Original article

Long-term visual acuity in patients with age-related macular degeneration and persistence of subretinal fluid after treatment with ranibizumab

C. Torrón, S. Fernández-Pérez, O. Ruiz, J. Leciñena, L. Pablo

Servicio de Oftalmología, Hospital Universitario Miguel Servet, Zaragoza, Spain

Abstract

Objective: To analyse the long-term visual acuity (VA) in patients with age-related macular degeneration (ARMD) treated with ranibizumab, and who had persistent subretinal fluid after the induction therapy and/or in the successive controls.

Materials and methods: We reviewed the medical records, optical coherence tomography (OCT) and fluorescein angiograms of 216 patients treated with ranibizumab between January 2008 and April 2010, selecting those who had persistent subretinal fluid or recurrent fluid for at least one year of follow-up.

Results: A total of 36 eyes from 34 patients were included, with 19 eyes (52.7%) having persistent, and 17 (47.2%) recurrent subretinal fluid throughout the follow-up (mean 29.06 ± 9.28 months). The average number of injections was 7.89 ± 3.2. The central macular thickness (CMT) at the start of follow-up was 330 ± 84 μm, at 3 months 265.2 ± 62 μm, and 294.5 ± 37 μm at the end of the follow-up. The initial mean VA was 0.3 ± 0.2, at 3 months 0.43 ± 0.2 (p < 0.05) and at the final review, 0.41 ± 0.22 (p < 0.05). Hemorrhages in recurrences were associated with a worse final VA (p = 0.004). At the end of follow-up, 18 eyes (50%) continued with ranibizumab treatment, 16 eyes (44%) were kept under observation, and 2 patients died. There were no differences between VA and CMT between the groups.

Conclusions: The persistence or recurrence of macular subretinal fluid in patients treated with ranibizumab does not significantly reduce the visual gain obtained after induction therapy, despite discontinuation of treatment during follow-up. Haemorrhages in the recurrences were associated with a worse final VA.

© 2011 Sociedad Española de Oftalmología. Published by Elsevier España, S.L. All rights reserved.
Agudeza visual a largo plazo en pacientes con degeneración macular asociada a la edad tratados con ranibizumab y persistencia de fluido subretiniano

Resumen

Objetivo: Analizar la agudeza visual (AV) a largo plazo en pacientes con DMAE tratados con ranibizumab con persistencia de líquido subretiniano después del tratamiento de inducción y/o en los controles sucesivos.

Método: Hemos revisado las historias clínicas, tomografías de coherencia óptica (OCT) y angiografías fluoresceínicas de los 216 pacientes tratados con ranibizumab entre enero de 2008 y abril del 2010, seleccionando aquellos que han presentado fluido subretiniano de forma persistente o recurrente a lo largo del seguimiento mínimo de un año.

Resultados: Hemos incluido 36 ojos de 34 pacientes; 19 ojos (52,7%) presentaban persistencia y 17 (47,2%) recurrencia de fluido subretiniano a lo largo del seguimiento (media 29,06 ± 9,28 meses). La media de inyecciones fue de 7,89 ± 2,41. El espesor macular central (EMC) inicial fue de 330 ± 84 μm, a los 3 meses de 265,2 ± 62 μm y de 294,5 ± 37 μm al final del seguimiento. La AV media inicial fue de 0,3 ± 0,2, a los 3 meses 0,43 ± 0,2 (p < 0,05) y al final del seguimiento de 0,41 ± 0,22 (p < 0,05). La aparición de hemorragias en las recurrencias se asoció con peor visión final en comparación con los que no las presentaron (p = 0,004). Al final del seguimiento 18 ojos (50%) continúan en tratamiento con ranibizumab, 16 ojos (44%) se mantienen en observación y 2 pacientes han fallecido. No existen diferencias entre AV y EMC entre ambos grupos.

Conclusión: La persistencia o recurrencia de fluido macular subretiniano en pacientes tratados con ranibizumab no disminuye significativamente la ganancia visual obtenida después del tratamiento de inducción, a pesar de la interrupción del mismo durante el seguimiento. La aparición de hemorragias en las recurrencias se asocia con peor AV final.

