Intravitreal anti-VEGF therapy for choroidal neovascularisation secondary to pathological myopia: 4-year outcome

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ABSTRACT

Ophthalmology, Castilla La Objective To report the visual outcome after 4-year follow-up in a series of highly myopic eyes with choroidal neovascularisation (CNV) treated with antivascular endothelial growth factor (anti-VEGF) drugs. Methods A retrospective, non-randomised, multicentre, consecutive, interventional case series study was performed. 92 highly myopic eyes with subfoveal CNV were treated with intravitreal injection (IVI) of anti-VEGF. The initial protocol (1 vs 3 injections) was dictated by surgeons' preferences and followed by an as-needed monthly regime. Best-corrected visual acuity (BCVA) was evaluated at baseline and then monthly. The primary aim was to analyse BCVA changes. The effect of age, spherical equivalent (SE) and treating drug were evaluated as secondary objectives.

Results The mean age of the patients was 57 years (SD 14, range 30–93). The mean number of letters read was 46.1 (SD 16.8, range 5-70) at baseline, 55.5 (SD 18.6, range 10-85) at 12 months, 50.1 (SD 20.1, range 5-82) at 24 months, 54.2 (SD 21.9, range 2-85) at 36 months and 53.1 (SD 22.5, range 1-83) at 48 months (p=0.000, initial vs 12, 24 and 36 months; p=0.01 initial vs 48 months; Student t test for paired data). The mean total number of IVI was 4.9 (SD 5.4, range 1-29). SE and treating drug had no influence on the final visual outcome and number of injections required.

Conclusions Intravitreal bevacizumab and ranibizumab are effective therapies and show similar clinical effects in highly myopic CNV. Visual acuity gain is maintained at 4-year follow-up.

INTRODUCTION

The standard care for myopic choroidal neovascularisation (CNV) is photodynamic therapy with verteporfin (PDT).¹ Antivascular endothelial growth factor (anti-VEGF) drugs such as ranibizumab² and bevacizumab3-6 have been used off-label to treat CNV secondary to high myopia with good results. Several studies have reported on the outcome of intravitreal bevacizumab (IVB) in the short term⁴ ⁶ at 1^{3 5} and 2 years follow-up,^{7 8} and intravitreal ranibizumab (IVR) at 2 years.^{9 10} More recently, Hefner and Peiretti reported on their results with IVR and IVB at 3 and 4 years, respectively.^{11 12} The initial therapeutic protocol has consisted of 3-monthly consecutive injections⁵ or one single injection.3 The results of three versus one loading dose have been published.¹³ The outcomes of PDT and IVB to treat myopic CNV have been compared,

suggesting that bevacizumab is more effective than PDT.14

The purpose of this study is to evaluate the visual acuity changes during a 4-year follow-up period in a large series of highly myopic eyes with CNV treated with anti-VEGF drugs.

MATERIALS AND METHODS

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A retrospective, non-randomised, multicentre, consecutive, interventional case series study was performed on 92 eyes from 92 highly myopic patients (spherical equivalent (SE) >-6.0 dioptres and/or axial length >26.0 mm) from five different centres in Spain and Portugal with more than 4 years follow-up. Patients with retinal drusen in the study or fellow eye or any evidence of age-related macular degeneration were excluded. All patients had presented with active subfoveal classic CNV and had been treated by intravitreal injections (IVI) of anti-VEGF drugs. The treating drug (IVR 0.5 mg or IVB 1.25 mg) and initial protocol (loading dose 3 vs 1 injection) were dictated by surgeon's preference. After the initial dose an as-needed (PRN) monthly regimen was used.

The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki, and data gathering was performed after obtaining written informed consent from each patient and approval from the local ethics committees.

A complete ocular examination including determination of best corrected visual acuity (BCVA) and macular examination by spectral domain optical coherence tomography (SD-OCT) was performed at the first visit and then monthly during follow-up. BCVA was determined at 4 m using standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Lighthouse, New York, USA) by certified optometrists. Fluorescein angiography (FA) was performed at baseline and whenever CNV activity was suspected. All patients completed the 4-year follow-up, attending at all visits. Patients previously treated by PDT were started on anti-VEGF therapy if they showed signs of CNV activity (decreased visual acuity associated with intraretinal or subretinal fluid and fluorescein leakage).

Patients were informed about the off-label condition of this therapy and women of childbearing age were also informed about the possible risks to the fetus; these patients agreed to use two forms of contraception (barrier and hormonal) throughout the following 3 months after injection. At each visit

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the patients were specifically asked about the appearance of systemic side effects (medication changes, high blood pressure, signs of cerebrovascular accidents, myocardial infarction or ischaemia) and ocular side effects (pain, floaters, reduced visual acuity).

