Sequenced Combined Intravitreal Triamcinolone and Indocyanine Green Angiography–Guided Photodynamic Therapy for Retinal Angiomatous Proliferation

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Objective: To study sequenced combined therapy using intravitreal triamcinolone acetonide followed by photodynamic therapy for the treatment of retinal angiomatous proliferation.

Methods: Patients newly diagnosed as having retinal angiomatous proliferation underwent intravitreal triamcinolone injection to reduce intraretinal and subretinal exudation, followed 7 to 14 days later by indocyanine green angiography–guided photodynamic therapy with verteporfin. Complete ocular examination, fluorescein angiography, indocyanine green angiography, and optical coherence tomography were performed at baseline and at standard intervals thereafter.

Results: Twenty-seven eyes of 26 patients underwent this sequenced combined treatment and were followed up for 12 months. The triamcinolone injection reduced the cystoid edema before photodynamic therapy. Complete resolution of the angiographic leakage was achieved in 89% of eyes. Visual acuity improved in 37% and was stable in 52% of eyes. Eight eyes developed recurrent leakage after 3 to 11 months. Complete resolution of leakage was observed after subsequent treatment.

Conclusions: This sequenced combined treatment in patients with retinal angiomatous proliferation was effective in reducing or eliminating the edema, achieving rapid regression of neovascularization, and stabilizing or improving visual acuity. To our knowledge, no study to date has achieved such promising results in the management of retinal angiomatous proliferation. A randomized clinical trial is under way to compare sequential and simultaneous combined therapy.

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Retinal Angiomatous Proliferation (RAP) is a well-described, distinct form of neovascular age-related macular degeneration (AMD). It is estimated to represent approximately 10% to 12% of patients newly diagnosed as having the condition in the overall spectrum of neovascular AMD. It is found more frequently in elderly patients, and there is a marked tendency toward bilateral, symmetric neovascular disease. Predominantly occurring in white individuals, it has rarely been identified in Asian people and to date not seen in African American individuals. A greater annual risk of neovascular involvement has also been reported in the second eye of these patients. On the basis of the presumed origin of the neovascular process in the retina, a 3-stage classification has been proposed to characterize the clinical manifestations and progressive vasogenic changes in this entity. In stage I, neovascular changes appear to originate in the middle retinal circulation, producing intraretinal neovascularization with a contiguous circumferential telangiectatic response. The angiomatic tissue extends into the subretinal space in stage II, forming subretinal neovascularization. Small preretinal and intraretinal hemorrhages, intraretinal edema, and pigment epithelium detachment (PED) are early clinical manifestations in the evolution of the vasogenic process. Eventually, choroidal neovascularization (CNV) evolves in stage III with a neovascularized complex that includes retinal-choroidal anastomoses. In some cases, preexisting occult CNV exists before the active proliferation of the intraretinal neovascularization. In either event, ultimately disciform scarring occurs, which evolves with severe central vision loss. Combined fluorescein angiography, indocyanine green (ICG) angiography, and optical coherence tomography (OCT) are useful and in some cases necessary to make the diagnosis. Fluorescein angiography may reveal these lesions in the transit phase of the study, but the later phases often show diffuse stain-...
ing of the neovascular lesion and associated exudative detachment. The ICG angiography displays the neovascularization in the middle to late phases, which appears as a hyperfluorescent spot (hot spot), and intraretinal staining of cystic spaces. This staining can lead to an overestimation of the extent of the CNV (lesion size). The OCT documents the intraretinal cystic changes, PED, and neurosensory retina detachment. These prominent exudative changes, intraretinal cystic spaces, and PED appear early in the vasogenic process and are characteristic features of RAP. Despite numerous publications on this distinct form of neovascular AMD, little is known regarding its natural course, and to date, no method of treatment has been established. Small uncontrolled series with diverse treatment modalities and variable success provide the only available data.7-14

Recently, combined intravitreal triamcinolone acetone and photodynamic therapy (PDT) with verteporfin was reported to be successful in the treatment of neovascular AMD.15 This approach is rational and attractive for modifying the vasogenic environment of the posterior fundus in conjunction with obliteration of the neovascular complex. Corticosteroids have antiangiogenic effects and anti-inflammatory properties. Histopathologic studies of a CNV complex have shown the presence of inflammatory cells.16,17 Triamcinolone might also support the antiangiogenic effect of PDT, since there is an up-regulation of vascular endothelial growth factor (VEGF) induced by the photosensitizing process.18

Both fluorescein and ICG angiography in eyes with stage II and III RAP show leakage into cystic retinal spaces. Given the similarity between ICG and verteporfin molecules, such as their size and protein-binding affinity, verteporfin may also fill cystic spaces in the retina in these eyes. Combined therapy, therefore, introduces a theoretical risk of photo-oxidative damage to the retina if the verteporfin molecule is activated while inside the retina. We hypothesized that triamcinolone resolves cystoid edema rapidly in these patients, reducing the risk of verteporfin staining in the perifoveal cystic spaces. On the basis of this theoretical concept, we investigated the combined sequenced therapy of triamcinolone administered to ameliorate or eliminate the cystic edema, followed after a delay of several days with PDT in a consecutive series of patients with RAP.