© 2011 Sociedad Española de Oftalmología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

At present, ranibizumab is the treatment of choice for exudative ARMD. The MARINA and ANCHOR multicenter, randomized and double blind studies have demonstrated that the monthly administration of ranibizumab during 2 years not only maintained vision but achieved significant improvements, with a mean game of 7.2 and 11.3 letters respectively. This pattern of treatment is not feasible in usual clinical practice due to organizational, social and economic reasons and for this reason studies have been developed to reach the VA improvement goals with a lower number of injections. The studies that have applied prescription of 3 injections, and in the beginning and quarterly injections thereafter (PIER, EXCITE) did not equal the good VA results, but the prescriptions based on the monthly injections in the beginning and thereafter according to the needs of each patient’s (PrONTO, SUSTAIN) in addiction, achieved very similar VA gains with a significantly lower mean number of injections. In addition, with the monthly regime it is likely that patients are being unnecessarily overtreated, causing alterations in the retina pigment epithelium (RPE) and damages in photoreceptors.

In our hospital, the usual regime generally consisted of 3 consecutive monthly injections in the beginning and individualized treatment for each patient thereafter taking into account the VA, biomicroscopy and optic coherence tomography (OCT) ocular fundus findings, according to the recommendations of the PrONTO study. Throughout the 5 years experience with anti-angiogenic treatments we have observed that in some patients ranibizumab injections were not able to completely eliminate subretinal fluid in the OCT, whereas in others it disappeared and appeared regularly regardless of the number of re-treatments. This required a close follow-up in order to avoid vision loss. For this reason, we consider carrying out this retrospective study with the main objective of researching the evolution of the VA in the long-term in this group of patients and to assess the influence of variable such as type or size of neovascular membrane, presence of PED and as well as the number of ranibizumab injections in the visual result of this type of patients.

Materials and methods

A retrospective and observational study comprising 216 patients with exudative ARMD treated with ranibizumab in our hospital between January 2008 and April 2010. The study included patients who exhibited persistent subretinal fluid after the 3 charge injections or recurrently throughout the minimum follow-up period of one year. Subretinal fluid recurrence was determined when it reappeared regardless of re-treatments after its initial disappearance with the 3 charge doses of ranibizumab. The study excluded the patients with suspected neovascularization clinic, retinal angiomatosus proliferation (RAP) in advanced stages, idiopathic polypoid choroidal vasculopathy (IPCV) or associated diseases that could cause exudation, as well as the study does have...
Fig. 1 – (A) Retinograph and (B–D) fluorescein angiography of a patient aged 64 with minimally classic lesion, cystic macular edema and retina pigment epithelium detachment. Initial visual acuity 0.1. Final visual acuity after 11 ranibizumab injections (24 months) 0.3.

the recent intraocular surgery history or previous laser or photodynamic therapy treatment if any.

Or the patients were assessed monthly or bi-monthly during the first year and every 1-3 months as of the second year of treatment. In each visit a complete ophthalmological exploration was carried out, which comprised VA (Snellen type optotypes), anterior pole biomicroscopy, applanation tonometry, ocular fundus exploration with binocular ophthalmoscope, posterior pole biomicroscopy with 78 dpt lens, fluorescein angiography (FA) and macular OCT, «macular cube» strategy 512 × 128 (Cirrus HD-OCT, Zeiss Meditec, Jena-Germany).

FA was performed before starting the treatment excepting 2 patients (3 eyes) and when deemed necessary during the follow-up to discard new neovascularization or therapeutic strategy changes. The main variables of the study were VA and the secondary variables included biomicroscopy and FA findings and macular OCT.

A descriptive statistical analysis was made, to calculate the frequencies and proportions of the qualitative variables and the mean values (typical deviation) or averages (ranges) for the quantitative variables. In order to compare the qualitative variables the Chi square test was applied. For the quantitative variables, normal distribution was verified applying the Kolmogorov–Smirnov tests because the data did not fit within the normal ranges. The mean values were compared by means of the U Mann–Whitney nonparametric test for independent samples and the W Wilcoxon for paired data. The significance level of 5% was taken: p < 0.05. The computer application was SPSS Inc., Chicago, IL, USA version 18.0.

