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Effect of a Single-Dose Regimen of Intravitreal Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration

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Abstract

Purpose: The purpose of this study was to demonstrate the effect of a single-dose regimen for treating AMD.

Methods: Patients (mean age, 75.5 years; range, 60-86) were enrolled who had AMD with a baseline Logarithm of Minimum Angle of Resolution (logMAR) Best-Corrected Visual Acuities (BCVAs) of 0.15 to 1.30 treated with intravitreal ranibizumab as the primary treatment. Eleven eyes (11 patients) received the three-injection loading regimen (3+PRN), and 21 eyes (20 patients) received the single-injection regimen (1+PRN). The mean follow-up period was 16.0 months. In the maintenance phase, additional treatment was administered when subretinal or intraretinal fluid persisted or recurred, BCVA decreased, new subretinal or retinal hemorrhage was observed, or choroidal neovascularization enlarged. The BCVAs and central retinal thickness were measured at baseline and months 3, 6, and 12 during the observation period.

Results: The mean number of injections in the 1+PRN group was 3.52 ± 1.97, significantly ($p<0.05$) fewer than the 4.83 ± 3.03 in the 3+PRN group. The mean BCVAs at baseline, 3, 6, and 12 months were 0.49, 0.37, 0.31, and 0.30 in the 3+PRN group and 0.57, 0.43, 0.38, and 0.41 in the 1+PRN group. The BCVA improved in six eyes (54.5%) in the 3+PRN group and 12 (57.1%) eyes in the 1+PRN group. At month 12, a 20% or greater decrease in central retinal thickness occurred in five (45.5%) eyes in the 3+PRN group and 12 (57.1%) eyes in the 1+PRN group. There was no significant difference in the BCVAs and central retinal thicknesses at any points in either group.

Conclusions: A single-dose regimen can lead to equivalent functional and morphologic retinal improvement with fewer injections compared with the loading regimen. Further studies are needed to determine the optimal intravitreal ranibizumab treatment regimen for the first 3 months.

This clinical trial is registered in UMIN-CTR (UMIN-ID: UMIN000006968).

Keywords: Intravitreal ranibizumab; Loading regimen; Neovascular age-related macular degeneration; Single-dose regimen

Introduction

Age-Related Macular Degeneration (AMD) is the leading cause of irreversible vision loss in elderly populations in developed countries [1-3]. Anti-Vascular Endothelial Growth Factor (VEGF) therapy is a standard effective strategy for treating neovascular AMD. Ranibizumab (Lucentis, Genentech Inc., South San Francisco, CA) is a recombinant, humanized antibody fragment designed to bind and inhibit all VEGF-A isoforms [4-6]. To date, a loading regimen with three initial monthly intravitreal injections of ranibizumab has been recommended widely for treating neovascular AMD [7-11]. However, some studies have reported an alternative single-dose regimen with a Pro Re Nata (PRN) dosing schedule after one injection [12-14]. More recently, the Comparison of AMD Treatment Trials (CATT) study suggested that a single-dose regimen yielded a comparable functional and morphologic retinal improvement [15]. The objective of the current study was to compare the outcomes of two treatment protocols: the conventional loading (3+PRN) regimen and a single-dose (1+PRN) regimen of intravitreal injections of ranibizumab for treating neovascular AMD.

Methods

Patients

Patients were enrolled who had been diagnosed with neovascular AMD with a baseline Logarithm of the Minimum Angle of Resolution (logMAR) Best-Corrected Visual Acuity (BCVA) of 0.15 to 1.30; all patients had been treated with intravitreal ranibizumab as the primary therapy at Nagoya City University Hospital between April 2009 and March 2010. Patients were grouped 3+PRN regimen group or 1+PRN regimen group by their first visiting date at our clinic. Exclusion criteria included patients who had undergone previous laser photocoagulation or were treated previously with intravitreal triamcinolone, intravitreal bevacizumab (Avastin, Genentech Inc.), or photodynamic therapy. Eleven eyes of 11 patients were treated with the 3+PRN regimen and 21 eyes of 20 patients were treated with the 1+PRN regimen. The mean patient age was 75.5 years (range, 60-86). The mean follow-up period was 16.0 months (range, 12-30).

Baseline examination

The BCVA, fundus examination, Optical Coherence Tomography (OCT) (Stratus III OCT; Carl Zeiss, Dublin, CA), and fluorescein and Indocyanine Green Angiography (ICGA) were performed to diagnose

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neovascular AMD. The Central Retinal Thickness (CRT) was measured using OCT to assess morphologic macular improvement.

