Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCITE Study

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Objective: To demonstrate noninferiority of a quarterly treatment regimen to a monthly regimen of ranibizumab in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Design: A 12-month, multicenter, randomized, double-masked, active-controlled, phase IIIb study.

Participants: Patients with primary or recurrent subfoveal CNV secondary to AMD (353 patients), with predominantly classic, minimally classic, or occult (no classic component) lesions.

Intervention: Patients were randomized (1:1:1) to 0.3 mg quarterly, 0.5 mg quarterly, or 0.3 mg monthly doses of ranibizumab. Treatment comprised of a loading phase (3 consecutive monthly injections) followed by a 9-month maintenance phase (either monthly or quarterly injection).

Main Outcome Measures: Mean change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) from baseline to month 12 and the incidence of adverse events (AEs).

Results: In the per-protocol population (293 patients), BCVA, measured by Early Treatment Diabetic Retinopathy Study-like charts, increased from baseline to month 12 by 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly (104 patients), 0.5 mg quarterly (88 patients), and 0.3 mg monthly (101 patients) dosing groups, respectively. Similar results were observed in the intent-to-treat (ITT) population (353 patients). The mean decrease in CRT from baseline to month 12 in the ITT population was -96.0 μm in 0.3 mg quarterly, -105.6 μm in 0.5 mg quarterly, and -105.3 μm in 0.3 mg monthly group. The most frequent ocular AEs were conjunctival hemorrhage (17.6%, pooled quarterly groups; 10.4%, monthly group) and eye pain (15.1%, pooled quarterly groups; 20.9%, monthly group). There were 9 ocular serious AEs and 3 deaths; 1 death was suspected to be study related (cerebral hemorrhage; 0.5 mg quarterly group). The incidences of key arteriothromboembolic events were low.

Conclusions: After 3 initial monthly ranibizumab injections, both monthly (0.3 mg) and quarterly (0.3 mg/0.5 mg) ranibizumab treatments maintained BCVA in patients with CNV secondary to AMD. At month 12, BCVA gain in the monthly regimen was higher than that of the quarterly regimens. The noninferiority of a quarterly regimen was not achieved with reference to 5.0 letters. The safety profile was similar to that reported in prior ranibizumab studies.

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**Group members listed online in Appendix 1 (available at http://aaojournal.org).*

Vascular endothelial growth factor (VEGF)-A is a key factor involved in the pathogenesis of choroidal neovascularization (CNV).[1–5] Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA) is a recombinant, fully humanized, affinity-matured monoclonal antigen-binding antibody fragment that inhibits the binding of multiple biologically active forms of VEGF-A to their receptors.[6–8]

Two pivotal Phase III trials, MARINA (*M*inimally classic/occult trial of the *A*nti-VEGF antibody *R*anibizumab *I*n the treatment of *N*eovascular *A*ge-related macular degeneration)[9] and ANCHOR (*AN*ti-VEGF antibody for the treatment of predominantly classic *CHOR*oidal neovascularization in age-related macular degeneration),[10,11] have previously demonstrated the efficacy of the monthly dosing regimens of ranibizumab in improving visual acuity (VA) in patients with subfoveal CNV secondary to age-related macular degeneration (AMD). These studies also described the safety and tolerability profile of intravitreal treatment using ranibizumab. Based on its favorable benefit/risk ratio, ranibizumab received marketing authorization for the treatment of CNV secondary to AMD from the US Food and

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Drug Administration, the European Medicines Evaluation Agency, and many other national health authorities around the world since 2006.

Although the monthly regimen of ranibizumab provides the best known treatment outcome as indicated by cumulative clinical evidence,[10,11] there was a need to evaluate whether a less frequent treatment regimen can also be effective, while decreasing the treatment burden caused by monthly intravitreal injections. In this context, the PIER (A *P*hase IIIb, Multicenter, Randomized, Double Masked, Sham *I*njection Controlled Study of the *E*fficacy and Safety of *R*anibizumab in Subjects with Subfoveal Choroidal Neovascularization [CNV] with or without Classic CNV Secondary to Age- Related Macular Degeneration) study of the 12-month efficacy of quarterly dosing of ranibizumab after 3 consecutive monthly injections (6 doses per year instead of 12 for the first treatment year) was the first to test an alternative maintenance regimen.[12] The 12-month efficacy result of PIER showed that both 0.3 mg and 0.5 mg ranibizumab injections provided statistically significant superiority in VA improvement as compared with sham treatment, with corresponding treatment differences of ≥3 lines. However, mean changes in best-corrected VA (BCVA) from baseline to month 12 in the quarterly ranibizumab dosing groups (−1.6 letters for 0.3 mg and −0.2 letters for 0.5 mg) was lower than that observed with the monthly dosing regimens of 0.3 mg and 0.5 mg ranibizumab in the MARINA (+7.2 letters) and ANCHOR studies (+11.3 letters). Importantly, because these studies did not directly compare the monthly and quarterly dosing regimens, an appropriate inference of the clinical benefits of the different maintenance treatment regimens is limited.

