Original article

Aflibercept in exudative age related macular degeneration refractory to ranibizumab

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ABSTRACT

Purpose: The aim of this study is to determine the effectiveness, safety and cost of aflibercept in the treatment of wet age-related macular degeneration (ARMD) refractory to ranibizumab.

Methods: Retrospective observational study was conducted on patients diagnosed with wet ARMD, and previously treated with ranibizumab. Efficacy variables assessed were changes in visual acuity (BCVA) and anatomical improvements in the most affected eye. Factors associated with improvement of BCVA with aflibercept were also studied. Adverse events related to the aflibercept administration were recorded. Cost analysis data were collected from the hospital perspective, and only taking the direct medical costs into account. Cost-effectiveness analysis was calculated using the aflibercept treatment cost, and effectiveness calculated as BCVA gained.

Results: A total of 50 eyes corresponding to 46 patients were included. The median follow-up period was 4.6 months (range: 1.0–6.0). Improvement in visual acuity after the first 2 doses and at the end of the follow-up period was observed in 32.0 and 28.0% of treated eyes, respectively. None of the variables studied was associated with an improvement in the BCVA after treatment. No significant differences were found in the average monthly cost between treatments.

Conclusions: Aflibercept is shown to be an effective treatment in a significant number of patients resistant to treatment with ranibizumab, presenting a cost similar to that generated during the final stages of treatment with ranibizumab.

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Resultados de aflibercept en degeneración macular asociada a la edad refractaria a ranibizumab

RESUMEN

Objetivo: El objetivo de este estudio es analizar la efectividad, seguridad y costes de aflibercept en el tratamiento de la degeneración macular relacionada con la edad (DMAE) refractaria al ranibizumab.

Métodos: Estudio observacional retrospectivo en el que se incluyó a pacientes diagnosticados de DMAE húmeda tratados previamente con ranibizumab. Las variables de eficacia evaluadas fueron cambios en la agudeza visual corregida (AV) y mejoras anatómicas en el ojo más afectado. Se estudiaron factores asociados a la mejora de la AV con aflibercept. Se recogieron los eventos adversos asociados con el tratamiento. El análisis de costes se realizó desde la perspectiva del hospital, teniendo en cuenta solo los costos médicos directos. El análisis coste-efectividad respecto a la terapia previa con ranibizumab se calculó mediante el coste del tratamiento y la efectividad del tratamiento calculada como AV ganada.

Resultados: Se incluyeron un total de 50 ojos correspondientes a 46 pacientes, con una mediana de seguimiento de 4,6 meses (rango: 1,0-6,0). El porcentaje de ojos tratados que mostraron una mejora en la AV después de las 2 primeras dosis y al final del período de seguimiento fue de 32,0 y 28,0%. Ninguna de las variables estudiadas se asoció con una mejoría en la AV corregida después del tratamiento. No se encontraron diferencias significativas en el coste medio mensual entre tratamientos.

Conclusiones: Aflibercept es un tratamiento efectivo en un número significativo de pacientes resistentes al tratamiento con ranibizumab, con un coste similar al generado durante las etapas finales de tratamiento con ranibizumab.

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Introduction

Age-related macular degeneration (AMD) is a chronic and progressive disease which mainly affects individuals over 50. It is characterized by degenerative changes in the macula leading to progressively diminishing visual acuity (VA).\(^{1}\) AMD accounts for 1 out of every 10 cases of blindness occurring in the world. The main risk factor for AMD is age and therefore, considering the progressive aging of the population, its prevalence will foreseeably increase in the next few years.\(^{2}\)

AMD has a significant impact in the quality of life of patients because the progressive loss of vision reduces their autonomy to carry out daily activities. In addition, AMD has high economic impact due to high direct costs (derived from treatments and dedicated health resources) as well as indirect costs (derived from the loss of productivity of individuals, increased dependency, depressive states and impaired quality of life).\(^{3}\)

The treatments available at this time are able to delay or stabilize the progression of the disease, although there are no healing treatments. Ranibizumab, a recombinant monoclonal antibody which is active against the vascular endothelial growth factor (VEGF-A), has brought about a significant advance in the management of this disease and at this date is considered as treatment of choice.\(^{4}\)

However, despite the efficiency demonstrated by ranibizumab, a significant proportion of patients who required treatment with injections for long periods of time develop a sort of resistance against this drug, evidenced in progressive loss of efficacy. The guidelines of the National Institute for Health and Clinical Excellence (NICE) for treating wet AMD recommend maintaining the treatment only in patients exhibiting adequate response.\(^{4}\)

Aflibercept is a fusion protein which, in contrast with bevacizumab and ranibizumab, acts as a receptor of the vascular endothelial growth factor (VEGF-A and VEGF-B) and the placenta growth factor (PlGF) which accounts for vasculogenesis and angiogenesis.

