TITLE PAGE

Full title: Treatment of peripapillary choroidal neovascular membranes with intravitreal bevacizumab.

Running title: Bevacizumab for peripapillary membranes

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ABSTRACT

Aims: To evaluate the effect of intravitreal injections of bevacizumab in the treatment of peripapillary choroidal neovascular membranes.

Methods: Interventional case series of patients with active peripapillary choroidal neovascular membranes. Ophthalmological examination included best-corrected visual acuity, fundus biomicroscopy, fluorescein angiography and optical coherence tomography (OCT). Bevacizumab injections (1.25 mg) were repeated monthly for the first three months. Re-treatment was considered if there were signs of membrane activity.

Results: Six eyes of five patients with peripapillary choroidal membranes were included in the study with a mean follow-up of 13 months (range 6 to 16). Bevacizumab was used as the initial treatment in four eyes and to manage recurrences after surgery in the other two. In five eyes three injections of bevacizumab led to a complete resolution of leakage on fluorescein angiography and OCT. In one eye, membrane activity persisted despite six injections of bevacizumab. Visual acuity improved in five eyes with a mean improvement of 4 lines (range: 2-10 lines). It deteriorated only in the eye that did not respond to treatment.

Conclusions: The results of this case series suggest that the intravitreal injection of bevacizumab may be an effective treatment for peripapillary choroidal membranes.
TEXT

Introduction
Choroidal neovascular membranes that develop contiguous to the optic nerve represent a therapeutical challenge for the vitreoretinal specialist. Common treatment options such as laser and photodynamic therapy may produce severe damage to the retina or to the optic nerve, leading to visual loss.[1-3] Until recently, surgery has been a valid treatment option, with satisfactory results in terms of improvement of visual acuity.[4-7] Anti-angiogenic therapies are being increasingly employed in the treatment of choroidal neovascularization. Encouraging results have been reported, with a decrease in membrane activity and, in some cases, an improvement in visual acuity. However, these studies have been performed mostly in subfoveal or juxtafoveal neovascularization due to age-related macular degeneration (AMD).[8-13] The purpose of this paper is to describe the response of peripapillary choroidal neovascular membranes to intravitreal bevacizumab in a short case series.

Patients and Methods

Patients with active peripapillary neovascular membranes were included in this prospective interventional case series. A membrane was considered peripapillary if the lesion was contiguous to the optic disc. The membrane was attributed to AMD if drusen or suggestive retinal pigment epithelium changes were present in either eye and was classified as idiopathic if fundus findings or patient history failed to reveal a specific cause. The lesion was considered active in the presence of the following findings:

- Intraretinal and subretinal fluid accumulation in optical coherence tomography (OCT).
- Intraretinal or subretinal hemorrhage in fundus examination.
- Leakage or growth of choroidal neovascularization on fluorescein angiography.

All patients underwent a complete ophthalmological examination at the time of inclusion into the study, including best-corrected visual acuity, biomicroscopic evaluation of the anterior and posterior segments, fluorescein angiography and OCT. Previous treatment of the peripapillary membrane was not an exclusion criterion. The natural history and current treatment options of peripapillary membranes were explained in detail to all patients. Treatment with bevacizumab was offered, taking special care to underline the off-label use of the drug and its potential side-effects. Patients willing to receive treatment provided written informed consent. The study adhered to the tenets of the declaration of Helsinki.

The procedure was performed under sterile conditions. Single use syringes of bevacizumab 1.25 mg (Avastin®, Genentech, Inc.) were prepared by the hospital pharmacy. The patient was instructed to apply ciprofloxacin 0.03% (Oftacilox®, Alcon) 1 drop four times daily starting three days before the injection and until one week after the procedure. Injections were repeated monthly for the first three months. After each injection, patients were seen one day, one week and one month later (just before the next treatment). After the third injection, patients were followed every two months. Retreatment was considered if there were signs of membrane activity.
Results

Six eyes of five patients were included in this case series. Patient demographic characteristics, etiology of the membranes and visual acuity results are reported in Table 1. In four eyes (patients 3, 4 and 5), bevacizumab was used as the initial treatment of the peripapillary membrane. In the other two eyes (patients 1 and 2), bevacizumab was used to treat recurrent neovascular activity five months and two years after surgical removal, respectively.

