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Efficacy of intravitreal bevacizumab to treat retinal angiomatous proliferation stage II and III

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PURPOSE. *To evaluate the efficacy of intravitreal bevacizumab to treat retinal angiomatous proliferation (RAP) stages II and III.*
METHODS. *A retrospective, interventional, nonrandomized multicentric study was performed. The files, optical coherence tomography (OCT) scans, indocyanine green, and fluorescein angiograms of patients with RAP stages II and III who had been treated by intravitreal bevacizumab were retrospectively examined. Final visual acuity, number of injections, and appearance of adverse events were considered as main outcome indicators.*
RESULTS. *Twenty-six eyes from 24 patients (9 male and 15 female) were treated by intravitreal bevacizumab. Fourteen eyes presented RAP stage II and 12 eyes presented RAP stage III. Mean age was 76±9 and 79±6 years, respectively. Mean initial best-corrected visual acuity (BCVA) was logMAR 0.60±0.24 and 1.13±0.37, respectively. Mean BCVA was 0.62±0.26 and 1.06±0.37, respectively, at 6 months (p=0.96 and 0.10, respectively, Student t test for paired data) and 0.63±0.26 and 1.04±0.37, respectively, at 12 months (p=0.82 and p=0.06, respectively, Student t test for paired data). The average number of injections during the first year was 3.4 and 3.2, respectively.*
CONCLUSIONS. *Intravitreal bevacizumab may stabilize visual acuity during the first year in RAP lesion stage II and III. Visual prognosis seems to be better in RAP II lesions. (Eur J Opjhthalmol 2009; 19: 448-51)*

KEY WORDS. *Bevacizumab, Choroidal neovascularization, Retinal angiomatous proliferation, Retinal pigment epithelium tear*

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INTRODUCTION

Retinal angiomatous proliferation (RAP) is a distinct form of neovascular age-related macular degeneration (AMD) characterized by angiomatous proliferation originating from the retina and extending into the subretinal space. It has been suggested that the neovascular complex may originate not only from deep retinal capillaries but also from the choroid as a retinal choroidal anastomosis without evidence of underlying occult Type 1 neovascularization. The term Type 3 neovascularization has been proposed for this entity, emphasizing the intraretinal location of the vascular complex and distinguishing this type from neovascularization beneath and above the retinal pigment epithelium (RPE), formerly alluded to as occult and classic (1). Different therapeutic approaches have been tried with limited success, as monotherapy or as combined treatments such as surgery, laser photocoagulation, intravitreal steroids, and photodynamic therapy with verteporfin (PDT). More recently, intravitreal antiangiogenic drugs

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such as bevacizumab (2-7) and ranibizumab (1, 8, 9) have been used to treat this condition, and some cases are known to resolve spontaneously without treatment.

RAP lesions stage II are characterized by the presence of intraretinal neovascularization beyond the photoreceptor layer, and may be associated with retinal pigment epithelium (RPE) detachment. RAP III lesions include choroidal neovascularization (CNV) with vascularized RPE detachment and retinal–choroidal anastomosis (Fig. 1).

The purpose of this article is to report the efficacy of intravitreal bevacizumab to treat RAP stages II and III.

METHODS

The files, optical coherence tomography (OCT) scans, indocyanine green, and fluorescein angiograms (FA) from 26 eyes (24 patients) with RAP lesions stages II and III who had been attended at two different centers were retrospectively examined. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. Written informed consent was obtained prior to the therapy.

Three consecutive monthly intravitreal injections of 1.25 mg bevacizumab (0.05 mL) were performed. The patients were followed monthly and bevacizumab was reinjected whenever intraretinal or subretinal fluid or visual acuity decrease was detected.

