Evaluation of Injection Frequency and Visual Acuity Outcomes for Ranibizumab Monotherapy in Exudative Age-related Macular Degeneration

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Objective: To evaluate the visual outcomes for intravitreal ranibizumab administered on an as-needed basis for exudative age-related macular degeneration (AMD) and to investigate the relationship between injection frequency and visual outcome in this setting.

Design: Retrospective, interventional case series.

Participants: A total of 131 eyes with treatment-naïve, exudative AMD undergoing ranibizumab monotherapy.

Methods: Intravitreal ranibizumab was administered on an as-needed basis guided by clinical examination and optical coherence tomography (OCT). The OCT scans were evaluated by the treating physicians for the presence of intraretinal fluid, subretinal fluid, intraretinal cysts, or increasing pigment epithelial detachment size. Clinical data including visual acuity (VA), choroidal neovascularization lesion morphology, and treatment course were collected retrospectively for analysis.

Main Outcome Measures: Mean change in best-corrected Snellen VA.

Results: The mean age was 81.3 years, mean follow-up was 12±4.3 months (minimum 6 months, median 12 months), and mean number of injections was 5.2±2.8. Mean baseline Snellen VA for the entire population was 20/110 and significantly improved at 6 months (20/80; $P = 0.0002$) and at last follow-up (20/90; $P = 0.0066$). At 6 months, 31% of eyes had gained at least 3 lines of VA and 90.5% had avoided loss of 3 lines. On average, it took 3.0 injections and 3.5 months to achieve a "dry" or "flat" macula on OCT after initiating treatment. Resolution of intra- and subretinal fluid on OCT did not correlate with the degree of vision improvement. Eyes receiving more frequent injections (defined as <2 months mean inter-injection interval) gained more vision (+2.3 lines at 6 months) than eyes receiving injections less frequently (+0.46 lines at 6 months; $P = 0.012$). At 6 months, 3.1% of those in the more frequent injection group lost >3 lines of vision compared with 15.9% in the >2 months interval group ($P = 0.011$).

Conclusions: In a population receiving as-needed injections of ranibizumab for exudative AMD, visual improvement was related to the frequency of injections received but not to the resolution of fluid by OCT. Treatment with ranibizumab on a strictly as-needed basis may result in undertreatment and significantly less visual gain.

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Age-related macular degeneration (AMD) is the leading cause of blindness among the aging population.[1] The introduction of molecular inhibitors of vascular endothelial growth factor (VEGF), such as pegaptanib, ranibizumab, and bevacizumab, as approved and off-label therapy for choroidal neovascularization (CNV) due to exudative AMD has revolutionized our management of these patients.[2] The phase III pivotal clinical trials, 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), have demonstrated the efficacy and safety of monthly ranibizumab injections (Lucentis, Genentech, South San Francisco, CA) for the preservation and improvement of visual acuity (VA) in patients with CNV due to exudative AMD.[3,4]

These key trials did not incorporate a treatment end point and continued injections irrespective of clinical course. Some emerging evidence has supported the adoption of a variable VEGF inhibitor dosing strategy guided by serial diagnostic reevaluation by optical coherence tomography (OCT).[5] The Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intra-ocular Lucentis (PrONTO) study was a prospective investigator-sponsored trial in 40 eyes that demonstrated 3 lines or more VA gain

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in 35% of patients and avoidance of 3 lines VA loss in 95% of eyes receiving 3 monthly ranibizumab injections followed by as-needed treatment based on clinical examination and serial OCT monitoring.[5] This as-needed dosing scheme based on OCT has largely been adopted without any clinical trial evidence. Ongoing studies are currently evaluating the effectiveness of as-needed dosing regimens compared with monthly dosing, different monitoring strategies, and combination therapies to determine the optimal niche for this new class of drugs in AMD management (Martin DF. The Comparison of Age-Related Macular Degeneration Treatments Trials [CATT]. Presented at: Annual Advanced Vitreoretinal Techniques and Technology Conference, September 8, 2007, Chicago, IL).

