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Retinal angiomatous proliferation treated with a combination of intravitreal triamcinolone acetonide and photodynamic therapy with verteporfin

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PURPOSE. *Retinal angiomatous proliferation (RAP) is a particularly aggressive form of exudative age-related macular degeneration. Response to laser photocoagulation or to photodynamic therapy (PDT) alone is often disappointing. The purpose of this study was to determine whether intravitreal triamcinolone acetonide (TA) injections followed by PDT in eyes with early stage RAP may be effective.*

METHODS. *Prospective uncontrolled study, enrolling 11 patients (11 eyes) with stage 2 RAP, treated with intravitreal TA injection followed by PDT. Patients with large pigment epithelium detachment, RAP stage 3, or pre-existing glaucoma and known steroid responders were excluded. All patients underwent a complete ophthalmic examination including fluorescein and indocyanine green (ICG) angiography and optical coherence tomography (OCT-3) at baseline and at 1, 3, 6, and 12 months. Informed consent was obtained from all patients.*

RESULTS. *Mean follow-up was 14.9 months (range 6–21 months). Mean age was 82 years. In four patients a small pigment epithelium detachment was found on tomography. Initial visual acuity (VA) ranged from 0.1 to 0.6 on the Snellen scale. After calculating the logarithmic values the authors found an initial mean VA of logMAR 0.61, which improved by 1.5, 0.9, and 0.9 log lines after 3, 6, and 12 months, respectively. Although the VA gain from baseline tended to decrease with time, only 2 patients (18%) had an actual loss of acuity (≥3 lines). Retreatment was required in 5 eyes.*

CONCLUSIONS. *In this prospective pilot study examining the use of intravitreal TA followed by PDT with verteporfin in eyes with stage 2 RAP, without a large pigment epithelium detachment, the authors found a potential benefit in terms of stabilization or even improvement of vision. (Eur J Ophthalmol 2006; 16: 705-10)*

KEY WORDS. *Age-related macular degeneration, Chorioretinal anastomosis, Intravitreal triamcinolone acetate, Photodynamic therapy, Retinal angiomatous proliferation, Visual acuity*

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INTRODUCTION

Advanced stages of age-related macular degeneration (ARMD), particularly exudative forms, are the main cause of severe loss of visual acuity (VA) in people over 65 years of age. Photodynamic therapy (PDT) with verteporfin has been shown to improve the visual outcome in patients with subfoveal choroidal neovascularization (CNV) (1, 2).

Additional intravitreal treatment with the steroid triamcinolone acetate (TA) may be more effective than PDT alone (3). Another study also showed reasonable results with good safety (4).

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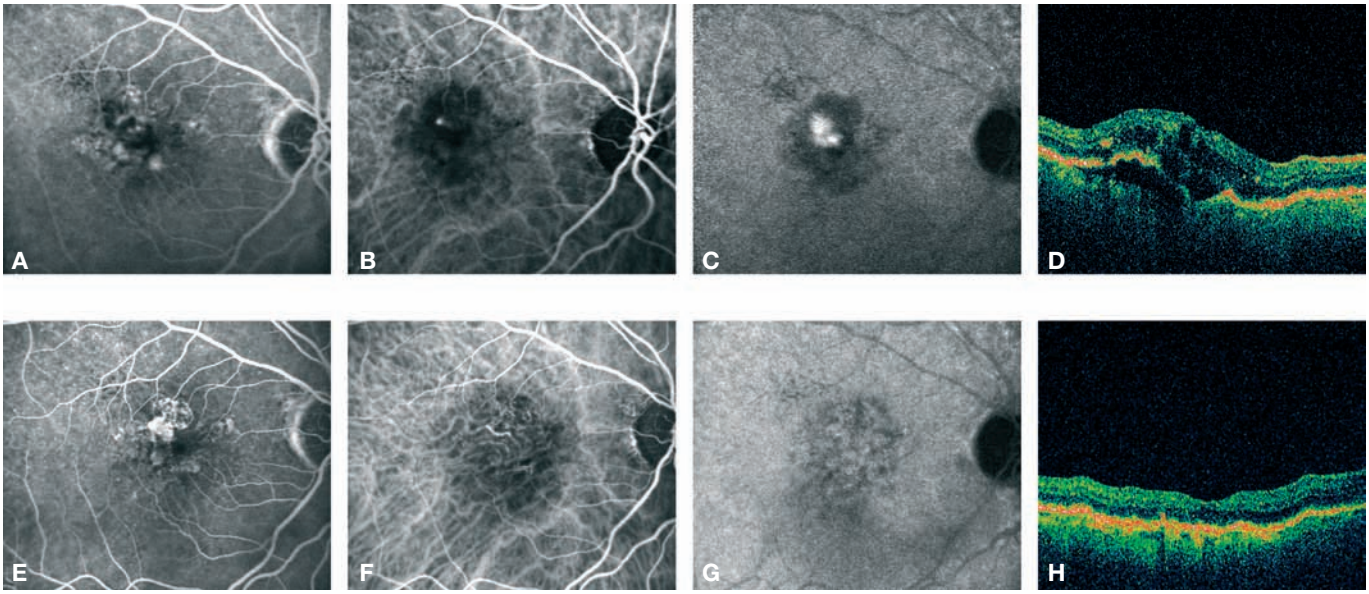