METHODS

We conducted a prospective pilot study of consecutive patients with sequenced combined intravitreal injection of triamcinolone and PDT with verteporfin in eyes newly diagnosed as having RAP. This study was approved by the institutional review board of the Manhattan Eye, Ear, and Throat Hospital. Informed consent was obtained from each patient. The patients were seen in the practice of Vitreous-Retina-Macula Consultants of New York, at offices in Brooklyn and Manhattan in New York City, in secondary and tertiary retina referral centers, respectively. Best-corrected visual acuity (Snellen) and intraocular pressure were measured, and ophthalmic examination results including slitlamp biomicroscopy, indirect ophthalmoscopy, fundus photographs, and OCT (Zeiss, Dublin, Calif) were recorded for every patient at each study visit (baseline, day 1, PDT day, after 6 weeks, and after 3, 6, 9, and 12 months). Digital fluorescein and ICG angiography were performed with a Topcon camera (Topcon, Tokyo, Japan) at baseline, before PDT, after 6 weeks, and after 3, 6, 9, and 12 months. If the patient noted a decrease in vision or increase in metamorphopsia or if clinical findings showed recurrences, the imaging was repeated earlier. Exclusion criteria included glaucoma, any other ocular condition that might lead to neovascularization (pathologic myopia or inflammatory diseases), and any ocular condition that might have compromised the visual acuity in the study eye.

At baseline, patients received intravitreal triamcinolone. Patients were given several drops of topical proparacaine hydrochloride and 1 drop of 5% povidone iodine solution. This was followed by a topical fluorourolina drop every 5 minutes for at least 4 doses. After 5 minutes, an additional drop of fluororquina was given and the lid speculum inserted. An intravitreal injection of 0.1 mL of triamcinolone acetonide (40 mg/mL; Kenalog; Bristol-Myers Squibb, New York, NY) was given using a 27-gauge needle. The intraocular pressure was measured 10 minutes afterward. The administration of topical fluororolina drop was continued for 3 days. After 7 to 14 days, PDT with verteporfin was performed with ICG angiographic guidance.19,20 Only the area of the hot spot in the ICG angiogram was treated. A spot size was chosen to cover the RAP lesion with a 200-µm border. When possible the fovea was not included in the treatment spot.

The data analyzed were extracted from the patients' records. Statistical analysis for descriptive statistics was performed with GB STAT software (Dynamic Microsystems Inc., Silver Spring, Md). The data obtained were analyzed with frequency and descriptive statistics. Decrease in visual acuity was considered significant with a loss of 3 or more lines. Improvement of visual acuity was considered as a gain of 3 or more lines. Any outcome in between was considered to be stabilization of visual acuity.

In this study, 27 eyes of 26 patients with newly diagnosed RAP were enrolled. The mean ± SD age was 82 ± 6 years (range, 71-94 years). There were 19 women and 7 men. All patients were white. The baseline Snellen equivalent was 20/150, with a range of 20/40 to 20/400. There were 2 eyes with RAP stage II without PED and 21 eyes with RAP stage II with PED. In 4 eyes, fluorescein and ICG angiograms revealed a choroidal component (stage III). All patients had a follow-up of 12 months.

Within 1 week after intravitreal triamcinolone injection, all eyes showed a significant reduction in intraretinal edema. A few eyes showed complete elimination of the edema. In 19 of 21 eyes with PED, a reduction in elevation of the serous PED was observed with OCT (Figure 1). The mean ± SD interval between triamcinolone injection and PDT with verteporfin was 8 ± 3 days (range, 7-14 days). At the 6-week follow-up visit, 24 eyes (88%) showed complete resolution of leakage on fluorescein angiography. The OCT revealed resolution of the cystic spaces as well as no intraretinal or subretinal fluid. The ICG angiogram showed disappearance of the hot spot. In 8 eyes, a recurrent leakage was observed after a mean ± SD follow-up of 8 ± 3 months with a range of 3 to 11 months. This was accompanied by a decline in vi-
tion of 2 lines in all patients. All 8 eyes were subsequently treated with the sequenced combined treatment (Figure 2). A complete resolution of fluid and increase in visual acuity was observed in all 8 eyes. The mean visual acuity after injection of triamcinolone before performing PDT was 20/150, with a range of 20/40 to 20/400 (Table). At 6 months, the mean visual acuity was 20/100 (range, 20/40 to 20/400). After 6 months, the visual acuity improved 3 or more lines in 5 eyes (19%), remained stable (±2 lines) in 19 eyes (70%), and lost 3 or more lines in 3 eyes (11%). After 12 months, the mean visual acuity was 20/100 (range, 20/50-20/400). In 10 eyes (37%) the visual acuity improved 3 or more lines, in 14 eyes (52%) the visual acuity was stable (±2 lines), and in 3 eyes (11%) it lost 3 or more lines (Figure 3). We treated only 4 eyes with stage III lesions. Therefore, we could not observe any difference in terms of visual outcome in such a small series. One of these eyes was stable at 12-month follow-up, 2 eyes improved 3 lines, and 1 eye was treated again after 6 months.

