Case Report

Therapeutic Improvement in the Contralateral Eye after Ranibizumab Intravitreal Treatment in a Patient Affected by Bilateral Subfoveal Choroidal Neovascularization

Nicola Pescosolido, Stefano Fazio and Dario Rusciano

1Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, Faculty of Medicine and Dentistry, Sapienza University of Rome, Italy.
2Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Italy.
3Scientific Department, Sooft Italia SpA, Rome, Italy.

Abstract

Aim of the present work has been to evaluate the effects in both the treated and the contralateral eye of mono-lateral intravitreal treatment with Ranibizumab (LUCENTIS®) in a 46-year-old woman affected by bilateral myopic choroidal neovascularization.

A 46-year-old woman presented a best-corrected visual acuity of 8/10 in the right eye, and 1/20 in the left eye. Fundus examination revealed a bilateral myopic choroiditis and a foveal neovascularization in the left eye that was confirmed by OCT analysis. The flicker ERG response was also altered in both eyes.

The subretinal neovascularization in the left eye was treated by an intravitreal injection of ranibizumab. After 8 days the OCT and the flicker ERG showed no improvement, and a second injection of ranibizumab was given one month after the first. Twenty days later OCT and flicker ERG showed a significant improvement both in the left, treated eye, but also in the right, untreated eye.

In conclusion, ranibizumab apparently inhibited VEGF induction of new vessel formation and the following edema due to the leakiness of these new vessels and the rupture of the blood-retinal barrier in the treated eye. Evidently, it also diffused via the hematic and/or neuronal route to the contralateral eye where it also exerted a detectable improvement of the local conditions.

ABBREVIATIONS


INTRODUCTION

Myopia and, above all, elevated myopia (>6 D) presents a high risk of ocular morbidity. It is an inherited condition characterized by a degenerative chorioretinal atrophy linked to an excessive lengthening of the eye ball [1]. Among the various alterations, myopia is associated with a greater risk of problems such as macular holes, lacquer cracks, and choroidal neovascularization (CNV).

It is known that vascular endothelial growth factors (VEGF) play a fundamental role in the formation of abnormal blood vessels and the increase of vascular permeability in many pathological conditions [2]. The inhibition of VEGFs, blocking angiogenesis and decreasing vascular permeability, could be an efficacious treatment for a variety of ocular diseases characterized by choroidal neovascularization. Bevacizumab (Avastin®) is a humanized monoclonal antibody that binds to VEGF-A. Ranibizumab (Lucentis®) is a fragment of a monoclonal antibody (Fab) derived from the similar murine antibody bevacizumab (Avastin®). Being bevacizumab a whole antibody, and ranibizumab an antibody fragment with a shorter half-life, it has been reported that the latter remains in circulation for a shorter time [3].

The use of bevacizumab has been well reported in the literature for the treatment of CNV both in senile macular...
degeneration [4] and in myopic pathologies [5]. However, the systemic administration of bevacizumab has a low but significative risk of thromboembolic events, such as ictus or infarct of the myocardium in cancer patients [6]. Ranibizumab is currently approved by the FDA for the treatment of neovascular age-related macular degeneration (ARMD).

We describe here the case of a 46-year-old patient with a choroidal neovascular membrane (CNVM) resulting from a CNV due to a myopic pathology, evaluating the effects of the intravitreal treatment with Ranibizumab (LUCENTIS®). A clinical evaluation of the subject’s visual acuity was carried out using optical coherence tomography (OCT) and flicker ERG, measured with the RETIMAX Advanced Plus® (CSO strumenti oftalmologici – Florence, Italy) calibrated according to the light adapted 3.0 flicker ERG protocol of the ISCEV standard. Amplitude and latency (peak time - PT) of the b-wave were evaluated and considered with respect to the values measured in normal and retinopathic individuals [7] as illustrated in (Table 1). The effects of the intravitreal treatment in the eye affected by CNV and eventual modifications of the contra lateral eye were observed.

CASE PRESENTATION

A 46-year-old woman with elevated myopia (-12.00 Sf in both eyes) presented with a best-corrected visual acuity of 8/10 in the right eye and 1/20 in the left eye.

The examination of the ocular fundus showed a myopic chorioretinopathy characterized by a tilted disc, posterior staphyloma and a peripheral area of paving stone degeneration in both eyes.

OCT revealed the presence of a neovascular choroidal membrane (CNVM), the result of choroidal neovascularization
Table 1: Latency (ms) of b-wave flicker ERG in normal and retinopathic patients*.

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Normal</th>
<th>Retinopathic</th>
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<tbody>
<tr>
<td>Latency (ms)</td>
<td>29.83</td>
<td>34.04</td>
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<tr>
<td></td>
<td>34.04</td>
<td>42.47</td>
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* see ref. 7

After 20 days the patient agreed to intravitreal treatment with ranibizumab for the left eye. After 8 days visual acuity was unchanged, while there was an improvement of the objective picture at OCT (Figure 2A) and no improvement of the PT of the b-wave of the flicker ERG (Figure 2B).