Fig. 1 - *Case 8 is an 86-year-old woman with stage 2 retinal angiomatous proliferation (RAP) plus small retinal pigment epithelial (RPE) detachment. At baseline, visual acuity (VA) is 0.5 (logMAR 0.3); many soft drusen are seen in the macular region as well as intraretinal edema with hard exudates and superficial hemorrhages.* (**A**) *Fluorescein angiography at baseline does not allow identifying the source of leakage.* (**B**) *Indocyanine green (ICG) angiography at baseline demonstrates the typical hot spot with an afferent retinal vessel.* (**C**) *Late ICG pictures show staining of the surrounding tissue.* (**D**) *Optical coherence tomography (OCT)-3 demonstrates well the intraretinal edema and the small RPE detachment.* (**E**-**H**) *Six months after a single treatment with the combination of triamcinolone acetate and photodynamic therapy with verteporfin, VA has improved to 0.8 (logMAR 0.1). Angiography shows some RPE atrophy* (**E**) *as well as delayed perfusion of the choriocapillaris* (**F**) *and the absence of the hot spot or late staining on ICG* (**G**)*. OCT* (**H**) *documents the absence of intra- or subretinal fluid. No RPE detachment can be found. This situation was maintained through to month 12 with VA increasing to 1.0.*

Recently, a form of exudative ARMD was recognized as a distinct entity with characteristics different from choroidal neovascularization. Yannuzzi and colleagues described it as retinal angiomatous proliferation (RAP) with signs of intraretinal origin of the neovascularization, in contrast to CNV (5). The pathology has also been described as retinal angiomatous lesion (6), while other publications used terms such as deep retinal vascular anomalous complex (7) or retinal choroidal anastomosis (8, 9).

The natural course of RAP tends to be particularly aggressive, and a therapeutic gold standard has not yet been developed (10).

Several reports of indocyanine green (ICG)-guided laser treatment suggested an extremely poor outcome in advanced cases with a pigment epithelium detachment (PED) (6, 7, 9, 11).

Surgical lysis of the feeding arteriole and draining venule of the RAP lesion has been reported by Borrillo and colleagues (12). However, recurrence 6 months after similar treatment of another patient was reported (13).

PDT seems to be less effective in eyes with RAP than would be expected on the basis of findings of the TAP and VIP studies (1, 2). A relatively poor outcome has been reported for stages 2 and 3 with PED, although some potential effectiveness was postulated for RAP accompanied by a only small PED (14-16). Another study, however, suggested some VA stabilization in eyes with established chorioretinal anastomosis treated with PDT (17).

PDT in combination with intravitreal TA has recently been reported to potentially stabilize or even improve VA in patients with RAP (18, 19).

The purpose of the study described herein was to investigate whether intravitreal injections of TA, followed by PDT with verteporfin, may be an effective treatment for less advanced stages of RAP.