The goal of the present study is to examine the effect of intravitreal ranibizumab monotherapy administered on an as-needed basis guided by OCT monitoring in treatment-naïve patients and to examine the relationship between dosing frequency and VA response to treatment in these patients.

Materials and Methods

After Cleveland Clinic Institutional Review Board approval, the charts of all patients with CNV due to exudative AMD receiving their first ranibizumab injection at the Cole Eye Institute (Cleveland, OH) between April 2006 and December 2007 were retrospectively reviewed. Patients were included in the study if they were older than 50 years of age, were treatment naïve and receiving their first ranibizumab injection for exudative AMD, and had at least 6 months of follow-up. Patients were excluded if there was documented evidence of diabetic retinopathy, vascular occlusion, epiretinal membrane, active uveitis, or any prior treatment for exudative AMD in the study eye before the initiation of ranibizumab monotherapy. In addition, patients with coexisting diagnoses that may lead to CNV, including 1 patient with lesions suggestive of presumed ocular histoplasmosis syndrome, 1 patient with myopic degeneration, 2 patients with vitelliform lesions, 1 patient with familial pattern dystrophy, and 1 patient with presumed idiopathic CNV, were excluded.

All eyes were treated with intravitreal injections of 0.5 mg ranibizumab per published guidelines. Injections were administered once at baseline and then on an as-needed basis at the discretion of the treating physician according to serial clinical evaluation and OCT monitoring using the Stratus OCT (software version 4.1, Carl Zeiss Meditec, Inc., Dublin, CA). All scans were obtained through a dilated pupil by experienced certified OCT photographers using Digital OCT Reading Center (DOCTR) Protocols consisting of a fast macular thickness map, which acquires six 6-mm radial lines consisting of 128 A-scans per line in 1.92 seconds of scanning; 3- and 6-mm horizontal and vertical linear cross-hair scans centered through the fovea as determined by evaluation of the red-free image on the computer monitor of the OCT scanner; and a custom posterior pole scan consisting of a 7-mm custom line scan that extends 5 degrees below horizontal from the temporal edge of the optic nerve toward the fovea. This custom scan pattern is based on a line extending from the center temporal edge of the optic nerve 5 degrees inferior-to-horizontal temporally. The treating physician evaluated the OCT images, and treatment was administered if there was evidence of any increased retinal thickening (i.e., intraretinal fluid), subretinal fluid (SRF), intraretinal cysts, or increasing pigment epithelial detachment (PED). Treatment was also delivered if there was clinical evidence of new or increasing subretinal or intraretinal hemorrhage on clinical examination.

Charts were reviewed for baseline demographic data, coexisting diagnoses, lens status, number of injections, and best-corrected Snellen VA at baseline, 1 month (±2 weeks), 2 months, 3 months, and 6 months (±4 weeks) after initiation of treatment and at the last documented follow-up visit. Snellen VA was converted to the logarithm of the minimal angle of resolution (logMAR) scale for statistical analyses based on formulas set forth previously.[6] Baseline fluorescein angiograms (FAs) were graded independently by 2 retina specialists (AV and JC) to determine CNV lesion composition, location, and size in disc areas using OIS WinStation Software (Medivision-OIS, Inc., Sacramento, CA). Baseline OCT scans were analyzed by 2 certified DOCTR readers (HD and SS) using DOCTR protocols for manual measurements of central retinal thickness, CNV thickness, SRF thickness, and PED height using Stratus OCT Reading Software version 4.1 (Carl Zeiss Meditec, Inc.).

