EFFICACY AND SAFETY OF INTRAVITREAL INJECTION OF BEVACIZUMAB IN THE TREATMENT OF NEOVASCULAR GLAUCOMA: SYSTEMATIC REVIEW

EFICACIA Y SEGURIDAD DE LA INYECCIÓN INTRAVÍTREA DE BEVACIZUMAB EN EL TRATAMIENTO DEL GLAUCOMA NEOVASCULAR: REVISIÓN SISTEMÁTICA

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ABSTRACT

Purpose: Systematic review on efficacy and safety of intravitreal bevacizumab (IVB) in the treatment of neovascular glaucoma (NVG). All original papers published in Medline (prior to August 2008) were included.

Methods: Search and selection of information on the internet and in Medline, validated by Kappa Index (K). Statistical and clinical study of the results in the selected articles on a one by one basis.

Results: 26 original papers analyzed the efficacy and safety of the procedure in case reports and short series of cases (127 eyes). The efficacy calculated in the sample was 68.7% and the recurrence rate was 18.6% in 4.2 months of follow-up. All studies were after 2006 and none of them was a clinical randomized controlled assay. Ophthalmic complications were under 0.78% and no systemic complications were found.

RESUMEN

Propósito: Revisión sistemática sobre la eficacia y seguridad de la inyección intravítreo de bevacizumab (IVB) en el tratamiento del glaucoma neovascular (GNV). Se incluyen todos los trabajos originales publicados en Medline hasta agosto de 2008.

Métodos: Búsqueda y selección de la información en Internet y Medline, validadas mediante el Índice Kappa (K). Estudio estadístico y clínico de los resultados en los trabajos seleccionados, uno a uno.

Resultados: Se encuentran 26 artículos originales que analizan la eficacia y seguridad del procedimiento en casos únicos y en series cortas de casos. 24 de ellos se analizan conjuntamente, con un total de 127 ojos intervenidos. La eficacia calculada para casos difíciles es del 68,7%. Las recidivas en un seguimiento de 4,2 meses son del 18,6%. Todos los trabajos son posteriores a 2006 y ninguno cumple criterios de ensayo clínico aleatorizado. Las com...
**Conclusions:** The use of bevacizumab demonstrates that intravitreal injections may be effective and useful to manipulate growth factors in the anterior chamber. IVB could serve as a first line treatment for NVG. Clinical trials are needed to confirm these results before its use is authorized (Arch Soc Esp Oftalmol 2008; 83: 579-588).

**Key words:** Bevacizumab, avastin, intravitreal injection, neovascular glaucoma, rubeosis iridis, laser photocoagulation, growth factors, systematic review.

In more advanced phases the fibrovascular tissue contracts, the iris is pulled until the camerular angle with an extensive iridic goniosynechia that finishes in closed angle glaucoma. However, the mere presence of neovessels in the angle, even for cells and exudations liberated at a microcirculatory level, can end with the same problem, of serious prognosis for the predictable ischemic retinal lesions (10).

In the middle of 2007 some experts posed the question whether the use of bevacizumab was a «compassionate» treatment or a way of making money for the ophthalmologists who were using it (11). It is being used more and more in ophthalmology, but is still not authorized. Its low cost with respect to other VEGF inhibitors could negatively influence its marketing and approval for intravitreal use, when scientific evidence suggests that its profile of efficacy and safety at doses of 1-2 mg/dL in vitro seem excellent for numerous indications. Since 2006 in our centre we have treated six cases of NVG with bevacizumab. The short and medium term response was excellent, coinciding with the publications, but a scientific coverage is needed to justify its use in this indication. At the moment the treatment of NVG by means of intravitreal injection of bevacizumab (IVB) is based on fairly limited experimental laboratory results and on clinical experience.

The proposal of this work is to study the efficacy and safety data of IVB in the NVG, according to the data appeared in specialized journals until August 2008. The systematic revision and the meta-analysis give the best available evidence on a topic of interest, although an objective and critical reading
of every work is indispensable to discuss the results. It is normal to talk about systematic revision on referring to the process of systematically identifying and evaluating various studies of the same type and with common objective. The meta-analysis consists in using statistical techniques that combine the results of a homogenous group of studies with global measures in quantifying and quality of results (12-15). Here we have tried both possibilities.

