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*Case Series*

# Treatment of Recurrent Retinal Angiomatous Proliferation With Intravitreal Triamcinolone Acetonide Followed by Photodynamic Therapy With Verteporfin: A Retrospective Case Series

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## ABSTRACT

**OBJECTIVE:** The aim of this study was to report the effect on tolerability of combined treatment with intravitreal triamcinolone acetonide (IVT) and photodynamic therapy (PDT) with verteporfin in patients with stage II retinal angiomatous proliferation (RAP) who had been treated previously with PDT and presented with recurrent RAP (R-RAP).

**METHODS:** This was a retrospective case series of patients with R-RAP after PDT (1–5 treatments) treated once with IVT followed 1 month later by PDT. A visual acuity test, fluorescein and indocyanine green angiography, and optical coherence tomography were performed at baseline and at 1, 3, and 6 months.

**RESULTS:** Five patients (4 men, 1 woman; mean [SD] age, 76.8 [3.9] years) with 6 eyes diagnosed with stage II R-RAP who had previously been treated with PDT and who received an IVT injection and PDT within 1 month were included in the study. Best corrected visual acuity (BCVA) remained stable after IVT in 5 eyes (83%) and deteriorated in 1 eye (17%). After PDT, BCVA remained stable in 2 eyes (33%) and deteriorated in 4 eyes (67%). IVT treatment combined with PDT also reduced fluorescein leakage. Median lesion size increased 24% before PDT and 61% at 6 months after PDT. One eye had intraocular hypertension at 3 months, and 1 eye developed a pigment epithelial tear after PDT.

**CONCLUSION:** The results were limited by the number of eyes and relatively short follow-up, but in this study, PDT after IVT did not appear to be as effective or well tolerated in 5 patients who had already been treated with PDT and presented with R-RAP. (*Curr Ther Res Clin Exp.* 2009;70:240–251) © 2009 Excerpta Medica Inc.

**KEY WORDS:** intravitreal triamcinolone acetonide, photodynamic therapy, retinal angiomatous proliferation.

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## INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative pathology of the posterior pole of the retina that is usually associated with visual impairment. It is the most common irreversible cause of severe vision loss among older people in Western countries.[1–3] Occult choroidal neovascularization (CNV) occurs in most patients with newly diagnosed exudative AMD.[4,5] In retinal angiomatous proliferation (RAP), neovascularization begins in the deep retina, extends through the subretinal space, and eventually communicates with the choroid, producing a CNV.[6] A controversial hypothesis suggests the initial event is the development of an occult chorioretinal anastomosis at the site of a type I CNV (subretinal pigment epithelium [sub-RPE] growth pattern) rather than an intraretinal neovascular process.[7,8] The prevalence of RAP in occult CNV ranges from 20%[6] to 28%.[9] Both theories describe the severe irreversible anatomical and functional course of such aggressive neovascularization.

Ocular photodynamic therapy (PDT) with verteporfin has been reported to reduce vision loss in patients with the classic or predominantly classic type of CNV lesions[10–12] and with occult CNV lesions but no classic lesions.[13] PDT was suggested to improve the anatomic and functional outcomes of RAP.[14] Triamcinolone and other steroids have been reported to be effective inhibitors of neovascularization in live and in vitro animal models.[15–18] In humans, intravitreal triamcinolone acetonide (IVT) combined with verteporfin PDT was well tolerated in classic, predominantly classic,[19,20] and occult[21] CNV lesions. In RAP, remodeling of the vascular lesions was found with the combined use of IVT and PDT,[22] which resulted in functional and anatomic improvement.[23] One prospective pilot study achieved promising results, but persistent neovascular activity was found in 7 treated eyes (26%).[24]

Methods of treating RAP have not been widely established. Surgical ablation of the feeding and draining vessels of RAP was reported to have transitory and limited beneficial effects.[25–28] PDT has been proposed to promote stabilization of visual acuity[29]; but the apparent lack of efficacy of this technique suggests that PDT alone does not prevent the natural course of the disease.[30] Because of the beneficial effects of IVT in the management of exudative AMD,[31,32] a combination of IVT and PDT was used to treat RAP.[33] Combination therapy offers the possibility of reducing the number of repeated treatments and improving visual acuity.[24,34]

The aim of this study was to present a case series of combined treatment with IVT injection followed 1 month later by PDT in eyes affected by recurrent RAP (R-RAP) that had previously been treated with PDT.