Mean best-corrected VA compared with baseline was calculated using paired *t* test analysis. Unpaired *t* test analyses were performed for comparisons of mean VA change among groups based on mean injection frequency and for comparisons of CNV size and OCT lesion thickness among subgroups. Injection number was compared among anatomic treatment response groups using 1-way analysis of variance (ANOVA). Pairwise correlations were performed using Spearman's coefficient. Analyses of proportions of eyes with vision gain or loss were performed using the likelihood-ratio chi-square statistic. All statistical analyses were performed using JMP Software Version 7.0 (SAS Inc., Cary, NC).

Results

A total of 446 patients were reviewed, and 131 treatment-naïve eyes in 124 patients met the inclusion criteria and were included in the analysis. Demographic and clinical data for these patients are summarized in Table 1. The mean age was 81.3±8.3 years, and the gender distribution was 64.5% female. Baseline FAs were available for 104 eyes, and these revealed a mix of baseline lesion types (16.3% predominantly classic CNV, 16.3% minimally classic CNV, 66.3% occult with no classic CNV) that were mostly subfoveal or juxtafoveal in location (75% subfoveal, 20.2% juxtafoveal, and 4.8% extrafoveal). The mean baseline center subfield

Table 1. Patient, Lesion, and Treatment Characteristics

Age	Median 83 yrs, mean 81.3±8.3 yrs
Gender	44/124 (35.5%) male, 80/124 (64.5%) female
Diabetes mellitus	15/124 (12.1%)
Glaucoma	16/124 (12.9%)
History of uveitis	3/124 (2.4%)
Follow-up (mos)	Median 12, mean 12.0±4.3
Injections (total)	Mean 5.2±2.8
Time to dry (mos)*	Mean 3.5±2.6
Injections to dry*	Mean 3.0±2.0
Baseline FA: lesion type	17/104 (16.3%) classic, 17/104 (16.3%) min. classic, 69/104 (66.3%) occult
Baseline FA: lesion loc.	78/104 (75%) subfoveal, 21/104 (20.2%) juxtafoveal, 5/104 (4.8%) extrafoveal

FA = fluorescein angiogram; OCT = optical coherence tomography.
Mean data are presented as mean ± standard deviation.
*Subgroups demonstrating resolution of subretinal and intraretinal fluid by OCT and clinical examination (groups 1 and 2; n = 98).

Table 2. Visual Acuity Change and Anatomic Subgroups

Anatomic Subgroups*	Total	Group 1 (No Recurrence)	Group 2 (Recurrent Fluid)	Group 3 (Always Wet)
No. (%)	131/131 (100)	36/131 (27.5)	62/131 (47.3)	33/131 (25.2)
Mos F/U mean (SD)	12.0 (4.3)	10.4 (3.7)	14.2 (3.9)	9.7 (3.5)
Mean VA baseline	0.75 [~20/110]	0.79 [~20/125]	0.63 [~20/85]	1.02 [~20/200]
Mean VA – month 1 (*P* vs. baseline)†	0.65 [~20/90] (0.0013)	0.71 [~20/100] (0.075)	0.56 [~20/70] (0.057)	0.84 [~20/140] (0.0093)
Mean VA – month 2 (*P* vs. baseline)	0.60 [20/80] (<0.0001)	0.64 [~20/90] (0.0091)	0.51 [~20/63] (0.0012)	0.82 [~20/125] (0.0095)
Mean VA – month 3 (*P* vs. baseline)	0.61 [20/80] (<0.0001)	0.71 [~20/100] (0.10)	0.51 [~20/63] (0.0012)	0.74 [~20/110] (0.0007)
Mean VA – month 6 (*P* vs. baseline)	0.60 [~20/80] (0.0002)	0.73 [~20/110] (0.26)	0.46 [~20/60] (<0.0001)	0.79 [~20/125] (0.06)
Mean VA – last F/U (*P* vs. baseline)	0.65 [~20/90] (0.0066)	0.77 [~20/115] (0.42)	0.54 [20/70] (0.05)	0.76 [20/114] (0.012)
Month 3				
≥3 lines gained (%)	33/120 (27.5)	8/33 (24.2)	16/57 (28.1)	9/30 (30.0)
<3 lines lost (%)	110/120 (91.7)	30/33 (90.9)	51/57 (89.5)	29/30 (96.7)
Month 6				
≥3 lines gained (%)	39/126 (31.0)	11/34 (32.4)	19/60 (31.7)	9/32 (28.1)
<3 lines lost (%)	114/126 (90.5)	29/34 (85.3)	56/60 (93.3)	29/32 (90.6)
Last F/U				
≥3 lines gained (%)	39/130 (30.0)	8/36 (22.2)	20/61 (32.8)	11/33 (33.3)
<3 lines lost (%)	109/130 (83.8)	29/36 (80.6)	51/61 (83.6)	29/33 (87.9)

