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Triamcinolone and PDT to treat exudative age-related macular degeneration and submacular hemorrhage

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PURPOSE. *To evaluate the efficacy of photodynamic therapy (PDT) with verteporfin and intravitreal injection of triamcinolone to treat choroidal neovascularization (CNV) with flat submacular hemorrhage in age-related macular degeneration (ARMD).*
METHODS. *A prospective, consecutive, noncomparative, interventional case series study was performed at the Instituto Oftalmologico de Alicante, Spain. Ten consecutive eyes from 10 patients with flat submacular hemorrhage secondary to ARMD were treated by PDT followed by intravitreal injection of 19.4±2.1 mg/0.1 mL triamcinolone 5 days later. PDT was repeated if leakage from the CNV appeared on fluorescein angiography (FA) at 3 months follow-up intervals. Main outcome measures were best-corrected visual acuity (BCVA) before and after treatment, post-treatment FA, results, and complications.*
RESULTS. *Stable or improved BCVA was achieved in seven eyes at 6 months follow-up. Complete absence of leakage in FA was observed in five and in eight eyes at 3 and 6 months follow-up, respectively. Intraocular pressure rose in seven eyes.*
CONCLUSIONS. *PDT followed by intravitreal triamcinolone seems useful to treat CNV with flat submacular hemorrhage in ARMD. However, further studies with longer follow-up and randomized controlled trials are necessary to assess its efficacy in the management of this difficult clinical problem. (Eur J Ophthalmol 2006; 16: 426-34)*

KEY WORDS. *Age-related macular degeneration, Intravitreous triamcinolone, Photodynamic therapy, Subretinal hemorrhage*

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INTRODUCTION

Visual prognosis in eyes with subretinal hemorrhage associated with age-related macular degeneration (ARMD) is generally considered to be poor (1, 2). Different mechanisms are considered to be responsible of this, such as a blockading effect of blood, which disturbs metabolic support from retinal pigment epithelium (RPE) and choroid to the photoreceptors, toxicity of iron released from blood, and mechanical damage of photoreceptors caused by the contraction of the fibrin clot (3). Different therapeutic approaches have been proposed. Some of them include removing submacular blood by vitrectomy (4) and subretinal injection of recombinant tissue plasminogen activator (rt-PA) followed by perfluoro-octane (5) or pneumatic displacement of the blood (6-11), in order to minimize the damage to the photoreceptors and RPE. Other authors propose perfluorohexyloctane (12) or gas endotamponade (13). There is evidence that visual outcome is poor when macular hemorrhage develops after being treated by PDT (14).

Photodynamic therapy (PDT) with verteporfin associated with intravitreal triamcinolone (IT) injection seems to