## PATIENTS AND METHODS

Best corrected visual acuity (BCVA) was measured by Snellen charts at baseline and at 1, 3, and 6 months. Six consecutive eyes diagnosed with stage II R-RAP after PDT in 5 patients who attended the Vitreo-Retinal Center (Policlinico of Bari, Bari, Italy) were selected for this single-center, retrospective case series. Institutional review board approval or informed consent was not obtained because of the retrospective nature of the study. Privacy and confidentiality were maintained per the requirements

of Italian law; only doctors from the ophthalmology department at the study site had access to the records. Recurrence was determined by residual neovascular activity after PDT was detected by fluorescein angiography (ie, leakage due to CNV beyond the area of the lesion noted at baseline, regardless of the amount of leakage noted within the area of the lesion identified at baseline, and the presence of fibrovascular pigment epithelial detachment) and optical coherence tomography (OCT) to identify persistent pigment epithelial detachment. Patients were scheduled for a single 25-mg dose of IVT followed by PDT 1 month later.

Visual acuity determined using the Early Treatment Diabetic Retinopathy Study refraction chart (Precision Vision, La Salle, Illinois) and ophthalmic examination, including slit-lamp biomicroscopy, indirect ophthalmoscopy, fluorescein (when available) and indocyanine green angiography (HRA, Heidelberg Engineering, Heidelberg, Germany), and OCT (OCT Stratus, Carl Zeiss Meditec, Inc., Dublin, California) were recorded at baseline and at 1, 3, and 6 months. A reduction in leakage was documented angiographically for occult components using the criteria developed by the Macular Photocoagulation Study Group[5] and the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group.[11,12] All evaluations were done by the same investigator (N.C.), who is an experienced retinologist. The greatest linear diameter was measured if the lesion was judged to be active. The greatest linear dimension (GLD) of the lesion was read on the screen using digital camera software; increases in GLD over time indicate worsening disease. The GLD was determined in all cases by the same investigator using Imagenet (Topcon TRC-50XT, Topcon Corporation, Tokyo, Japan) digital fluorescein angiography. The GLD measurement included all lesion components: the CNV lesions and features that could obscure the lesion boundaries (thick blood, hypofluorescence not corresponding to blood, serous detachment of the RPE, and hyperfluorescent staining from fibrous tissue).[35] Reduction in retinal thickness and in pigment epithelial detachment was documented by OCT, based on the morphology of a 6-mm cross-hair scan centered on the RAP.[27] None of the treated patients had a history or diagnosis of glaucoma.

### Intravitreal Triamcinolone Acetonide Injection

Patients received an intravitreal injection of 25 mg of crystalline triamcinolone acetonide in 0.1 mL of balanced salt solution. All injections were performed in the operating room by the same surgeon (F.B.). Before the intravitreal injection, topical 5% povidone/iodine (Alcon Laboratories, Fort Worth, Texas) was applied, and then the patients were completely draped. An eye speculum was inserted, and paracentesis was done to decrease the volume of the eye. Crystalline triamcinolone acetonide 25 mg was injected using a sharp 27-gauge needle through the temporal inferior pars plana 3 to 3.5 mm from the limbus. A combination antibiotic ointment (polymyxin B sulfate and neomycin sulfate) was then applied. The triamcinolone acetonide had been prepared by extracting 0.62 mL from an ampule (Kenacort, Bristol-Myers Squibb, New York, New York) containing 40 mg of triamcinolone acetonide in 1 mL of balanced salt solution (BSS). The extracted volume was placed in a tuberculin syringe (1 mL) filled with BSS. A Millipore filter (pore size, 5 µm [Sterifix Pury, Braun Mel-

sungen AG, Melsungen, Germany]) was placed on top of the syringe, and most of the contents of the syringe were pressed through the filter with the triamcinolone crystals remaining in the syringe. The syringe was then refilled with BSS, and the same procedure was repeated 3 times. At the end, 0.1 mL of solution was left in the syringe and injected transconjunctivally into the vitreous cavity. (To our knowledge, there have been no studies of this method that validate the actual concentration being injected or its reproducibility.) To avoid an increase in intraocular pressure, all patients were given a topical β-blocker (timolol 0.5%) BID for the entire follow-up period.

### Photodynamic Therapy

One month after triamcinolone acetonide injection, all eyes underwent PDT. The GLD of the lesion was measured on the fluorescein angiogram. Any area of hypofluorescence due to overlying blood or a serous detachment of the RPE contiguous with CNV was considered to be part of the GLD of the lesion. Verteporfin (6 mg/m$^2$) was infused intravenously for 10 minutes. Fifteen minutes after starting the infusion, a laser beam set at 689 nm was delivered at 50 J/cm$^2$ at an intensity of 600 mW/cm$^2$ for 83 seconds without a safety margin. Each patient was instructed to wear protective sunglasses and not expose their eyes to sunlight for the next 2 days.[35]

### Statistical Analysis

All of the data were analyzed using GraphPad Instat (GraphPad Software Inc., San Diego, California). Repeated measures analysis of variance tests were used. $P < 0.05$ was considered statistically significant.