VA = visual acuity (mean logMAR format with Snellen conversion in brackets); SD = standard deviation; F/U = follow-up.
*Subgroups defined by anatomic response to treatment. Group 1 = resolution of subretinal/intraretinal fluid by OCT and clinical examination without recurrence, no further injections after "dry." Group 2 = resolution of fluid at some time with at least 1 recurrence based on OCT and clinical examination. Group 3 = persistent subretinal or intraretinal fluid throughout the follow-up period.
†Paired *t* test analyses restricted to datasets with observations at all timepoints (total n = 99; group 1 n = 26; group 2 n = 53; group 3 n = 20).

thickness by OCT was 299.2 μm. Detectable SRF was present in 75.7% of eyes at baseline, and a PED was present in 68.9%.

Both mean and median follow-ups from the time of the first injection were 12 months. The mean total number of injections was 5.2±2.8 over this follow-up period. For those eyes demonstrating complete resolution of intraretinal fluid and SRF on follow-up OCT (i.e., "dry" or "flat" OCT), the mean number of injections to achieve this anatomic end point was 3.0±2.0 injections over 3.5±2.6 months from the time of the initial injection.

As shown in Table 2, the mean baseline VA was 20/110 and there was a statistically significant improvement in vision to 20/90 as early as month 1 (i.e., after a single injection; paired *t* test, $P = 0.0013$). At month 6, average VA was 20/80 ($P = 0.0002$) and mean VA at last follow-up was approximately 20/90 ($P = 0.0066$). The mean change in Snellen VA from baseline was +1 line, +1.5 lines, +1.4 lines, +1.5 lines, and + 1 line at months 1, 2, 3, and 6, and last follow-up, respectively. At 6 months, 31% of eyes had gained at least 3 lines of VA, 57.1% had gained more than 0 letters, and 90.5% had avoided the loss of 3 lines or more of VA. The proportion of eyes with 3 lines or more gained remained 30% at last follow-up; however, the proportion gaining any VA was 49.2% and only 83.8% avoided loss of 3 or more lines VA at last follow-up.

On the basis of the anatomic response to treatment (as determined by the presence of any retinal fluid on follow-up OCT), we defined 3 subgroups (Table 2). Group 1 (n = 36) included those eyes that showed completely resolved intraretinal fluid and SRF, that showed no evidence of recurrence clinically or by OCT on serial reexaminations during the study follow-up, and that required no further treatment. Group 2 (n = 62) included those eyes that demonstrated resolution of fluid as described previously, but then had at least 1 recurrence of either subretinal or intraretinal fluid on repeat examination during follow-up that required reinitiation of injections after they were initially stopped. Group 3 (n = 33) included those eyes that had persistent leakage by OCT throughout the follow-up period, and injections were never stopped. These groups were defined for demonstrative purposes within the context of this study, and it is understood that given a sufficiently long follow-up the majority of eyes in group 1 would likely cross over into group 2 as defined previously.