In five eyes (patients 1, 2, 3, 5 and in the left eye of patient 4), bevacizumab injection led to a complete resolution of leakage from the neovascular complex on fluorescein angiography and absence of subretinal and intraretinal fluid in OCT. In all five eyes, no signs of membrane activity were detected during the follow-up period (mean: 13 months; range: 6 to 16). In the right eye of patient 4, bevacizumab was not effective and the membrane remained active throughout the study period despite 6 intravitreal injections. Visual acuity improved after treatment in five of the six eyes. Changes in visual acuity are shown in table 1.

Table 1. Patient demographic characteristics, etiology of the membranes and visual acuity results.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Eye</th>
<th>Etiology</th>
<th>Previous treatment</th>
<th>Baseline VA</th>
<th>Number of injections</th>
<th>Follow-up (months)</th>
<th>Final VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>Female</td>
<td>LE</td>
<td>AMD</td>
<td>Surgical removal</td>
<td>CF</td>
<td>3</td>
<td>12</td>
<td>20/50</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>Male</td>
<td>RE</td>
<td>AMD</td>
<td>Surgical removal &amp; PDT</td>
<td>20/40</td>
<td>3</td>
<td>16</td>
<td>20/30</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Female</td>
<td>LE</td>
<td>Idiopathic</td>
<td>No</td>
<td>CF</td>
<td>3</td>
<td>12</td>
<td>20/25</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>Female</td>
<td>RE</td>
<td>Angioid streaks</td>
<td>No</td>
<td>20/100</td>
<td>6</td>
<td>16</td>
<td>CF</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
<td>Male</td>
<td>RE</td>
<td>AMD</td>
<td>No</td>
<td>20/40</td>
<td>3</td>
<td>6</td>
<td>20/30</td>
</tr>
</tbody>
</table>

RE right eye; LE left eye; AMD age-related macular degeneration; PDT photodynamic therapy; VA visual acuity; CF counting fingers

Case 2

A 79-year-old male patient presented in April 2004 with visual acuity loss (20/40) in his right eye due to a peripapillary choroidal neovascular membrane. Several years earlier, he had suffered a similar process in his left eye, which resulted in a visual acuity of 20/200 in this eye. Pars plana vitrectomy with surgical removal of the neovascular complex was performed in the right eye in May 2004. After surgery, vision remained stable at 20/40 for one year, when a membrane recurrence produced a one-line drop in visual acuity. Photodynamic therapy was successful and visual acuity returned to 20/40. However, in December 2006, fluorescein angiography showed a predominantly classic peripapillary membrane in the right eye (Figure 1A). At that time, the patient
had a visual acuity of 20/40. Three intravitreal injections of bevacizumab were performed in December 2006 and January and February 2007. As of April 2008, visual acuity had improved to 20/30, with no signs of membrane activity (Figure 1B).

**Case 4**

A 51-year-old female patient presented in December 2006 with visual acuity loss in her right eye. Visual acuity was 20/100 in the right eye and 20/32 in the left eye. Fundus examination revealed the presence of angioid streaks and peripapillary choroidal neovascular membranes in both eyes. Fluorescein angiography showed bilateral, active peripapillary membranes; in the right eye, the neovascular complex extended beneath the fovea (Figure 2). Bevacizumab injections were performed in both eyes in January, February and March 2007. The right and left eyes were injected in separate sessions, 7 to 10 days apart. In the left eye, subretinal fluid disappeared one week after the first injection. However, the complete cycle of three injections was administered. In contrast, the right eye showed no response to 6 intravitreal injections of bevacizumab. In April 2008, visual acuity was counting fingers in the right eye and 20/20 in the left eye (Figure 3).

**Discussion**

Peripapillary choroidal neovascular membranes represent an uncommon type of neovascularization that can be associated with several ocular diseases.[14] Age-related macular degeneration and idiopathic cases are the most common causes in older patients. Peripapillary neovascular membranes in younger patients may be associated to a wider spectrum of diseases such as myopia, inflammation, optic nerve drusen or angioid streaks. The natural history of these membranes is variable, since they can remain stable or produce severe central visual loss due to subfoveal extension of the membrane or through exudation and hemorrhage. Thus, in approximately 25% of cases, visual acuity is 20/500 or less 3 years after diagnosis.[6,14-16] The risk of bilateral involvement can be as high as 25%.

