RANIBIZUMAB AS TREATMENT FOR MYOPIC CHOROIDAL NEOVASCULARIZATION

TRATAMIENTO DE MEMBRANAS NEOVASCULARES MIÓPICAS CON RANIBIZUMAB

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OBJECTIVE

To evaluate the efficacy of intravitreal Ranibizumab as treatment for choroidal neovascularisation due to pathological myopia.

MATERIALS AND METHODS

A retrospective, non-comparative study of 18 eyes treated with intravitreal injections of Ranibizumab. Ten eyes had been treated previously with photodynamic therapy and eight received Ranibizumab as first therapy. After thorough ophthalmologic examination, fluorescein angiography (FAG) and optical coherence tomography (OCT), intraocular injection of Ranibizumab was performed. In subsequent monthly follow-ups and taking into account visual acuity, presence or absence of metamorphopsia, biomicroscopy and OCT examination, further treatment was decided.

RESULTS

Eighteen eyes from 16 patients were finally included. Patients were followed up for a minimum of 6 months. The mean age at initial treatment was 56.4 years. Mean refractive error was -13.3 diopters. Regarding FAG, all neovascular membranes were classical and sub or juxtafoveal localised. At the end of the sixth month after treatment fourteen eyes (77.7%) showed better visual acuity ranging from one or more lines on the Snellen chart, eleven eyes (61.1%) improved two lines or more, three eyes (16.6%) did not show any change and one eye (5.5%) worsened by one line. At 6 months the mean best-corrected visual acuity improved from 0.25 to 0.46 (p = 0.001). The mean thickness of the macula on OCT was reduced from 344.9 microns to 212.6 (p = 0.015).

RESUMEN

Objetivo: Determinar la eficacia de Ranibizumab intravítreo, como tratamiento de la neovascularización coroidea asociada a miopía patológica.

Materiale y métodos: Estudio retrospectivo, no comparativo de 18 ojos tratados con inyecciones intravítreas de Ranibizumab. Diez de los casos se habían tratado previamente con Terapia Fotodinámica, los 8 restantes recibieron Ranibizumab como primera terapia. Tras realizar angiografía fluoresceínica (AGF) y tomografía de coherencia óptica (OCT), se inyectaba ranibizumab, en los controles mensuales posteriores y teniendo en cuenta la agudeza visual (AV), presencia de metamorfopsias, biomicroscopia de polo posterior y características de la OCT se decidía el retratamiento.

Resultados: Se analizaron 18 ojos de 16 pacientes, con un seguimiento mínimo de 6 meses. La edad media fue de 56,4 años y el equivalente esférico medio de -13,3 dioptrias. Todas las membranas neovasculares fueron angiográficamente clásicas y de localización sub o juxtafoveal. La AV mejoró en 14 ojos (77,7%) al menos 1 línea y 11 ojos (61,1%) mejoraron 2 o más líneas a los 6 meses de la inyección, 3 ojos no mostraron cambio (16,6%) y sólo 1 empeoró 1 línea (5,5%). A los 6 meses la AV media mejoró de 0,25 a 0,46 (p = 0,001). La media del espesor macular en la OCT se redujo de 344,9 micras a 212,6 (p = 0,015).
INTRODUCTION

Myopic maculopathy is one of the main causes of irreversible blindness in the world. It also affects young and middle-aged patients. In most cases, vision loss is caused by chorioretinal atrophy or the development of choroidal neovascularization (CNV). In general, myopic neovascularizations are more frequent in women, related to the presence of lacquered fissures, classical at the angiographic level and smaller than a disc diameter (1-5).

At present the only treatment approved for CNV associated to pathological myopia is Photo-Dynamic Therapy (PDT) with verteporfin. PDT has proven to stabilize vision in treated eyes in comparison to placebo groups (4-6). However, the emergence of a new group of drugs, called anti-angiogenics, and their increasing utilization for treating Age Related Macular Degeneration (ARMD) after demonstrating not only stabilization but also visual acuity improvements (7-11), has opened a new path for the therapeutic management of myopic CNV patients.