The first prospective trial designed to directly compare monthly and quarterly ranibizumab dosing regimens, EXCITE evaluated patients with subfoveal CNV secondary to AMD. This 1-year study had an active control arm of continuous monthly injections (0.3 mg) versus the less frequent dosing schedules of 3 initial monthly injections of 0.3 mg or 0.5 mg ranibizumab followed by quarterly injections of the respective doses. The primary objective of this study was to investigate whether a maintenance strategy using a quarterly dosing regimen (0.3 and 0.5 mg) was noninferior to a monthly dosing regimen as determined by the mean change in BCVA from baseline to month 12 in the study population. The key secondary objectives were to assess possible differences in the proportion of patients with loss or gain of BCVA of ≥15 letters, loss of BCVA of ≥30 letters, mean change in central retinal thickness (CRT) from baseline, overall safety, and tolerability.

Methods

Study Design

The EXCITE study was a 1-year, randomized, double-masked, active-controlled, multicenter, Phase IIIb study in patients with subfoveal CNV secondary to AMD, comparing the efficacy and safety of quarterly dosing regimens of ranibizumab with a monthly dosing regimen during the maintenance phase, that is, from month 3 onward.

Eligible patients were randomly assigned in a 1:1:1 ratio to any of the following 3 double-masked treatment arms (Fig 1): loading doses of 3 initial monthly intravitreal injections of 0.3 mg (arm A) or 0.5 mg (arm B) ranibizumab followed by quarterly injections of the respective doses at months 5, 8, and 11 (i.e., a total of 6 injections) or 0.3 mg ranibizumab administered monthly from baseline to month 11 (arm C, active control) (i.e., a total of 12 injections). Primary end point analysis was at month 12. To maintain masking, patients in treatment arms A and B were administered a sham injection during the monthly visits for which no intravitreal injection was scheduled.

This study was conducted in a total of 59 study centers in 16 European countries, Australia, Brazil, Israel, and Turkey in accordance with the declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Approval was obtained from the independent Ethics Committee or Institutional Review board at each participating center. All patients provided signed informed consent before participating in the study. The trial is registered at clinicaltrials.gov (NCT00275821).

Inclusion and Exclusion Criteria

Patients aged ≥50 years and suffering from primary or recurrent subfoveal CNV secondary to AMD, with predominantly classic, minimally classic, or occult (with no classic component) lesions were included in the study. The reading center (DARC) required active CNV for confirmation of the patient inclusion. Other inclusion criteria, based on study eye characteristics were as follows: total area of CNV (including classic and occult components) ≥50% of the total lesion area; the total lesion area ≤12 disc areas for minimally classic or occult with no classic component or ≤9 disc areas (5400 μm) for predominately classic lesions; and BCVA score between 73 and 24 letters (approximately 20/40 to 20/320 Snellen equivalent).

Exclusion criteria were as follows: BCVA score of <34 letters in both eyes; previous treatment or participation in a clinical trial (for either eye) with antiangiogenic drugs; use of any other investigational drugs at the time of screening, or within 30 days or 5 half-lives of screening; prior treatment in the study eye with verteporfin, external-beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy, or transpupillary thermotherapy; operative intervention for AMD in the past in the study eye; laser photocoagulation in the study eye within 1 month preceding baseline; angioid streaks or precursors of CNV in either eye due to

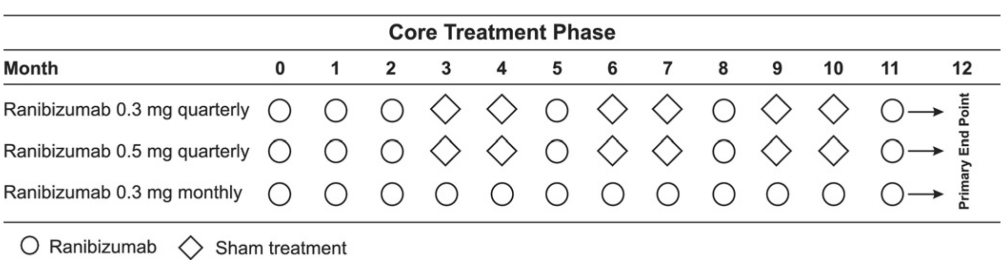

Figure 1. Dosing schedule of ranibizumab regimen in the EXCITE study.

other causes; clinically significant subretinal hemorrhage in the study eye that involved the foveal center; or any other significant clinical condition detrimental to the study outcome.

