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The 12-Month Outcome of Three Consecutive Monthly Intravitreal Injections of Ranibizumab for Myopic Choroidal Neovascularization

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Abstract

Purpose: The aim of this study was to evaluate the 12-month outcomes, efficacy, and safety of three consecutive monthly intravitreal ranibizumab injections for myopic choroidal neovascularization (CNV).
Methods: We retrospectively reviewed the medical records of 25 consecutive eyes that received a loading dose of three consecutive monthly intravitreal injections of ranibizumab for myopic CNV between February, 2008, and March, 2010, with a follow-up of 12 months. Eyes with persistent or recurrent CNV after 3 months received additional ranibizumab injections as needed. Patients' demographic data, best corrected visual acuity (BCVA), CNV findings on fluorescent angiography (FAG), central macular thickness (CMT) on optical coherence tomography (OCT), total number of treatments, and complications were recorded.
Results: Mean baseline BCVA was 0.73 logarithm of the minimum angle of resolution (logMAR) (standard deviation [SD] 0.63), and improved significantly to 0.42 logMAR (SD 0.43) at 1 month, 0.38 logMAR (SD 0.47) at 2 months, 0.34 logMAR (SD 0.43) at 3 months, and 0.34 logMAR (SD 0.40) at 12 months (all $P < 0.001$, Wilcoxon signed-rank test). The average number of injections was 3.44 (SD 0.92). At 12 months, mean improvement was 2.88 lines (SD 2.35), and 20 eyes (80%) showed a gain of at least one line after treatment. At 3 months, OCT showed significant reduction in CMT ($P = 0.012$, two-tailed t-test), and FAG showed significant reduction of mean CNV size from 0.3 (SD 0.16) to 0.19 (SD 0.12) disc area ($P = 0.007$, two-tailed t-test). No angiographic leakage was evident at 3 months in 21 eyes (84%); four eyes (16%) required additional injections for persistent leakage. Two eyes (8%) had recurrent CNV during follow-up and required retreatment. No complications were noted after treatment.
Conclusions: An initial loading dose of three ranibizumab injections is safe and effective in treating myopic CNV, with visual improvement maintained over 12 months.

Introduction

Choroidal neovascularization (CNV) is one of the important causes of vision loss in pathologic myopia.[1] Currently, photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis, Basel, Switzerland) is the only approved standard treatment for myopic CNV. Although PDT with verteporfin was more likely to stabilize vision in patients with myopic CNV compared with a placebo at 1 year, the differences were not statistically significant at 2 years, and the visual improvements were limited.[2,3] In recent years, anti-vascular endothelial growth factor (VEGF) drugs have become a mainstream therapy for CNV secondary to age-related macular degeneration (AMD).[4] In addition, several clinical studies have showed promising results for a variety of diseases involving CNV.[5,6] In CNV secondary to pathologic myopia, some case series showed significant vision improvement with anti-VEGF drugs.[7] Despite fewer reports than bevacizumab (Avastin, Genentech, South San Francisco, CA), treatment with ranibizumab (Lucentis, Novartis, Basel, Switzerland) in myopic CNV resulted in significant visual improvement.[8–14] Most of these studies adopted the regimen of a single injection with retreatments as needed.[8,9,11–13] However, in the Prospective OCT Imaging of Patients with

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Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO) study of AMD, eyes treated with a loading dose of three consecutive, monthly ranibizumab injections, with retreatments as needed, achieved optimal visual outcomes comparable to those of the phase III studies with monthly dosing over 2 years and required fewer injections.[15] In light of this result, we sought to further evaluate the 12-month outcomes of a loading dose with three consecutive monthly injections of ranibizumab to treat CNV secondary to pathologic myopia.

Methods

This study was approved by the Hospital Institutional Review Board, and followed the tenets of the Declaration of Helsinki. We retrospectively reviewed the medical records of 25 consecutive eyes with CNV secondary to pathologic myopia that were treated with a loading dose of three consecutive monthly intravitreal injections of ranibizumab between February, 2008, and March, 2010. The inclusion criteria included high myopia with spherical equivalent of −6 diopters or more and axial length of 26 mm or more, active subfoveal or juxtafoveal CNV, at least three consecutive monthly intravitreal ranibizumab injections, and a follow-up of at least 1 year. Exclusion criteria were CNV secondary to causes other than myopic CNV (such as AMD, ocular histoplasmosis syndrome, angioid streaks, choroiditis, or trauma), any chorioretinopathy other than pathologic myopia (including central serous chorioretinopathy, diabetic retinopathy, retinal vein occlusion, vasculitis or uveitis), and previous treatment or surgery for myopic CNV within the previous 3 months.