After 1 month from the first injection a second was given and 20 days later the visual acuity, OCT and the PT of the b-wave of the flicker ERG were repeated. At the visual acuity examination the patient presented a visual acuity of 1/10 with best correction. OCT showed a further improvement of the clinical picture, characterized by an almost complete regression of the CNVM (Figure 3A). The PT of the b-wave of the flicker ERG revealed a reduction in latency (Figure 3B). Therefore, the PT of the b-wave...
of the left eye, at the initial examination, was 38.26 ms, and in the right eye it was 34.37 ms, both values in the pathological range according to our previous observations (Table 1). Thus, following the first IV injection with ranibizumab, there were no notable modifications, while following the second IV injection the PT of the b-wave of the flicker ERG reached, respectively for RE and LE, a value of 32.10 ms and 31.45 ms. These values now fall within the range of normal values (Table 1) that would objectively confirm an improvement of the photoreceptors trophism in both eyes.

**DISCUSSION**

VEGF-A is the principal vascular endothelial cell growth factor of arteries, veins and lymphatic vessels and is necessary as a vascular endothelial cell survival factor [8]. According to Nguyen et al. [9]
VEGF-A plays an important role in the development of myopic CNV. Examples of VEGF inhibitors include pegaptanib (Macugen®), ranibizumab (Lucentis®) and bevacizumab (Avastin®). The intravitreal use of bevacizumab in myopic CNV, a cheaper alternative and closely linked to ranibizumab, has been reported in retrospective [10,11] and prospective studies [12,13] that have shown the remission of the CNVM and an improvement of visual acuity. Ranibizumab was developed following the discovery that this molecule can penetrate the layers of the retina and reach the choroid after intravitreal injection. Various trials (MARINA, ANCHOR and HORIZON) have been carried out on the safety and efficacy of these drugs at the ocular level [14]. These studies demonstrate the improvement of visual acuity and the usefulness of OCT in guiding the decisions for re-treatment and timing.

The evaluation of the b-wave PT of the flicker ERG shows the effect of the intravitreal injection with ranibizumab in the treated eye and also in the contralateral untreated eye (Table 2). The effect of the improvement on the b-wave PT of the flicker ERG needs to be compared to the inhibition of VEGF side effects induced by ranibizumab. We believe that ranibizumab would inhibit the rupture of the blood-retinal barrier with the consequent freeing of cytokines that are toxic for photoreceptors. This mechanism has already been reported in the literature following the administration of brimonidine in rats with induced streptozotocin diabetes [15]. Kusari et al. demonstrated the reduction of VEGF expression induced by brimonidine and its capacity to attenuate the increase in vascular permeability and the rupture of the blood-retinal barrier in diabetic rats.

Moreover, to explain the effect in the contralateral untreated eye we hypothesize a neuronal or systemic diffusion of ranibizumab that is able to induce the same effects in the contralateral eye as in the treated eye. The same mechanism could also be beneficial at the retina level; however, this is not detectable with the measurement of visual acuity and OCT but only with the b-wave of the flicker ERG. In the literature, the contralateral action of ranibizumab has already been described by Acharya et al. [16] after the evaluation with OCT. Therefore, this event should always be considered when there are numerous intravitreal injections and thus an accurate evaluation of the cardiovascular state of the subject must be taken into consideration.

The evaluation of the b-wave PT with flicker ERG is in our experience less subject to intrinsic variables, and therefore could objectively detect physiologic and functional changes occurring in the retina.

These data confirm the beneficial effect of ranibizumab without a risk for retinal cells, due to the decrease of a trophic factor such as VEGF. Thaler et al. [17] evaluating the toxicity of bevacizumab, ranibizumab and pegaptanib at the electronic microscope did not observe statistically significant differences in the number of retinal ganglion cells, and the structure and the morphology of RGC both in normal rats and in rats with progressive retinal damage. This study is in agreement with two previous papers studying bevacizumab [18,19]. The same conclusions were found in the study by Spitzer et al [20] in which the comparison of the same anti-VEGF molecules showed no cytotoxic effect on the ganglion retinal cells of rats and neither anti-proliferative effects of ranibizumab on human retinal pigment epithelium cells.

CONCLUSIONS

We have presented a case of a patient affected by myopic CNVM treated with intravitreal injections of ranibizumab. We have shown, by means of OCT, the net improvement of the CNVM following the first injection and the complete regression after the second injection both with OCT and the Peak Time of the b-wave of the flicker ERG. This finding, objectively confirmed by the latter examination, allowed us to not give the patient a third intravitreal injection as the resolution of the clinical picture with positive economic and clinical/toxic results was already clear. Thanks to the use of the flicker ERG we were able to evaluate the effect of the drug also on the contralateral eye, in agreement with other studies in the literature in which the bilateral action of the intravitreal injection of VEGF inhibitors was evaluated, both as regards ranibizumab [21,22] and bevacizumab [23-24]. This finding could be useful to obtain bilateral clinical benefit following a unilateral injection of the drug. It is clear that further studies are needed on the pharmacokinetics and the systemic bioavailability of the drug above all in patients who are more exposed to the systemic effects of VEGF inhibitors.

ACKNOWLEDGEMENTS

The authors wish to thank Dr Antony Bridgewood for critical proofreading of the manuscript.

REFERENCES