Patients' eligibility was confirmed by an independent masked Central Reading Center, DARC, at screening by fundus photography and fluorescein angiography. The DARC also classified the lesion types and assessed lesion area, area of CNV, and leakage activity based on fluorescein angiography at months 6 and 12. A separate independent masked Central Reading Center (Vienna Reading Center) reviewed optical coherence tomography (OCT) images to provide an objective assessment of retinal thickness for each monthly assessment of all patients.

Study Assessments

Efficacy. Visual acuity was assessed in both eyes at each study visit using Early Treatment Diabetic Retinopathy Study-like charts at an initial testing distance of 4 m. The change in BCVA from baseline to each visit was assessed. The mean change in BCVA from baseline to month 12 was the primary end point. In addition, change in BCVA was assessed as the proportion of patients with <15 letters loss, ≥30 letters loss, ≥0 letters gain, and ≥15 letters gain in BCVA from baseline to month 12. The CRT was measured in both eyes by time domain OCT at screening, and at each monthly visit until month 12. Baseline BCVA and OCT were performed before treatment. Fluorescein angiograms were used to evaluate CNV lesions at screening, month 6, and month 12. In 84% of patients (296 out of 353 patients), visual function contrast sensitivity was assessed in both eyes at baseline, month 6, and month 12 using Pelli-Robson charts.

Safety. Adverse events (AEs), serious AEs, and changes in vital signs were assessed monthly during the study. Biochemical values were measured at screening and at the end of the study visit (month 12), and hematology, blood chemistry, and urine were regularly monitored. Intraocular pressure measurement (before and after each administration by tonometry) and standard ophthalmic examination were also performed monthly.

Statistical Analysis

A population size of 350 randomized patients was planned to reach a sample size of 101 per protocol (PP) patients per treatment arm, assuming a dropout and protocol deviation rate of 13%. The dropout rate and protocol deviation calculations were based on results of the MARINA clinical study data. The PP population was chosen as the primary analysis population to assess the primary end point and to evaluate the null hypothesis of noninferiority of quarterly treatment regimen to monthly treatment regimen in terms of change in BCVA from baseline to month 12. Assuming that there is no difference between quarterly and monthly treatment regimens, there was a power of ≥83% to reject this null hypothesis and therefore conclude that quarterly treatment is noninferior to monthly treatment using 6.8 letters as the noninferiority margin.

For both alternative dosing treatment arms (0.3 and 0.5 mg quarterly), the noninferiority to the reference arm (0.3 mg monthly) was tested using 1-sided testing procedures (or equivalent, using 1-sided confidence intervals [CIs]), while keeping an overall type I error level of 0.025. The Hochberg procedure was used to control for multiplicity; that is, the null hypothesis was rejected if either or both comparisons were statistically significant at a 0.025 level or ≥1 comparison was statistically significant at a 0.0125 level. For both quarterly dosing arms (0.3 and 0.5 mg), the null hypothesis H_0: $u_q - u_m \leq -6.8$ and the alternative hypothesis H_a: $u_q - u_m > -6.8$ were tested, where u_q and u_m were the mean changes in BCVA from baseline/month 3 to month 12 in the quarterly dosing treatment arms (q) and the monthly reference arm (m), respectively, with a noninferiority limit of −6.8. The noninferiority limit was based on the results of a previous study in which the value of 6.8 was approximately one half of the minimum estimated difference (13.6; lower limit of a 2-sided 95% CI) in the mean change in BCVA from baseline to month 12, with testing distance of 4 m between the ranibizumab 0.3 mg and sham injection groups.[9] Noninferiority of 0.5 mg quarterly to 0.3 mg monthly was assessed based on the change from baseline to month 12, and noninferiority analysis of 0.3 mg quarterly versus 0.3 mg monthly could be based on the change from month 3 to month 12 because any differences at month 3 between the 0.3 mg groups could be attributed to chance (up to the month 3 assessment there was no difference in the corresponding treatment regimen).

The mean change in BCVA from baseline to month 12 was analyzed by using an analysis of variance with treatment, baseline BCVA (≤52 vs ≥53 letters), and lesion type as factors.

The primary end point was analyzed for both PP and intent-to-treat (ITT) populations. The PP population was a subset of the ITT population and included patients who had an assessment for BCVA at month 12 and with no major study protocol deviation. The ITT population comprised all randomized patients. The last observation carried forward method was used to impute missing values for the ITT population for all efficacy measures. All the

