±0.3. In Group 2, the previous PDT performed before the triple therapy was 2.0±0.3 (range 1 to 4).

In addition to triple therapy during the study course, extra injections of intravitreal triamcinolone and/or bevacizumab were performed in 5 eyes in Group 1 and in an eye in Group 2.

At the last follow-up, hyperfluorescence on angiography due to membrane activation was evident in 8 out of 17 eyes (47%) in Group 1, and in 10 out of 12 eyes (83%) in Group 2. At the final visit, totally 11 out of 29 eyes (38%) were leakage-free.

Overall, 3 eyes underwent cataract surgery during the follow-up. Two eyes had transiently elevated IOP that was managed with topical anti-glaucoma medication.

In one of the resistant cases in Group 2 having RPE rip from previous treatment, the membrane activity could never be eradicated despite the intense treatment with 4 sessions of triple therapy.

In two other eyes in Group 1, macular subretinal hemorrhage was present before the initial therapy. They received tissue plasminogen activator and intravitreal $C_3F_8$. The therapy was applied after the resolution of the subretinal hemorrhage. Both cases had inactive SCNM at the last visit.

## DISCUSSION

This study showed that a better visual acuity can be obtained with combination of PDT and intravitreal injection of bevacizumab and triamcinolone for SCNM when used as primary option as compared to that of secondary option over a mean of 7.6 months. The triple treatment increased visual acuity when used as primary therapy (Group 1) while keeping visual acuity stable in eyes with previous treatments (Group 2).

PDT with vertoporfin is the major treatment for SCNM and is in use since 1999.[1,2] During the treatment course, PDT should be repeated as many times as the membrane gets active components. The aim of treatment with PDT is to slow down the progression of visual loss and stabilize the visual acuity while halting the membrane spread during the course of the disease. With the new treatment modalities as an adjunct to PDT not only the

stabilization but also improvement in vision further and decrease in number of repeated treatments is the goal of the treatment.

Vertoporfin is an anti cancer drug that has an angio-occlusive effect. Because the drug is specifically taken up by the endothelium of newly formed abnormal vessels there is little damage to the surrounding tissue. When irradiated with 689 nm light coagulative necrosis in the newly formed abnormal vessels occurs. Liberated oxygen radicals from the process and the large ischemic area initiate an inflammation cascade where the RPE cells secrete vast amount of inflammatory mediators and growth factors like VEGF.[10,11]

With the inflammation blood retinal barrier is broken up, which results in edema formation in the early post treatment period. In addition, inflammation also promotes continued VEGF production which in turn contributes to further neovascularization and therefore to the relapse of the lesion.[12-14] Intravitreal steroids limit inflammation by blocking the mediator and cytokine release. They close the gap junctions between the endothelial cells and decrease the vascular permeability. They also have anti-fibrotic activity which minimizes the retinal scarring.[5]

VEGF plays an essential role in the regulation of embryonic and postnatal physiological angiogenesis processes, such as skeletal growth and bone formation and angiogenesis in endocrine glands. VEGF is essential also for tissue repair and reproductive functions. Besides physiological angiogenesis, VEGF also plays role in pathological conditions such as tumor formation, hematological malignancies, inflammatory disorders, brain edema and pathological intraocular neovascularization.[15,16]

The anti-VEGF drugs block the action of VEGF receptors. Because VEGF is essential for the new vessels to emerge and grow, applying anti VEGF inhibits continuing neovascularization in the process of SCNM formation. However they have a limited effect on already existing membrane. Our study confirmed better visual acuity results with primary triple therapy with bevacizumab.

Anti-VEGF drugs, on the other hand, when gain access to systemic circulation after the intravitreal injection may block the physiological VEGF actions posing great risk especially in elderly. Mc Gimpsey et al. reported three patients in a series of 126 injections who developed a thromboembolic event soon after treatment.[17] We did not observed such complication following the injection of bevacizumab.

Studies are done to show the efficacy of intravitreal coricosteroids and the anti-VEGF agents in the SCNM treatment. Having good short term and long term results, intravitreal agents needed repeated administration for their maintenance.[7,18-23] Gragoudas et al. reported improvement in visual acuity in patient with SCNM treated with intravitreal pegaptanib, an anti-VEGF agent, but only when treated monthly.[20] Intravitreal ranibizumab was found superior to PDT while improving visual acuity on average at one year in eyes with predominantly classic SCNM with AMD in ANCHOR study.[23] Intravitreal administration ranibizumab for 2 years prevented vision loss and improved mean visual acuity in patients with minimally classic or occult SCNM from AMD in MARINA study.[21] The FOCUS study, on the other hand, found ranibizumab + PDT was more efficacious than PDT alone for treating neovascular AMD for all primary and secondary efficacy outcomes, including based on visual acuity, lesion characteristics, and need for PDT retreatment.[24] We think that, the synergetic effect of the three different treatment modalities is expected to give better results with destroying both the new and old vessels and limiting ongoing inflammation. In our study, cataract extraction due to cataract progression probably due to 2 mg intravitreal triamcinolone injection was conducted in 3 of 22 phakic eyes (13.6%).Study reported cataract extraction rate was 26.1% after 4 mg triamcinolone injection.[25] Two eyes (6.9%) showed transient IOP rise that was controlled with topical glaucoma medication in our study. A 4-mg intravitreal triamcinolone injection was associated with elevated intraocular pressure in 32.0% of treated eyes.[26] Two mg triamcinolone seems to induce less ocular hypertension and cataract than that of 4 mg.

In conclusion, the triple therapy with PDT, intravitreal triamcinolone and bevacizumab injection is a novel approach which seems to be more beneficial when applied primarily (as in Group 1 in this study) in terms of improvement in visual acuity. However, dosages, timing of injection and treatment sequences of triple therapy still needs to be clarified. In our study, triple therapy for SCNM improved visual acuity when used as a primary treatment (Group 1) and stabilized visual acuity in eyes refractory to prior PDT (Group 2). Ongoing membrane activity, need for repeated triple therapy or additional intravitreal injections as well as cataract progression due to intravitreal steroid were the detected weak points of triple therapy in the current study.

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