## RESULTS

Six eyes diagnosed with stage II R-RAP of 5 patients (4 men, 1 woman; mean [SD] age, 76.8 [3.9] years) who had previously been treated with PDT (mean [SD] number of previous PDT treatments, 1.8 [1.6]; range, 1–5 treatments) and who received an IVT injection (period between primary diagnosis and IVT, 132.3 [143.7] days; range, 11–408 days) and PDT within 1 month (18.3 [6.6] days; range, 11–27 days) were included in the study. The BCVA remained stable after IVT in 5 eyes (83%) and deteriorated (3 fewer lines on Snellen charts) in 1 eye (17%). After PDT, BCVA remained stable in 2 eyes (33%) and deteriorated in 4 eyes (67%) (**Table I**). Overall, IVT treatment combined with PDT reduced fluorescein leakage (**Figures 1–4**). Based on GLD, median lesion size increased 24% before PDT and 61% in 4 eyes 6 months after PDT (**Table II**). OCT showed a resolution or reduction of intraretinal and subretinal fluid accumulation (**Figures 5–7**).[14] One eye had intraocular hypertension at 3 months and was treated with a combination of topical antiglaucomatous drops (β-blocker and carbonic anhydrase inhibitor). One eye developed a pigment epithelial tear after PDT (**Figures 4–7**). There was 1 case of sterile endophthalmitis, which was treated with topical dexamethasone, tetracycline, and atropine.

## DISCUSSION

In this study, we used the combination of IVT and PDT to treat R-RAP,[33] because combining therapies offers the possibility of reducing the number of repeated treat-

**Table I. Demographic and clinical characteristics in a retrospective case series of 5 patients (6 eyes) diagnosed with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy (PDT) before and 1 month after intravitreal triamcinolone acetonide (IVT).**

| Pt | Sex | Age, y | Follow-up, d | Baseline BCVA | Baseline IOP, mm Hg | Previous PDT | Pre-IVT BCVA | Time to IVT, d | Post-IVT BCVA | Post-IVT IOP, mm Hg | Post-IVT AE | Time to PDT, d | BCVA at 1 mo | BCVA at 3 mo | BCVA at 6 mo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 79 | 225 | 20/40 | 14 | 1 | 20/40 | 67 | 20/100 | 15 | None | 22 | 20/200 | 20/200 | 20/200 |
| 2 | M | 73 | 194 | 20/50 | 15 | 1 | 20/320 | 120 | 20/320 | 14 | None | 11 | 20/400 | 20/320 | 20/320 |
| 3 | F | 73 | 119 | 20/50 | 14 | 2 | 20/400 | 11 | 20/400 | 25 | Ocular hypertension | 27 | 20/400 | 20/400 | 20/400 |
| 4 | M | 74 | 232 | 20/50 | 13 | 1 | 20/63 | 145 | 20/63 | 15 | RPE tear | 10 | 20/100 | 20/100 | 20/200 |
| 5 | M | 81 | 123 | 20/20 | 15 | 1 | 20/100 | 43 | 20/100 | 14 | None | 20 | 20/400 | 20/400 | 20/400 |
| 5 | M | 81 | 488 | 20/40 | 16 | 5 | 20/200 | 408 | 20/200 | 16 | None | 20 | 20/2000 | 20/2000 | 20/2000 |

Pt = patient; BCVA = best corrected visual acuity; IOP = intraocular pressure; AE = adverse event; M = male; F = female; RPE = retinal pigment epithelium.

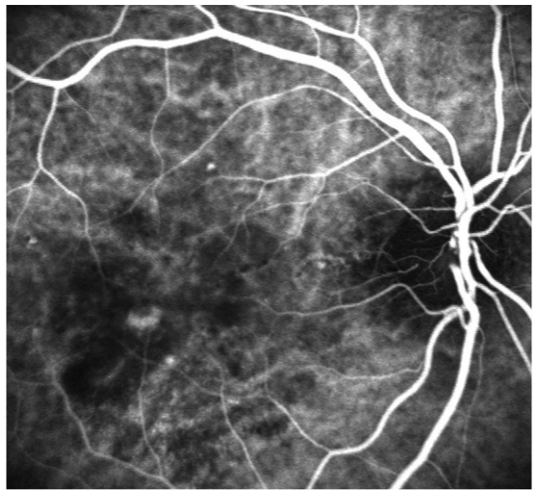

**Figure 1.** Fluorescein angiography image of lesion of patient 4 at baseline, showing juxtafoveal retinal angiomatous proliferation (RAP) surrounded by pigment epithelial detachment, in a case series of 5 patients with stage II recurrent RAP who received photodynamic therapy before and 1 month after intravitreal triamcinolone acetonide.