The therapeutic approaches developed in recent years have several limitations. Thermal laser leads to destruction of the overlying outer retinal layers and occasionally the nerve fiber layer. Therefore, it is presently applied only in well-defined extrafoveal membranes in which there is no risk of damaging the fovea, avoiding the production of residual scotomas. The Macular Photocoagulation Study Group (MPS) warns against the use of laser if at least one clock-hour and a half of the retina around the optic nerve cannot be spared.[15] Moreover, there is a high recurrence rate after thermal laser. Even if we set aside these limitations, visual success is questionable: the MPS found that only 50% of patients with idiopathic or inflammatory membranes achieved a visual acuity of 20/40 or more after thermal laser compared to 43% of patients in the control group.[15] Success after photodynamic therapy is also limited. Recommendations for its application include sparing 200 µm from the edge of the optic disk. Several treatments are usually required in order to elicit resolution of active leakage.[9] Intravitreal triamcinolone has managed to reduce the number of treatment sessions when applied in combination with photodynamic therapy. However, it has a high rate of side effects, including an increase in intraocular pressure and an increased rate of cataract progression.[17-20] Surgery can be performed only when the membrane is above the retinal pigment epithelium.[4] Some case series of patients with peripapillary choroidal membranes undergoing surgery have reported excellent visual results, with visual acuity
remaining stable or improving in between 35 and 87% of patients.[4-7,21] The main drawbacks of this invasive procedure are its cost and the frequent development of local side effects such as nuclear cataract progression.

The process of new vessel formation from pre-existing vessels is called angiogenesis. Although it is an essential part of several biological processes, it is also implicated in the pathogenesis of eye diseases such as choroidal neovascularization and proliferative retinopathies.[22] Bevacizumab (Avastin®, Genetech, Inc., South San Francisco, CA) is a monoclonal antibody that targets VEGF, one of the main factors involved in angiogenesis. Compared to other anti-VEGF drugs, bevacizumab may be the most cost-effective.

Several papers have reported the results of bevacizumab in the treatment of choroidal neovascularisation due to AMD.[8-13] However, to our knowledge, there are only three published cases of peripapillary choroidal membranes treated with bevacizumab. A series of 26 patients with choroidal neovascularization included one eye with a peripapillary choroidal membrane; however because the results are provided only for the series as a whole, the result in this particular case is unknown.[23] The others are single case reports in which the injection of bevacizumab led to an improvement of visual acuity to near normal levels.[16,24] Our results support the use of bevacizumab in the treatment of peripapillary choroidal neovascular membranes, both for newly diagnosed membranes and for recurrences. In our series, leakage in fluorescein angiography resolved in all but one eye. Subretinal and intraretinal fluid disappeared in all but one eye. Membrane inactivation was reflected in an improvement in visual acuity in five eyes. In our series, among the six eyes treated, only one did not respond to a cycle of three monthly injections of bevacizumab and showed a persistence of membrane activity in OCT and fluorescein angiography and a final visual acuity of counting fingers. After a mean follow-up of 13 months, no recurrences developed in any of the cases that responded to bevacizumab.

Compared to other treatment modalities, the injection of bevacizumab has the advantage of preserving the integrity of the papillomacular bundle. The intravitreal injection of bevacizumab has not been clearly associated with significant systemic side effects and the incidence of severe ocular complications is low.[25]

In summary, the results of this case series suggest that the intravitreal injection of bevacizumab may lead to peripapillary membrane regression with a limited number of injections. No patients in our series had significant side-effects. The high rate of recurrences in this type of membranes makes it even more important to provide a less aggressive treatment modality. Treating the membrane before it extends to the subfoveal area, seems to have a vital role in improving visual prognosis. Although further studies are needed in order to determine the true usefulness of bevacizumab in the treatment of peripapillary choroidal membranes, initial results are encouraging.

None of the authors have any competing interests in this manuscript.
Figure Legends

Figure 1. Patient 2.  A. Pre-treatment. Fundus photography and fluorescein angiography show a recurrent choroidal peripapillary neovascular membrane in the upper edge of the membrane.  B. Post-treatment. Fundus photography and fluorescein angiography show an absence of active leakage.

Figure 2. Patient 4, pre-treatment.  A. Fundus photography, fluorescein angiography and optical coherence tomography of the right eye. The choroidal peripapillary membrane spreads subfoveally, with extensive leakage and hemorrhages in its temporal edge. Angioid streaks are visible, distributed radially from the optic nerve.  B. Fundus photography, fluorescein angiography and optical coherence tomography of the left eye. The choroidal peripapillary membrane does not affect the fovea. Angioid streaks are also present.

Figure 3. Patient 4, post-treatment.  A. Fundus photography, fluorescein angiography and optical coherence tomography of the right eye. Extensive subfoveal fibrosis and subretinal fluid.  B. Fundus photography, fluorescein angiography and optical coherence tomography of the left eye. Complete inactivation of the membrane.
References


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