SUBJECTS, MATERIAL AND METHODS

The search, selection and quantification of results was made by two independent investigators (PMC y EBM), with the following pre-established consensus:

Search strategy

The Medline database and the internet network were used. To obtain data on IVB efficacy and safety in the NVG on Medline, between January 2003 and October 2008, the scrutiny options recommended by the experts were used (12-14). Different key words, compound describers and meta-terms were tried in increasing order of specificity towards the topic studied, selecting and crossing the most productive and selective ones (12-14). The summaries of each of the works were read and all the complete articles included in this study were compiled. The search was complemented with a cleaning out on Internet (Firefox-Google) to the effect of finding reliable scientific publications missed on Medline (14,15).

Selection of articles for analysis

Inclusion criteria:
– The main work objective is to evaluate the efficacy and safety of the IVB in the treatment of NVG.
– The study gave necessary data of the ophthalmological clinical history and detail of ocular problems before intervention.
– The materials and methods allow a reproduction of the investigation.
– It specified when and how the results were observed, giving objective proof.
– It concerns a publication recognized by a scientific body.

Exclusion criteria:
– Articles on the efficacy of IVB in intraocular vascular neoformation processes, including the GNV in an accessory manner, without data related to efficacy or that give rise to confusion.
– Communications in congresses, unpublished experiences of investigators, opinions of authors, etc.

Descriptive group statistics

The number of eyes intervened in each study (n) is considered, the time of maximum follow up after the IVB, in months (t) and the loss or persistence of efficacy during the follow up. Throughout the analysis the arithmetical mean (m=average) was used as descriptive indicators, as a measurement of

Table I. Grouped data analysis of 24 selected publications, indicating the average and the range between brackets

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\( \Sigma n = 127; \Sigma EC = 2.59 (r=2.3); \Sigma ECP = 262; \Sigma ECM = 3n = 381; \Sigma E = 248/360= 68.9\%; t = 4.2; (t = 0.25-13.3) \) (maximum follow-up time, in months); (*) t follow-up average; Open angle NVG (1); closed angle NVG (2).
the central tendency, and the trajectory (r= range) as a level of dispersion.

To evaluate the clinical efficacy of the treatment (EC) in each article the following semi-quantitative scale was established: worsening [-1], without efficiency [0], moderate efficiency [1], good efficiency [2], and excellent efficiency [3]. To mark each work we had to take into account the results of the diagnostic tests and the rest of the applied treatment, as well as the IVB.

We noted down for each work the dose of the medicament administered, the possible photoocoagulation before and/or after the IVB, the need for filtering surgery, medical and conventional treatment applied, percentage of relapses and complications observed. We also noted the most relevant data of the discussion and conclusion of each work.

The EC marks were previously established used by both researchers. When the works were studied series of cases, with results for each case, the average value was taken. It was defined as pondered clinical efficacy (PCE) the product EC x n, and global efficacy, or group (EG), to the quotient ECP/ECM, where ECM is the maximum clinical efficiency (=3n).

Validation of results

To validate the inter-observer search reliability, selection of articles and efficacy marks in the semi-quantitative scale the Kappa index was calculated (K). A match was considered valid if K>0.7. The discrepancies between both researchers were annulled by consensus using the critical deductive reasoning (16,17).

RESULTS

Search results on MEDLINE 2003-January 2008: (O: original articles / R: revisions).
  - Avastin/Bevacizumab (O1167/R371).
  - Avastin/Bevacizumab/ophthalmology/eye therapy (O199/R15).
  - Avastin/Bevacizumab/neovascular glaucoma (O19/R2).
  - Avastin/Bevacizumab/treatment neovascular glaucoma (O18/R2).

Search results on MEDLINE (2003-October 2008):
  - Avastin/Bevacizumab (O1991/R739).
  - Avastin/Bevacizumab/neovascular glaucoma (O37/R4).
  - Avastin/Bevacizumab/treatment neovascular glaucoma (O28/R4).

Search results on INTERNET (October 2008): 30900 entries appeared for Bevacizumab/Glaucoma. It was found in 14 publications and communications proceeding from organisms and societies, which did not appear in Medline.