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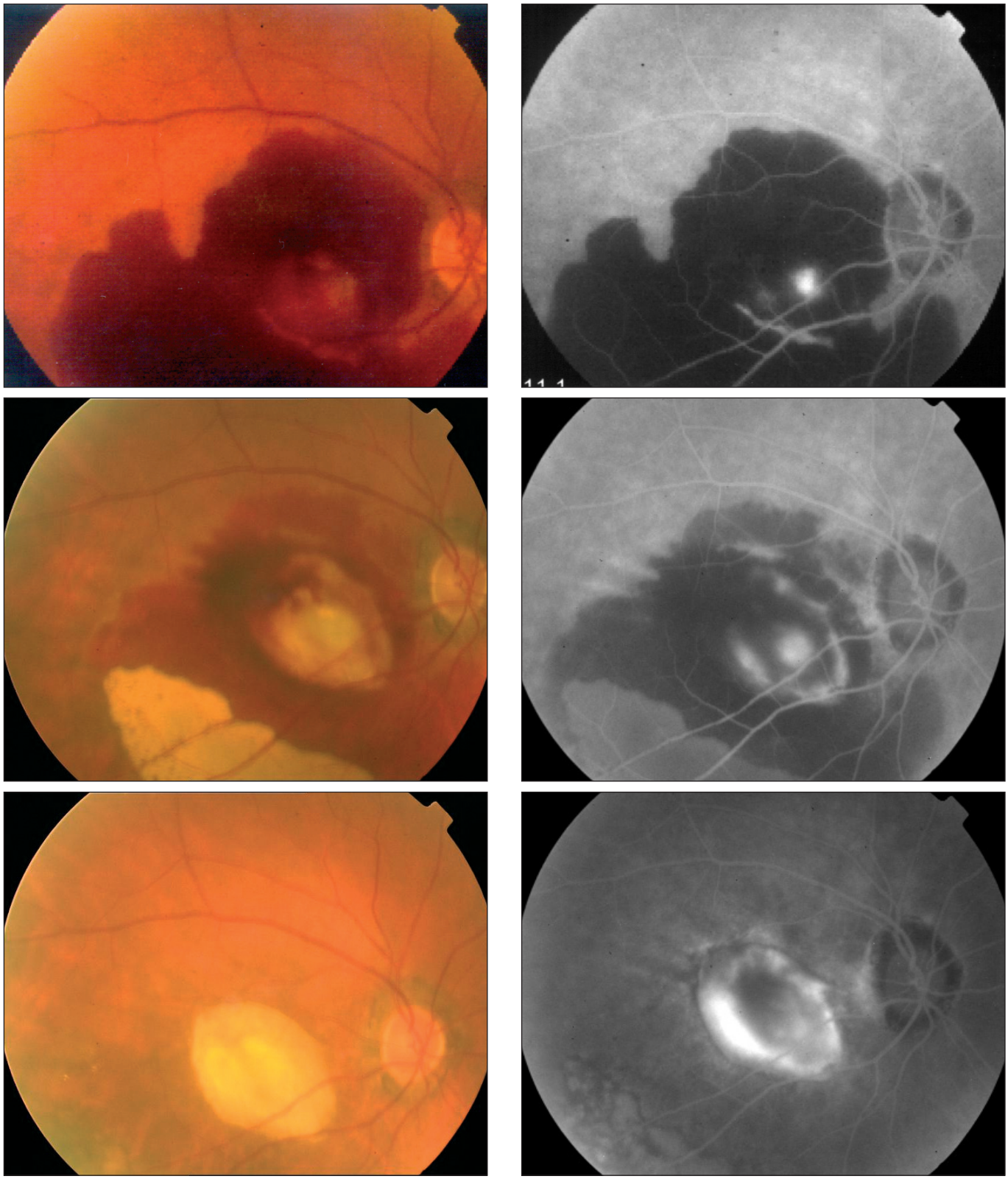

Fig. 1 - *Case 3. Top: Initial color and fluorescein angiography (FA) (late). Middle: Color and late FA 3 months after treatment. Bottom: Color and late FA 6 months after treatment showing late staining. The hemorrhage has disappeared.*