Main outcome variables were best-corrected visual acuity

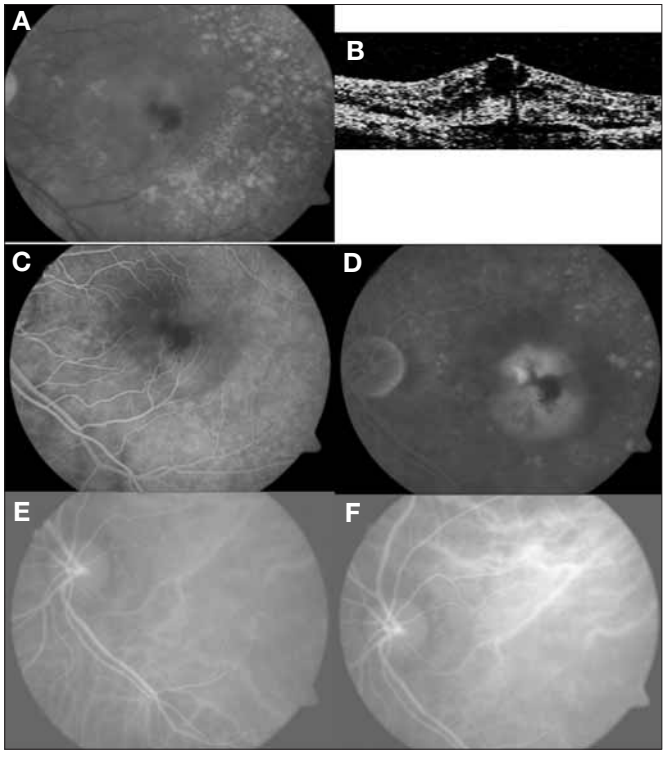

Fig. 1 - *Retinography* **(A)** *and horizontal optical coherence tomography (OCT) scan* **(B)** *in a patient with a retinal angiomatous proliferation (RAP) III lesion. OCT revealed a retinal pigment epithelium (RPE) detachment with subretinal and intraretinal fluid. Early and late frame fluorescein angiography* **(C, D)** *show a hot spot corresponding to the intraretinal neovascularization surrounded by a vascularized RPE detachment. LogMAR best-corrected visual acuity was 0.70. Early and late green indocyanine frames* **(E, F)** *reveal an intraretinal angiomatous proliferation.*

TABLE I - DEMOGRAPHICS OF THE PATIENTS, CHANGES IN LOGMAR BEST-CORRECTED VISUAL ACUITY (BCVA), AND NUMBER OF INJECTIONS PERFORMED

	Total	RAP II	RAP III	p
Age, yr	78±8	76±9	79±6	0.32*
Sex, M/F	9/15	5/9	5/7	
No. injections	3.3±0.6	3.4±0.8	3.2±0.4	0.4*
BCVA baseline	0.84±0.40 n=26	0.60±0.24 n=14	1.13±0.37 n=12	0.0006*
BCVA 3 mo	0.77±0.44 p=0.08† n=26	0.48±0.08 p=0.05† n=14	1.09±0.35 p=0.64† n=12	0.0003*
BCVA 6 mo	0.81±0.28 p=0.35† n=23	0.62±0.26 p=0.96† n=13	1.06±0.37 p=0.10† n=10	0.008*
BCVA 9 mo	0.76±0.29 p=0.15† n=20	0.59±0.28 p=0.77† n=12	1.02±0.41 p=0.06† n=8	0.02*
BCVA 12 mo	0.78±0.35 p=0.15† n=18	0.63±0.26 p=0.82† n=11	1.04±0.37 p=0.06† n=7	0.01*

*Kruskall-Wallis test.
†Student t test for paired data.
RAP = retinal angiomatous proliferation.

(BCVA) at baseline and at the end of follow-up, changes in visual acuity, number of injections, and appearance of adverse events.

RESULTS

Twenty-six eyes from 24 patients (9 male and 15 female) were treated by intravitreal bevacizumab. Fourteen eyes presented RAP stage II and 12 eyes presented RAP stage III. Mean age was 76±9 and 79±6 years, respectively.