The results of phase III VIEW1 and VIEW2 trials demonstrated that monthly or bi-monthly administrations of aflibercept are not inferior to monthly treatments with ranibizumab, exhibiting a similar safety profile\(^{1}\) in both drugs. Other studies have demonstrated that aflibercept is an efficient alternative in patients with persistent lesions despite multiple ranibizumab injections.\(^{5-9}\)

The objective of this study is to analyze the efficacy, safety and cost of aflibercept in the treatment of wet AMD resistant to ranibizumab.

Subjects, materials and methods

A retrospective and observational study was designed which included patients diagnosed with wet AMD previously treated with ranibizumab who were administered aflibercept between December 2012 and November 2013. Aflibercept was administered under the mode of foreign drug, obtaining the...
informed consent of all patients prior to administration. Intravitreal administration was carried out according to the sterility protocol of the hospital, including previous disinfection with iodine povidone and administration in a sanitized room.

Demographic data of each patient were collected as well as data related to the treatments with aflibercept and ranibizumab during the latter 6 months of treatment before the switch to aflibercept. Said data included diagnostic date, treatment initiation date, number of visits, number of injections, duration treatment and other drugs received for treating AMD (intravitreal dexamethasone and triamcinolone).

Assessed efficacy variables included changes in VA (obtained by means of the Snellen scale) and anatomic changes in the most impaired eye. Anatomical improvements were measured through the persistence of sub- and intraretinal fluid (SRF, IRF) and through central macular thickness (CMT) variations, as well as variations in the height of the retina pigment epithelium detachment (PED). The anatomical evolution of patients was analyzed with spectral domain optic coherence tomography equipment (Heidelberg Engineering, Heidelberg, Germany), with an image quality requirement of at least 7/10.

After treatment with aflibercept, factors associated to VA improvement were analyzed, including age, time elapsed since diagnostic, baseline VA, presence of IRF and SRF, PED height and CMT at aflibercept treatment baseline and number of previous injections with ranibizumab. In addition, VA improvements between the groups of patients with over and under 6 months of previous treatments with ranibizumab. The safety of aflibercept was assessed collecting administration-related adverse events.

Cost analysis was made from the hospital perspective, taking into account only direct medical costs, including the cost of ranibizumab and aflibercept, the cost of concomitant medications utilized for managing AMD as well as the cost of the medical visits and tests performed during patient follow-up. Said analysis also included costs associated to adverse effects of the treatment as well as the cost derived from the visits to emergency services due to causes related to the disease or the treatment thereof (Table 1).

The costs associated to aflibercept treatment was compared with those associated to ranibizumab treatment during the last 6 months before switching treatments. The cost-effectiveness analysis was carried out considering the cost of treatment with ranibizumab and aflibercept and the efficacy of each, calculated as VA improvement during the follow-up period.

The study was approved by the Ethical Committee of the hospital.

## Results

The period of the study included 50 eyes of 46 patients. Patient characteristics are detailed in Table 2.

The average time elapsed between consecutive administrations of aflibercept was 51.0 days (range: 41.0–182). No statistically significant differences were found regarding the time between injections during the 6 months of previous treatment with ranibizumab (56.2 days [23.8–182]) (p = 0.380; t for Student test).

### Efficacy

The percentage of treated eyes that exhibited VA improvement (regarded as increases of 0.1 or greater) after the first

### Table 1 – Direct medical costs considered by the study.

<table>
<thead>
<tr>
<th>Cost of treatments (PVL)</th>
<th>Cost (€)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept vial</td>
<td>742.0</td>
<td>10</td>
</tr>
<tr>
<td>Ranibizumab vial</td>
<td>742.0</td>
<td>10</td>
</tr>
<tr>
<td>Dexamethasone ITV</td>
<td>0.60</td>
<td>10</td>
</tr>
<tr>
<td>Triamcinolone ITV</td>
<td>1.53</td>
<td>10</td>
</tr>
<tr>
<td>Ozurdex® ITV</td>
<td>950.0</td>
<td>10</td>
</tr>
<tr>
<td>Cost of visits to ophthalmology office</td>
<td>112.0</td>
<td>11</td>
</tr>
</tbody>
</table>

ITV: intravitreal; LSP: laboratory sale price.