The Kappa inter-observer match rates were: search on Medline (K=1), search on Internet (K=0.83), work selection (K=0.92) and efficient clinical evaluation (K=0.80). Of the 37 selected articles, 26 had the inclusion criteria (18-42). For the group analysis it was agreed to exclude the Biancito study because the cause of NVG was tumoral and the response to the medication could be different (41). Also eliminated from the work was Avery and cols. (42) because NVG patients could not be well differentiated from those that only had retina lesions. The article of Wakabayashi (34) is divided into two parts to differentiate between NVG of the open angle and closed and homogenize the clinical efficacy according to the severity of the glaucoma. The characteristics of the works made meta-analysis impossible: none complied with the criteria of controlled clinical trials and are heterogeneous in the selection of patients, in the indications and application of procedure and in the concomitant treatments that were used. They are retrospective studies that do not include easily handed statistical data in conventional meta-analysis. However, some important variables are susceptible to descriptive and critical analysis of maximum interest. The 24 works submitted to this analysis of data integration faithfully reflect the present state of knowledge in this matter. The average variables include the dose used, the gonioscopic alterations and clinical cases found and all the medical and surgical treatment that is used to resolve the case, as well as the IVB.

Descriptive statistics and clinical results in the selected works

All appeared on Medline, except one (33). No publications were found before 2006, 38% are from 2006, 29% from 2007 and 33% from January to
August 2008. 79% of the works study short series of cases with less than 6 eyes operated on. The largest study is that of Wakabayashi (34), which treats 41 eyes, 9 with rubeosis iridis without glaucoma, 17 with open angle NVG and 15 with closed angle NVG. The articles of Ehlers (n=23) and Chalam (n=16) can also be stressed for their sample size. The studies appeared in 2008, of higher quality, include 65% of eyes analyzed and clear up some of the unknown factors posed at the time.

The global clinical efficiency (GE) calculated on 127 eyes with an average maximum follow up of 4.2 months was of 68.7% and the percentage of relapses 18.6%. The response to second treatment dose was effective in all the relapse cases. The most frequently utilized dose of bevacizumab was 1.25 mg/0.05 mL (m= 1.29 mg, r= 1-2.5 mg). The ophthalmological complications are situated below 0.78% (1 eye), with no proof of causality. No systemic complication was detected.

In the sample studied here, the main causes of NVG were diabetic retinopathy and the occlusion of the central retina vein, including two cases of retina central artery occlusion (23,26), a case of meningioma of the orbital apex treated with radiotherapy (21), one case of a diabetic patient with choroid melanoma (30) and an iris melanoma treated with radiotherapy (41). Generally the use of IVB was justified by the failure of previous treatments or because of a difficult approach.

In all the eyes treated where glaucoma is minimum or inexisten the efficiency of IVB in reducing the iridis and angular rubeosis is 100% (angio-graphically demonstrated), and 85% in eliminating it, regardless of the etiology. In more than 80% of the eyes treated before 2008 the neovascularization associated to the glaucoma completely disappears, the IOP is normalized in a few days without filtrating surgery being necessary and the visual acuity improves. The bleeding is reduced and the comfort of the patient is improved when glaucoma surgery is performed, at the same time or after the IVB (24, 26, 37, and 40). The IVB treatment does not seem enough in the case of consolidated anterior peripheral synechia (18, 25) and when a pronounced closure of the angle exists (34).

There is a lack of medium and long term studies to be able to confirm figures. The pharmacological effect is drastic and very early for gonioscopic visualization. The effects are observed at 48 hours, with a range between 24 hours and the first week (23, 25-29, 32, 33, 37-39). In the 127 intervened eyes, only one case of infectious keratitis was detected, without demonstrating causality (21) and no systemic complication. The dose of 1 mg, or even less, could be more effective than 1.25 mg for treating NVG, perhaps reducing relapses (26, 28, 29, and 34). Whereas the dose of 2.5 mg seems to facilitate them and it is important to advise against this indication (20). when the a second IVB is necessary complications do not appear either and it is possible to resolve the case (18, 20, 32). The majority of patients are treated with panretinal photocoagulation before and/or after IVB, generally avoiding the trans-scleral cyclophotocoagulation and filtrating surgery. The results are also satisfactory when panphocoagulation and prior cyclophotocoagulation fail (29).