MATERIALS AND METHODS

In this prospective interventional case study, all patients seen in the medical retina department of the Jules Gonin Hospital, Lausanne, Switzerland, who were diagnosed with RAP between October 2003 and October 2004 were considered for enrollment to this study according to the following criteria: best-corrected VA (BCVA) between 0.6 and 0.08, consent given for the suggested treatment regi-

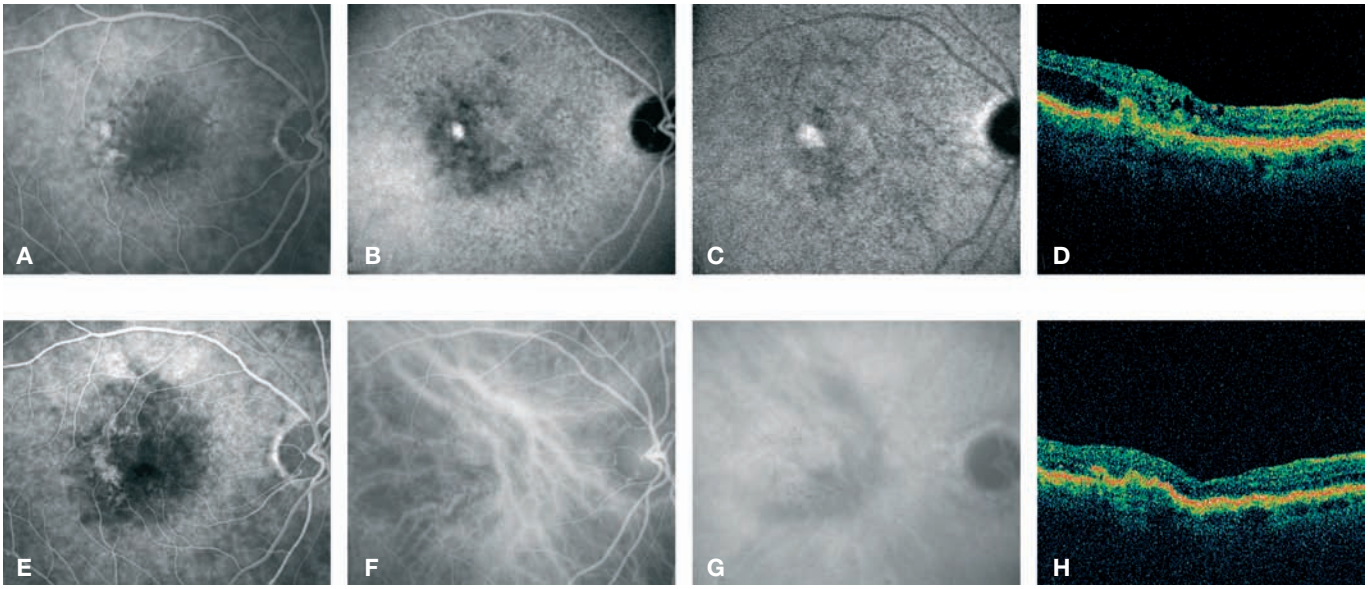

Fig. 2 - *Case 9 is a 79-year-old woman with stage 2 retinal angiomatous proliferation (RAP). At baseline, visual acuity (VA) is 0.5 (logMAR 0.3); many soft drusen are seen in the macular region as well as intraretinal edema with some hard exudates and superficial hemorrhages.* (**A**) *Fluorescein angiography at baseline shows diffuse leakage temporal to the fovea.* (**B**) *Indocyanine green angiography (ICG) at baseline demonstrates the typical hot spot. However, an afferent retinal vessel cannot be clearly identified.* (**C**) *The hyperfluorescence area on late ICG is hardly larger than on early frames.* (**D**) *Optical coherence tomography (OCT)-3 demonstrates well the intraretinal edema. Six months after the initial combined treatment, VA improved to 1.0 (logMAR 0), but soon after further treatment was needed for recurrence (2 photodynamic therapy treatments, the last again combined with intravitreal triamcinolone acetate). At 12 months, VA stabilized at 0.5 (logMAR 0.3).* (**E**) *Fluorescein angiography shows some retinal pigment epithelial changes as well as mild subretinal fibrosis temporal to the fovea.* (**F**) *Early perfusion of the choriocapillaris appears near normal on ICG and* (**G**) *on late frames only faint hyperfluorescence is noted.* (**H**) *OCT documents the absence of intra- or subretinal fluid. During follow-up to month 20 no further treatment was needed and VA was 0.6.*

men with intravitreal TA injection and PDT with verteporfin. Patients with very small RAP lesions of stage 1 were alternatively offered treatment with ICG-guided laser photocoagulation. Eyes with stage 3 RAP were excluded from this study, as were eyes with significant PED (>1 disc diameter) in stage 2 RAP, because of the increased risk for pigment epithelium tear (14, 20-22). A small PED of less than 1 disc diameter, however, was not considered an exclusion criterion. Patients with glaucoma and known steroid responders were also excluded from this study, because of the high risk of intraocular pressure (IOP) rise after intravitreal injection of TA.