The primary aim of the study was to analyse the changes in the number of letters read during the 4-year follow-up period after anti-VEGF therapy for subfoveal myopic CNV. The role of age ($<50 \text{ vs} \ge 50$ years of age), SE, anti-VEGF drug and previous PDT on the visual outcome were evaluated as secondary objectives.

Anti-VEGF re-injections were performed following the same criteria in all the centres during follow-up in those cases with signs of CNV activity: visual acuity loss ≥ 1 ETDRS line associated with increased central foveal thickness <30 microns and/ or macular haemorrhage and/or increased intraretinal or subretinal fluid. FA was performed in order to confirm the presence of fluorescein leakage in the macular area.

RESULTS

The mean age of the patients was 57 years (SD 14 years, range 30-93); 27 (29%) were men. The right eye was affected in 48 patients. The mean SE was -12.4 dioptres (SD 4.4, range -5.0 to -25). Thirty-seven eyes (40%) had undergone previously unsuccessful PDT to treat myopic CNV: seven times in one eye, six times in five eyes, four times in three eyes, three times in four eyes, twice in nine eyes and once in 14 eyes. The last PDT session had been performed at least 3 months prior to the first injection with anti-VEGF in all cases. All these cases presented with fluorescein leakage when they were included. Twenty-four eyes were treated with IVR and 68 eyes with IVB. Seventy-seven patients were treated with one single IVB or IVR as initial protocol. The demographic characteristics of these patients are shown in table 1.

A 4-year follow-up was completed in all cases. The mean number of ETDRS letters read was 46.1 (SD 16.8, range 5–70) at baseline, 55.5 (SD 18.6, range 10–85) at 12 months, 50.1 (SD 20.1, range 5–82) at 24 months, 54.2 (SD 21.9, range 2–85) at 36 months and 53.1 (SD 22.5, range 1–83) at 48 months (p=0.000, initial vs 12, 24 and 36 months and p=0.01 initial vs 48 months, Student t test for paired data).

The mean number of re-injections after the loading dose was 3.6 (SD 5.4, range 0–28) and the mean total number of injections was 4.9 (SD 5.4, range 1–29). Seventeen patients required

seven or more re-injections (six of them had been previously treated by PDT) and 10 cases required 12 or more IVI (three of them previously treated by PDT). No systemic adverse reactions were detected during follow-up. Two cases with lens opacity progression were detected during follow-up that were not attributed to the treatment.

Average BCVA gain in treatment-naïve eyes was $+3.7\pm21.8$ letters (p=0.21) versus $+7.1\pm15.0$ letters in previously PDT-treated eyes (p=0.007, both Student t test for paired data). Previous PDT did not seem to influence BCVA changes after anti-VEGF treatment (p=0.4, Student t test for unpaired data) or the number of IVI required (5.3 ± 5.9 vs 4.4 ± 4.5 , respectively; p=0.5, Student t test for unpaired data). However, PDT treatment-naïve eyes showed better initial and final visual acuity than previously PDT-treated eyes, even though BCVA gain was lower in the former group (figure 1).

Considering BCVA changes in the treatment-naïve or PDT-treated eyes that underwent IVB or IVR injections, the differences were not statistically significant: 4.5 vs 1.5 letters gained for the treatment-naïve eyes treated by IVB and IVR, respectively; 6.8 vs 7.6 letters gained for the previously PDT-treated eyes injected with IVB and IVR, respectively (p=0.56, ANOVA test).

The type of drug injected did not affect the visual outcome $(+5.3\pm19.3 \text{ letters}$ with IVB and $+4.3\pm14.8 \text{ letters}$ with IVR; p=0.85, ANOVA test). The influence of the anti-VEGF drug used (bevacizumab, ranibizumab) on the number of re-injections performed was not significant (post hoc Bonferroni test).

The initial loading dose had no effect on the number of re-injections required $(3.9\pm5.7 \text{ injections vs } 2.1\pm3.6 \text{ in eyes}$ treated with one or three previous injections, respectively; p=0.2, Student t test).

The correlation between BCVA change and age was low but significant (r=-0.19; p=0.04; Pearson correlation test) but non-significant for SE (r=0.12; p=0.22; Pearson correlation test).

