ORIGINAL ARTICLE

Bevacizumab versus ranibizumab in the treatment of exudative age-related macular degeneration: A retrospective study of 58 patients

Bevacizumab versus ranibizumab dans la prise en charge de la dégénérescence maculaire liée à l’âge exsudative : étude rétrospective chez 58 patients

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Received 21 November 2011; accepted 27 January 2012
Available online 4 October 2012

Summary
Aim. — To compare the efficacy and safety of bevacizumab versus ranibizumab in the treatment of patients with neovascular age-related macular degeneration (AMD).

Patients and methods. — Retrospective case-controlled series of 30 patients treated with intravitreal bevacizumab and 28 patients treated with intravitreal ranibizumab for exudative AMD. Main outcomes measured included best-corrected visual acuity (BCVA), central macular thickness (CMT) and foveal thickness, quantity of subretinal fluid, neovessel size and total number of injections over the first year treatment period. A secondary outcome was the report of any adverse events in both groups.

Results. — BCVA stabilized and increased from LogMAR 0.70 to 0.47 in the bevacizumab group and from 0.55 to 0.54 in the ranibizumab group (P > 0.05). CMT decreased in the bevacizumab group from 369 to 284 µm and in the ranibizumab group from 340 to 271 µm (P > 0.05). The number of injection was significantly lower (4.8) in the bevacizumab group than in the ranibizumab group (5.8) (P < 0.05). No serious ocular adverse events were noted in both groups.

Conclusion. — This retrospective study failed to show a difference in visual and anatomic outcomes between bevacizumab and ranibizumab. The number of re-treatment was lower in the bevacizumab group (P = 0.03).

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http://dx.doi.org/10.1016/j.jfo.2012.01.015
Introduction

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in patients over the age of 50 in occidental countries [1]. One of the key factors implicated in the pathogenesis of choroidal neovascularization is the vascular endothelial growth factor (VEGF). Antiangiogenic drugs that inhibit active forms of VEGF have been shown to be effective in the treatment of wet AMD. Three agents (pegaptanib sodium [Macugen], ranibizumab [Lucentis], and bevacizumab [Avastin]) inhibit some or all VEGF-A isoforms and are currently in clinical use. Pegaptanib sodium was the first effective and safe treatment for wet AMD. It received approval by the US Food and Drug Administration (FDA) in 2004. In 2006, ranibizumab was approved by the FDA for the treatment of choroidal neovascularization in wet AMD. Ranibizumab is a humanized antibody Fab fragment which can inhibit the action of VEGF-A in order to prevent blood vessel growth and leakage. The Minimally Classic/Occult Trial of the anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR), prospective and randomized studies, established the efficacy and safety of ranibizumab [2,3]. In contrast, bevacizumab is a full-length monoclonal antibody that blocks the action of all isoforms of VEGF. It was initially developed as an intravenous drug in the treatment of metastatic colorectal cancer. Philip Rosenfeld pioneered the off-label use of bevacizumab in the eye. After Rosenfeld, the use of intravitreal bevacizumab for treatment of AMD spread all over the world. A lot of uncontrolled case series report the efficacy and safety in the use of intravitreal bevacizumab for wet AMD [4–10]. It is now probably the most widely used agent to treat neovascular AMD in the USA, because of its similarity with ranibizumab and its low cost. Indeed, Brechner et al. suggest that most US patients receive bevacizumab rather than ranibizumab for the treatment of neovascular AMD [11]. However, bevacizumab and ranibizumab are not the same molecule. The CATT study [12] is a multicenter, single-mind, non-inferiority trial that enrolled 1208 patients with neovascular AMD. At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. We herein report a retrospective study that observes the efficacy and safety of bevacizumab versus ranibizumab in the treatment of 58 patients with neovascular AMD.

Patients and methods

After obtaining the Institutional Review Board’s approval, a retrospective chart review was performed of 58 patients who were treated with intravitreal anti-VEGF for neovascular AMD in two ophthalmological university hospitals in Lyon, France, from March 1, 2007 to October 31, 2010. Thirty patients, in the bevacizumab group, were treated in the Croix-Rousse University Hospital and 28 patients, in the ranibizumab group, in the Edouard-Herriot University Hospital. All patients were naive to anterior anti-VEGF treatment and received three initial intravitreal injections (1.25 mg bevacizumab or 0.5 mg ranibizumab in 0.05 mL) every month as a loading dose. There were no limitations based on visual acuity for the inclusion in this study. Intravitreal injections were performed according to French Governmental Health Authority recommendations’ under sterile condition. Each patient had received clear and loyal information about the anti-VEGF treatment and the existence or not of a label for the molecule. A consent signed by the patient was got back in a systematic way before every intravitreal injection.