According to the above criteria, 11 eyes of 11 patients (5 men and 6 women) were included in the study. All 11 underwent intravitreal injection of 4 mg TA, followed by PDT within 1 week. During the first month after injection, they were seen weekly for early side effects. Visits at 1, 3, 6, and 12 months included determination of BCVA, IOP, anterior segment and dilated fundus examination, as well as fluorescein and ICG angiography (Heidelberg scanning laser ophthalmoscope for most angiograms), and optical coherence tomography (OCT-3). Scheimpflug imaging of the lens was performed in phakic eyes at baseline, and at month 6 and 12, allowing observation of the nuclear density (median density level in comparison with the corneal density on a slit image) and cortical opacifications (transparent surface in percentage) over time.

Eyes with recurrent exudation on angiography, confirmed by OCT in order to exclude potential confusion with pigment epithelium changes, were considered for retreatment with the same regimen. However, in eyes in which VA was better than 0.6, only PDT with verteporfin was suggested, because of the potentially serious side effects of intravitreal TA. No further treatment was suggested for eyes that had lost VA to levels worse than 0.08 or if significant PED became apparent.

Follow-up data were analyzed primarily for change in VA. In addition, recurrence of exudative activity (retreatments) and angiographic evidence of progression of the disorder were analyzed.

RESULTS

Eleven patients met the entrance criteria (5 men and 6 women); their average age was 82 years (standard devia-

tion [SD] 3.1). At baseline visit, each study eye had stage 2 RAP. Two showed two simultaneous RAP lesions. No eye had a clinically evident PED, but four eyes had a small PED as shown by OCT (<1 disc diameter on angiography). Two eyes had previously undergone focal ICG-guided laser treatment with recurrence 1 month after photocoagulation (Patients 1 and 2). Patient 4 was pretreated with a single session of PDT but had a recurrence 10 months later. Patient 5 had a recurrence 2 months after surgical intervention of the feeder vessel. None of the remaining seven eyes had received any treatment prior to inclusion in our study. Patients were followed for an average of 14.9 months (range, 6–21 months).

Visual outcome

Average baseline BCVA was logMAR 0.61 (decimal equivalent, 0.25; SD, 0.34), and ranged from logMAR 1 to logMAR 0.2. The average BCVA improved within 3 months by 1.5 lines to logMAR 0.46 (decimal equivalent, 0.32-0.4; SD, 0.43). At the 6-month visit, it decreased slightly to logMAR 0.52 (decimal equivalent, 0.25-0.32; SD, 0.40) and remained stable through to month 12. However, the average BCVA at last follow-up tended to decrease further (logMAR 0.58; decimal equivalent, 0.25-0.32; SD, 0.43). The final VA was improved by 3 lines or more in 4 patients (36%), stable (±2 lines) in 5 patients (45%), and worse 3 lines or more in 2

TABLE I - OVERVIEW OF THE MORE ESSENTIAL DATA OF THE STUDY PATIENTS

Patient no.	Age, y	Baseline VA, log MAR	VA 1 mo, logMAR	VA 3 mo, logMAR	VA 6 mo, logMAR	VA 12 mo, logMAR	final VA, logMAR	VA changes, in lines	Retreatments	Follow-up, mo
1	83	1	0.9	0.9	0.5	0.6	0.7	3	PDT2, PDT3	21
2	79	1	1.3	1.3	1.3	1.3	1.3	-3	Photocoagulation	18
3	83	0.6	0.4	0.3	0.4	0.2	0.3	3		18
4	87	1	0.8	1	0.7	0.9	1	0		18
5	82	1	0.7	0.5	1	NA	1	0		6 - lost
6	86	0.2	0.1	0	0.1	0.2	0.2	0	PDT 2, IVTA+PDT3, IVTA+PDT4, IVTA+PDT5	15
7	80	0.7	0.2	0	0.4	0.3	0.3	4		15
8	86	0.3	0	0.2	0.1	0	0	3		12
9	79	0.3	0.1	0.1	0	0.3	0.2	1	PDT 2, IVTA+PDT 3	20
10	84	0.3	0.3	0.3	0.4	0.4	0.4	-1		12
11	78	0.3	0.4	0.5	0.8	NA	1	-7	PDT 2, IVTA+PDT 3	9
Mean		0.61	0.47	0.46	0.52	0.52	0.58	0.27		14.9