Treatment

In the 3+PRN group, patients received three monthly intravitreal injections of ranibizumab (0.5 mg/0.05 ml) according to the loading regimen, and the patients in the 1+PRN group received one injection. Thereafter, both groups were followed according to the re-treatment criteria (PRN regimen) (Figure 1). The BCVAs were measured and fundus and OCT examinations were performed. Fundus fluorescein and ICGA were repeated only if lesion sizes increased or new hemorrhages developed. The re-treatment criteria included persistent or recurrent subretinal or intraretinal fluid seen on OCT, decreased BCVAs associated with fluid seen on OCT, and new retinal or subretinal hemorrhages or angiographic evidence of increased lesion size. The presence of a pigment epithelial detachment was not considered as a re-treatment criterion.

Visual outcome

The main outcome variables in the two treatment groups were the BCVA and CRT at different time points. Changes in the BCVA of 0.3 or more logMAR unit were considered improved or worsened. Changes in the CRT of 20% or more from baseline were defined as improved or worsened. P<0.05 (analysis of variance) was considered significant for all analyses.

Results

Patient profiles

Eleven eyes of 11 patients (mean age, 74.6 ± 8.0 years) were treated with the 3+PRN regimen; the mean follow-up period was 14.5 ± 2.9 months, the mean baseline BCVA was 0.49 ± 0.25, and the mean baseline CRT was 325 ± 109μm. Twenty-one eyes of 20 patients (mean age, 76.0 ± 6.6 years) were treated with the 1+PRN regimen; the mean follow-up period was 16.8 ± 4.2 months; the mean baseline BCVA was 0.57 ± 0.32, and the mean baseline CRT was 343 ± 79 μm.

Visual outcome

The mean BCVAs at baseline and months 3, 6, 9, and 12 were 0.49 ± 0.25, 0.37 ± 0.39, 0.31 ± 0.34, 0.30 ± 0.29, and 0.30 ± 0.30 in the 3+PRN group and 0.57 ± 0.32, 0.43 ± 0.36, 0.38 ± 0.29, 0.41 ± 0.30, and 0.41 ± 0.31 in the 1+PRN group. There were no significant changes from baseline in BCVAs at any time points (Figure 2). In the 3+ PRN groups, the BCVAs significantly improved in six (54.5%) eyes; at month 12, the BCVAs improved in six (54.5%) eyes, while the BCVA deteriorated in one (9.1%) eye. In the 1+PRN group, BCVAs improved significantly and in 12 (57.1%) eyes; at month 12, the BCVAs improved in six (28.7%) eyes and decreased in one (4.8%) eye. There were no significant differences in the distributions of the patients in the two groups at any time points (Figure 3).

During the first 3 months of treatment in the 1+PRN group, seven (33.3%) eyes received one injection, nine (42.9%) eyes received two injections, and five (23.8%) eyes received three injections. The mean change from baseline in the BCVA at month 12 was -0.18 in seven eyes treated with one injection during the first 3 months, -0.21 in nine eyes treated with two injections, and -0.05 in five eyes treated with three injections.

CRT

The mean CRTs at baseline and months 3, 6, 9, and 12 were 325 ± 110 μm, 232 ± 46 μm, 243 ± 62 μm, 242 ± 62 μm, and 248 ± 55 μm in the 3+PRN group and 343 ± 79 μm, 275 ± 102, 281 ± 120, 305 ± 142, and 311 ± 120 in the 1+PRN group. The mean change in the CRTs in the 1+PRN group was less than in the 3+PRN group (p<0.05)

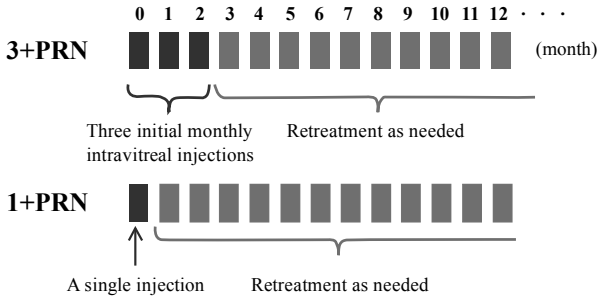

Figure 1: The 3+PRN and 1+PRN treatment protocols. Patients on the 3+PRN regimen received two additional consecutive monthly intravitreal ranibizumab injections independent of clinical findings compared with patients treated according to the 1+PRN protocol. The need for additional injections was determined by the same retreatment criteria as patients assigned to the 1+PRN schedule from baseline.