Although all groups demonstrated some improvement in VA with treatment, there was a clear trend toward greater improvement in groups 2 and 3 (Fig 1). Although group 1 appeared to exhibit moderate VA improvement within the first few months, the vision gradually drifted toward baseline VA (20/125) by the last follow-up (20/115, $P = 0.42$). At last follow-up, 22.2% of eyes in group 1 had gained at least 3 lines of VA, compared with 32.8% and 33.3% in groups 2 and 3, respectively. Although there was a trend toward greater VA improvement in groups 2 and 3 compared

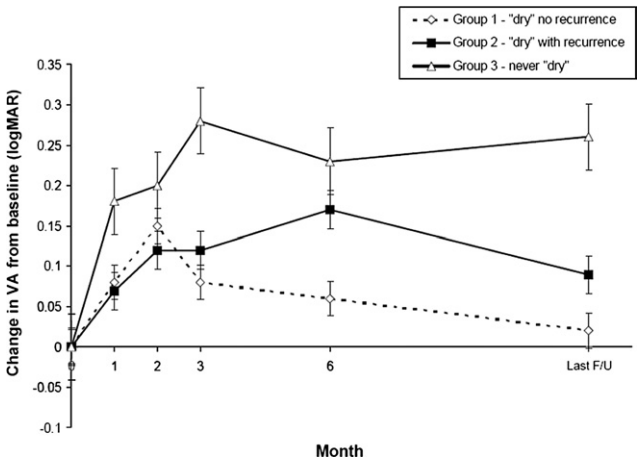

Figure 1. Visual acuity change by anatomic response group. Mean VA change from baseline was plotted for each group at the indicated time intervals and at last follow-up. Error bars indicate standard error. VA = visual acuity; logMAR = logarithm of the minimal angle of resolution; F/U = follow-up.

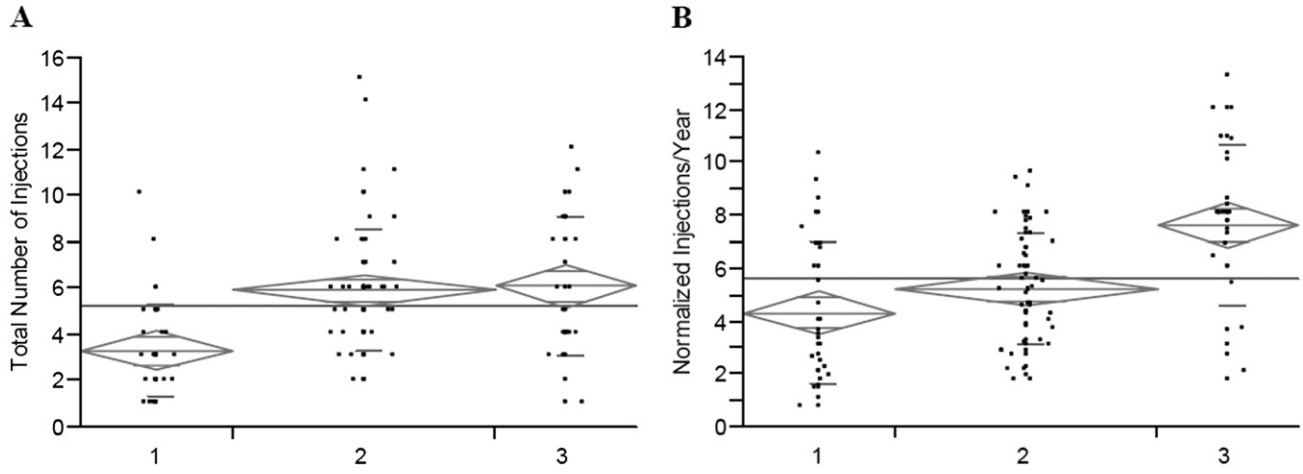

Figure 2. Injection number by anatomic response group. Scatter diagrams depict total number of injections **(A)** and number of injections normalized by follow-up period to approximate injections per year **(B)** for anatomic response groups 1, 2, and 3 (defined above). Diamonds indicate means and 95% CIs for each group. Outer lines indicate standard deviation. All means were compared by 1-way ANOVA.

with group 1, the differences in VA change at month 3, month 6, and last follow-up were not significantly different between the 3 groups (ANOVA, all $P>0.4$; pairwise t tests, all $P>0.2$).