In the past 3 years some studies were published about clinical cases and small series of patients having myopic membranes treated with Bevacizumab (Avastin®), both systemic and intraocular, with promising results (12-25). Bevacizumab is a humanized recombinant antibody which blocks all the isoforms of the Vascular Endothelium Growth Factor (VEGF). However, this drug is not approved for intra-ocular use like Ranibizumab (Lucentis®). Ranibizumab if a Fab fraction of humanized recombinant antibody which, like, Bevacizumab, blocks all the active forms of VEGF. In randomized, double blind studies this drug has proved its efficiency in intravitreal use for treating any type of neovascular membrane, substantially improving the PDT results and achieving visual acuity improvements in a high percentage of ARMD patients (7-9).

In this small retrospective series we present the results of treatment with Ranibizumab in patients with myopic membranes.

SUBJECTS, MATERIAL AND METHODS

We present a study assessing the response of 18 eyes diagnosed with myopic CNV treated with intravitreal Ranibizumab in our Service.

In all cases a complete ophthalmological exploration was made in each visit, including VA (Snellen-type standard optotypes), anterior pole biomicroscopy, applanation tonometry, ocular fundus exploration with binocular ophthalmoscopy, posterior pole biomicroscopy with 78-dioptre lens and macular qualitative and quantitative examination with Stratus OCT 3000 (Zeiss Meditec, Jena-Germany). All patients were submitted to fluorescein angiography (FAG) before beginning the treatment and subsequently when considered necessary.

The patients were informed verbally and in writing of the treatment characteristics and the utilization of the drug on compassionate grounds, and were asked to sign their consent. Antibiotic eye drops were prescribed (Ciprofloxacin, Oftacilox®, Alcon-Cusí, Barcelona, Spain), to be utilized 4 times a day 3 days before the intraocular injection and 4 days after it.

Prior to the injection, on two occasions anesthetic eye drops were instilled (0.4% oxibuprocaine and 0.5% tetracaine: Colircusí double anesthetic®, Alcon-Cusí, Barcelona, Spain), and 5% iodated povidone. 0.05 ml of Ranibizumab 0.5 mg (Novar-
Ranibizumab in myopic membrane

tis, West Sussex, United Kingdom) were injected in the lower temporal quadrant at 3.5-4 mm of the limbus. The patients were advised to visit the emergency ward if they noticed abnormalities in their vision, pain or other complication.

The check-ups were made at 4 weeks, repeating the injection whenever necessary due to persistence of intra- or sub-retinal liquid in OCT, pigmentary epithelium detachment (PED), appearance of hemorrhage, new CNV or growth of the existing one. In case of doubt, in addition to the clinical signs, we considered the persistence of metamorphopsia when pondering retreatment.

All the variables of the analysis were checked to verify they were within normal ranges by means of a Kolmogorov-Smirnov test. The results of each group were compared with the t for student test. The computer program was SPSS version 15.

RESULTS

Eighteen eyes of 16 patients were analyzed (seven men and nine women). The mean age was 56.44 (range 33-78), the mean spherical equivalent was of –13.36 diopters (range –6 to –24). The mean follow-up was 7.5 months (range 6-12) with a mean number of Lucentis® injections of 2.61 (range 1-6).

Table I describes the base characteristics of the patients.

Ten eyes had undergone previous treatment: 8 eyes received PDT, one was treated with laser due to extrafoveal membrane prior to PDT (subfoveal relapse). In these patients the Lucentis® medication was injected after the third month from the PDT. One eye was treated with PDT and 1 injection of Avastin®, in this case Lucentis® was injected 2 months after the Avastin® injection.

Table II illustrates the mean and standard deviation for VA and central macular thickness in OCT at one, 3 and 6 months and at follow-up termination.

