Terapia Sistémica con Bevacizumab (Avastin) para Degeneración Macular relacionada con la Edad Exudativa

Enrique L. Sgattoni*, Alejandra Larregina MD**

Resumen

Objetivo: Evaluar seguridad sistémica y efecto en la agudeza visual a largo plazo del bevacizumab intravenoso en pacientes con membrana neovascular coroidea (MNVC) por degeneración macular relacionada con la edad (DMRE).

Métodos: Se incluyeron pacientes con DMRE exudativa y MNVC de cualquier tipo en ambos ojos, con o sin tratamiento previo y agudeza visual entre 20/40 y 20/1600. Previo consentimiento informado y evaluación clínica, se administró bevacizumab en forma intravenosa a una dosis de 3mg/kg de peso. Una administración adicional fue realizada a los 14 días. Se realizaron controles, mensuales durante 2 años, e incluyeron agudeza visual y OCT 3d. En control se registro el perfil de seguridad sistémica, los cambios en agudeza visual y espesor retinal central.

Resultados: El único efecto adverso identificado fue un leve aumento de la presión arterial sistólica, que se mantuvo durante 7 días y fue controlado con medicación antihipertensiva. La agudeza visual en los ojos estudiados mejoró durante las primeras 6 semanas y al final del seguimiento la agudeza visual media fue de +11,4 letras. El espesor retinal medio disminuyó a la semana ciento 102 en 124µ con respecto al valor medio inicial. No fueron necesarios re-tratamientos durante el seguimiento.

Conclusión: El tratamiento sistémico con bevacizumab fue bien tolerado por todos los pacientes y efectivo para todos los ojos. A pesar de los buenos resultados obtenidos en el estudio SANA, el bevacizumab sistémico no está siendo estudiado en grandes estudios multicéntricos por los potenciales efectos adversos relacionados a los antiangiogénicos y por la percepción de que la terapia intravítrea sería más segura. Sin embargo, creemos que debería ser evaluado. *Oftalmol Clin Exp 2007;1: 21-25*

Palabras clave: bevacizumab, sistémico, neovascular, DMRE

Systemic Bevacizumab (Avastin) Therapy for Neovascular Age-Related Macular Degeneration

Abstract

Purpose: To evaluate the safety, efficacy, and durability of systemic bevacizumab for the treatment of choroidal neovascularization (CNV) in patients with bilateral neovascular age-related macular degeneration (AMD).

Methods: Age-related macular degeneration patients with bilateral CNV and best-corrected ETDRS visual acuity (VA) of 20/40 to 20/1600 were included. Patients were treated at baseline with an intravenous infusion of bevacizumab (3 mg/kg) followed by one additional dose given at 2-weeks interval. Safety assessments were performed at all visits. Ophthalmologic evaluations included VA measurements, ocular examinations, and 3D optical coherence tomography (3D OCT) imaging at each visit. Assessments of safety and changes from baseline in VA scores and 3D OCT measurements were performed through 102 weeks.

Results: No serious ocular or systemic adverse events were identified through 102 weeks. The only adverse event identified was a mild elevation of mean systolic blood pressure measurements evident by 7 days and controlled with antihypertensive medications. Visual acuity in the study eyes improved within the first 6 weeks, and by 102 weeks, the mean The mean VA letter score increased by 11.4 letters. The mean 3D OCT central retinal thickness measurement decreased by 124 µm. No retreatments were needed.

Conclusions: Systemic bevacizumab therapy for neovascular AMD was well tolerated and effective for all 24 patients (48 eyes). Despite these results and the SANA Study results, systemic bevacizumab is not being studied in a large clinical trial because of the potential risks associated with systemic anti-VEGF therapy and the perception that intravitreal therapy is safer. *Oftalmol Clin Exp 2007;1: 21-25*

Key words: bevacizumab, systemic, neovascular, AMD

Recibido: 01/07/08
Aceptado: 18/07/08
*Megavisión Centro Privado de Oftalmología. Bahía Blanca, Buenos Aires, Argentina.
**Hospital Municipal de Agudos Dr. Leónidas Lucero. Bahía Blanca, Buenos Aires, Argentina.
Autor responsable:
Dr. Enrique L. Sgattoni
Megavisión Centro Privado de Oftalmología.
Eliseo Casanova 248. (8000).
Bahía Blanca, Buenos Aires, Argentina. E-mail:
sgattoni@bblanca.com.ar