### Table 2 – Characteristics of patients treated with aflibercept (n = 46).

| Mean age (years) (SD)    | 76.1 (7.9) |
| Sex (%)                  |            |
| Male                     | 21 (45.6)  |
| Female                   | 25 (54.4)  |
| Mean age (years) from diagnostic (SD) | 2.49 (1.47) |
| Number of previous ranibizumab administrations (%) |        |
| ≤5                       | 11 (23.9)  |
| 6–10                     | 12 (26.1)  |
| 10–15                    | 8 (17.3)   |
| 15–20                    | 15 (32.7)  |
| Visual acuity at treatment baseline (n = 50) |          |
| Period with ranibizumab |            |
| ≥0.5                     | 16 (32.0)  |
| 0.5–0.1                  | 22 (52.0)  |
| ≤0.1                     | 8 (16.0)   |
| Period with aflibercept  |            |
| ≥0.5                     | 6 (12.0)   |
| 0.5–0.1                  | 36 (72.0)  |
| ≤0.1                     | 8 (16.0)   |
| Average baseline CMT (SD) | 379.7 (150.5) |
| Average PED height (SD)  | 204.2 (145.6) |
| % Eyes with intraretinal fluid | 29 (63.0) |
| % Eyes with subretinal fluid | 41 (89.0) |
| Follow-up time (median) (range) | 4.6 (1.0–6.0) |
| Average number of aflibercept doses (SD) | 2.26 (1.19) |

CMT, central macular thickness; PED, pigment epithelium detachment.
2 doses and at the end of the follow-up period was of 32.0 and 28.0%, respectively. Only in 2 patients VA improvement was evidenced after the third dose of aflibercept. No statistically significant differences were found between the eyes that received ranibizumab during a period above or below 6 months (25.6% vs 25.0%; p = 0.384, Chi square). None of the other variables of the study was associated to VA improvements (Pearson: previous number of injections with ranibizumab: p = 0.405; age: p = 0.730; time since diagnostic: p = 0.748; PED height: p = 0.847; CMT: p = 0.734; initial VA: p = 0.777; IRF: p = 0.108; SRF: p = 0.203).

On the other hand, no correlation was found between VA and anatomical improvements in the treated eyes (Pearson: p = 0.638 for PED height and p = 0.495 for CMT).

In what concerns anatomical improvements, 54.4% of treated eyes exhibited lower PED heights, with a mean difference between baseline and end of treatment of −8 μm (range: −222 to 477 μm). In 38.0% of eyes, CMT reduction was observed, with a mean difference of −38.7 μm (range: −375 to 164 μm). Overall, 20.0% of patients exhibited a reduction exceeding 100 μm.

21.8% and 18.2% of patients with IRF and SRF at the beginning of the treatment with aflibercept exhibited the disappearance of these at the end of the follow-up period.

Safety

As regards the safety profile, 3 adverse events were identified in 3 patients: one aseptic endophthalmitis episode, one lens opacity case and one hypertensive crisis which required referral to the emergency section after administering the first dose of aflibercept.

In the course of the 6 months of follow-up with ranibizumab, 3 cases of hemorrhage secondary to drug administration were recorded.

Cost-effectiveness

The use of aflibercept was associated to a mean monthly cost per treated eye that exceeded the mean cost of the 6 previous months of treatment with ranibizumab. However, no statistically significant differences were found between both treatments in this regard (684.4 [SD: 302.5] vs 616.0€ [SD: 271.3]; p = 0.523: t for Student test). The cost per patient with VA improvement after switching to aflibercept was of 734.2€.

Discussion

In accordance with the results of this study, in patients with previous ranibizumab treatment aflibercept achieved anatomical improvements in the majority of cases, including a reduction in the PED height in over half of treated eyes. However, the improvement obtained in VA terms is more limited: approximately one-third of treated patients exhibited improved VA at the end of the study period.

The main limitations of this study is its retrospective design, the small number of patients and the short follow-up period, which has prevented an assessment of effectiveness and cost related to aflibercept in the medium and long-term.