When the mean number of injections was compared among groups 1 (3.3±2.0), 2 (5.9±2.6), and 3 (6.1±3.0), there were significantly more injections in groups 2 and 3 (Fig 2; ANOVA, $P<0.0001$). A normalized measure representing the average number of injections per year also was calculated for every eye in each group. By using this measurement, the normalized injections for groups 1 (4.3±2.7), 2 (5.2±2.1), and 3 (7.6±3.0) also were significantly different (ANOVA, $P<0.0001$). Normalized injections per year then were compared against VA change at last follow-up, and bivariate analysis revealed a weak association with a trend toward greater VA gain with a larger number of injections per year (Spearman $r = 0.21$, $P = 0.014$).

An approximation of injection frequency was obtained by dividing the total follow-up duration by the total number of injections to determine the relationship between injection frequency and VA change. The study population was then divided into 2 groups on the basis of injection frequency: those who received repeat injections at a mean interval of ≤2 months throughout the follow-up period (<2 months; n = 65) and those with an average injection interval of >2 months (>2 months; n = 66). In the <2 months and >2 months groups, the percentages of female patients were 60% and 69.7%, respectively ($P = 0.24$), and the mean ages were 81±8.4 years and 81.5±8.0 years, respectively ($P = 0.74$). The mean baseline VA (logMAR) was 0.70±0.50 for the <2 months group and 0.84±0.57 for the >2 months group ($P = 0.15$). Baseline OCT characteristics were compared among the 103 eyes for which baseline OCTs were available. Baseline central retinal thickness measurements for the <2 months group (n = 52) and >2 months group (n = 51) were 261 μm and 288 μm, respectively ($P = 0.38$), and there were no significant differences in the distribution of specific morphologic features on baseline OCT: SRF present in 78.9% versus 72.6%, respectively ($P = 0.46$); intraretinal fluid present in 90.4% versus 88.2%, respectively ($P = 0.72$); lipid exudates present in 61.5% versus 54.9%, respectively ($P = 0.49$); and PED present in 73.1% versus 64.7%, respectively ($P = 0.36$). Also, for those lesions with measurable CNV, SRF, or PED on baseline OCT, there was no statistically significant difference between the <2 months group and the >2 months group in mean CNV thickness ($P = 0.91$), mean SRF thickness ($P = 0.3$), or mean PED height ($P = 0.14$). Baseline angiographic characteristics were compared among the 104 eyes for which baseline FAs were available. Mean CNV lesion sizes in the <2 months group (n = 53) and >2 months group (n = 51) were 5.5 and 5.6 disc areas, respectively ($P = 0.95$). The percentages of predominantly classic, minimally classic, occult, and indeterminate CNV types were 11.3%, 18.9%, 67.9%, and 1.9%, respectively, for the <2 months group and 21.6%, 13.7%, 64.7%, and 0%, respectively, for the >2 months group, ($P = 0.32$). Lesion locations were subfoveal, juxtafoveal, and extrafoveal in 79.3%, 17.0%, and 3.8%, respectively, for the <2 months group and 70.6%, 23.5%, and 5.9%, respectively, for the >2 months group ($P = 0.59$). Thus, we were unable to identify any baseline feature that differed significantly between these 2 groups.