Bevacizumab (Avastin, Genentech/Roche) is a full-length, humanized, murine monoclonal antibody, [1] directed against all the biologically active forms of vascular endothelial growth factor-A (VEGF). Bevacizumab, was developed as an intravenous therapy for cancer patients because VEGF is one of the major angiogenic stimuli responsible for neovascularization in tumors. Anti-VEGF therapy has shown promising results in several forms of cancer. When used in cancer therapy, bevacizumab is infused at a dose of 5 mg/kg every two weeks until the patient dies or significant disease progression is observed. In clinical trials, the most common adverse event caused by bevacizumab was hypertension. Whatever the mechanism of action, an anti-VEGF drug like bevacizumab may be

beneficial for any ocular disease in which neovascularization and edema play a major role, particularly diseases like neovascular AMD, diabetic retinopathy, vein occlusions, neovascular glaucoma and retinopathy of prematurity.[2]

When Philip Rosenfeld observed the beneficial responses in patients receiving ranibizumab during the Phase I/II studies, he proposed that bevacizumab, could also be used as a treatment for neovascular AMD. One potential advantage is the use of intravenous injection, which avoids the discomfort and risks associated with an intraocular injection. In addition, a single systemic dose can treat both eyes. The disadvantages of systemic therapy, however, include systemic exposure to an antiangiogenic drug at therapeutic levels, resulting in a higher risk of systemic adverse events compared to intravitreous injection.[4-8]

SANA

In the spring of 2004, Rosenfeld initiated the Systemic Avastin for Neovascular AMD (SANA) study at the Bascom Palmer Eye Institute. In this study he offered systemic bevacizumab as salvage therapy for patients who were not candidates for verteporfin photodynamic therapy. Unlike the regimens used in cancer therapy, he proposed treating patients only two or three times followed by a period of close observation, with retreatment possible if the leakage from the neovascularization recurred. Since this article was published, a total of 18 patients have been followed for at least 24 weeks, and the 24-week results confirmed and improved upon the preliminary results observed at 12 weeks. Of the 18 patients, seven initially received three treatments, and eleven received only two treatments. The majority of patients did not require another treatment through 24 weeks. With improvement in visual acuity, OCT and angiographic outcomes, the systemic use of bevacizumab appeared to be both effective and durable. The only significant adverse event observed in the study group was a mild elevation of blood pressure that was easily controlled with antihypertensive medication.

Observing the results of the SANA Study we designed an open-label, single-center, uncontrolled clinical study since October 2005. The purpose was to evaluate the safety, efficacy and durability of systemic bevacizumab with a lower dose of 3mg/kg for the treatment of choroidal neovascularization (CNV) in patients with bilateral neovascular age-related macular degeneration (AMD).

Materials and Methods

Age-related macular degeneration patients with bilateral CNV (n= 24 / 48 eyes) and best-corrected ETDRS visual acuity (VA) Snellen equivalent of 20/40 to 20/160 were included. At baseline, patients underwent VA testing (Fig. 1), ophthalmoscopic examination, 3D OCT imaging (Topcon) (Fig. 3), and fundus angiography.

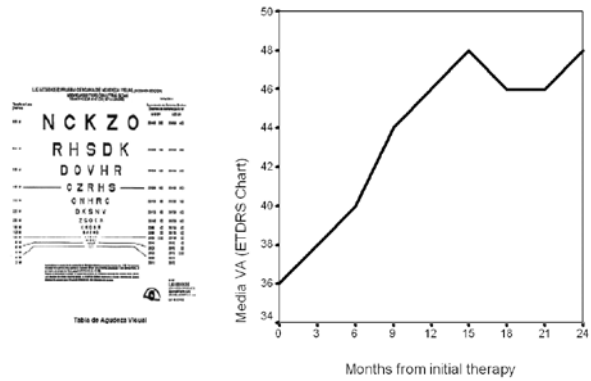

Figure 1. ETDRS VA chart.
Figure 2. Evolution of the median visual acuity from initial therapy to 24 months.