Mean initial BCVA was logMAR 0.60±0.24 for RAP stage II eyes and 1.13±0.37 for RAP stage III eyes. Mean BCVA was 0.62±0.26 and 1.06±0.37, respectively, at 6 months (p=0.96 and 0.10, respectively, Student *t* test for paired data) and 0.63±0.26 and 1.04±0.37, respectively, at 12 months (p=0.82 and p=0.06, respectively, Student *t* test for paired data).

BCVA at baseline was significantly better among the eyes with RAP stage II and this difference was maintained at 3 months and at 1 year (p=0.0006, p=0.008, and p=0.01, respectively, Kruskal-Wallis test).

The average number of injections during the first year was 3.4 and 3.2, respectively. The demographics of the patients and changes in visual acuity are shown in Table I.

All the eyes were naïve for treatment of their chorioretinal lesions. One eye with RAP II developed RPE tear at month 3 after three consecutive injections of bevacizumab. Macular fibrosis appeared in one eye with RAP II and two eyes with RAP III.

DISCUSSION

Since RAP lesions were first reported by Yannuzzi et al (10), different therapeutic approaches have been tried with limited success. Early stage lesions (stage I RAP) seem to be associated with better anatomic and functional outcome, whereas anatomic closure is seldom achieved in well-established lesions (11). This situation has prompted the association of other therapeutic approaches such as the intravitreal injection of steroids and more recently, antiangiogenic drugs.

RAP III lesions are considered untreatable to some authors since they often already have a disciform scar with irreversible overlying photoreceptor dysfunction. A retrospective study on the outcome of RAP III lesions reported that six out of seven eyes failed to respond to laser photocoagulation treatment showing persistent or recurrent CNV and progressive disciform scar formation within 6 weeks to 16 months follow-up (12).

Intravitreal antiangiogenic drugs have been used to treat CNV secondary to AMD for the past 3 years. However, the use of antivascular endothelial growth factor (anti-VEGF) drugs to treat RAP lesions was not reported until 2007 (13).

Intravitreal bevacizumab has been used to treat stage I and II RAP lesions with good results after short follow-up. Different therapeutic schedules have been reported, such as uploading treatment until resolution of macular edema (2), isolated injections (6, 7), or three consecutive injections (5). These series report improvement in 30 to 75% of the cases, some of them gaining more than two ETDRS lines (3, 4). However, recurrences are common and need for repeated injections is frequent. We have found similar improvement during the first 3 months, though visual acuity decreased progressively during the following months, even in the absence of anatomic worsening. Joeres et al reported on the lack of effect of intravitreal bevacizumab on RAP III lesions after anatomic improvement (6, 7). In our series, we have found visual acuity improvement among patients with RAP II lesions whereas visual acuity remained stable in patients with RAP III lesions in spite of the treatment and macular edema resolution.

Reduction of subretinal fluid and visual acuity improvement has been reported by Lai et al in a short series after three consecutive ranibizumab injections (8) though lack of visual improvement was frequent as occurs with other therapeutic approaches. Other authors have reported similar results with treatment as needed (9). Freund et al reported improvement after one single injection, as well as spontaneous resolution of the edema in other cases (1).

PDT does not seem to alter the natural course of RAP (14). Combined therapy PDT and intravitreal bevacizumab has been reported, achieving visual acuity improvement without recurrences during a 6-month follow-up (3). Combined PDT and intravitreal triamcinolone does not seem to achieve better results than PDT monotherapy (15).

Regarding the appearance of local side effects, we have detected one case of RPE tear and three cases of macular fibrosis; however, the sample is too small to draw any conclusions from these data.

Among the limitations of this study is that it is a nonrandomized, short series of patients without a controlled group for spontaneous evolution. Randomized, controlled prospective studies including other possible therapeutic possibilities will probably establish the optimal treatment for these cases.

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