<table>
<thead>
<tr>
<th>Table 1 – Characteristics of baseline fluorescein angiography and optic coherence tomography.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Lesion size (μm)</td>
</tr>
<tr>
<td>Membrane type</td>
</tr>
<tr>
<td>Hidden</td>
</tr>
<tr>
<td>Classical</td>
</tr>
<tr>
<td>RAP (IA stage)</td>
</tr>
<tr>
<td>Without angiograph</td>
</tr>
<tr>
<td>Membrane location</td>
</tr>
<tr>
<td>Subfoveal</td>
</tr>
<tr>
<td>Juxtafoveal</td>
</tr>
<tr>
<td>Extrafoveal</td>
</tr>
<tr>
<td>Without angiograph</td>
</tr>
<tr>
<td>Central macular thickness (μm)</td>
</tr>
<tr>
<td>OCT description</td>
</tr>
<tr>
<td>Cysts</td>
</tr>
<tr>
<td>PED</td>
</tr>
<tr>
<td>NSD</td>
</tr>
</tbody>
</table>

SD, standard deviation; PED, pigment epithelium detachment; NSD, neurosensory detachment; OCT, optic coherence tomography; RAP, retinal angiomatous proliferation.
Table 2 – Mean visual acuity and macular thickness comparison between eyes with continued ranibizumab treatment and patients who interrupted treatment.

<table>
<thead>
<tr>
<th></th>
<th>Continued treatment</th>
<th>Interrupted treatment</th>
<th>Statistical significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of cases (%)</td>
<td>25 (69.4%)</td>
<td>11 (30.5%)</td>
<td></td>
</tr>
<tr>
<td>Final VA (mean ± SD)</td>
<td>0.38 ± 0.20</td>
<td>0.45 ± 0.27</td>
<td>0.406</td>
</tr>
<tr>
<td>Final central macular thickness (µm)</td>
<td>261.36 ± 63.61</td>
<td>279.91 ± 50.20</td>
<td>0.164</td>
</tr>
</tbody>
</table>

VA, visual acuity; SD, standard deviation.

Results

The study included 36 eyes of 34 patients, with a mean age of 76.1 ± 5.67 years, 11 males (32.3%) and 33 females (67.6%); 19 eyes (52.7%) exhibited persistence and 17 (47.2%) subretinal fluid recurrence in OCT throughout the various assessments (Figs. 1 and 2). The mean follow-up was of 29.06 ± 9.28 months (range 12–48) and the mean number of injections was of 7.89 ± 3.21 (range 3–14). Twenty of the 34 patients of the study (58.8%) exhibited bilateral exudative ARMD. Only 2 follow-ups were lost at 30 and 18 months involving two patients with Alzheimer disease who died aged 87 and 85.

In 9 of the 36 eyes (25%), biomicroscopy ocular fundus assessment revealed subretinal hemorrhage and in 13 (36%) pigment epithelium detachment (PED) at diagnostic time.

The characteristics of baseline FA and OCT are shown in Table 1.

![Macula thickness: Macular cube 512x128](image)

Fig. 2 – (A) Initial optic coherence tomography and (B–F) optic coherence tomography at month 3, 6, 9, 12 and 24 from the 1st ranibizumab injection. Initial central macular thickness 658 µm, final 323 µm. Note the persistence of subretinal fluid in all controls despite the treatment.
The mean initial VA was of 0.30 ± 0.20 (range 0.02–0.9), 3 months after the first injection of 0.43 ± 0.22 (p = 0.00035; ratio 1.96; CI 95% 1.27–2.65), at 12 months of 0.39 ± 0.2 (p = 0.008; ratio 1.89; CI 95% 1.08–2.69), at 24 months of (No. = 30) of 0.42 ± 0.2 (p = 0.006; ratio 2.03; CI 95% 1.22–2.84), and at the end of the follow-up of 0.41 ± 0.22 (p = 0.02; ratio 2.0; CI 95% 1.27–2.73). Significant differences were observed between the initial mean VA and all the assessments. In the comparison of the mean VA in 3 months after the first injection with the assessments at 12 and 24 months and at the end of the follow-up no significant differences were observed (p = 0.247; p = 0.818 and p = 0.631, respectively).

