Original article

Responses to ranibizumab in wet age-related macular degeneration patients with vitreomacular traction

A. Filloy*, L. Arias

Servicio de Oftalmología, Hospital Universitari de Bellvitge-Institut d’Investigació Biomèdica de Bellvitge, Universitat de Barcelona, L’Hospitalet de Llobregat, Barcelona, Spain

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ABSTRACT

Purpose: The purpose of the present study is to compare the responses to ranibizumab between wet age-related macular degeneration patients, with and without accompanying vitreomacular traction syndrome.

Methods: Our database of optical coherence tomography files was searched for eyes of age-related macular degeneration patients that had been treated with ranibizumab, and that had evidence of vitreomacular traction. A control group was selected from the same database for comparison.

The case history of each selected individual was reviewed for data regarding the evolution of visual acuity in that patient, and the number of intravitreal injections that had been required to date.

Results: From a database of 373 eyes, clear images of vitreomacular traction were obtained for a total of 18 eyes.

The mean follow-up period was 20.6 months (SD = 10.6, range = 10.4–31.7).

Patients in the vitreomacular traction group had been given an average of 5.1 injections versus an average of 4.2 injections in patients in the control group.

The mean changes in visual acuity (which was measured using ETDRS charts) were −15 letters and −4 letters in the vitreomacular traction and control groups (p = 0.07), respectively.

Conclusions: After ranibizumab treatment, age-related macular degeneration patients with accompanying vitreomacular traction showed a tendency to have a poorer prognosis in terms of visual acuity than patients without this finding. In addition, higher numbers of intravitreal injections were required to obtain clinical responses in patients with vitreomacular traction.

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* Corresponding author.
E-mail address: alejandrolilloy@gmail.com (A. Filloy).

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Anti-VEGF
Mácula

Resposta a ranibizumab en pacientes con degeneración macular húmeda con tracción vitreomacular

RESUMEN

Objetivo: Comparar la respuesta a ranibizumab entre pacientes con degeneración macular asociada a la edad con y sin tracción vitreomacular acompañante.

Métodos: Nuestro archivo de imágenes de tomografía de coherencia óptica de pacientes con degeneración macular ha sido examinado en busca de imágenes de tracción vitreomacular. Un grupo control fue seleccionado de la misma base de datos para la comparación.

La historia clínica de los pacientes fue examinada en busca de datos acerca de la evolución de la agudeza visual y del número de inyecciones intravitreales necesarias para controlar la enfermedad.

Resultados: La base de datos estaba formada por 373 ojos. Entre ellos, 18 mostraron imágenes de tracción vitreomacular.

La media de seguimiento fue de 20,6 meses (desviación estándar [DE] = 10,6; rango = 10,4−31,7).

Los pacientes del grupo de tracción vitreomacular recibieron un promedio de 5,1 inyecciones mientras que un promedio de 4,2 inyecciones fue necesario en los pacientes en el grupo control.

La media del cambio en la agudeza visual (tablas ETDRS) fue de −15 letras para el grupo de la tracción vitreomacular, y −4,9 letras para el grupo control (p = 0,07).

Conclusiones: Después del tratamiento con ranibizumab, los pacientes de nuestro estudio con degeneración macular asociada a la edad y tracción vitreomacular coexistente han mostrado tendencia a alcanzar una peor agudeza visual que los pacientes sin este hallazgo. Además, estos pacientes han necesitado un mayor número de inyecciones intravitreales para obtener respuesta clínica.

No existen en la literatura actual estudios previos sobre este aspecto.

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Introduction

Age-related macular degeneration (ARMD), particularly the exudative form, is the main cause of him visual loss and legal blindness in the elderly population. At present, the standard treatment for exudative ARMD consists in intravitreal injections of vascular endothelial growth factor antibodies (anti-VEGF). The genetic and environmental factors have been widely discussed in studies researching the pathogenesis of ARMD. The biological interactions between the various compartments of the eye have attracted growing attention in recent years, above all the interactions in the vitreoretinal interface.

The vitreomacular traction syndrome (VMT) consists in an anomalous relationship between the central retina and the posterior surface of the hyaloids with a partial separation from the vitreous body while the posterior hyaloids remain adhered to the central retina. Optic coherence tomography (OCT) has significantly facilitated the identification of this characteristic in ARMD patients, revealing the anteroposterior traction exerted by the hyaloids on the central retina as well as the resulting anatomic distortion.