Until 2008, relapses appeared in16% of the cases and generally occurred between the second and the fifth month (18, 20, 32). However, the data is not very orientative because many of the follow ups are less than two months. Until then, only 11 eyes are examined consecutively for longer than 3 months, with a relapse rate of 27%. In 2008 Wakabayashi and Ehlers cleared up the truth of this result, in wider samples. Patients with rubeosis iris without glaucoma where the neovessels disappeared could have up to 40% of relapses during the first six months, but all were satisfactorily resolved with a second IVB (34). The early relapses (before 1 month) could appear in more than 12% of cases (36). The average of relapses calculated in this work is of 18.6% in an average follow up of 4.2 months.

In cases of rubeosis iridis and minimum glaucoma, IVB could be enough to treat the problem on its own. When the angle traction is significant, the efficacy depends on whether it is open or closed. In open NVG, IVB could be efficient in over 70% of the cases, avoiding many cases of surgery. However, when the angle is closed, over 90% of the cases need surgery (34). Ehlers also confirms the previous investigations comparing the advantages of the IVB associated to the panretinal photocoagulation, with respect to the panretinal photocoagulation alone. In a 4 month follow up, the neovascular regression was greater, and earlier, in the group treated with both methods (35). The cases of NVG due to tumors also respond positively, but deserve a separate study (21, 23, 26, and 41). The effects of IVB as sole treatment have not been studied.
In 24 different studies (127 eyes) a very favorable benefit/risk to IVB on treating NVG was found. In cases of neovascularization in the iris and angle without glaucoma, and in incipient cases of glaucoma, the IVB per se could be decisive. Also, as it avoids the risk of hemorrhage, the prognosis of NVG is improved with photocoagulation and/or surgery. There is a common agreement in that the IVB provided the added value of an early regression of the neovessels and a greater and faster normalization of the IOP. Some works suggest that the success of the treatment produces an improvement of visual acuity but were unable to demonstrate this with the methodology used. Various authors note that the IVB is capable of controlling the IOP refractory NVG to the treatment, in the terms of Sothornwit (40).

**DISCUSSION**

The first works of Linch (9) and Rosenfeld (8) suggest good possibilities for IVB at a pharmacological level to favor the regression of vascular neoformations. Among the clinical studies that appear in Medline, Avery (34) is noteworthy with a total of 45 eyes operated on for a heterogeneous group of vascular intraocular proliferations. The efficacy results were 73% in retina and 82% in iris. 24 hours post-injection the first signs appear of neovascular involution in all treated patients, with no ophthalmological or systemic secondary effect, maintained for at least 11 weeks. Our results support the safety and speed of the effect, with more modest success (68.7%) because we dealt with numerous established glaucomas of difficult response. The most recent publications confirm the previous results, minimizing the publication slant known as the «iceberg phenomenon». The 26 works selected, and the 24 analyzed, conclude that IVB has a clear therapeutic value added to the rest of treatments, showing efficacy and with no complications. The benefit/risk is very favorable and raises the question of IVB and retinal panphotocoagulation as initial treatment of NVG, independent of whether filtrating surgery is applied or not. When the NVG is associated to vitreous hemorrhage, it could be resolved with success. This has been reported by some media and on the Internet, but these reports are not assessed here. The results coincide with publications in journals with impact factor and suggest that the experimental clinical practice of the intervention is greater than that communicated in the literature.

The official and valid mode to study the efficacy and safety of a drug is the controlled and random clinical trial in phases II-IV. At present, the information precedes short retrospective series of cases which do not comply with clinical trial criteria for a pharmacological study. The original revised articles tried to prove if intravitreal bevacizumab is efficient and safe in the treatment of NVG, but on the other hand the designs and methodology employed only allow suggestion and not demonstration. This revision clears up the need to prioritize the pertinent clinical trials given the severity of NVG and the good results that the preliminary clinical investigations observed.