On the other hand, measuring VA with the Snellen scale as the main criterion for assessing efficacy limits the interpretation of results.

Several studies have demonstrated the efficacy of aflibercept in patients resistant to treatment with ranibizumab or bevacizumab. In a prospective study, after 24 weeks of treatment Chang et al. observed VA increases exceeding 10 letters (equivalent to VA gains of 0.1) in 26% of treated patients. In addition said author founded a CMT reduction above 100 μ in 33% of patients. The results obtained in the present study are similar to said referenced study and other published series. The different action mechanism of aflibercept seems to account for the response to treatment of patients who received multiple doses of ranibizumab. Accordingly, aflibercept is a highly valuable alternative for these patients.

As in other published studies, anatomical improvements have not been correlated with VA increases in treated patients. Accordingly, the loss of VA associated to AMD seems to be a prolonged and irreversible process. In a prospective study, Oishi et al. identified the presence of limiting external membrane and polypoid lesions as factors associated to improved VA in patients treated with aflibercept. However, additional studies are required to assess the factors associated to VA improvements experienced by some patients treated with anti-VEGF drugs.

The present study was unable to identify groups of patients who could derive greater benefit from treatment with aflibercept. Patients with less pre-treatment time and lower number of injections did not obtain better responses to aflibercept. Accordingly, switching patients exhibiting good response to the first line of treatment does not appear to be justified. The study published by Chan et al. reported that patients who did not respond to bevacizumab or ranibizumab treatment exhibited greater improvements with the switch to aflibercept when compared to the group which responded positively to the first line of treatment. In the present study, aflibercept was applied only to patients who proved refractory to the first line of treatment, and this prevents the confirmation of said hypothesis.

Only 2 patients exhibited VA improvements after not exhibiting any response to the first 2 injections of aflibercept. Accordingly, treatment with aflibercept should be considered for interruption in patients who do not respond to the first doses.

No differences were found between the time intervals between the administration of consecutive doses between ranibizumab and aflibercept. This has prevented assessing the efficacy of aflibercept in prolonged administration intervals, with the corresponding reduction of associated costs. One of the advantages attributed to aflibercept is its long mean life and duration of its action compared to ranibizumab and bevacizumab, which has given rise to the possibility of increasing the interval between doses. This could increase the quality of life of patients as well as reduce side effects related to the administration of the drug and a significant reduction in treatment costs. However, several authors question this theory. The study by Chang et al. on pretreated patients, treatment with aflibercept increasing the dosage interval from 4 to 8 weeks, produced a significant increase in CMT, which means that the
effect of aflibercept may not be as lasting as expected for this group of patients.

As regards adverse effects, no significant differences were found between both treatments, although the small number of study patients does not enable conclusive results. The development of a hypertensive crisis after the administration of a dose of aflibercept requiring the involvement of the emergency ward was the only identified severe adverse effect. Said effect was shown in the pivotal studies and its possible appearance should taken into account. On the other hand, a recent review of intraocular inflammation secondary to aflibercept concluded that it was a frequent but self-limited adverse effect, with positive response to topical treatment. This is in agreement with the endophthalmitis case encountered in the present study, which exhibited positive evolution after topical treatment with corticoids without the need to interrupt treatment. Finally, the patient who developed ocular opacity suspended treatment after the appearance of this symptom even though it was not attributed to the drug being studied.

Treatment with aflibercept is associated to high costs. It has been published that switching treatment to aflibercept involves a relevant increase in the treatment cost, with limited benefit for a high number of patients. However, the results obtained in the present study demonstrate that the costs associated to aflibercept and ranibizumab treatments were similar, being the cost for the patient with VA improvement of 734.2 €. Accordingly, it is very useful to identify the patients who could most benefit from the treatment in order to increase the efficacy thereof. On the other hand, it would be necessary to relate variations in VA improvements with changes in the daily activities carried out by patients in order to assess the actual impact of the changed treatment in quality of life terms.

Aflibercept is an efficient treatment for a significant number of patients who are resistant to treatment with ranibizumab, with a cost similar to that of the latter stages of ranibizumab treatment. Even so, it is necessary to carry out studies with higher numbers of patients to identify those who would obtain greater benefit from this drug and to establish termination criteria in order to amortize its high cost.

Conflict of interest

No conflict of interest was declared by the authors.

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