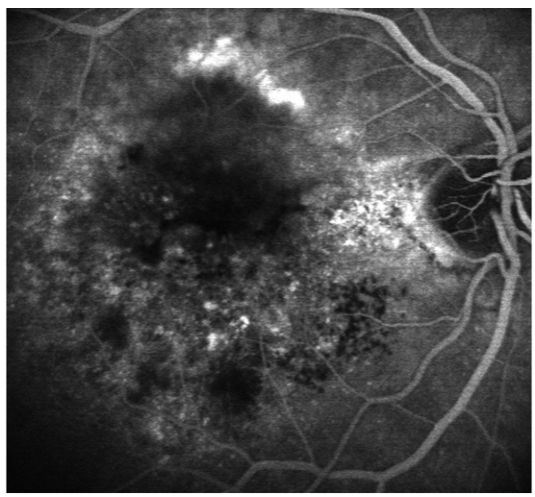

**Figure 2.** Fluorescein angiography image of lesion of patient 4 at 15 days before intravitreal triamcinolone acetonide (IVT), showing extensive pigment epithelial detachment, in a case series of 5 patients with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy before and 1 month after IVT.

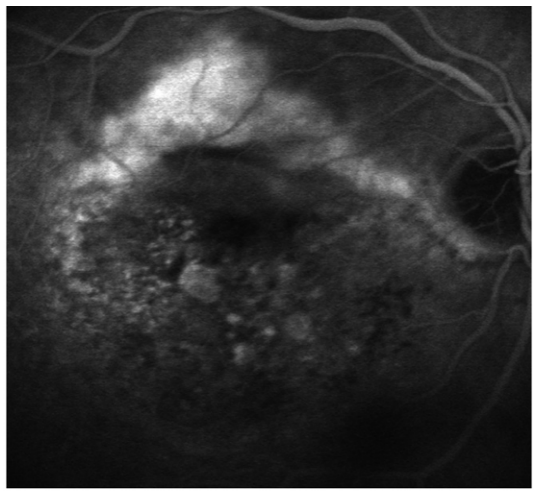

**Figure 3. Fluorescein angiography image of lesion of patient 4 at 3 months after photodynamic therapy, showing persistent pigment epithelial detachment and pigment epithelial tear, in a case series of 5 patients with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy before and 1 month after intravitreal triamcinolone acetonide.**

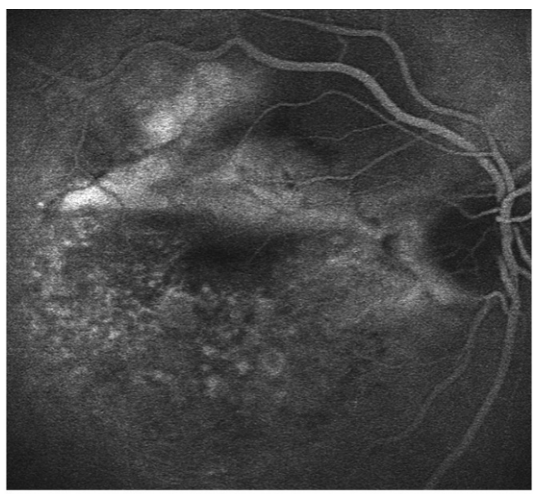

**Figure 4. Fluorescein angiography image of lesion of patient 4 at 6 months after photodynamic therapy, showing a reduction in pigment epithelial detachment and of the pigment epithelial tear, in a case series of 5 patients with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy before and 1 month after intravitreal triamcinolone acetonide.**

**Table II. Lesion size in microns, calculated using greatest linear dimension, in a retrospective case series of 5 patients (6 eyes) diagnosed with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy (PDT) before and 1 month after intravitreal triamcinolone acetonide (IVT). Increase in lesion size indicates worsening disease.**

| Patient | Baseline | IVT | 6 Months Post-PDT | Difference, % |
|---|---|---|---|---|
| 1 | 2550 | 4997 | 5142 | 202 |
| 2 | 3670 | 5288 | 6075 | 166 |
| 3 | 2625 | 2175 | 2186 | 83 |
| 4 | 2775 | 6073 | 6089 | 219 |
| 5 | 3832 | 3696 | 6022 | 157 |
| 5 | 4095 | 4555 | 6085 | 149 |