VA = Visual acuity; PDT = Photodynamic therapy; NA = Not available; IVTA = Intravitreal triamcinolone acetate

TABLE II - DEVELOPMENT OF NUCLEAR LENS DENSITY (as measured by the intensity of light scatter on scheimpflug imaging) AND CORTICAL OPACITIES (as measured by retroillumination on scheimpflug imaging) OVER TIME

Patient no.	Increase of cortical opacities after 6 mo, %	Increase of cortical opacities after 12 mo, %	Increase of nuclear density after 6 mo, %	Increase of nuclear density after 12 mo, %
1	+4		+1	
3	+3	+8	+2	+13
4	+2	+1	+1	+1
5	Missing data			(Clinical progression)
9	0	+65	+4	+18
10	+2		+1	
11	0		+1	

In order to quantify the nuclear lens density, the mean intensity of light scatter was compared with the corneal scatter on the slit image (in percentage). The table shows the difference of this percentage over time. Cortical opacities were calculated as no-transparent surface area in the percentage of a circle, with maximal size according to the worst dilatation

patients (18%) (Tab. I). Patients who had undergone other treatment modalities before intravitreal TA and PDT had no worse visual outcome than previously untreated patients.

Angiographic outcome

Favorable angiographic outcome without recurrence after a single treatment was found in 5 eyes (45%) with disappearance of the hyperfluorescent hot spot on ICG angiography. Figure 1 shows one example.

Recurrence of leakage was noted in 6 eyes (55%) at month 3–7 after treatment. Four of these six eyes underwent retreatment (Patients 1, 6, 9, 11). The kind and number of retreatments is shown in Table I. An example is given in Figure 2 (initial and final angiograms) with an inactive end result.

In Patient 5, the condition was considered to be too far advanced for any potential treatment benefit (stage 3 RAP with chorioretinal anastomosis), however, she maintained her visual acuity until month 6 and was then lost to follow-up. Patient 2 was treated with photocoagulation because of low VA. Progression of the subretinal neovascular membrane was observed in 3 eyes (27%).

Complications

Looking at the previously reported side effects of TA, we found only 1 eye (9%) where intraocular pressure increased to greater than 21 mmHg. The eye responded well to topical treatment.

Some cataract progression was observed in 3 (43%) of the 7 phakic patients. Table II shows measurements of the nuclear density on Scheimpflug slit image and transparency on retroillumination. One of these eyes (Patient 9) had a rapidly progressive intumescent cataract that developed 2 weeks after the third treatment, and which required surgical intervention.

None of our patients developed either infectious or sterile endophthalmitis.

DISCUSSION

This prospective pilot study examined the use of intravitreal TA followed by PDT in eyes with RAP stage 2 (without large PED), and found a potential benefit in terms of visual stabilization or even improvement within the first 12 months (average gain 0.9 log lines). Although the VA gain from baseline tended to decrease with time, only 2 (18%) of the patients experienced an actual loss of three lines or more. Retreatment was necessary in four eyes, which is probably less than what would be expected if PDT alone had been used. We cannot compare our results with those of PDT alone or with the natural course of the disorder. However, given the tendency of RAP to be more aggressive than CNV, and given the commonly encountered mild visual loss in eyes with CNV treated by PDT alone (1, 2), our preliminary results are encouraging for the treatment of eyes with RAP with a combination of intravitreal TA and PDT. However, we excluded eyes with more advanced disease (large PED or stage 3 RAP), and this may have biased our results, possibly increasing the apparent responsiveness to treatment.

Complications that could arise from our study regimen include all of those that may occur from intravitreal TA injections or from PDT. Nonetheless, we observed only 1 incidence (9%) of increased IOP; this particular patient responded well to topical medication. Progression of an existing cataract, however, was observed in 3 of 7 phakic patients (43%), one of whom required surgery for an intumescent cataract. In our small series, there was no case of endophthalmitis, either infectious or sterile.

We acknowledge that our study has numerous limitations. Only a small number of patients were enrolled and the follow-up time is limited. Furthermore, the study is a noncomparative case series, so the findings cannot be used for justification of any treatment. Our results, however, are strongly suggestive of a potential benefit of intravitreal TA injection combined with PDT in eyes with RAP. There is obviously a need for large prospective and comparative studies in order to develop a treatment gold standard for these patients. This preliminary study provides useful information for the design of these future studies.

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