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

K. Bailey Freund, MD; Christina M. Klais, MD; Chiara M. Eandi, MD; Michael D. Ober, MD; Daniel E. Goldberg, MD; John A. Sorenson, MD; Lawrence A. Yannuzzi, MD

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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RETNAL 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 vasoergic 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 angiomatous tissue extends into the subretinal space in stage II, forming subretinal neovascularization. Small preretinal and intraretinal hemorrhages, preretinal edema, and pigment epithelium detachment (PED) are early clinical manifestations in the evolution of the vasoergic 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.\textsuperscript{7-14}

Recently, combined intravitreal triamcinolone acetonide and photodynamic therapy (PDT) with verteporfin was reported to be successful in the treatment of neovascular AMD.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

### RESULTS

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-
sion 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 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 antiglaucomatus 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 mice21,22 and in idiopathic perifoveal telangiectasia.23 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 photocoagula-
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...
a different effect on RAP than on “classic CNV” or “occult CNV.”39 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.7 Therefore, a theoretical possibility exists that the verteporfin may leak into the retinal cystic spaces, predisposing patients to photochemical damage to the retinal layers. This might also explain the presence of foveal atrophy after PDT of RAP.25 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.30,37

Furthermore, triamcinolone persists in the vitreous, extending the duration of treatment by modifying the biological environment in the posterior fundus,38 whereas PDT has a strong but short-term effect.39 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).35

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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Correspondence: K. Bailey Freund, MD, LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Hospital, 210 E 64th St, New York, NY 10021 (vrmny@aol.com).

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