Multiple regression analysis for the main variables (age, SE, initial BCVA, letters gained, SD-OCT findings, previous PDT, anti-VEGF drug, initial protocol, number of re-injections, total injections) showed similar results, with significant correlation for visual acuity gain and age (R^2 =0.220; p<0.001). SE and treating drug had no influence on final visual acuity and the number of injections required, and the number of injections was not related to visual gain.

| | Bevacizumab (n=53) | Ranibizumab (n=24) | p Value |
|----------------------------------|-----------------------|-----------------------|---------|
| Age (years) | 57±14 (31–93) | 54±15 (35–75) | 0.48* |
| Sex (M/F) | 14/39 | 6/18 | 0.85† |
| Eye (R/L) | 26/27 | 15/9 | 0.58† |
| Spherical equivalent (D) | -12.5±4.1 (-6 to -25) | -12.4±4.5 (-5 to -21) | 0.91* |
| % photodynamic therapy | 17 (32%) | 13 (54%) | 0.86† |
| BCVA initial | 44.3±19.2 (5-70) | 50.1±12.6 (20-68) | 0.18* |
| BCVA final | 49.8±24.2 (5-82) | 54.5±17.9 (15–83) | 0.40* |
| Change in number of letters read | 5.4±20 (-53 to 67) | 4.3±14.8 (-23 to 36) | 0.81* |
| Number of retreatments | 4.7±6.4 (0–15) | 2.3±3.0 (0–10) | 0.10* |
| Total intravitreal injection | 5.7±6.4 (1–16) | 3.3±3.0 (1–11) | 0.10* |

Data shown are mean±SD (range).

*Mann–Whitney U test.

 $\dagger \chi^2$ test.

BCVA, best-corrected visual acuity letters read; D, dioptres; L, Left eye; R, Right eye.



Figure 1 Best-corrected visual acuity changes in treatment-naïve and previous photodynamic therapy (PDT)-treated eyes.

DISCUSSION

The good results obtained by intravitreal anti-VEGF therapy in CNV secondary to age-related macular degeneration⁹ and the increased VEGF expression in myopic CNV¹⁵ have set the rationale for anti-VEGF therapy in myopic CNV.

Our results and those of several series in the literature show that intravitreal anti-VEGF drugs are effective in treating myopic CNV. However, Sawada *et al*¹⁶ and Shin *et al*¹⁷ have recently reported that the VEGF concentration in the aqueous humour of patients with myopic CNV is lower than in normal controls. These authors have hypothesised that decreased aqueous VEGF levels may be secondary to a disruption of the VEGF/pigment epithelial derived factor balance in retinal pigment epithelium (RPE) cells in highly myopic eyes. Nevertheless, high levels of VEGF might be localised in or around the CNV, explaining the anti-angiogenic benefit of anti-VEGF therapy.

Bevacizumab has been the most widely used drug, and several short series have reported good visual and anatomical outcomes.⁴ ⁶ ¹⁸ These results are maintained after 1 year of follow-up.⁵ ¹⁹ ²⁰ Gharbiya *et al*,²⁰ Chan *et al*¹⁹ and Ruiz-Moreno et al⁵ reported very similar visual outcomes and significant visual improvement at 1-year follow-up using a three consecutive IVB loading phase with no treatment-related systemic or ocular complications. Peiretti et al^{12} have reported on the persistent effectivity of IVB even after 4 years of follow-up. However, the initial use of three IVB injections as a therapeutic protocol is controversial due to the usually low activity of myopic CNV.²¹ Further studies at 1-year follow-up used one single initial dose of IVB. Ikuno *et al*³ treated 63 eyes with 1 mg IVB; LogMAR BCVA improved from 0.57 to 0.33 at 12 months. Ruiz-Moreno et al^{22} reported a significant improvement in the number of ETDRS letters read (mean 8.7 letters) during a 12-month follow-up; visual improvement occurred during the first 3 months and remained stable.

Similarly good results have been reported after one single injection of ranibizumab followed by PRN treatment. Silva *et al*² reported an average visual acuity gain of eight letters from baseline to 12 months after an average of 3.6 injections and no systemic or ocular side effects, and Hefner *et al*²³ have reported good results after 1 year of follow-up.

In our series, some patients presented with persistent CNV and required a higher number of re-injections. Those patients who required a higher number of IVI showed a poorer final visual gain. We have not observed any singular pattern among such patients in terms of age or SE. Series of eyes treated with one versus three consecutive injections have been compared showing that one single initial injection followed by PRN therapy is usually enough,¹³ probably because of the low activity of myopic CNV.¹⁹ We have not found differences in our series after 4 years of follow-up; the initial loading dose had no effect on the number of re-injections required.