In the case of NVG, bevacizumab could be more effective than the rest of the VEGF inhibitors on the market, such as ranibizumab and pentaganib, for their molecular characteristics. The proposed advantage for ranibizumab, as a smaller molecule and more appropriate for penetrating the retina, does not justify in the anterior segment. Bevacizumab is possibly the best studied drug for the intravitreal treatment of NVG, both in the laboratory and with patients. It has just been proved that in cases of rubeosis iridis and NVG the concentrations of VEGF in the aqueous humor are increased and that these are drastically reduced with IVB (43). Our results suggest that the efficacy of IVB to resolve glaucoma depend on structural lesions of the trabecule and the physiopathology related with the fibrovascular membrane that is developed on the surface of the iridocorneal angle. At first, this membrane provokes an open angle NVG that can disappear with IVB. When the membrane is fibrous and is transformed into a goniosynechia iridiana, it traditionally closes the angle and filtrating surgery is normally necessary. The IVB eliminates the neovessels, but is not capable of undoing the fibrous tissue and the synchecia. In this process of the VEGF other growth factors also intervene.

The greatest importance of this work is that it demonstrates the capacity that intravitreal injections have for modifying growth factors in the anterior chamber, with results in patients that confirm laboratory studies. The advantage is that very small doses of the pharmaceutical cross the means well.
and reach effective concentrations in the target areas. This shows that the functioning growth factors in the trabecule and in the aqueous humor could be pharmacologically manipulated with intravitreous injections. If you think about the growth factors signaled in the introduction the future possibilities are important (1-6). Although the efficacy of bevacizumab in iris, choroids and the retina seem evident, it is not possible to specify if the benefits of this molecule exclusively depend on the blocking or inactivation of VEGF or on other growth and cytokine factors, regulated by VEGF, that trigger complex cascades of intracellular signaling (44). Other cellular growth factors could be more important in diminishing the fibrosis or the proliferation of certain cells. In cultures of human MDA-MB-231 tumoral line important interactions between the VEGF, EGF y TGF-beta factors have been shown, which have also been seen in epithelial, endothelial and immunitary cells, in both healthy tissues and cancerous ones (1-4). The aqueous humor and the trabecule are very rich in growth factors and in molecules and cells related with inflammatory and immune processes (45). Under our criteria, the most important are VEGF, EGF y TGF-beta (45-48) for two reasons: the three have crucial implications in NVG etiopathogeny and could simultaneously be manipulated with intravitreous injections that combine pharmaceuticals and immuno-pharmaceuticals. There are EGF and TGF-beta activators and inhibitors which directly operate on them and on their membrane receptors. In the cellular proliferation in the intracoilar lens the MAPK/ERK1/2 and ERK1/2 pathways play a very important role, related with tyrosine-kinase receptors, with EGF and with their receptors (EGFR). The pharmacological inhibitors that already exist could be effective in intravitreous administration to prevent or undo epithelization processes, but experimentation on animals is lacking (44,46). It has also been proved that TGF-beta determines the quantity and composition of the matrix in the juxtacanalicular region of the trabecule, and that, similarly to the case of VEGF, the concentrations of TGF-beta in the aqueous humor are increased when there is glaucoma. The BMP-7 protein in the laboratory behaves like a potent inhibitor of fibrinogenesis measured by the TGF-beta in the trabecule cells (45), and their combination with bevacizumab in experimentation animals has not been proved either.

In NVG the VEGF inhibitors could solve the vascular problem, while the inhibitors or enhancers of EGF and TGF-beta could act on the formation of fibrovascular membrane and its progressive retractibility, that is to say, on the structure responsible for the glaucoma and on that which determines the type of glaucoma in terms of evolution time. Intravitreous injection in cocktail could achieve the normalization of the vascularization and interrupt or regress the formation of membranes and synechiae.

The importance of bevacizumab in the treatment of NVG exceeds the particular interest of this disease. It has a strong relationship with some publications appearing in previous numbers of this journal (48, 49). Anterior uveitis is one of the most important manifestations of idiopathic juvenile arthritis. Among the complications are glaucoma, cataract and corneal alterations. The growth factors previously indicated could play an important role, with the intravitreous injections being an effective and secure approach to achieve pharmacological effects, at low doses, in the entire anterior segment (48). The sapphire titanium laser is capable of producing a trabeculoplasty on rabbits, with minimum or null thermal effect, only with the biomodular activity typical for low potency laser therapy. The growth factors and their receptors are especially sensitive to this type of stimulation, where the photochemical effects predominate (49). These are apparently disconnected lines of research where cellular growth factors should play a predominant role.

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585


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