The objective of this study is to determine whether the response to treatment with ranibizumab in wet ARMD can be altered by the coexistence of VMT.

Subjects, materials and methods

The study was designed as a retrospective case and control study. The sample included patients with wet ARMD who had received or were receiving treatment with ranibizumab in one or both eyes in the Ophthalmology Service of the Bellvitge University Hospital. Some patients were excluded from the study due to the poor quality of OCT images.

The OCT images taken as from the first visits (OCT-2000, Topcon, Oakland, USA) are stored in the hospital database. A search was made in said images to identify the patients exhibiting VMT with central macular adhesion (Fig. 1).

A control group of ARMD patients with OCT images clearly showing the absence of VMT was randomly selected for comparison purposes (Fig. 2).

The clinical records of each participant were reviewed for obtaining relevant clinical data. The data included in the study comprised the evolution of patient visual acuity (VA) according to the ETDRS records and the number of ranibizumab injections required to achieve control over the disease, understood as macular fluid resolution.

Results

The database used in this study comprised 373 ARMD patients treated with ranibizumab.
The inclusion criteria for the study were: established wet ARMD diagnostic in one or both eyes, not having received another treatment against ARMD after beginning the ranibizumab treatment, with the exception of oral antioxidants, and a follow-up period of at least 6 months. The exclusion criteria were follow-up period under 6 months, the use of other treatments concomitant with ranibizumab or the coexistence of another ocular disease which could cause progressive visual loss (for example, developing cataracts or uncontrolled glaucoma).

The study included only OCT images showing clear evidence of VMT with central adhesion and edges raised from the vitreous body. Blurry or low quality images were discarded together with images in which the presence or absence of VMT could not be determined.

Overall, 18 eyes were identified with clear VMT, corresponding to 17 patients.

The control group comprised 50 eyes randomly selected among patients without VMT signs. Due to lack of key information in the clinical records, 3 of these patients had to be excluded during the data recovery stage.

The mean follow-up was of 20.6 months (SD = 10.6; range = 10.4–31.7) (Table 1).

The mean age of patients in the VMT group was of 75.4 years with SD of 5.6 years and an age range of 69.7–81 years. The mean age of patients in the control group was of 75.6 years with SD of 8.8 years and an age range of 66.7–84.5 years.

The male/female proportion was of 0.8 (VMT) and 0.9 (control).

The right/left eye proportions were of 1.0 (VMT) and 1.0 (control).

The phakic/pseudophakic eye proportions in both groups were of 2.0 (VMT) and 1.1 (control).

Three patients in the VMT group had received previous treatment for ARMD (2 had received bevacizumab and one had received photodynamic therapy). Twelve eyes included in the control group had previously taken treatment for ARMD (5 had received bevacizumab, 4 photodynamic therapy and 3 a combination of bevacizumab and photodynamic therapy).

The types of neovascular lesions observed in the eyes of VMT group patients were predominantly classical, concealed retinal angiomaticus proliferation (RAP) and minimally classical. The lesions in the eyes of control group patients were predominantly classical (15), hidden, RAP and minimally classical.

Of the contralateral eyes of VMT group patients, 7 were normal, 5 had with ARMD, a further 5 exhibited disk-shaped scarring and one active ARMD. Among the control group patients, 22 contralateral eyes exhibited normal OCT images, 6 wet ARMD, 16 eyes with disk-shaped scarring and 3 eyes had atrophic ARMD.

Due to advanced ARMD stages, it was not possible to identify the original lesion type in some patients of both groups.

The control group patients required an average of 4.2 intravitreal injections to achieve control over the disease,
whereas the VMT group patients required an average of 5.1 (p = 0.31) (t for Student test) (Tables 1 and 2).

The mean baseline VA was of 44.8 and 48.8 letters for the control group and VMT, respectively (p = 0.41).

The mean VA change was of −4.9 and −15 letters in the control and VMT groups, respectively (p = 0.07).

No local or systemic side effects were observed as a result of treatment in the patients of both groups.

The data were statistically analyzed by means of the t for student (SPSS statistics, IBM, Baltimore, USA).