**Table 3 - Mean visual acuity comparison of eyes with and without cysts in optic coherence tomography throughout the follow-up period.**

<table>
<thead>
<tr>
<th></th>
<th>No cysts</th>
<th>Cysts</th>
<th>Statistical significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of cases (%)</td>
<td>VA (mean ± SD)</td>
<td># of cases (%)</td>
</tr>
<tr>
<td>Initial</td>
<td>25 (69.4)</td>
<td>0.29 ± 0.23</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>3 months</td>
<td>26 (72.2)</td>
<td>0.48 ± 0.18</td>
<td>10 (27.7)</td>
</tr>
<tr>
<td>12 months</td>
<td>22 (61.1)</td>
<td>0.43 ± 0.20</td>
<td>14 (38.8)</td>
</tr>
<tr>
<td>24 months</td>
<td>17 (56.6)</td>
<td>0.46 ± 0.20</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Final</td>
<td>25 (69.4)</td>
<td>0.46 ± 0.23</td>
<td>11 (30.6)</td>
</tr>
</tbody>
</table>

SD, standard deviation.

* Statistically significant.
Figs. 3 and 4 illustrate the evolution of the mean VA and the mean CMT of all the patients in the various assessments. Prior to treatment only 7 eyes (19.4%) exhibited a VA $\geq 0.5$, while at the end of the follow-up 15 eyes had a VA $\geq 0.5$ (41.6%) $p = 0.005$; ratio 2.60; CI 95% 1.13–4.06.

In what concerns the evolution of subretinal fluid in relation to the ranibizumab injections, 11 eyes (30.5%) exhibited diminished amounts in over 50% of re-treatments, 9 eyes (25%) did not exhibit any reduction in any re-treatment and 16 (44.4%) exhibited diminished subretinal fluid in less than half of re-treatments.

No significant differences were found in the final VA or the CMT, comparing the patients who continued to receive ranibizumab injections during the entire follow-up period (No. = 25, 69.4%) with those who at a given point in time stopped treatment but continued assessments (No. = 11, 30.5%) (Table 2).

No significant differences were found in the comparison of baseline VA or baseline CMT in the OCT, according to the angiographic type of neovascular membrane. Likewise, no significant differences were found between the baseline existence of PED, intraretinal cysts or intra- or sub-retinal hemorrhage.

The variables analysis between patients with persistent and recurring fluid (initial and final VA, lesion size, number of injections), the only significant differences were found in the initial CMT ($p = 0.01$; mean 330.52; CI 95% 299.62–361.41) and also in the final CMT ($p < 0.001$; mean 267.03; CI 95% 246.81–287.24), which was lower in patients with recurring fluid.

In eyes with the appearance of hemorrhage in recurrences, the final VA was significantly poorer than in those who did not have hemorrhage ($p = 0.004$; mean VA hemorrhage in recurrences 0.21; CI 95% 0.08–0.34 versus no hemorrhage 0.47; CI 95% 0.40–0.55). In contrast, the appearance of cysts in OCT in said recurrences was not associated with worse final VA against those who did not exhibit cysts ($p = 0.442$), although it was significantly poorer in eyes with cysts at the three-month assessment (Table 3).
## Discussion

Treatment with ranibizumab has achieved an important change in the management of ARMD patients, enabling the majority to stabilize or improving their vision. However, 8–10% of patients suffer significant visual loss even with monthly treatment as demonstrated by the MARINA and ANCHOR clinical studies. In a recent retrospective study, Rosenfeld researched the main causes of vision loss in these patients, comparing several variables between patients with a gain of ≥15 letters and those who lost ≥15 letters, on the hypotheses that increases in exudation derived from neovascularization would explain the difference between both groups. However, the comparison between both groups demonstrated the absence of differences at baseline or at month 3, 6, 12 and 24. Likewise, no association was found between visual loss and hemorrhage, fibrosis or presence of PED. However, significant differences were observed in the extension of RPE anomalies and increases in the atrophy area, above those of the visual loss group. In his viewpoint, said changes could be due to the ranibizumab therapy.

The PrONTO study included the presence of subretinal fluid in OCT as a criterion for re-treatment, regardless of the VA values. However, after the 3 charge injections, the SUSTAIN study treated only the patients who exhibited a loss exceeding 5 VA letters or a CMT increase exceeding 100 µm.