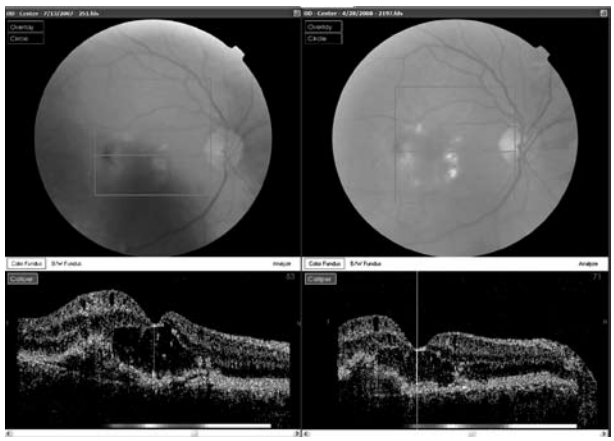

Figure 3. Patient with AV 20/125 to 20/32 - 504µ to 277µ with evident less intraretinal fluid.

Table 1. Entry criteria

Inclusion Criteria
Age > 60 years
Primary or recurrent bilateral subfoveal CNV due to AMD
Central 1-mm retinal thickness (OCT) ≥ 300 µm
Best-corrected visual acuity (ETDRS) of 20/40–20/1600

Exclusion Criteria
Uncontrolled blood pressure
Coagulation abnormalities
Renal dysfunction
History of thromboembolic events
Need for surgery within 1 month of enrollment

Once the study consent form was signed the drug was infused if all entry criteria were fulfilled (Table 1). Patients were treated at baseline with an intravenous infusion of

bevacizumab (3 mg/kg) followed by one additional dose given at 2-weeks interval. The intravenous infusion was performed by an expert physician in cancer treatments. Safety assessments and ophthalmologic evaluations included VA measurements, ocular examinations, and 3D OCT imagings performed at each visit through 2 years (102 weeks).

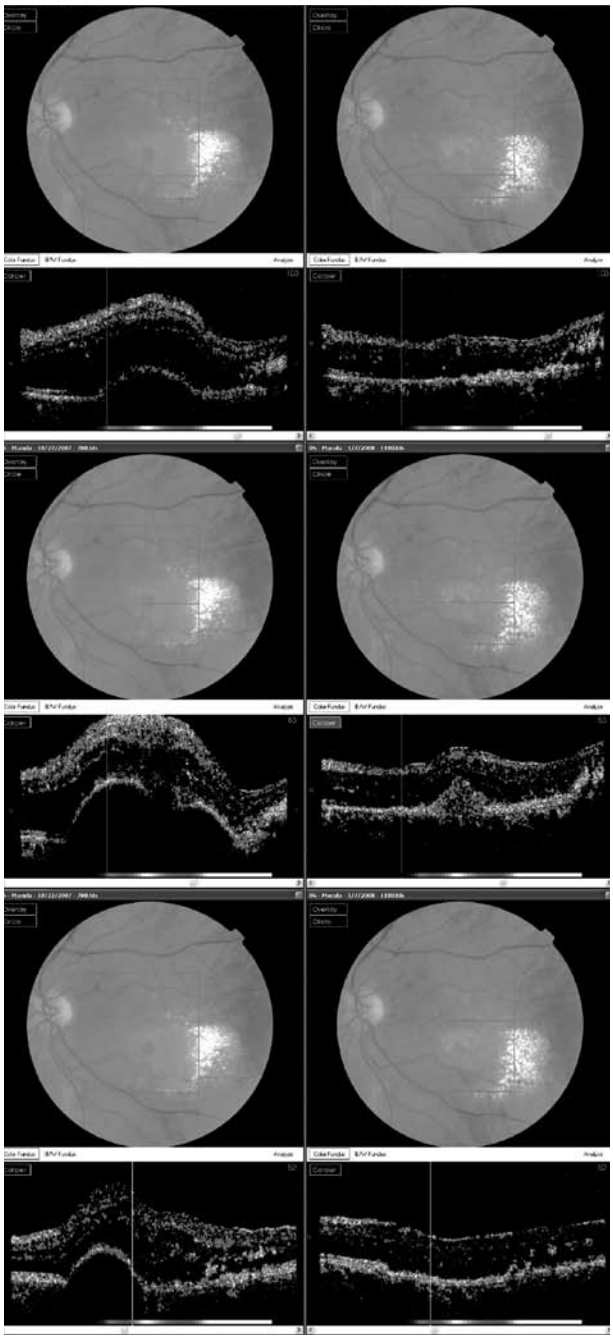

Figure 4. Patient with AV 20/160 to 20/50 – RPE detachment resolution in three different sections.