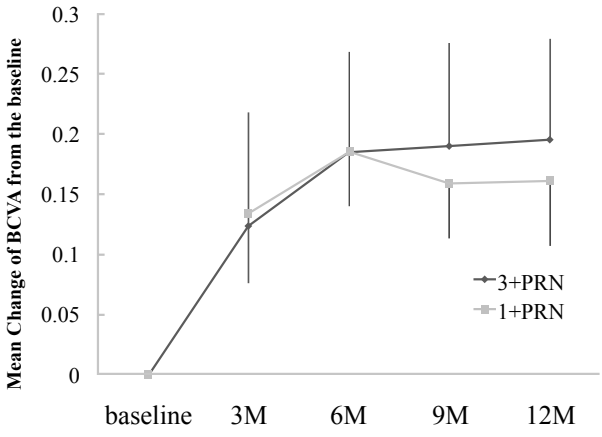

Figure 2: The mean changes in the BCVAs in each group. Neither regimen is associated with a significant difference in BCVAs at any time points. (Error bar shows SE: standard error).

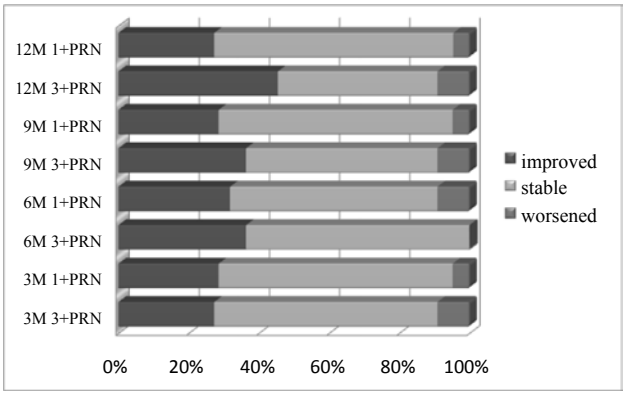

Figure 3: Distributions of the changes in the BCVAs in each group. Changes of 0.3 or more in logMAR VA are defined as improved or decreased. There are no significant differences in the distributions of the patients in the two groups.

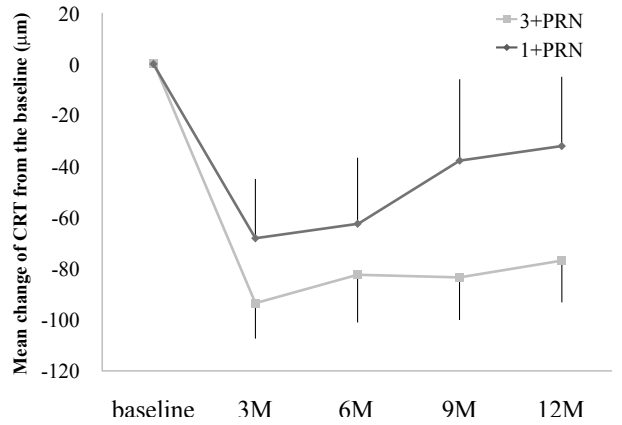

Figure 4: The mean change in the CRTs in each group. The mean changes in the CRTs in the 1+PRN group are significantly ($p<0.05$) less than in the 3+PRN group. (Error bar shows SE: standard error).

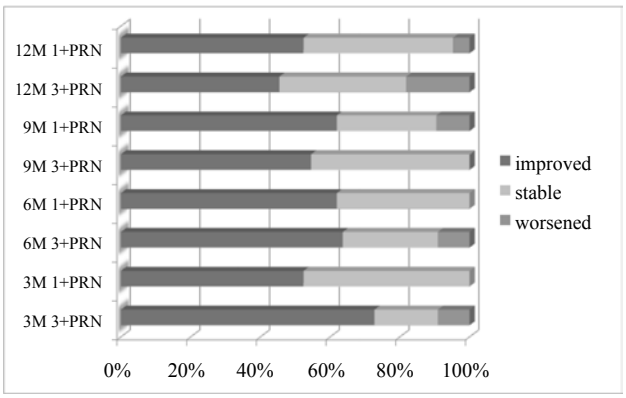

Figure 5: The distributions of the changes in the CRTs in each group. Changes of 20% in the CRTs from baseline are defined as improved or worsened. There are no significant differences in the distributions of the CRTs in the two groups.

(Figure 4). Figure 5 shows the distributions of the change of the CRTs in the two groups. In the 3+PRN group, the CRTs improved in five (45.5%) eyes and worsened in two (18.1%) eyes at month 12. At month 12 in the 1+PRN group, the CRTs improved in 12 (57.1%) eyes and worsened in two (9.5%) eyes. There were no significant differences in the distributions of the changes in the CRTs in the two groups at any time points.