We reported results of the initial visits (VI), 1 month (M1), 4 months (M4) and 13 months (M13) after the first
Bevacizumab injection. At the preinjection visit and the follow-up visits, best-corrected visual acuity (BCVA), aplanation tonometry, slit-lamp evaluation and dilated biomicroscopic fundus examination were performed in addition to ancillary tests. BCVA was measured using the decimal chart, and a converted logarithm of the minimum angle of resolution (LogMAR) was used for statistical analysis. Optical coherence tomography (OCT) was performed for each visit (Stratus OCT-3 and Cirrus SD-OCT, Zeiss). Some patients included in 2007 received Stratus OCT-3 evaluation. However, Cirrus OCT measures 57 μm greater than Stratus OCT, which is likely attributable to Cirrus OCT detection of the outer band of the retinal pigment epithelium versus Stratus OCT detection of the inner/outer segment photoreceptor junction. To this end, we converted the measures Stratus OCT-3 by adding 57 microns [13,14]. Central macular thickness (CMT) which is a mean value of the 1 mm central region, foveal thickness (FT), subretinal fluid (SRF) and size of the neovessel, measured in micrometers were assessed by OCT. Fluorescein angiography (FA) (Heidelberg Engineering, Germany) was necessarily performed for initial visit to show the subfoveal subretinal leakage of active choroidal neovascularization (CNV). All patients were monthly followed and re-treatment was performed if visual acuity deteriorated more than 0.1 LogMAR and presence of intraretinal or subretinal fluid in OCT or persisting leakage on FA or intraretinal or subretinal bleeding. Treatment and re-treatment protocols were the same for both groups of patients. At each visit, patients were examined for systemic and ocular adverse event. Statistical analysis was performed using Student t-test. Fisher’s exact test was used for comparison of re-treatment rates.

Results

Thirty eyes were included in the bevacizumab group and 28 eyes in the ranibizumab group. The number of intravitreal injections in both groups was 308. The follow-up was 12 months for all patients in both groups. Demographic and preinjection characteristics of the study patients are summarized in Table 1. Comparison of preinjection parameters showed no statistically significant difference between the two groups (P > 0.05).

Visual acuity

In the bevacizumab group, BCVA mean increased from 0.70 LogMAR before the first treatment to 0.48 LogMAR after the last loading dose. This gain in visual acuity was maintained over the 9 months following the last loading-dose injection, with a BCVA mean at 0.47 LogMAR at last follow-up termed M13 in the analysis. In the ranibizumab group, the mean of BCVA increased from 0.55 LogMAR equivalent before the first treatment to 0.51 LogMAR after the last loading dose and to 0.54 LogMAR at M13. The proportion of patients who had less than an increase of 0.3 LogMAR, that is to say a loss of three lines of visual acuity, over the period of follow-up was 93% and 89% in the bevacizumab and ranibizumab groups, respectively. In both groups, mean LogMAR BCVA values improved between the first injection and M13. However, comparing the course of visual acuity, there was no statistically significant difference between both groups (Table 2).

OCT measurements

Mean central macular thickness (CMT) measured by OCT decreased in the bevacizumab group from 369 μm (±77) before treatment to 284 μm (±87) at last follow-up. In the ranibizumab group, CMT also decreased from 340 μm (±78) before initial treatment to 271 μm (±59) at M13. Between both groups, there was no statistically significant difference for the CMT (P > 0.05 all time points). It was the same for all the criteria measured by OCT (FT, NV size, SRF) (Table 2).

Number of intravitreal injections

The number of injection was statistically significantly lower (P = 0.03) in the bevacizumab group (average of 4.8 per eye) than in the ranibizumab group (average of 5.8 per eye).

Adverse events

In the bevacizumab group, one patient (3%) had a non-infectious epithelial keratitis. No patient displayed signs of intraocular inflammation or endophthalmitis. No other ocular or systemic adverse events were reported.

Discussion

Intravitreal inhibition of VEGF has evolved to be the “first-line” therapy in neovascular AMD. Ophthalmologists can use three anti-VEGF agents to treat this pathology: two
Table 2  Mean LogMAR BCVA, CMT, FT, NV size, SRF at four follow-up visits in both treatments groups. No statistically significant difference could be shown between both groups at any time points.

<table>
<thead>
<tr>
<th></th>
<th>Initial (mean ±SD)</th>
<th>1 month (mean ±SD)</th>
<th>4 months (mean ±SD)</th>
<th>13 months (mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCVA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucentis</td>
<td>0.55 (0.33)</td>
<td>0.45 (0.32)</td>
<td>0.51 (0.33)</td>
<td>0.54 (0.37)</td>
</tr>
<tr>
<td>Avastin</td>
<td>0.70 (0.46)</td>
<td>0.63 (0.51)</td>
<td>0.48 (0.37)</td>
<td>0.47 (0.37)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.11</td>
<td>0.09</td>
<td>0.71</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>CMT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucentis</td>
<td>340 (78)</td>
<td>286 (46)</td>
<td>299 (82)</td>
<td>271 (59)</td>
</tr>
<tr>
<td>Avastin</td>
<td>369 (77)</td>
<td>307 (76)</td>
<td>285 (78)</td>
<td>284 (87)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.16</td>
<td>0.2</td>
<td>0.48</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>FT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucentis</td>
<td>264 (87)</td>
<td>215 (60)</td>
<td>226 (74)</td>
<td>203 (62)</td>
</tr>
<tr>
<td>Avastin</td>
<td>258 (81)</td>
<td>203 (59)</td>
<td>198 (53)</td>
<td>194 (67)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.8</td>
<td>0.45</td>
<td>0.1</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>NV size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucentis</td>
<td>139 (71)</td>
<td>117 (32)</td>
<td>118 (36)</td>
<td>120 (36)</td>
</tr>
<tr>
<td>Avastin</td>
<td>132 (47)</td>
<td>115 (59)</td>
<td>105 (55)</td>
<td>105 (60)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.67</td>
<td>0.86</td>
<td>0.29</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>SRF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucentis</td>
<td>83 (54)</td>
<td>30 (46)</td>
<td>33 (46)</td>
<td>48 (48)</td>
</tr>
<tr>
<td>Avastin</td>
<td>112.2 (78.01)</td>
<td>47.7 (61.80)</td>
<td>35.6 (45.56)</td>
<td>35.0 (47.11)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.11</td>
<td>0.22</td>
<td>0.82</td>
<td>0.29</td>
</tr>
</tbody>
</table>