Results

A total of 48 eyes were treated. The 24 patients enrolled in the study had a median age of 82 years (range, 64–89), with 16 women and 8 men. At baseline, study eyes median VA was 20/360, with a range of 20/40 to 20/1600. Baseline median 1-mm central retinal thickness measurements were 457 µm. No serious ocular or systemic adverse events were identified through 102 weeks. No vision loss was observed in either the study eyes. The only adverse event identified was a mild elevation of mean systolic blood pressure measurements evident by 7 days and controlled with antihypertensive medications. By 3 weeks, the systolic and diastolic mean blood pressures were at baseline measurements. Visual acuity in the study eyes improved within the first 6 weeks, and by 102 weeks, the mean VA letter score increased by 11.4 letters (+2.5 to +30 letters) (Fig. 2). The mean 3D OCT central retinal thickness measurement decreased by 124 µm (Figs. 3-7). No retreatments were needed. By week 102, the median VA had stabilized at 20/150 (+11.4 letters), with a stable reduction in median central retinal thickness measurements (–124 µm). At week 102, there were 24 eyes (50%) with at least 3 lines of VA improvement and 48 eyes (100%) with at least 1 line of improvement.

Discusion

After 24 months, systemic bevacizumab therapy for neovascular AMD seemed to be well tolerated and effective in 24 patients who received 2 intravenous infusions. VA improved in the study eyes in which leakage from neovascularization was detected at baseline. No VA was lost from either eye, with 50% of study eyes gaining 3 or more lines of VA.

Systemic Bevacizumab therapy eliminated or greatly reduced leakage from neovascularization, and this could be observed by 3D OCT. The major variables that may affect the extent of vision improvement after the resolution of macular fluid include the baseline VA, the amount of fluid in the macula, the size and type of CNV, and the extent of irreversible damage sustained by the retina and the retinal pigment epithelium. The therapy was durable.

When compared with pegaptanib therapy, which requires an injection every 6 weeks, and ranibizumab therapy, which requires a monthly injection, systemic bevacizumab therapy could be one of the most effective and durable therapies for the treatment of neovascular AMD.

Although the efficacy seems very promising, the safety of systemic bevacizumab in neovascular AMD patients has yet to be determined. All the study patients were monitored closely with multiple measurements at each visit,

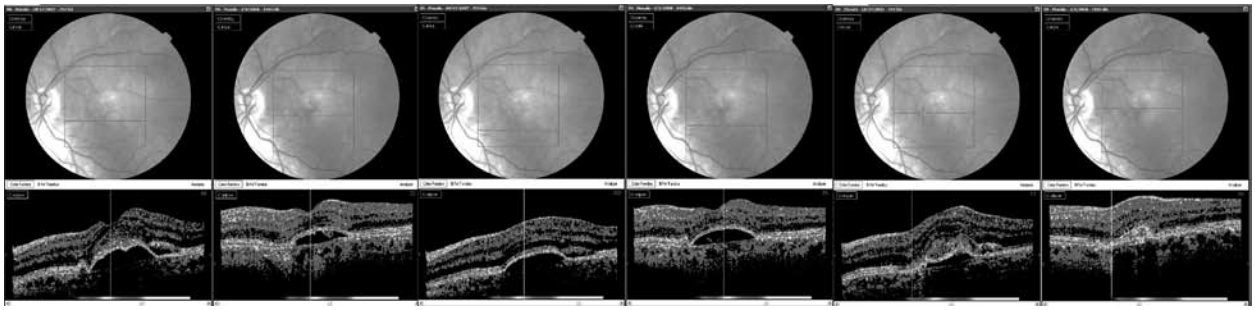

Figure 5. Patient with AV 20/125 to 20/32 - RPE detachment resolution in three different sections

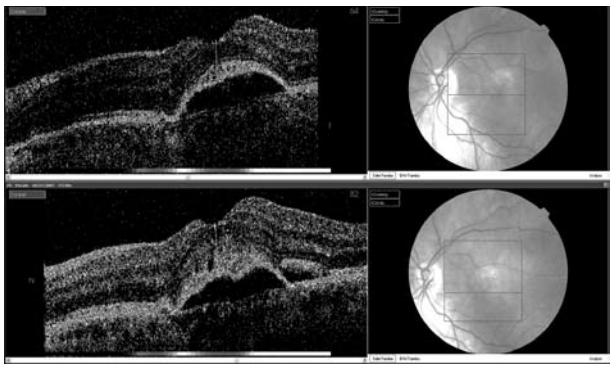

Figure 6. Patient with AV 20/80 to 20/50 – 216μ to 161μ with neuroepithelial detachment resolution

and their antihypertensive medications were adjusted.