Every patient underwent a comprehensive ophthalmologic examination before the operation, with the following recorded: best corrected visual acuity (BCVA), intraocular pressure, and results of slit lamp biomicroscopy, dilated fundus examination, fluorescent angiography (FA), and optical coherence tomography (OCT) (Stratus OCT, Carl Zeiss Meditec, Dublin, CA, or RTVue Scanner; Optovue, Inc., Fremont, CA). The CNV lesion was evaluated for size, location and composition on FA, and central macular thickness (CMT) was measured using OCT.

After we explained the procedure, we obtained written, informed consent from each patient. All patients were scheduled at baseline, 1 month, and 2 months for three consecutive monthly injections of ranibizumab. The surgical procedure was performed in an outpatient setting. Under topical anesthesia, we placed each patient in a supine position and then prepped the affected eye with 5% betadine solution. We injected 0.05 mL of ranibizumab (0.5 mg) using a 30-gauge needle through the pars plana into the vitreous cavity.

All patients were followed 1 week after injection and then monthly thereafter for 1 year. Retreatment was done with a single ranibizumab injection in eyes with persistence or recurrence of CNV, defined by a visual loss of at least one Snellen line, metamorphopsia, macular edema or subretinal fluid on the OCT, or CNV leakage on FA. Monthly follow-up examinations included BCVA, intraocular pressure, slit lamp biomicroscopy, dilated fundus examination, and OCT. FA was performed at baseline and at 3 months after the first ranibizumab injection, with eyes needing retreatment receiving additional FA as required.

We recorded patients' baseline demographic data and findings of examinations at baseline and at every follow-up visit, including BCVA, findings of FA and OCT, total number of injections, and adverse events after injections. We measured BCVA using Snellen charts and converted visual acuities into the logarithm of the minimum angle of resolution (logMAR) for data analysis. For calculation, we converted counting fingers (CF) into 1/400 (2.60 logMAR).

We used SPSS statistical software, version 12.0 (SPSS, Inc., Chicago, IL) for statistical analysis. The Wilcoxon signed-rank test was used to compare paired data of BCVA, and the two-tailed *t*-test was used to compare changes in CMT on OCT and CNV sizes. We used an independent *t*-test to compare continuous variables between groups. Categorical variables were compared using the Fisher exact test. We regarded a *P* value of less than 0.05 as statistically significant.

Results

In this retrospective study, we enrolled 25 eyes (13 right eyes and 12 left eyes) of 23 patients (13 women and 10 men) with a mean age of 49.16 years (standard deviation [SD] 13.97; range 22–71 years). The average spherical equivalent was −9.45 diopters (SD 3.12; range −6.00 to −18.00); the average axial length was 28.24 mm (SD 1.09; range 26.07–29.63). Three eyes (12%) had received prior PDT treatment. In angiographic appearance, all CNVs were predominantly classic. In all, 16 eyes (64%) had subfoveal CNVs, whereas 9 (36%) were juxtafoveal. The mean CNV size was 0.3 disc area (SD 0.16; range 0.1–0.8).

The average number of ranibizumab injections was 3.44 (SD 0.92; range 3–6). During the 12-month period, 19 eyes (76%) received only three intravitreal ranibizumab injections. Another six eyes (24%) required an additional one to three injections after 3 months due to persistent leakage in four eyes (16%) and recurrent CNV in two (8%).

Figure 1 shows the changes in mean logMAR BCVA during the 12-month follow-up. Mean baseline BCVA was 0.73 logMAR (SD 0.63). During the 12-month follow-up, mean BCVA was 0.42 logMAR (SD 0.43) at 1 month, 0.38 logMAR (SD 0.47) at 2 months, 0.34 logMAR (SD 0.43) at 3 months, 0.33 logMAR (SD 0.41) at 6 months, and 0.34 logMAR (SD 0.40) at 12 months. The differences in mean BCVA at each follow-up visit over baseline were significant ($P < 0.001$, Wilcoxon signed-rank test). Mean BCVA was also significantly different between 1 month and 2 months ($P = 0.040$) and between 2 months and 3 months ($P = 0.042$, Wilcoxon signed-rank test).