In 3 eyes, the intraocular pressure increased within 3 months but was stable with topical antiglaucomatous therapy. No optic nerve damage was evident. No other adverse effects occurred (eg, intraocular inflammation, endophthalmitis, or progression of lens opacities).

COMMENT

The peculiar vasogenic sequence in retinal angiomatous proliferation with neovascularization originating in the retinal circulation is reminiscent of the vascular proliferation known to occur in certain transgenic mice and in idiopathic perifoveal telangiectasia. There are, however, major differences among RAP, these animal experimental models, and the human retinal vascular counterpart. In RAP, the retinal pigment epithelium degenerates, predisposing individuals to PED, CNV, and retinal-choroidal anastomoses. The dual circulation that evolves in the RAP vascular process may constitute a degree of combined neovascularization that is resistant to therapy. To date, there is no known successful form of therapy. Some investigators noted that patients with RAP have a poor visual outcome after thermal laser photocoagle-

Figure 1. Sequenced combined therapy for retinal angiomatous proliferation (RAP). A, Red-free photograph showing intraretinal hemorrhage, serous pigment epithelium detachment (PED), and large drusen. B, Late-phase fluorescein angiogram (FA) demonstrating leakage of the fluorescein dye into the PED. C, Horizontal scan with optical coherence tomography (OCT) confirming the presence of the stage III RAP lesion (arrow) as well as a PED and intraretinal cystic changes. Vision acuity was 20/60. Nine days after intravitreal triamcinolone acetonide injection but prior to photodynamic therapy, a red-free photograph (D), FA (E), and horizontal OCT (F) revealed reduction of the intraretinal edema and elevation of the serous PED. G, Six months after sequenced combined treatment, there was a reduction in the neovascular process associated with the resolution of lipid exudation. H, The FA revealed the presence of a small area of occult choroidal neovascularization. I, The corresponding vertical section with OCT demonstrated resolution of the PED and the intraretinal cystic changes. Visual acuity improved to 20/40. Arrows in A, D, and G indicate where the OCT slice was obtained.
tion even when the focal neovascular lesion is in an extrafoveal location. Surgical ablation of retinal feeder vessels, transpupillary thermotherapy, and PDT have been proposed as producing possible therapeutic results in small, uncontrolled case series. Only surgical excision of the lesion combined with diathermy of the retinal feeding vessels, which has had promising results, warrants further investigation, but again this was a small series of patients followed up for a limited period and also treated with coagulation. In a longer series, a pharmacologic approach using anecortave acetate in 34 patients was ineffective. These authors concluded that monotherapy was inadvisable. The same recommendation was made in another report that investigated PDT to treat RAP. Combined therapy seems like the next logical approach for treating this resistant form of neovascular AMD. In our study we chose to investigate the effect of triamcinolone, a corticosteroid with anti-VEGF properties.

Corticosteroids in general have anti-inflammatory and antiangiogenic effects. The anti-inflammatory effect is effective not only against cellular mediators of inflammation but also in the expression of cell surface markers, secretion of proinflammatory and angiogenic cytokines, and stabilization of cell membranes and tight junctions. Corticosteroids modulate the production of VEGF and therefore can reduce permeability. Histopathologic studies have shown the presence of inflammatory cells in CNV. Intravitreal triamcinolone was reported to have a short-term but not a long-term benefit in the treatment of neovascular AMD. Eyes treated with triamcinolone appeared to have a favorable effect on visual acuity and fundus appearance, although a significant proportion of eyes still lost vision. The use of this drug was also rational based on its known ability to reduce or eliminate macular edema in other entities such as diabetic retinopathy and vein occlusion.