As with most prospective studies, our patients were closely followed up and managed with internists conveniently available. There is concern that systemic bevacizumab could put patients at a higher risk for uncontrolled hypertension and thromboembolic events. This concern is exacerbated by the high prevalence of hypertension and thromboembolic events in our older patients with neovascular AMD. Although it is true that bevacizumab has never been shown to cause this increased risk of thromboembolic events in any population other than cancer patients who receive bevacizumab therapy in combination with chemotherapy every 2 weeks for many months, the potential for thromboembolic events cannot be ignored. Strategies to avoid the adverse events associated with anti-VEGF therapy include using a lower systemic dose of drug.

Interestingly, our results with systemic bevacizumab therapy seem to be very similar to the VA, angiographic, and OCT outcomes from the ranibizumab studies. This should not be surprising in light of the pharmacologic similarities between bevacizumab and ranibizumab.

Despite these results and the SANA Study results, systemic bevacizumab is not being studied in a large clinical trial because of the potential risks associated with systemic anti-VEGF therapy and the perception that intravitreal therapy is safer.[9-10]

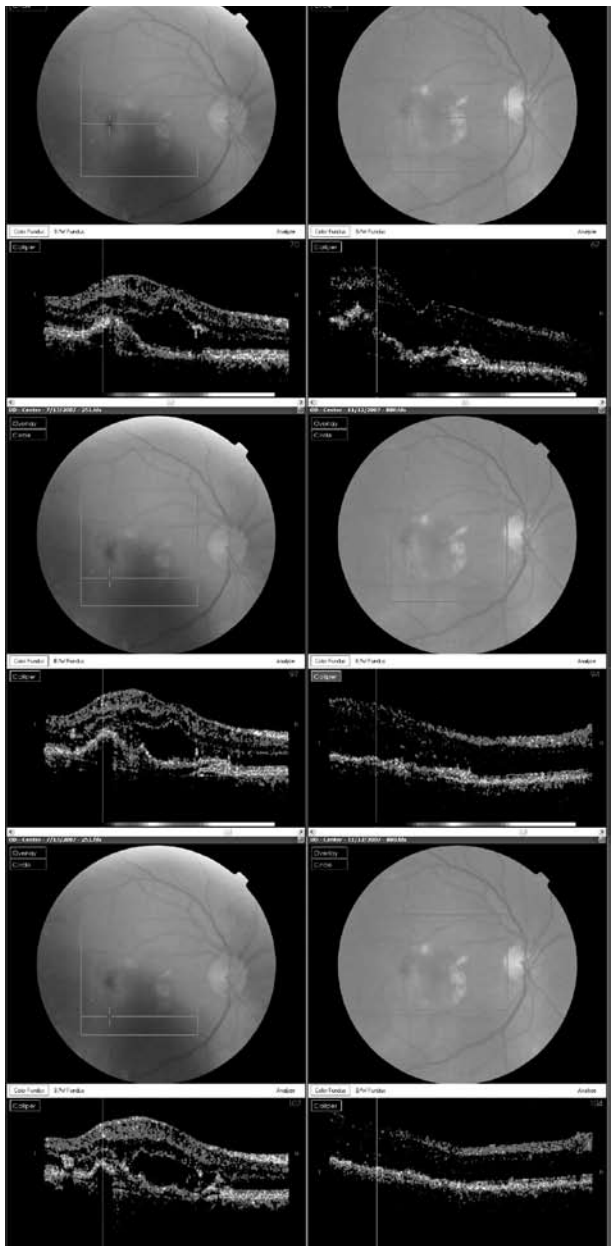

Figure 7. Patient with AV 20/400 to 20/100 – RPE detachment and neuroepithelial resolution in three different sections

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