As shown in Figure 3, those who received repeat injections at a mean interval of 2 months or less throughout the follow-up period had a greater improvement in VA at month 6 (mean change in vision +2.3 lines, 95% confidence interval [CI] +0.14 to +0.32 logMAR) and at last follow-up (mean change in vision +2.1 lines, 95% CI +0.11 to +0.31 logMAR) compared with those with >2 months average injection interval at 6 months (mean change in vision +0.46 lines, 95% CI −0.087 to +0.18 logMAR; $P = 0.012$) and at last follow-up (mean change in vision −0.22 lines, 95% CI −0.14 to +0.095 logMAR; $P = 0.0015$). Similarly, there was a trend toward a higher percentage of eyes gaining at least 3 lines of VA in the <2 months injection interval group compared with the >2 months group (37.5% vs. 24.2% at 6 months follow-up, $P = 0.11$), but this difference did not reach statistical significance. The difference in percentage of eyes with 3 lines of VA loss, however, was statistically significant (Fig 4) with less loss in the <2 months group (3.1% at 6 months, 7.8% at last follow-up) compared with the >2 months group (15.9% at 6 months, $P = 0.011$; 24.2% at last follow-up, $P = 0.0093$).

Discussion

Determining the optimal dosing schedule for anti-VEGF therapy for exudative AMD remains a challenge because neither the effect of the drugs in human eyes nor the nature of the disease itself is fully understood. On the basis of the MARINA and ANCHOR trial data, the best reported efficacy, in terms of VA preservation and gain, is seen with

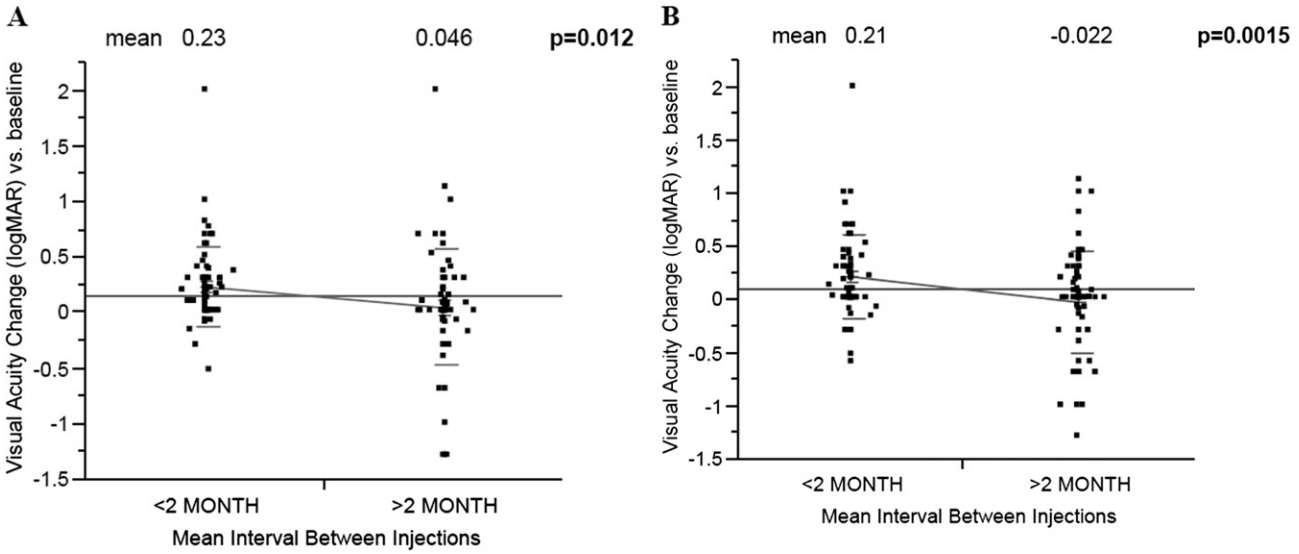

Figure 3. Greater mean VA improvement with higher injection frequency. Scatter diagrams depict mean VA change (logMAR) from baseline at 6 months **(A)** and at last follow-up **(B)** for eyes receiving injections at an average interval of ≤2 months versus an average interval of >2 months over the follow-up period. Means were compared by unpaired *t* test. Inner error lines represent mean and standard error, and outer error lines represent standard deviation. VA = visual acuity; logMAR = logarithm of the minimal angle of resolution.