The initial mean VA (SD) was of 0.25 (0.17), at 6 months was of 0.46 (0.3), a highly significant difference (p = 0.001). The final mean VA was of 0.44 (0.26) with a mean gain of 2 lines. In 14 eyes (77.7%) an improvement of at least one VA line was observed and 11 eyes (61.1%) improved 2 or more lines. Three eyes remained the same (16.6%) and only one eye worsened 1 line (5.5%) 6 months after the Lucentis® injection.

The initial mean central macular thickness (SD) was of 344.93 microns (202.90) with significant reduction in the first and third monthly controls. At 6 months said thickness was of 212 microns (74.02), a statistically significant difference (p=0.015) (table II).

Comparing the patients treated with PDT, in those treated primarily with Lucentis® we observed a lack of statistically significant differences in what concerns VA, central macular thickness in OCT or number of injections (table III) (figs. 1-4).

<table>
<thead>
<tr>
<th>Eyes</th>
<th>Sex</th>
<th>Age</th>
<th>Spherical Equivalent</th>
<th>Follow-up Time</th>
<th>Membrane Type</th>
<th>Previous Treatment</th>
<th># of Lucentis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>73</td>
<td>–11</td>
<td>7</td>
<td>Classic/subf.</td>
<td>Yes, PDT laser</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>40</td>
<td>–15</td>
<td>6</td>
<td>Classic/subf.</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>36</td>
<td>–24</td>
<td>9</td>
<td>Classic/juxt.</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>59</td>
<td>–13</td>
<td>6</td>
<td>Classic/subf.</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>51</td>
<td>–17</td>
<td>6</td>
<td>Classic/subf.</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>46</td>
<td>–13</td>
<td>6</td>
<td>Classic/subf.</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>76</td>
<td>–12</td>
<td>8</td>
<td>Classic/subf.</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>56</td>
<td>–6</td>
<td>7</td>
<td>Classic/subf.</td>
<td>Yes, PDT</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>43</td>
<td>–13,50</td>
<td>6</td>
<td>Classic/juxt.</td>
<td>Yes, PDT</td>
<td>1</td>
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<tr>
<td>10</td>
<td>F</td>
<td>77</td>
<td>–13</td>
<td>9</td>
<td>Classic/subf.</td>
<td>Yes, PDT</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>61</td>
<td>–9</td>
<td>6</td>
<td>Classic/subf.</td>
<td>Yes, PDT</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>61</td>
<td>–10</td>
<td>7</td>
<td>Classic/subf.</td>
<td>Yes, PDT</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>39</td>
<td>–17</td>
<td>6</td>
<td>Classic/subf.</td>
<td>Yes, PDT</td>
<td>2</td>
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<tr>
<td>14</td>
<td>F</td>
<td>33</td>
<td>–13</td>
<td>12</td>
<td>Classic/subf.</td>
<td>Yes, PDT Avastin</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>56</td>
<td>–20</td>
<td>12</td>
<td>Classic/juxt.</td>
<td>Yes, PDT</td>
<td>3</td>
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<tr>
<td>16</td>
<td>M</td>
<td>56</td>
<td>–18.75</td>
<td>6</td>
<td>Oculta/yuxt.</td>
<td>Yes, PDT</td>
<td>2</td>
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<tr>
<td>17</td>
<td>M</td>
<td>78</td>
<td>–6.75</td>
<td>6</td>
<td>Classic/subf.</td>
<td>Yes, PDT</td>
<td>4</td>
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<tr>
<td>18</td>
<td>F</td>
<td>75</td>
<td>–8.5</td>
<td>10</td>
<td>Classic/subf.</td>
<td>Yes, PDT</td>
<td>2</td>
</tr>
</tbody>
</table>

Likewise, comparing patients under 50 with those over that age we observed the lack of statistically significant differences in what concerns VA and number of injections. However, the central macular thickness in OCT was significantly greater than in the over-50 group (table IV).

We did not observe systemic or local treatment-derived complications. One case exhibited a CNV relapse with bleeding and VA reduction against the best obtained value, but maintaining the initial VA (case 7).