At 12 months, the mean improvement was 2.88 lines (SD 2.35; range −1 to 7 lines). At last follow-up, 20 eyes (80%) showed a gain of at least 1 line after treatment, with 16 eyes (64%) improved by 2 or more lines and 15 eyes (60%) improved by 3 or more lines; 4 eyes (16%) remained unchanged and only one eye (4%) lost one line from baseline. Among 17 eyes with baseline BCVA better than 6/60, 15 (88.2%) achieved BCVA of 6/12 or more at 12 months; however, among eyes with baseline BCVA of 6/60 or worse, only 25% (2 of 8 eyes) achieved this level ($p = 0.004$).

Figure 2 shows the changes in mean CMT on OCT after treatment. At baseline, the average CMT was 261 μm (SD 90.41). The mean CMT reduced gradually to a minimum of 213.4 μm (SD 41.88) at 3 months, a reduction that was statistically significant ($P = 0.012$, two-tailed *t*-test).

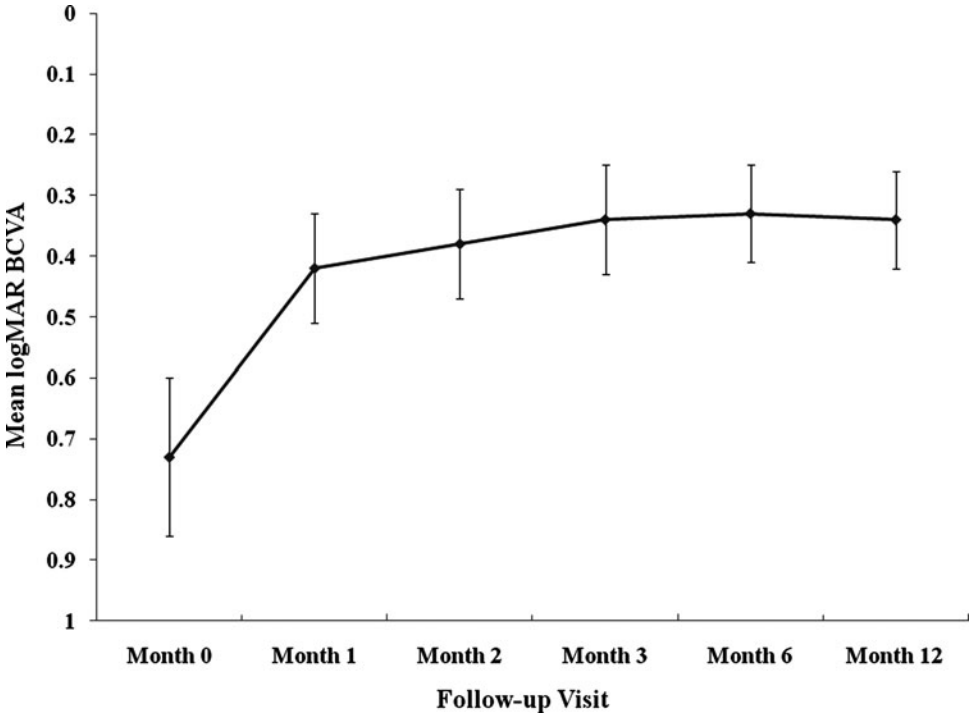

FIG. 1. Changes in the mean logarithm of the minimum angle of resolution (logMAR) best corrected visual acuity (BCVA) during the 12-month follow-up visits shows the benefit of three consecutive monthly intravitreal injections of ranibizumab. The error bars illustrate one standard error of the mean. Compared with baseline, vision improved significantly at each follow-up visit ($P < 0.001$). In addition, mean BCVA improved significantly between 1 and 2 months ($P = 0.040$) and between 2 and 3 months ($P = 0.042$).

FA at three months showed significant reduction of mean CNV size from 0.3 disc area (SD 0.16) at baseline to 0.19 disc area (SD 0.12) ($P = 0.007$, two-tailed *t*-test). Twenty-one eyes (84%) showed no angiographic leakage after three consecutive monthly injections; four eyes (16%) had reduced but persistent leakage and required one to three additional injections in subsequent months. Two eyes (8%) developed recurrent CNV during follow-up visits. One had recurrence at 9 months and needed one additional injection; the other had recurrence at 6 months and received three additional injections in subsequent months because of persistent macular edema on the OCT and reduced vision. There were no leakages on FA after retreatment. None of the patients had any systemic or ocular complications after injections.