mandated monthly dosing.[3,4] However, these trials did not follow a clinical end point for treatment cessation, and such a regimen raises concerns for overtreatment. Because VEGF is a survival factor, long-term VEGF suppression may lead to ocular problems that we have not yet identified. Although reported risks of injection-related adverse events such as retinal detachment or endophthalmitis are low,[3,4,7,8] they are not zero, and the results can be devastating. Minimizing the number of injections would decrease this risk. Finally, overuse of such treatments is certain to present an unnecessarily heavy financial burden on society given the cost of ranibizumab.[9,10]

Thus, for multiple reasons, it is desirable to find a dosing regimen that is maximally effective at preserving or improving VA while at the same time is intended to avoid treatment when it is not needed. The Phase IIIb, Multi-center, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab (PIER) assessed the efficacy of fixed quarterly dosing by evaluating a regimen of 3 monthly injections on enrollment, followed by mandated injections every 3 months thereafter for a total of 2 years.[11] In the ranibizumab groups, there was an initial mean improvement in VA by approximately 1 line after the loading phase of 3 monthly injections. However, at 12

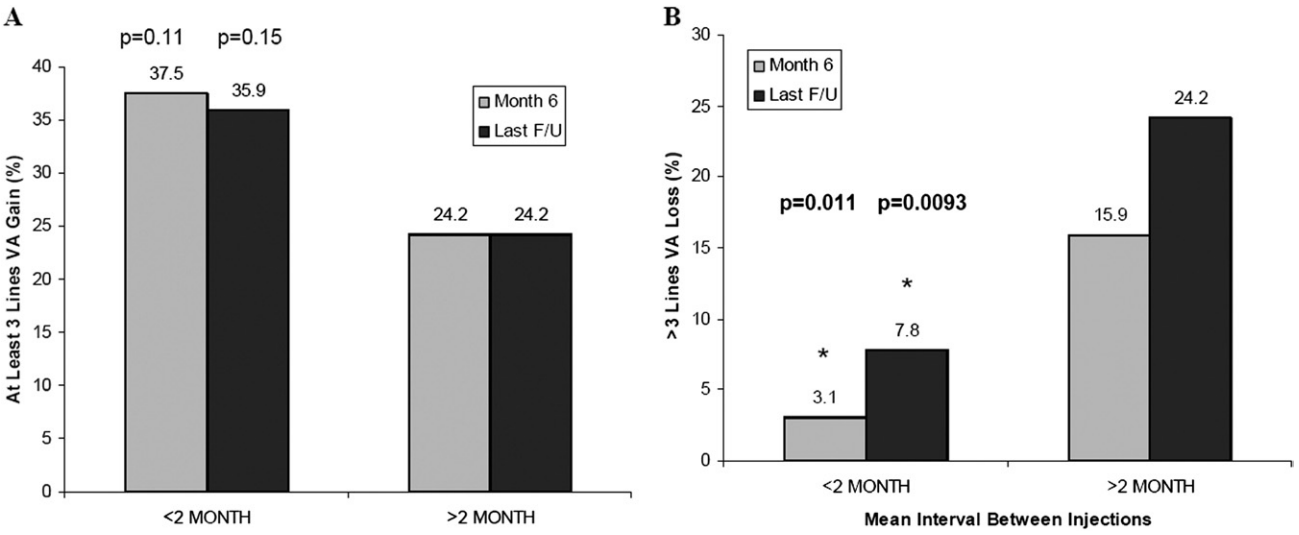

Figure 4. Moderate vision gain and loss by injection interval. Percentage of eyes in each group with at least 3 lines VA gain **(A)** or >3 lines VA loss **(B)** at 6 months and at last follow-up for each injection frequency group was compared by likelihood-ratio chi-square test. VA = visual acuity; F/U = follow-up.

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