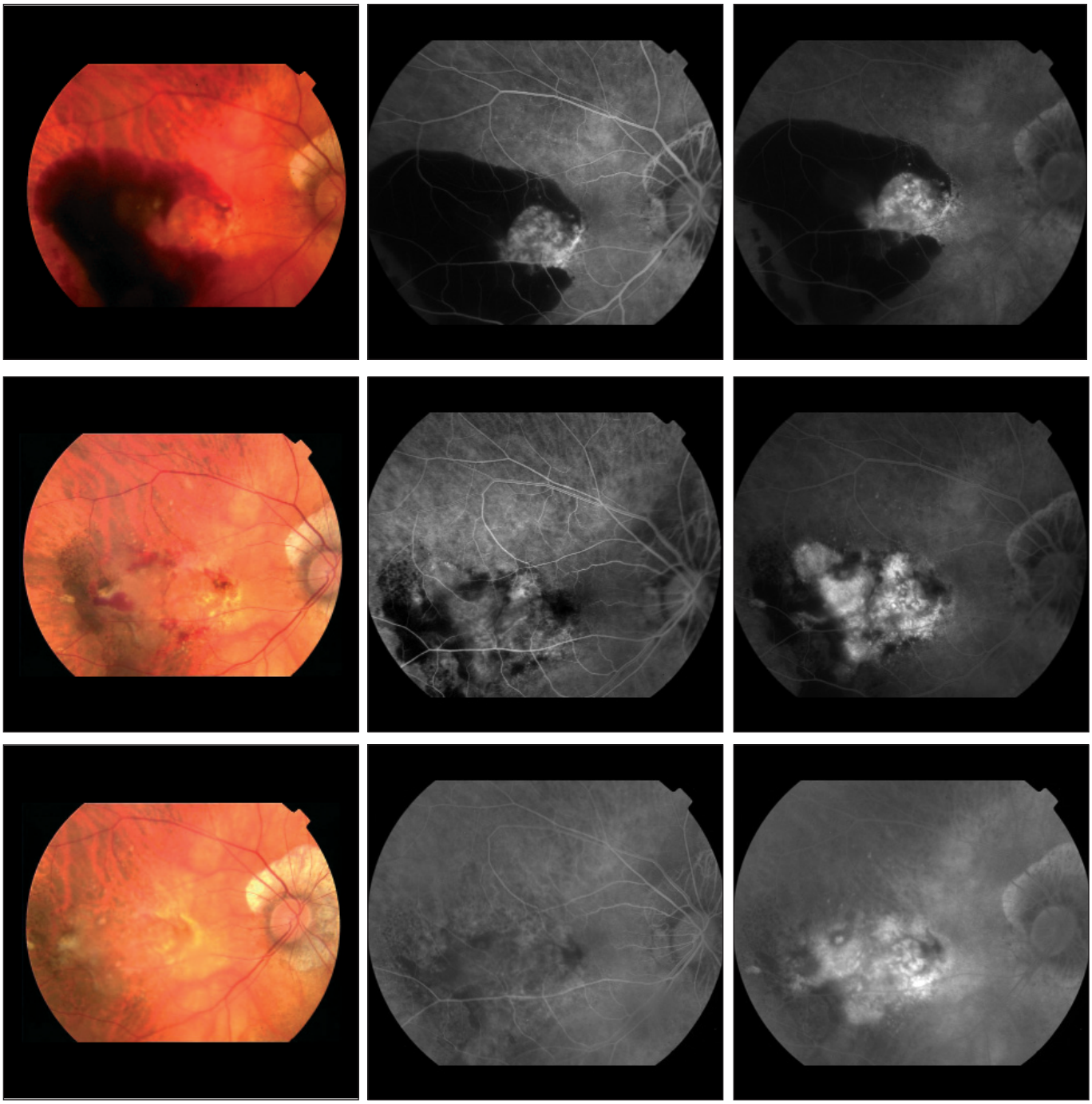

Fig. 2 - *Case 2. Top: Color and late fluorescein angiography (FA) before treatment. Middle: Color and FA after photodynamic therapy and intravitreal triamcinolone. Subretinal fibrosis can be appreciated. Bottom: Color and FA 9 months after treatment with increased subfoveal fibrosis.*

offer better results to treat choroidal neovascularization (CNV) than PDT or thermal laser alone (15-17).

The purpose of our study is to report the 6 months preliminary outcome of eyes with flat submacular hemorrhage, associated with ARMD treated by PDT and IT.

PATIENTS AND METHODS

We have analyzed the results obtained after treating 10 consecutive eyes (10 patients) with CNV and flat submacular hemorrhage associated with ARMD, by PDT fol-

lowed by IT. The study took place between January and March 2004 at the Instituto Oftalmologico de Alicante–VISSUM, with a minimum follow-up of 6 months after treatment. The study conformed to the provisions of the Declaration of Helsinki. All the procedures, diagnostic and therapeutic, were performed after obtaining written informed consent from the patients. The procedure and the data accumulation were approved by the ethical committee of the clinic.

Inclusion criteria were as follows:

- Sub- or juxtafoveal CNV secondary to ARMD with fluorescein angiography (FA) evidence of leakage.
- Subretinal hemorrhage greater than 50% of the total lesion size.
- Absence of retinal thickening caused by the hemorrhage as appreciated by biomicroscopy with +90 D lens.
- Intraocular pressure (IOP) lower than 21 mmHg.
- Older than 50 years of age.
- Written informed consent.

Exclusion was not determined either by lesion size or by initial best-corrected visual acuity (BCVA).

Photodynamic therapy

PDT with verteporfin (Visudyne®, Novartis AG, Bülach, Switzerland) was performed as described previously (18). Patients received further treatments with PDT in those cases when leaking CNV could be angiographically demonstrated, and it was performed not earlier than 3 months after the last session, and not later than 1 week after the last angiography.