Numbers of injections

The mean number of injections at months 3, 6, and 12 were 3.00, 3.55, and 4.82 in the 3+PRN group and 1.90, 2.71, and 3.52 in the 1+PRN group (Figure 6), with a significantly ($p<0.05$) lower mean number of injections in the 1+PRN group throughout the observation period. Figure 7 shows the frequency of treatments in eyes with different injection number during the first 3 months in the 1+PRN group. Seven eyes that received one injection during the first 3 months had an average of 0.7 and 1.0 additional injection by months 6 and 12, respectively. Nine eyes that received two injections during the first 3 months had an average of 0.8 and 1.8 additional injections during months 6 and 12, respectively. Five eyes that received three injections during the first 3 months received an average of 1.0 and 2.2 additional injections by months 6 and 12, respectively. On the other hand, the 11 eyes in the 3+PRN group received an average of 0.55 and 1.82 additional injections by months 6 and 12, respectively.

Complications

No cases of endophthalmitis, retinal detachment, increased intraocular pressure, traumatic cataract, or any other major complications related to the injection procedure developed.

Discussion

The current study compared two regimens for treating neovascular AMD with intravitreal ranibizumab. The 3+PRN group received a loading dose of three monthly ranibizumab injections followed by an as-needed dosing schedule. In contrast, the 1+PRN group received one ranibizumab injection and additional injections as needed. There were no significant differences in the BCVA outcomes (Figures 2, 3). The mean change in the CRT in the 1+PRN group was less than in the 3+PRN groups, while the percentages of eyes with improved or thickened CRTs did not differ significantly between the groups (Figures 4, 5). The patients in the 1+PRN group received fewer injections than those in the 3+PRN group (Figure 6).

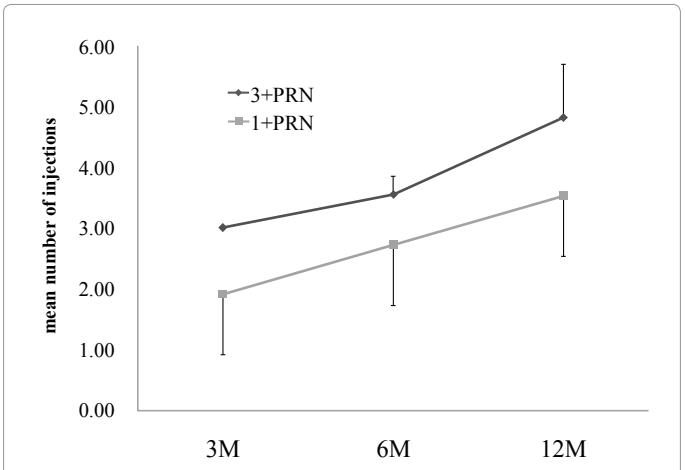

Figure 6: Average number of injections in each group. A significantly ($p<0.05$) lower average number of injections was administered in the 1+PRN group compared with the 3+PRN group. (Error bar shows SD: standard deviation).

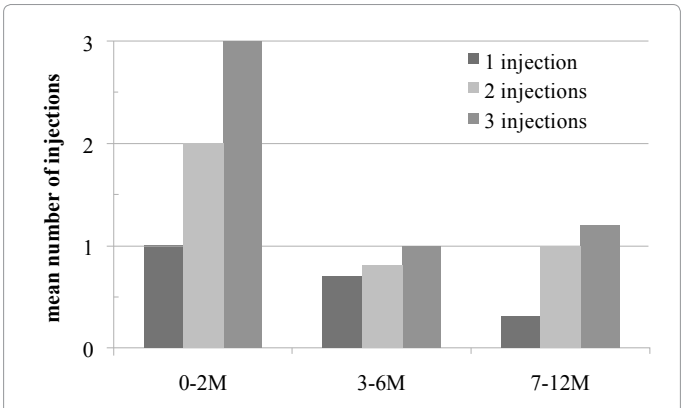

Figure 7: Relationship of injection number during the first 3 months and frequencies of following additional treatments in the 1+PRN group. The fewer injection number during the first 3 months, the less frequent additional treatments during the following months.

	MARINA [7]	ANCHOR [8]	PrONTO	Gupta et al.[14]		CATT [15]		Current Study	
Treatment regimen	Monthly	Monthly	3+PRN	3+PRN	1+PRN	monthly	1+PRN	3+PRN	1+PRN
No. injections at 12 months	12	12	5.6	6	4.5	11.7	6.9	4.83	3.52
Mean letters* improved at 12 months	7.2	11.3	9.3	4.4	4.1	8.5	6.8	9.5**	8.0**
Eyes losing fewer than 15 letters	94.6	96.4	95.0	89.4	93.5	94.0	95.0	90.1	95.2
Eyes gaining 15 letters or more	33.8	40.3	35.0	52.4	48.5	34.0	25.0	54.5	28.7

* Measured by Early Treatment of Diabetic Retinopathy Study (ETDRS) chart
** Letters on the ETDRS chart calculated a letter equivalent to -0.02 of logMAR equivalent

Table 1: Comparison of studies of intravitreal ranibizumab for neovascular AMD.