Table II. Visual Acuity (VA) and central macular thickness: mean and standard deviation (SD) at base, after 1, 3 and 6 months and at follow-up termination

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>Follow-up end</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA visual parameters (Snellen)</td>
<td>0.251 (0.17)</td>
<td>0.413 (0.26)</td>
<td>0.392 (0.25)</td>
<td>0.464 (0.30)</td>
<td>0.442 (0.26)</td>
</tr>
<tr>
<td>OCT: central macular thickness</td>
<td>344.93 (202.90)</td>
<td>246.37 (86.80)</td>
<td>221.15 (100.19)</td>
<td>212.6 (74.02)</td>
<td>219.33 (58.32)</td>
</tr>
</tbody>
</table>

* Statistically significant difference.

Table III. Comparison of mean values at 6 months for visual acuity (VA), central macular thickness in Optical Coherence Tomography (OCT) and number of injections between patients with and without previous photodynamic therapy (PDT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without PDT</th>
<th>With PDT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>0.538</td>
<td>0.406</td>
<td>0.383</td>
</tr>
<tr>
<td>OCT</td>
<td>216.7</td>
<td>209</td>
<td>0.849</td>
</tr>
<tr>
<td>Number of injections</td>
<td>2.18</td>
<td>2.60</td>
<td>0.507</td>
</tr>
</tbody>
</table>

* Diferencias estadisticamente significativas con p<0.05.

Likewise, comparing patients under 50 with those over that age we observed the lack of statistically significant differences in what concerns VA and number of injections. However, the central macular thickness in OCT was significantly greater than in the over-50 group (table IV).

We did not observe systemic or local treatment-derived complications. One case exhibited a CNV relapse with bleeding and VA reduction against the best obtained value, but maintaining the initial VA (case 7).

Fig. 1: Case 4: Female, age 59, 3 ranibizumab injections with 6 months follow-up. Initial VA 0.12, at 6 months 0.3. A: Retinography; B, C and D: Angiography: classical active subfoveal membrane.
DISCUSSION

For many years, the treatment of choice for CNV secondary to pathological myopia has been PDT with verteporfin. Although its initial results were highly encouraging, in long-term studies it was unable to avoid loss of vision in affected patients (4,5). In the VIP study with 2 years follow-up, 36% of eyes treated vs. 51% of the placebo group lost at least 8 letters in their visual acuity, a non-significant change. In the same study, 40% of treated eyes vs. 13% of the placebo group improved at least 5 letters and only 12% of treated eyes vs. 0% of the placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients &lt;50</th>
<th>Patients &gt;50</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>0.617</td>
<td>0.388</td>
<td>0.141</td>
</tr>
<tr>
<td>OCT</td>
<td>169.33</td>
<td>241.44</td>
<td>0.034*</td>
</tr>
<tr>
<td>Number of injections</td>
<td>2</td>
<td>2.57</td>
<td>0.39</td>
</tr>
</tbody>
</table>

* Statistically significant difference with p<0.05.

Fig. 2: Optical Coherence Tomography. A: initial; B: at month 1; C: at month 3; D: at month 6. Initial central thickness 775 µm at 6 months 356 µm.

Fig. 3: Case 14: Female, age 33, previous treatment with PDT and one Avastin injection, 4 injections of ranibizumab, initial VA 0.3, at month 6, A: Retinography; B, C and D: Angiography: classical active subfoveal membrane on edge of scar.
group improved 3 lines of vision, with this result being significant (5).

The above results and the experience obtained in ARMD with the new group of anti-angiogenic drugs has led some authors to utilize them in myopic CNV therapy. The most widely utilized drug is Avastin® for rescue treatment, failed PDT as well as first choice treatment. In 2005, Nguyen (12) published the first article about the use of IV Avastin® in two myopic CNV patient in which several PDT sessions had failed, with spectacular results. Shortly afterwards, Laud (18) published the first article about intra-vitreous Avastin® in myopic membranes (13-25). All authors seem to agree on the promising results of the treatment even though the series are short, lack control groups and have little follow-up. To date there are only 4 publications about the results of Lucentis® in myopic CNV (26-29). The probable reason is that, as both drugs are for «compassionate use», the choice was for the cheapest drug, about 20 Euros, for a dose of Avastin® against the 1,200 Euros for the Lucentis® injection. Rosenfeld (30) admits that at this time there is an important controversy about whether the «off label» use of Avastin® as a primary treatment for myopic CNV is ethical when PDT is approved for treating the same patients.