All these series show the same limitation-namely, the lack of a PDT-treated control group as the first-line therapy approved for myopic CNV following the results of the VIP 1 trial.¹ Series comparing PDT versus IVB to treat myopic CNV agree in a higher visual acuity gain with anti-VEGF after 1 and 2 years of follow-up.¹⁴ ^{24–27} Yoon *et al*²⁷ retrospectively compared the results of 51 eyes with myopic CNV treated by PDT, 63 eyes treated with intravitreal anti-VEGF drugs and 28 eyes treated with a combined therapy PDT plus anti-VEGF at 1-year follow-up. The authors concluded that intravitreal anti-VEGF was more effective than PDT alone or combined therapy to treat myopic CNV. Ikuno *et al*²⁵ analysed the results after treating 31 eves with myopic CNV in Japanese women who received either PDT or IVB. Baba et al^{14} compared 12 eyes treated with PDT with 12 eyes treated by IVB. Both groups concluded that IVB was superior to PDT in myopic CNV. Hayashi et al performed a prospective non-randomised study comparing the results of 44 eyes with myopic CNV treated by PDT and 43 eyes treated by IVB. IVB was more effective and BCVA improved from 0.68 to 0.45 (LogMAR) in the bevacizumab group versus 0.61 to 0.54 in the PDT group.²⁴ Ruiz-Moreno et al performed a prospective randomised multicentre study comparing the results of 28 eyes with myopic CNV treated by PDT and 27 eves treated by IVB. Bevacizumab was more effective at 1 year and BCVA changed from 53.0 to 64.2 ETDRS letters in the bevacizumab group versus 52.8 to 52.5 in the PDT group.²⁶

Reported series with 2 years follow-up show a decline in BCVA²⁸ that has been attributed to atrophic changes associated with high myopia.²⁴ However, the extent of this 2-year decline is controversial. Hayashi⁷ (75 eyes) and Ruiz-Moreno and Montero²⁹ (19 eyes) did not find a statistically significant decline in BCVA between baseline and 2 years, and Chen³⁰ (26 eyes) reported a significant gain in BCVA by the end of the second year.

To the best of our knowledge, only one retrospective nonrandomised study with 4 years of follow-up has been published on 21 eyes with myopic CNV treated with bevacizumab.¹² In this series, 15/21 eyes gained one or more lines, three eyes remained stable within one line and three eyes lost one or more lines.

OCT findings were significantly related to final BCVA. Best results were observed for eyes without significant OCT changes after treatment and the poorer results occurred in eyes with atrophic changes, probably associated with damage to the RPE and the outer segment of the photoreceptors.³¹ The response to IVI was poorer in eyes with subfoveal lesions in terms of re-injections and VA gain, as has been previously reported.⁷

It has been reported that previous PDT may lead to a poorer visual outcome in eyes treated with anti-VEGF drugs,³² whereas other series have shown that previous PDT had no influence on the final visual acuity.²² PDT might influence visual acuity outcomes by varied mechanisms including choroidal ischaemia or damage to the RPE and photoreceptors. According to our findings, previous PDT did not affect the final visual outcome or the number of IVI.

Our results confirm the statistically significant visual acuity gain in myopic eyes treated with anti-VEGF drugs. The type of

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anti-VEGF drug used and previous PDT did not induce any difference. Correlation with SE was not statistically significant and a low but significant correlation was found between BCVA change and age. BCVA gain was more marked in younger patients. The comparative efficacy of bevacizumab and ranibizumab was similar. No systemic adverse reactions were detected during follow-up.

Among the limitations of the current study we should highlight that this is a non-randomised retrospective study and that more eyes were treated with bevacizumab than with ranibizumab (68 and 24 eyes, respectively). We also lack a control group with PDT; however, following the recent reports comparing PDT and anti-VEGF drugs, the latter are markedly superior. The strengths of the study are the high number of treated eyes (92 eyes) with long follow-up (4 years), based on real practice in different centres.

According to our results, anti-VEGF drugs are useful for the treatment of CNV associated with high myopia, achieving significant BCVA gain at long follow-up, and must be considered as first-line therapy. Bevacizumab and ranibizumab had similar clinical effects in BCVA gain and number of IVI required.

Contributors JMR-M and JAM: concept and design, analysis and interpretation, writing, obtaining funding and literature search. JMR-M, LA, AC, RS and JAM: critical revision and final approval, data collection and provision of patients. JMR-M: statistical expertise and technical support.

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Competing interests None.

Ethics approval Local ethics committees approved retrospective data gathering (Alicante Institute of Ophthalmology, VISSUM; Department of Ophthalmology, Bellvitge University Hospital; Pio del Rio Hortega University Hospital, Hospital São João, and University Hospital of Coimbra).

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