The diameter of the laser spot was calculated to cover the whole area of the lesion, including the subretinal hemorrhage. Whenever lesion size was greater than the maximum spot size (7300 µ), the maximum spot was used centered in the CNV, as identified by indocyanine green angiography.

Intravitreal injection of triamcinolone

Five days after PDT, IT injection was performed in the preoperative room. After three consecutive drops topical ofloxacin 0.3% and a 5% povidone-iodine flush of the fornices and caruncle with 5 cc of solution, the injection was carried out in the inferotemporal quadrant, 3.0 to 3.5 mm from the limbus in aphakic/pseudophakic and 3.5 to 4.0 mm in phakic patients, with a 30 gauge needle.

Topical anesthesia of the eye, eyelid speculum, and forceps were used to stabilize the globe and two drops of antibiotic were placed over the injection site before and at the end of the procedure. IOP was measured by applanation tonometry. The same antibiotic drops were used three times a day for 5 days after the injection.

The concentration of triamcinolone injected averaged 19.4±2.1 mg in 0.1 mL.

This concentration was obtained by allowing the 40 mg/mL triamcinolone suspension (Trigon“ Depot, Squibb Industria Farmaceútica, SA. Barcelona, Spain) to precipitate inside the injecting syringe for 90 minutes at an inclination of 45º.

The overlying clear fluid was removed by gently ejecting the overlying supernatant out of the syringe. The remaining 0.1 mL with higher concentration suspension was used for injection. The amount of triamcinolone injected was calculated after performing the same injection procedure in ten Eppendorf tubes and weighing the powder in each tube obtained after its ultracentrifugation at 14,000 rpm during 10 minutes and desiccation at 45ºC during 24 hours to eliminate the solvent. The average weight was 19.4±2.1 mg.

Follow-up and re-treatments

Follow-up examination was performed the day after IT injection, 15 days, 1 month, and every 3 months afterwards. BCVA and IOP were determined and fundus examination carried out in every visit. FA was performed 3 and 6 months after PDT treatment. PDT was repeated whenever any leakage appeared. A second IT injection, when needed, was performed 6 months after the first IT injection if leakage persisted.

Outcome measurements

BCVA with ETDRS charts at 3 and 6 months were analyzed. FA absence of leakage and number of PDT treatments required were recorded at the same period of follow-up.

RESULTS

Five patients were male and five were female. Mean age was 76.1±8.1 years (ranging 61 to 86). Hemorrhage had appeared after two previous PDT sessions to treat CNV in Case 5. Subfoveal blood was present in five cases. In five more cases subretinal hemorrhage had spared the center

of the fovea. Table I summarizes the data of this series of patients.

Five eyes showed FA leakage at month 3 (Tab. II). BCVA remained unchanged (within one line from baseline) or improved in eight eyes: one eye did not change, one lost one line, four improved two lines, one improved five lines, and one improved 14 lines. BCVA decreased in two eyes. One eye lost two lines and one lost four lines. Blood had completely disappeared in five eyes and was markedly reduced in five eyes (Tab. II).

Six months after IT injection two eyes still had CNV leakage (Tab. II). BCVA was stable or better in eight eyes: two eyes remained unchanged, one lost one line, one improved one line, two improved two lines, one improved six lines, and one improved 11 lines. BCVA was worse than baseline in two eyes: one eye lost two lines and one lost four lines.

Mean initial BCVA (LogMAR) was 0.86±0.51 (ranging 2 to 0.4) and 0.74±0.54 (ranging 2 to 0.3) at 6 months (p=0.52, Student t test for paired data). Blood had completely disappeared in all cases at month 6 (Tab. II).

BCVA improved in three of five cases in which subretinal blood had spared the center of the fovea (+11, +6 and, +2 lines), remained unchanged in one case, and decreased in one case (-1 line, Fig. 1). Among those cases with subfoveal hemorrhage, BCVA improved in two cases (+2 and +1 lines), remained unchanged in one case, and decreased in two cases (-2 and -4 lines).

Subretinal fibrosis with submacular scar developed in two cases (Fig. 2). Subretinal fibrosis developed in both cases in the same site as CNV. IOP rose in seven cases; all of them could be controlled by topical medication (Tab. III). In two cases IOP was less than 10 mm Hg higher than baseline and in five cases it rose over 10 mm Hg. The elevation of IOP appeared in the first month after IT injection in six cases.