In our study we have observed how in a group of patients ranibizumab therapy was not able to completely eliminate subretinal fluid in the OCT, so that in some cases the usual therapeutic approach was to assess the patient without treatments as long as the VA did not diminish or no hemorrhages or intraretinal cysts appeared to indicate the reactivation of the lesion. In contrast, others were treated for fear that their vision might diminish due to the fact of being single eyes in many cases. However, the analysis of our results seems to indicate that only the presence of hemorrhages associated to the appearance of subretinal fluid was accompanied by a

---

### Macula thickness: Macular cube 512x128

<table>
<thead>
<tr>
<th>ILM-RPE thickness (µm)</th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>352</td>
<td>333</td>
</tr>
<tr>
<td>342</td>
<td>311</td>
<td>361</td>
</tr>
<tr>
<td>398</td>
<td>352</td>
<td>352</td>
</tr>
</tbody>
</table>

---

### Distribution of normals

- 99%
- 95%
- 9%
- 1%

---

### Overlay: ILM RPE transparency: 50%

- Fovea: 289, 64

---

### Discussion

Treatment with ranibizumab has achieved an important change in the management of ARMD patients, enabling the majority to stabilize or improving their vision. However, 8–10% of patients suffer significant visual loss even with monthly treatment as demonstrated by the MARINA and ANCHOR clinical studies. In a recent retrospective study, Rosenfeld researched the main causes of vision loss in these patients, comparing several variables between patients with a gain of ≥15 letters and those who lost ≥15 letters, on the hypotheses that increases in exudation derived from neovascularization would explain the difference between both groups. However, the comparison between both groups demonstrated the absence of differences at baseline or at month 3, 6, 12 and 24. Likewise, no association was found between visual loss and hemorrhage, fibrosis or presence of PED. However, significant differences were observed in the extension of RPE anomalies and increases in the atrophy area, above those of the visual loss group. In his viewpoint, said changes could be due to the ranibizumab therapy.

The PrONTO study included the presence of subretinal fluid in OCT as a criterion for re-treatment, regardless of the VA values. However, after the 3 charge injections, the SUSTAIN study treated only the patients who exhibited a loss exceeding 5 VA letters or a CMT increase exceeding 100 µm.

In our study we have observed how in a group of patients ranibizumab therapy was not able to completely eliminate subretinal fluid in the OCT, so that in some cases the usual therapeutic approach was to assess the patient without treatments as long as the VA did not diminish or no hemorrhages or intraretinal cysts appeared to indicate the reactivation of the lesion. In contrast, others were treated for fear that their vision might diminish due to the fact of being single eyes in many cases. However, the analysis of our results seems to indicate that only the presence of hemorrhages associated to the appearance of subretinal fluid was accompanied by a
poorer visual result. In addition, it demonstrates that patients who remain in observation without treatment do not have a worse VA than those who continue to be treated throughout the entire year follow-up.

We consider that these patients are not “nonresponders” because VA improves with the initial treatment and then remains stable. Accordingly, they could be considered to be “partial responders”. In addition to the possible persistence of exudation derived from neovascularization, perhaps due to possible tachyphylaxis, other mechanisms may be involved in the persistence of subretinal fluid, such as retinal pigment epithelium dysfunction or vitreomacular adherence.

Even though the percentage of patients is just about 15%, it involves a significant workload in practices because they reach quiet indefinite controls at short intervals when they are retreated and also when they are not retreat, thus becoming chronic patients and developing hospital dependency. We believe it is important to recognize this type of behavior, probably called by quiescent or less aggressive lesions derived from the treatment or due to unknown factors. These particular characteristics mean that, in these patients the presence of intra-or subretinal fluid is not an absolute criterion for retreatment provided it is not accompanied by visual loss.

To conclude, we have verified that about 15% of our patients have exhibited subretinal fluid persistence or recurrence associated to other exudation expressions such as PED or intraretinal cysts. In these patients, the mean VA gain obtained after the 3 charges injections was maintained in the long-term even though nearly half of the patients abandoned treatment. The presence of hemorrhages these relapses associated poorer final VA.

This study involves some limitations such as its retrospective nature, the small number of eyes and the expiration with Snellen optotypes. However, we believe that it provides useful information for the management of these patients in daily clinic.
Fig. 2 – (Continued)

Fig. 3 – Evolution of the mean visual acuity (VA) in each assessment.
**Conflict of interests**

The authors have not declared any conflict of interests.

**References**