Treatment with intraocular ranibizumab injections has been evaluated prospectively. In those studies, Early Treatment of Diabetic Retinopathy Study (ETDRS) chart was used to evaluate the BCVAs [7-11]. The MARINA and the ANCHOR studies have shown the efficacy of monthly intravitreal ranibizumab injections on neovascular AMD [7,8]. In the MARINA study [7], the mean BCVA improved by 7.2 letters, and in the ANCHOR study [8], the mean BCVA improved by 11.3 letters at 12 months. In the PrONTO study [11], in which the loading regimen of three initial monthly injections of ranibizumab was followed by a PRN schedule based on the BCVAs and findings on OCT, the mean BCVA improved by 9.3 letters with an average 5.6 injections in month 12. In the current study, in which the logMAR VA was recorded, a letter on the ETDRS chart is equivalent to -0.02 of logMAR equivalent [16]. Accordingly, our results showed that the mean BCVA improved about 9.5 letters in the 3+PRN group and about 8.0 letters in the 1+PRN group at month 12. These results were comparable to those of the PrONTO study [11].

Regarding the total number of injections, 4.82 injections in the 3+PRN group were fewer than those in the PrONTO study [11]. Other studies have reported on the effects of a 3+PRN regimen. Rothenbuehler et al. reported a mean number of injections of 5.6 at month 12, and a mean change in VA of 7.3 letters [12]. Querques et al. reported that the mean number of injections at month 12 was 5.1 and the mean change in VA was 9 letters [13]. In the current study, the reason for the fewer number of injections compared with previous reports might be related to the small number of patients and different characteristics and background of AMD in a Japanese population [2,3].

No evidence supports the need for a loading dose with three initial monthly injections. Bolz et al. showed that the initial administration of intravitreal ranibizumab induced a significant effect on intraretinal and subretinal fluid and visual function, while subsequent injections had a less pronounced effect [17]. Recently, Gupta et al. [14] compared a loading regimen and a one-dose regimen of ranibizumab and reported that the 3+PRN group required a mean of 6.0 injections by month 12 and had a mean BCVA improvement of 4.4 letters, while the 1+PRN group required a mean of 4.5 injections at month 12 with a mean BCVA improvement of 4.1 letters; there were no significant differences in the mean changes in VA at any time point during the 12 months of the study. In April 2011, the CATT Research Group reported the results of a multicenter, single-blind, noninferiority trial, in which 1,208 patients with neovascular AMD were randomized to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or an as-needed schedule with monthly evaluations [15]. The as-needed group was treated with the PRN dosing schedule after one dose or ranibizumab or bevacizumab. At 12 months, the mean number of injections was 11.7 and the mean change in VA was 8.5 letters in the monthly group and 6.9 injections and 6.8 letters in the as-needed group. In that study, there were also no significant differences in the mean VA changes at any time points during the 12 months. Those results were similar to the current results (Table 1). In the current study, patients who received only one or two injections during the first 3 months in the 1+PRN group did not require an increased number of injections during the latter half of the year but rather required fewer injections (Figures 6, 7). Moreover, the improvement in the mean BCVA in these cases was significantly higher than in eyes that received monthly injections for the first 3 months in the 1+PRN group. Taken together, the results suggested that the loading regimen with three initial monthly intravitreal injections of ranibizumab might be unnecessary, at least in some cases, for treating neovascular AMD.

The current study, which of Gupta et al. [14], and the CATT study [15] showed that the 3+PRN or monthly group achieved more morphologic improvement than the 1+PRN group. We speculated that in some cases the intraretinal or subretinal fluid recurred in patients assigned to the PRN schedule even during the first 3 months in the 1+PRN group and affected the average decrease in the CRT. In fact, some PRN schedules in the PrONTO Study [11] ignored CRT thickening of less than 100 μm. It remains to be elucidated whether less morphologic improvement affects functional outcomes.

In conclusion, the current results suggested that the 1+PRN regimens led to equivalent functional and morphologic retinal improvements with fewer injections compared with the 3+ PRN regimens. Further studies are needed to determine the optimal intravitreal ranibizumab regimen for neovascular AMD during the first 3 months of treatment.

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Disclosure

The authors have no financial relationships with any organizations.

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