TABLE I - CHARACTERISTICS OF PATIENTS WITH SUBMACULAR HEMORRHAGE ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION (ARMD)

No.	Age, y	Sex	Eye	Subfoveal blood	BCVAi, Snellen LogMAR	BCVA3, Snellen LogMAR	BCVA6, Snellen LogMAR	Visual acuity change	Complications
1	73	F	L	No	20/200 1.0	20/63 0.5	20/50 0.4	+6 lines	› IOP
2	86	F	R	Yes 1.0	20/200 1.0	20/200 1.0	20/200 change	No	Fibrosis
3	79	M	R	No	20/50 0.4	20/100 0.7	20/63 0.5	-1 line	› IOP
4	75	M	R	Yes	20/50 0.4	20/63 0.5	20/80 0.6	-2 lines	› IOP Fibrosis
5*	65	F	L	No	20/200 1.0	20/125 0.8	20/20 1.0	No change	› IOP
6	81	F	R	No	20/80 0.6	20/50 0.4	20/50 0.4	+2 lines	
7	77	M	L	Yes	20/50 0.4	20/32 0.2	20/40 0.5	+1 line	› IOP
8	61	M	L	No	20/2000 2	20/40 0.3	20/80 0.6	+11 lines	› IOP
9	86	F	L	Yes	20/400 1.3	20/2000 2	20/2000 2	-4 lines	
10	78	M	R	Yes	20/63 0.2	20/40 0.3	20/40 0.5	+2 lines	› IOP

*Case treated with photodynamic therapy twice previously
BCVAi-3-6 = Best-corrected visual acuity initial, at 3 months, at 6 months; IOP = Intraocular pressure

DISCUSSION

In order to treat patients with CNV associated with AR-MD in the presence of large subretinal hemorrhages two approaches can be considered: to treat the CNV, which is the origin of bleeding and will eventually be the reason of loss in VA; and to remove subretinal blood, reducing the damage caused to photoreceptors by blood.

PDT is presently considered the best way to treat some types of subfoveal CNV (18), even though the appearance of recurrences and the need to retreat is still high. This therapy is known to reduce the patient's perception of scotoma (19). The use of an infrared laser to activate verteporfin allows its use even when the area to be treated is covered with blood (20). The need to retreat CNV reactivation is well known, and recent studies have described an increased local production of vascular endothelial growth factor (VEGF) induced by PDT, which contributes to the reappearance of choroidal vessels (21).

The use of high doses of IT is primarily based on its antiangiogenic properties (22). After achieving CNV inhibition in an animal model by the injection of a sustained release triamcinolone device (23), Jonas et al have performed 25 mg triamcinolone intravitreal injections in patients with CNV, improving VA (24).

The presence of blood in a tissue and iron release is known to induce inflammation, in part by its role in the formation of free radicals (3, 25). Triamcinolone acetonide has been used to treat articular inflammation for years (26), and has also proved its anti-inflammatory ability after intravitreal injection (27). The use of intravitreal steroids as free radicals removers (28-30) may reduce the toxic effect of iron on the photoreceptors.

Blood induced subretinal fibrosis is known to reduce VA

TABLE II - FINDINGS OF FLUORESCEIN ANGIOGRAPHY

Number	GLD	1 month, blood/GLD	3 months, blood/GLD/leakage	6 months, blood/GLD/leakage
1	5988	Yes/4806	Yes/4036/leakage	No/—/no leakage
2	10,333	Yes/10,906	Yes/10,838/leakage	No/5148/leakage
3	8489	Yes/7656	Yes/7525/leakage	No/—/no leakage
4	8397	Yes/6715	Yes/6430/leakage	No/6207/leakage
5	7238	Yes/1235	No/—/no leakage	No/—/no leakage
6	8937	Yes/2211	No/—/no leakage	No/—/no leakage
7	6243	Yes/3895	No/—/no leakage	No/—/no leakage
8	6017	Yes/3942	No/3806/leakage	No/—/no leakage
9	6322	Yes/6437	Yes/6260*/no leakage	No/—/no leakage
10	5143	Yes/5930	No/—/no leakage	No/—/no leakage