Groups with subfoveal and non-subfoveal CNV did not differ significantly in age, axial length, total number of treatments, CNV size, baseline BCVA, or lines of improvement at last follow-up. Although the mean VA of the subfoveal group at 12 months was worse than that of the non-subfoveal group, the difference was not statistically significant (0.41 logMAR [SD 0.42] vs.0.21 logMAR [SD 0.33], $P = 0.225$).

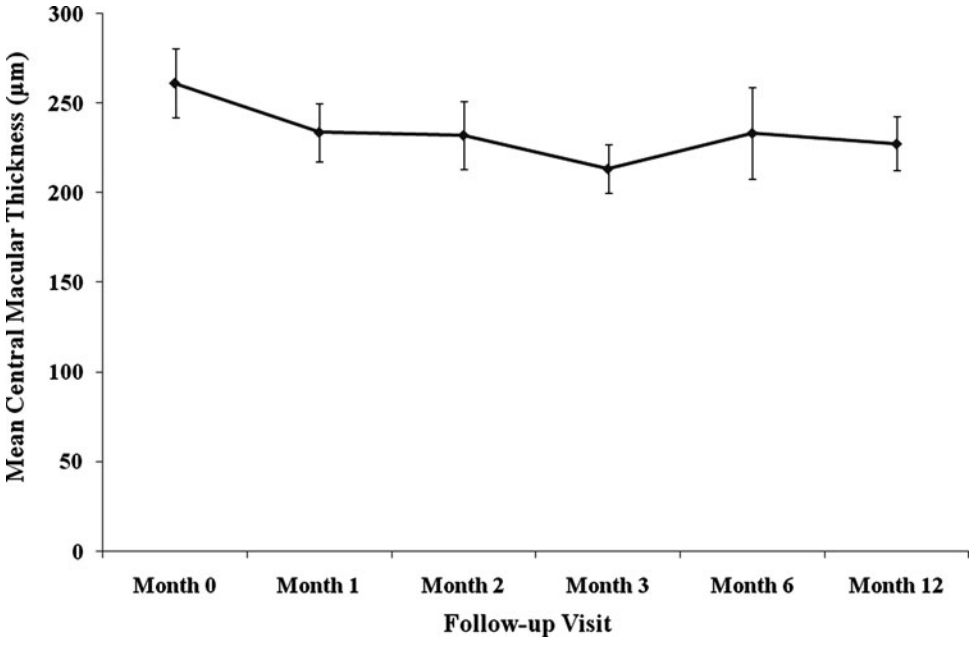

FIG. 2. The changes in mean central macular thickness (CMT) on optical coherence tomography (OCT) during follow-up visits shows the benefit of three consecutive monthly intravitreal injections of ranibizumab. The error bars illustrate one standard error of the mean. The mean CMT reduced gradually to a minimum of 213.4 μm (standard deviation [SD] 41.88) at 3 months, a reduction that was statistically significant ($P = 0.012$).

Discussion

Eyes with pathologic myopia are known to have extremely elongated axial length, chorioretinal degeneration, and lacquer cracks, and CNV is an important cause of visual loss in these eyes. Although self-limiting, CNV may cause subretinal hemorrhage, exudation, fibrosis, and atrophic scars, leading to permanent visual loss.[1] Tong et al. found that VEGF concentrations in aqueous humor were markedly increased in patients with CNV secondary to pathologic myopia when compared with the controls.[16] This result indicated that the angiogenic activity of VEGF might be associated with the pathogenesis of CNV.

Ranibizumab, an antiangiogenic medication, can block the effects of VEGF. It has been approved and widely used as the primary treatment in CNV secondary to AMD.[4] On the basis of its theoretical and therapeutic effects on CNV, it may also effectively treat CNV secondary to pathologic myopia. In a short-term study of 26 eyes treated with intravitreal ranibizumab for myopic CNV by Silva et al.,[8] 65% of eyes gained at least 1 line at 3 months after a mean 1.9 treatments, and significant improvement was seen only in treatment-naïve eyes. In another study of 14 eyes by Konstantinidis et al.,[9] 93% showed visual improvement at a mean follow-up of 8.4 months after a mean 2.36 injections, and vision improved by a mean 3.86 lines.