BCVA: best-corrected visual acuity; CMT: central macular thickness; FT: foveal thickness; SRF: subretinal fluid.

antibodies (ranibizumab and bevacizumab) and an aptamer (pegaptanib sodium). The use of bevacizumab is still an off-label therapy. Nevertheless, bevacizumab is performed in many countries because of its lower price. But we cannot only choose a therapeutic drug for its lower cost. Reviewing the literature, retrospective and uncontrolled case series show a similar efficacy and safety of both treatments. The CATT study shows that both molecules have equivalents effects on visual acuity when administered according to the same schedule. We are waiting for other results with GEFAL in France.

Here, we retrospectively compared intravitreal bevacizumab and ranibizumab in patients with neovascular AMD. All the 58 patients included were naive to treatment and received in the first place, three intravitreal injections every month as a loading dose and in the second place a clinical and OCT guided re-treatment. The results of our study show no significant difference between bevacizumab and ranibizumab in terms of safety and efficacy for both treatments. The CATT study showed a significantly decrease in the mean CFT from 340 μm at baseline to a mean of 213 μm at month 3 after treatment with bevacizumab. Moreover, the number of bevacizumab injections was statistically lower during the following period of 12 months with only an average of 4.8 injections per eye (P=0.03). Landa et al. found similarly results in their study with an average of 4.7 bevacizumab injections per eye. In that case, if patients are less injected, the incidence of adverse effects and the cost of the treatment will be lower for the bevacizumab [18]. Our study limitations are a retrospective design, a low number of patients, treatment of patients in two different centers and the use of two different OCT (Stratus and Cirrus).

In the literature, intravitreal anti-VEGF are used to be well tolerated as in our study [19–21]. Nevertheless, taking account of the small sample of patients, we can conclude, in our study, about the safety of these two drugs. We only found one case of ocular effect in the bevacizumab group.
as an epithelial keratitis probably due to the asepsis during the injection. Endophthalmitis was not observed in any patient during all the following period. The incidence of endophthalmitis with ranibizumab injections reported in MARINA, ANCHOR, PIER [22] and CATT studies was less than 0.1%. Spaide et al. reported no case of endophthalmitis in any of 266 patients. Fung et al. in an electronic retrospective study reported an incidence of endophthalmitis less than 0.01% after 7113 injections [23]. According to their internet-based survey, the most common adverse event related to bevacizumab injection included corneal abrasion (0.15%) and ocular inflammation (0.14%). Also, we do not note any systemic side effects during the 12 months. Curtis et al. recently reported that the use of bevacizumab or ranibizumab was not associated with increased risks of mortality, myocardial infarction, bleeding or stroke in contrast to photodynamic therapy and pegaptanib sodium [24]. Moreover, they showed in a secondary analysis of sub-groups a better safety in the ranibizumab group. Gower et al. [25], at ARVO, showed more hemorrhagic diseases with bevacizumab. The absence of potential adverse events in our study is explained by a relatively small sample size (58 eyes). In reality, to show statistically significant difference from 0.1 to 0.2% in a study, more than 50,000 patients have to be included. Incidences of myocardial infarction and stroke are high in the population like 2.2% and 4% respectively [26]. As a result, in AMD study which are older populations studies it is not a surprise to find some cases of these cardiovascular pathologies.

Conclusion

While the main limitations of our study are its retrospective nature and relatively small sample size, the results seem to be closely related with the literature and the prospective studies as MARINA, ANCHOR and CATT. Bevacizumab seems to be a safety and above all an effective treatment in neovascular age-related macular degeneration. The CATT study showed no equivalent effects on visual acuity throughout the first year of follow-up. More prospective and randomized trials are still necessary to define more precisely the role of bevacizumab in the treatment of wet AMD. In France, the multicenter, randomized study, called GEFAL, will prospectively compare bevacizumab and ranibizumab and should provide an answer about their equivalence on efficacy and safety. Our retrospective study adds to the literature that supports the off-label use of bevacizumab in the treatment of wet AMD.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