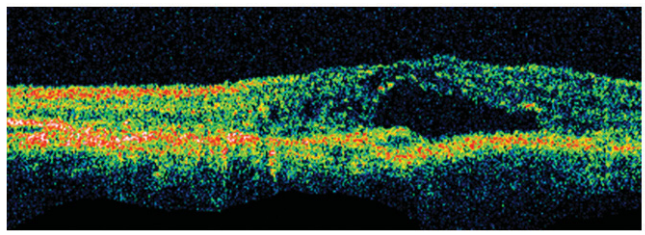

**Figure 5. Optical coherence tomography image of patient 4 at baseline, showing pigment epithelial detachment contiguous to retinal angiomatous proliferation, in a case series of 5 patients with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy before and 1 month after intravitreal triamcinolone acetonide.**

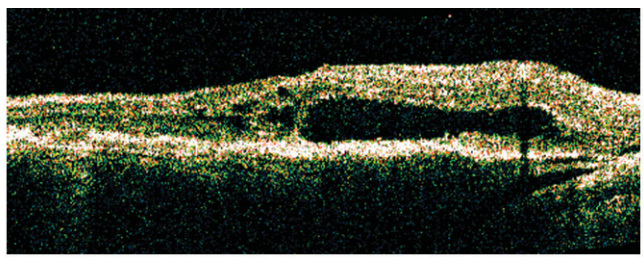

**Figure 6. Optical coherence tomography image of patient 4 at 15 days before intravitreal triamcinolone acetonide (IVT), showing extensive pigment epithelial detachment, in a case series of 5 patients with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy before and 1 month after IVT.**

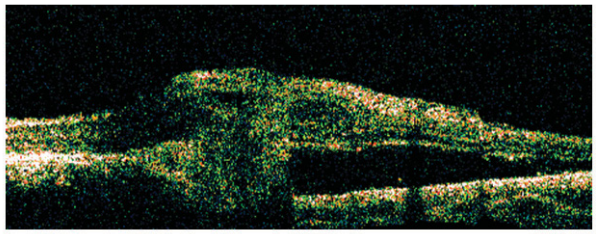

**Figure 7. Optical coherence tomography image of patient 4 at 6 months after photodynamic therapy, showing fibrovascular tissue of the retinal pigment epithelium tear, in a case series of 5 patients with stage II recurrent retinal angiomatous proliferation who received photodynamic therapy before and 1 month after intravitreal triamcinolone acetonide.**

ments, thereby improving visual acuity.[24,34] Despite the resolution of fluorescein and indocyanine leakage, visual acuity decreased by 2 lines[36,37] and lesion size increased 61% in 4 eyes (66%). The reduction of fluorescein and indocyanine leakage could be related to the antiangiogenic effect and anti-inflammatory properties of corticosteroids. In particular, corticosteroids can modulate the production of cytokines and reduce the permeability induced by vascular endothelial growth factor.[37–39] These secondary effects would not be expected with PDT with verteporfin alone. The sequence and temporal interval of the combined treatments are likely to be important. In our study, PDT was performed within 1 month after IVT injection. During this period, triamcinolone could reduce fluorescein leakage and facilitate RPE reattachment, diminishing the risk of an RPE tear and sudden decrease in vision.[40–43]

Adverse events arising from the combined treatment may be expected to include all of those associated with PDT, as well as the incremental risks of IVT injection (eg, increased intraocular pressure, accelerated progression of cataract formation, endophthalmitis).[43] To balance intraocular pressure, we prescribed hypotensive topical therapy (β-blocker) after IVT injection for the entire follow-up period. Only 3 eyes needed to be treated with combination topical therapy (β-blocker and dorzolamide). Cataract progression was not observed because of the short duration of follow-up. There was 1 case of sterile endophthalmitis, which was treated with topical dexamethasone, tetracycline, and atropine. A pigment epithelial tear occurred in 1 eye after PDT.

Limitations and potential biases of the present study were the retrospective nature of the investigation, the limited number of eyes, and the short follow-up period. Moreover, the small sample size and the relatively short follow-up period did not allow calculation of the power to detect complications throughout the follow-up period. Krebs et al[44] did not find a beneficial effect of triamcinolone combined therapy versus PDT alone, suggesting new therapeutic strategies might be required in RAP lesions, probably including therapy with antiangiogenic agents.[45]

## CONCLUSIONS

The findings of the present case series suggested that combination treatment with IVT injection followed 1 month later by PDT with verteporfin was not an effective or well-tolerated strategy to treat the eyes of these patients affected by R-RAP.

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