In other longer-term studies, 65–92.7% of eyes with myopic CNV achieved visual improvement of at least one line after intravitreal injections of ranibizumab[10–14]; 80% of eyes in our study also achieved this level of improvement. These results seem superior to those in eyes treated with PDT at 1 year. However, the broad range of variation in results is probably due to lack of uniformity in study design and variety in CNV severity, percentages of eyes with prior treatment, follow-up durations, baseline visual acuities, sample sizes, study designs, and treatment dosing regimens. Even so, our results seem promising.

Because of the potential risk of retinal break, retinal detachment, and other complications in these highly myopic eyes and the fact that most eyes improved after a single injection, most studies adopt the regimen without a loading dose of three consecutive monthly injections.[8,9,11–13] They chose to retreat eyes when needed. However, in some studies, a longer follow-up showed an average number of treatments similar to ours with a loading dose of three injections. Silva et al.[13] reported a mean 3.6 treatments in 34 eyes with myopic CNV during a 12-month prospective study; of these, only 65% experienced visual improvement. In another prospective study of 32 eyes by Lalloum et al.[12] with a median follow-up of 17 months (range 7–29 months), the median number of injections was three (range 1–12), with 81.2% gaining 1 line or more of visual acuity at the last examination.

So far, despite the paucity of studies evaluating the outcomes of a loading dosing of three consecutive ranibizumab injections for myopic CNV, the results are encouraging. In a retrospective study, Lai et al.[10] pioneered the use of a loading dose in 16 eyes with myopic CNV, and 92.7% gained visual improvement at 12 months after a mean 3.8 ranibizumab injections. The mean improvement was 3.0 lines, and 81.3% eyes required only three (*i.e.*, the loading dose) intravitreal ranibizumab injections. In Calvo-Gonzalez et al.'s prospective study of 67 eyes,[14] 79.1% showed visual improvement after an average 4.2 injections over a mean follow-up of 15.9 months. In both of these studies, despite any mention of statistical significance, the figures clearly showed a trend in visual improvement over the first 3 months after each injection of the initial loading doses.[10,14] In addition, the treatment effects were maintained over time—12 months for Lai[10] and 24 months for Calvo-Gonzalez.[14]

Similarly, in our study, 80% of eyes achieved a gain after a mean 3.44 injections over a 12-month period, and 76% needed only a loading dose. Compared with baseline, vision improved significantly at each follow-up visit ($P < 0.001$). In addition, mean BCVA improved significantly between 1 and 2 months ($P = 0.040$) and between 2 and 3 months ($P = 0.042$) (Fig. 1). The second and third doses seemed to reinforce the visual improvement, respectively, as also seen in the studies of Lai et al. and Calvo-Gonzalez et al.[10,14]

Calvo-Gonzalez et al.[14] pointed out that the positive predictive factors for improved visual acuity at the end of follow-up were baseline visual acuity and a non-subfoveal CNV. Our study also found that 15 of 17 eyes (88.2%) with initial BCVA better than 6/60 achieved BCVA of 6/12 or more at 12 months, compared with only 25% (2 of 8 eyes) with initial BCVA of 6/60 or worse ($P = 0.004$). Baseline BCVA did affect the visual outcomes in our study; however, we did not find any significant differences in visual outcomes between groups with subfoveal and non-subfoveal CNV. This result may have been because our sample size was not large enough to distinguish differences between these two groups.

In terms of complications, neither retinal break nor retinal detachment was noted in our study or other studies using the regimen of initial loading dose.[10,14] Also, none had other systemic or ocular side effects, except two eyes with mild acute anterior uveitis in the study of Calvo-Gonzalez et al. that responded well to topical medications.[10,14] Moreover, the total number of treatments during the study period were not apparently higher than in other studies, and around 80% or more of eyes treated with an initial loading dose gained at least one line of visual improvement after the study period.[10,14] Accordingly, we consider that the initial loading dose of three monthly ranibizumab injections is a safe and effective treatment for myopic CNV that will maintain visual improvement.

In conclusion, a loading dose of three monthly ranibizumab injections was an effective and safe treatment for eyes with CNV secondary to pathologic myopia. However, our study had several limitations: small sample size, a retrospective design, nonstandardized visual acuity testing, short follow-up duration, and lack of a control group. Future long-term prospective, randomized trials are needed to compare the safety and outcomes for different dosing regimens of intravitreal ranibizumab.

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Author Disclosure Statement

The authors have no conflicts of interest or relevant commercial associations to disclose. No competing financial interests exist.

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