The advent of PDT with the photosensitizing dye verteporfin has introduced a means of treating neovascular AMD with the promise of modest but meaningful success. In the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy and Verteporfin in Photodynamic Therapy studies, patients with RAP were generally excluded because of either the size of their lesion, which is increased by the presence of a PED, or their fluorescein angiographic characteristics, which are usually "occult CNV" or less frequently "minimally classic CNV." Neither ICG angiography nor OCT imaging was used in these studies. Photodynamic therapy may have

### Table. Visual Acuity of Eyes With Retinal Angiomatous Proliferation After Sequenced Combined Triamcinolone Acetonide and Photodynamic Therapy

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Visual Acuity, Mean (Range)</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>20/150 (20/40-20/400)</td>
</tr>
<tr>
<td>Before PDT</td>
<td>20/150 (20/40-20/400)</td>
</tr>
<tr>
<td>3 mo</td>
<td>20/100 (20/40-20/400)</td>
</tr>
<tr>
<td>6 mo</td>
<td>20/100 (20/40-20/400)</td>
</tr>
<tr>
<td>9 mo</td>
<td>20/100 (20/40-20/400)</td>
</tr>
<tr>
<td>12 mo</td>
<td>20/100 (20/50-20/400)</td>
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Abbreviation: PDT, photodynamic therapy.

*Sample size for all time points was 27.
a different effect on RAP than on “classic CNV” or “occult CNV.” The ICG dye is similar to verteporfin in its biophysical properties. It has been shown that ICG has a high affinity for protein, including fibrin, which is commonly present in the intraretinal edema in RAP lesions and visible as leakage in ICG angiography. Therefore, a theoretical possibility exists that the verteporfin may leak into the retinal cystic spaces, predisposing patients to phototoxic damage to the retinal layers. This might also explain the presence of foveal atrophy after PDT of RAP. Accordingly, it appears rational to resolve the exudation within the retina before the use of PDT with verteporfin to avoid this risk of phototoxic damage to the retina, the method used in our study. Since ICG angiography images the vascular component to the RAP lesion and not the exudative detachments that stain with fluorescein, we used only the ICG angiography to guide the PDT.

There are several other possible reasons why the sequenced combined therapy, which we have termed PPP (pharmacology–pause–photodynamic therapy), may have a more favorable outcome in patients with RAP than monotherapy. Even in the earliest stage of RAP, which is limited to the retina, there is considerable retinal cystic change. This is distinctly different from other forms of neovascular AMD, in which extensive CNV with or without a PED may occur without cystic changes in the retina. Our data indicate that triamcinolone reduces vascular permeability and resolves macular edema and even a PED promptly in patients with RAP, not unlike the macula edema response known to occur in central retinal vein occlusion or diffuse diabetic macular edema.

Furthermore, triamcinolone persists in the vitreous, extending the duration of treatment by modifying the biological environment in the posterior fundus, whereas PDT has a strong but short-term effect. In the present study, a significant reduction in intraretinal and subretinal fluid was observed in all eyes shortly after treatment with triamcinolone and even before PDT was performed. After a mean time of 8.5 days, standard PDT with verteporfin was performed, using a spot size corresponding to the lesion size with a border of 200 μm. To reduce the theoretical risk of collateral retinal and choroidal damage, only the vascular area of the active lesion (hot spot), identified with ICG angiography, was treated. This method is in reality ICG-guided PDT of the vascular component of the RAP lesion, avoiding laser energy to the serous detachments, which stain with fluorescein angiography. A reduction in PDT exposure has the secondary benefit of minimizing fluency by reducing the possibility of VEGF up-regulation and collateral choroidal damage to nonvascular tissue. After this sequenced combined treatment, most of our patients had stabilization (70%) or improvement (19%) in vision after 6 months. This tendency was also observed after 1 year (52% and 37%, respectively). No other method of therapy for this form of neovascular AMD or any other form has resulted in such improvement in vision or even such a high frequency of stabilization of vision. In the present study, improvement or stabilization of vision was observed in 89% after 1 year.

Another promising aspect to our study was the low rate of additional treatment. The rate of additional treatment in this study was 1.3 during the 1-year follow-up, which is lower compared with the frequency of additional treatment during the first year of the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy Study (3.3).

There are several obvious limitations to this pilot study. The sample size is small, the follow-up period is short, and the series is uncontrolled. We also do not know the optimal interval between injection of triamcinolone and PDT, yet our results indicate that the sequenced combined treatment with intravitreal triamcinolone and PDT with verteporfin is effective in achieving rapid resolution of angiographic leakage and fluid in OCT imaging. This specific sequenced approach for treating patients with RAP may result in a better visual outcome by reducing the treatment area with the ICG-guided PDT effect and the risk of PDT-induced foveal atrophy. The inherent concept in our study, reduction of intraretinal edema with a pharmacologic agent before the use of ICG-guided PDT, may be applicable to other forms of neovascular AMD. Future research on a larger series with a longer follow-up is needed to study this technique designed to reduce the need for subsequent treatment and to improve the visual outcome in neovascular AMD. A randomized clinical trial is currently under way at our research facility to compare simultaneous (PDT-Plus) to sequenced (PPP) combined therapy with intravitreal triamcinolone and PDT. These results may have implications for treating other neovascular lesions associated with intraretinal fluid accumulation in AMD.

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