**Discussion**

To date, literature on the coexistence of ARMD and VMT is not abundant. An interesting review by Green-Simms et al. summarized current knowledge on the coexistence of vitreomacular adhesion and ARMD. Ondes et al. described that posterior vitreous detachment (PVD) was significantly less frequent in eyes of patients with ARMD than in healthy eyes and accordingly postulated that PVD has a protective effect against the development of wet ARMD. However, said study did not utilize OCT to determine the vitreomacular relationship, which is the method applied in the remainder of studies. Krebbs et al. described that complete PVD is more common among eyes with dry ARMD and among healthy eyes than in eyes with wet ARMD. Similarly, Mojana et al. concluded that the detection of a tractional vitreomacular component was significantly more frequent among eyes with exudative ARMD and that the area on which the hyaloids adhered tended to overlap the choroidal neovascularization area (CNV). The latter finding was supported by a further study carried out by Lee et al.

It has been proposed that chronic traction on the macula would produce local inflammation or mechanical stress which could facilitate the appearance of wet ARMD. It has also been suggested that in the vitreoretinal adhesions the hyaloids could act as a sort of cupula, promoting prolonged contact between the free oxygen radicals and the retinal surface, while the presence of PVD would enable the clearing of said substances.

However, a recent longitudinal and prospective four-year study (Waldstein et al.) has not found a correlation between the presence of VMT and the risk of dry ARMD transforming into the wet form. This study also suggested the previously formulated hypotheses that VMT could be an effect of ARMD instead of a cause thereof, and could be produced by the pro-inflammatory environment of ARMD which would enhance the adhesion of the posterior vitreous.

A study on 7 patients carried out by Rotso et al. focused on the efficacy of intravitreal anti-VEGF in the treatment of CNV with the coexistence of VMT found that after the injections vision improved or stabilized in 71% of the studied eyes.

**Table 1 – General results.**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean age (years)</th>
<th>Follow-up (months)</th>
<th>MiVA</th>
<th>MfVA</th>
<th>MVAv</th>
<th>Inj.</th>
</tr>
</thead>
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<tr>
<td>VMT Group</td>
<td>18</td>
<td>75.4</td>
<td>20.2</td>
<td>48.8</td>
<td>33.8</td>
<td>−15</td>
<td>5.1</td>
</tr>
<tr>
<td>control Group</td>
<td>47</td>
<td>75.6</td>
<td>20.9</td>
<td>44.8</td>
<td>39.9</td>
<td>−4.9</td>
<td>4.2</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td>0.46</td>
<td>0.07</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

VA, visual acuity; MfVA, mean final VA; MiVA, mean initial VA; Inj., number of injections; n, number; VMT, vitreomacular traction; MVAv, mean VA variation.

**Table 2 – Data belonging to the cases group.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Eye</th>
<th>Previous treatments</th>
<th>IVI</th>
<th>IVA</th>
<th>FVA</th>
<th>VAV</th>
<th>Current condition</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85</td>
<td>LE</td>
<td></td>
<td>5</td>
<td>60</td>
<td>30</td>
<td>−30</td>
<td>In trt.</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>RE</td>
<td></td>
<td>14</td>
<td>69</td>
<td>45</td>
<td>−24</td>
<td>In trt.</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>RE</td>
<td></td>
<td>2</td>
<td>38</td>
<td>61</td>
<td>23</td>
<td>In trt.</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>RE</td>
<td></td>
<td>4</td>
<td>28</td>
<td>3</td>
<td>−25</td>
<td>Macular fibrosis</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>LE</td>
<td></td>
<td>1</td>
<td>36</td>
<td>8</td>
<td>−28</td>
<td>Macular fibrosis</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>RE</td>
<td></td>
<td>6</td>
<td>81</td>
<td>74</td>
<td>−7</td>
<td>In trt.</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>RE</td>
<td></td>
<td>3</td>
<td>55</td>
<td>10</td>
<td>−45</td>
<td>Stable without trt.</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>LE</td>
<td></td>
<td>6</td>
<td>69</td>
<td>3</td>
<td>−66</td>
<td>Macular fibrosis</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>LE</td>
<td></td>
<td>3</td>
<td>31</td>
<td>20</td>
<td>−11</td>
<td>In trt.</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>−</td>
<td>RE</td>
<td></td>
<td>4</td>
<td>49</td>
<td>51</td>
<td>2</td>
<td>In trt.</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>RE</td>
<td>1 Luc.</td>
<td>3</td>
<td>55</td>
<td>41</td>
<td>−14</td>
<td>Stable without trt.</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>LE</td>
<td></td>
<td>1</td>
<td>16</td>
<td>19</td>
<td>3</td>
<td>Stable without trt.</td>
<td>7</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>RE</td>
<td>PDT</td>
<td>13</td>
<td>60</td>
<td>35</td>
<td>−25</td>
<td>Stable without trt.</td>
<td>47</td>
</tr>
<tr>
<td>14</td>
<td>75</td>
<td>RE</td>
<td></td>
<td>1</td>
<td>18</td>
<td>9</td>
<td>−9</td>
<td>Fibrosis macular</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>82</td>
<td>LE</td>
<td></td>
<td>5</td>
<td>30</td>
<td>80</td>
<td>50</td>
<td>Stable without trt.</td>
<td>33</td>
</tr>
<tr>
<td>16</td>
<td>71</td>
<td>LE</td>
<td></td>
<td>9</td>
<td>65</td>
<td>60</td>
<td>−5</td>
<td>Stable without trt.</td>
<td>14</td>
</tr>
<tr>
<td>17</td>
<td>72</td>
<td>RE</td>
<td></td>
<td>5</td>
<td>70</td>
<td>10</td>
<td>−60</td>
<td>Macular fibrosis</td>
<td>31</td>
</tr>
</tbody>
</table>