GLD of blood
GLD = Greatest linear dimension (μ) including choroidal neovascularization and blood

TABLE III - EVOLUTION OF INTRAOCULAR PRESSURE (IOP)

Case	IOP baseline	Intravitreal injection	IOP 1 month	IOP 3 months	IOP 4 months	IOP 6 months	Treatment
1	15	Yes	34	20		20	2 Drugs
2	12	Yes	12	12		15	
3	20	Yes	17	20	35	27	2 Drugs
4	16	Yes	26	18		17	1 Drug
5	18	Yes	28	21		17	1 Drug
6	17	Yes	20	17		20	
7	10	Yes	31	27	22	30	2 Drugs
8	16	Yes	48	27	25	26	2 Drugs
9	16	Yes	13	15		14	
10	15	Yes	32	34	23	23	2 Drugs

Values are mmHg

(3), and may also be inhibited by the use of steroids (31).

Different therapeutic approaches have been used to treat submacular hemorrhages in ARMD. Merrill et al described a large series of 64 patients being treated by surgical removal of CNV followed by subretinal r-TPA injections and perfluoro-n-octane, and air-fluid exchange (32). BCVA improved among these patients, within a wide range of final VA (hand motion to 20/20), mainly because of the original localization of the CNV, with better results in patients with initially poorer vision, larger subfoveal CNV, and small hemorrhages.

The use of PDT to treat CNV with hemorrhages is easier to perform and associated with less morbidity than vitreoretinal surgery and subretinal injection of r-TPA (33). PDT shows the additional advantage of treating CNV, which is the primary cause of the hemorrhage and often causes decrease in visual acuity in spite of blood removal (5-7).

We have been treating CNV associated with flat subretinal hemorrhages in order to ensure the capability of laser to activate verteporfin. We have called them flat hemorrhages in contrast to what Olivier et al (6) defined as thick hemorrhages: those "causing retinal elevation detectable on stereo fundus photographs." Even though infrared laser is not absorbed by blood, the amount of energy to reach the CNV will depend on the thickness of the hemorrhage, making it highly unpredictable if the amount of blood cannot be determined.

We have tried to follow these patients by OCT in order to evaluate the changes in subretinal hemorrhages. However, even though subretinal hemorrhages were considered to be "flat," they did not allow the red laser used by OCT through them. The light was completely reflected by the blood making it impossible to measure hemorrhage thickness.

The results have been analyzed at 6 months in order to ensure that changes in VA were caused by the presence of the hemorrhage and not by the evolution of ARMD. It has been previously demonstrated that patients with retinal hemorrhages of recent onset show better visual outcome (7, 34) and that final prognosis is determined by the underlying disease (5).

Considering the limited number of cases in our series, visual outcome was better among those cases in which the fovea was free of blood (+11, +6, + 2, unchanged, and -1 lines), compared to those five cases with subfoveal hemorrhage (+2, +1, unchanged, -2, and -4 lines, respectively). These results confirm the better prognosis of those cases without subfoveal hemorrhage.

At 3 months 50% of our cases showed leakage in FA. Other series using PDT combined with IT injection (15-17) have shown a lower proportion of leakage at 3 months; in these cases blood was occupying less than 50% of the total lesion area, which makes it impossible to compare the results with our series (15-17).

The purpose of our study was to associate the short term positive effect of PDT in closing CNV (35) to the antiangiogenic (23, 36-38) and anti-inflammatory effect of triamcinolone. The rationale for first performing PDT and then IT injection was to avoid triamcinolone opacification of the vitreous, which might make PDT difficult, and avoiding steroids action inhibiting free-radicals (28-30) interfering with the way PDT works (39). The reason for choosing a 5-day lapse for performing IT has been to avoid Visudyne photosensitizing effect (2 days) in case any problem with the injection might appear (retinal detachment, endophthalmitis), and before neither reperfusion nor new vessels growth might take place (40).

According to our results, PDT followed by intravitreal triamcinolone at high dose could be useful to treat CNV with submacular hemorrhage without thickening in ARMD. However, further studies with longer follow-up and randomized controlled trials are necessary to assess the real efficacy of this combined treatment.

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