In our hospital the decision of establishing treatment with the Lucentis drug in myopic CNV was taken considering the failure of PDT to deactivate the injury in some patients. The results obtained in these cases encouraged us to treat other patient as first treatment in order to improve the visual results of PDT.

In our series of 18 eyes, 14 (77.7%) improved their VA at least one line and 11 eyes (61.1%) exhibited improvements exceeding 2 lines 6 months after the Lucentis® injection. Three eyes remained unchanged (16.6%) and only one exhibited a VA decrease of one line (5.5%). The mean initial VA was of 0.23 while the mean final VA was of 0.44, with a mean VA gain of 2 lines. These results are comparable to those of Monés (29) but not as good as those of Silva (26), Konstantinidis (28) and Lai (27), which demonstrated mean improvements between 2.5 and 3.8 lines.

Our results are also similar to those obtained by other authors with Avastin®. In the Sakaguchi series of 8 eyes (20), 75% of eyes exhibited a 2-line VA improvement, with the remaining 25% unchanged. In the 22-eye series of Chan (13), 68.2% of eyes exhibited improvements of 2 or more lines, with a mean visual increase of 2.6 lines after 6 months and 2.4 lines after 1 year (23). The best results were obtained by Yamamoto (15), Gharbiya (24) and Mandal (16) with increases ranging between 3.5 and 5.1 VA lines.

As other authors, (13,15-17,19-29), we have also observed a statistically significant central macular thickness reduction in all OCT controls.

When comparing previously treated with untreated patients, the mean VA was better and the number of injections lower in the second group, even though the differences were not significant. In contrast, Monés (29) did find better visual results in untreated patients with gains of 12.7 letters against the 7.4 letters of those with previous treatments. This difference was also seen in the study of Avastin made by Arias (21).

At this time, myopic CNV treatments have a number of questions which have yet to be answered. Firstly, whether anti-angiogenics are more efficient than PDT, secondly which is the anti-angiogenic of choice and thirdly which is the most adequate administration regime.

The results of the above small series seem favorable to the use of anti-angiogenics but we must take into account that these are only short series, without a control group and with very little follow-up.

In what concerns the anti-angiogenic of choice, while we don’t have studies comparing both drugs, the design for intra-ocular use would be favorable to Lucentis® while the lower cost would tilt the balance towards Avastin®.

As in the case ARMD, the administration regime must be independent for each patient to achieve the best results with the lowest possible number of injections (31-33). In the majority of studies with
Avastin® (15-17,20-22,24) and Lucentis® (26,28-29), the therapeutic regime was based on the patient’s needs. In our study with Lucentis® the mean was of 2.5 injections, similar to that of Silva (26) and Konstantinidis (28). In the Monés series (29) with a longer follow-up of 1 year, the mean number of injections was 1.5. The largest series, that of Ikuno (22), 63 eyes treated with Avastin® with a follow-up of at least one year, the mean was of 2.4 injections, higher than the mean of 1 injection of the Arias (21) and Yamamoto (15) studies, albeit with a follow-up of only 6 months. In contrast, Chan (13,23) and Ruiz-Moreno (25) propose a regime comprising 3 injections of Avastin® to consolidate the effect as well as additional treatment when necessary, as Lai (27) suggest for Lucentis®.

To conclude, we believe that even though the results obtained with intra-ocular injections of Lucentis® for treating myopic CNVs are highly encouraging, broader, randomized studies are required with longer follow-up in order to clarify the questions posed above and others.

REFERENCES