VA, visual acuity; FVA, final VA; IVA, initial VA; Bev, bevacizumab; IVI, received intravitreal injections; Luc, luteinis; RE, right eye; LE, left eye; PDT, photodynamic therapy; previous trt., previous treatments; trt., active treatment; VAV, VA variation.
Said authors recommend treating CNV with the coexistence of VMT as in the typical CNV cases. They also recommend considering surgery for VMT once CNV has stabilized by means of a conventional medical therapy.\textsuperscript{13}

A search through the literature has not produced previous studies that researched the influence of VMT in the response of patients to ranibizumab or other type of anti-VEGF. Accordingly, there is no information on previous studies on the specific prognosis for the subgroup of patients with coexisting ARMD and VMT.

Before arriving at conclusions, the authors would like to point out one specific case of the study: a patient who exhibited bilateral wet ARMD but only had evidence of VMT in one eye. Three ranibizumab injections were administered in each eye and even though the eye without VMT maintained vision and through OCT exhibited a complete resolution of the intraretinal fluid, the eye with VMT experienced progressive loss of vision and evolved to macular fibrosis. Despite being a unique case, it was surprising to observe such a different response in each eye of the same patient (Figs. 3 and 4).

**Fig. 3** – Evolution of OCT throughout the treatment in both eyes of a patient with bilateral wet ARMD and unilateral VMT. Eye exhibits vitreomacular adhesion. (A) Subretinal fluid prior to the first injection does not show resolution. (B and C) In contrast, it evolves to a larger pigment epithelium detachment which does not exhibit signs of regression after 2 additional doses. The evolution of the VA was from 48 to 14 letters.
Throughout the series of cases of said database, only 7 patients required 12 or more anti-VEGF injections in the course of their disease. Two of these patients were in the VMT group, representing a VMT incidence of 28.7% among the patients who required 12 or more injections. This incidence is higher than would be expected if the presence of VMT did not influence patient response to ranibizumab, taking into account the incidence of VMT in the series.

The conclusion of this study is that the patients with coexisting wet ARMD and VMT of this study have exhibited a tendency to diminished VA and requiring more treatment than patients in which OCT did not show VMT. The statistical significance results are not sufficient to state an established evidence of the difference.

The reasons for the observed difference between ARMD patients with and without VMT remain in the field of speculation. Literature suggests an area in which the adhered posterior hyaloids would create microenvironments maintaining high VEGF and pro-inflammatory concentrations in the vicinity of the macula, at the same time preventing access of the injected drugs (which would be the case in complete PVD), according to Waldstein et al. However, VMT has no influence in the development of wet ARMD and therefore

Fig. 4 – Evolution of OCT throughout the treatment in both eyes of a patient with bilateral wet ARMD and unilateral VMT. Eye does not exhibit vitreomacular adhesion. (A and B) The fluid present at the beginning disappeared after the first dose. (C) The fluid did not reappear after completing the charging load. VA evolved from 32 to 30 letters.
perhaps VMT begins to act as a factor which influences the course of the disease once it has taken hold.

Some of the limitations of this study are the small number of included patients, its retrospective nature and limited follow-up periods. Additional studies with larger samples, longer follow-up periods and ideally a prospective structure would be necessary to confirm the differences described in this paper and endow them with sufficient statistical significance.

Conflict of interests

No conflict of interests has been declared by the authors.

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