Table 1. Summary of the EXCITE Patient Disposition

	0.3 mg Quarterly, *n* (%)	0.5 mg Quarterly, *n* (%)	0.3 mg Monthly, *n* (%)	Total, *n* (%)
Enrolled	—	—	—	482
Randomized	120	118	115	353
Completed*	106 (88.3)	95 (80.5)	103 (89.6)	304 (86.1)
Early discontinued from study	14 (11.7)	23 (19.5)	12 (10.4)	49 (13.9)
Adverse event(s)	4 (3.3)	12 (10.2)	5 (4.3)	21 (5.9)
Administrative problems	3 (2.5)	4 (3.4)	4 (3.5)	11 (3.1)
Patient withdrew consent	0	2 (1.7)	1 (0.9)	3 (0.8)
Lost to follow-up	0	1 (0.8)	1 (0.9)	2 (0.6)
Death	0	2 (1.7)	1 (0.9)	3 (0.8)
Abnormal test procedure result(s)	0	0	0	0
Unsatisfactory therapeutic effect	2 (1.7)	1 (0.8)	0	3 (0.8)
Protocol deviation	5 (4.2)	1 (0.8)	0	6 (1.7)

*Completed the study and underwent visual acuity assessment at month 12.

safety parameters were calculated for the safety (i.e., ITT, in this study) population.

Results

Patients

A total of 482 patients were screened and 353 patients were randomized for treatment with the study medication. As per the study design, patients received ranibizumab 0.3 mg quarterly (120 patients), ranibizumab 0.5 mg quarterly (118 patients), or ranibizumab 0.3 mg monthly dosing (115 patients). The PP population included 104 patients (86.7%) from the 0.3 mg quarterly, 88 (74.6%) from the 0.5 mg quarterly, and 101 (87.8%) from the 0.3 mg monthly dosing groups. The study was completed by 106 patients (88.3%) in the ranibizumab 0.3 mg quarterly group, 95 (80.5%) in the ranibizumab 0.5 mg quarterly group, and 103 (89.6%) in the ranibizumab 0.3 mg monthly treatment group. In all 3 treatment groups, the most frequently reported reason for early discontinuation from study was AEs (3.3% in 0.3 mg quarterly; 10.2% in 0.5 mg quarterly; 4.3% in 0.3 mg monthly). Details of patient disposition are given in Table 1.

Baseline Characteristics and Treatment Exposure

Baseline demographic and ocular disease characteristics of patients (ITT population) in the EXCITE study are summarized in Table 2. The treatment groups were balanced with respect to baseline BCVA, CRT, and fluorescein angiography of the study eye. Approximately 20% of patients had predominantly classic lesion, 40% patients had minimally classic lesion, and 40% patients had occult (with no classic component) lesion.

The mean (standard deviation) number of active treatment injections received over the study treatment period from baseline to month 11 were 5.7 (0.80), 5.5 (1.05), and 11.4 (1.69) in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively.

Efficacy

The mean change in BCVA in the study eye from baseline over time (PP population) is shown in Figure 2A. In the PP population,

Table 2. Demographics and Baseline Characteristics of the Study Eye of Patients who Entered Treatment in the EXCITE Study (Intent-to-Treat Population)

Characteristic	0.3 mg Quarterly (n = 120)	0.5 mg Quarterly (n = 118)	0.3 mg Monthly (n = 115)	Total (n = 353)
Gender, n (%)				
Women	70 (58.3)	73 (61.9)	66 (57.4)	209 (59.2)
Men	50 (41.7)	45 (38.1)	49 (42.6)	144 (40.8)
Race, n (%)				
Caucasian	118 (98.3)	117 (99.2)	113 (98.3)	348 (98.6)
Asian	1 (0.8)	0	0	1 (0.3)
Other	1 (0.8)	1 (0.8)	2 (1.7)	4 (1.1)
Age (yrs)				
Mean (SD)	75.1 (7.45)	75.8 (6.96)	75 (8.26)	75.3 (7.56)
Age group, n (%)				
50–64	13 (10.8)	12 (10.2)	10 (8.7)	35 (9.9)
65–74	37 (30.8)	28 (23.7)	45 (39.1)	110 (31.2)
75–84	61 (50.8)	72 (61.0)	46 (40.0)	179 (50.7)
≥85	9 (7.5)	6 (5.1)	14 (12.2)	29 (8.2)
History				
Years since first diagnosis, mean (SD)	0.57 (1.424)	0.52 (1.14)	0.56 (2.177)	0.55 (1.629)
BCVA (letters)*				
Mean (SD)	55.8 (11.81)	57.7 (13.06)	56.5 (12.19)	56.7 (12.4)
≤52	46 (38.3)	33 (28.0)	36 (31.3)	115 (32.6)
≥53	74 (61.7)	85 (72.0)	79 (68.7)	238 (67.4)
BCVA (Snellen equivalent)*				
≤20/200	5 (4.2)	8 (6.8)	6 (5.2)	19 (5.4)
>20/200 and <20/40	94 (78.3)	84 (71.2)	86 (74.8)	264 (74.8)
≤20/40	21 (17.5)	26 (22.0)	23 (20.0)	70 (19.8)
CNV classification				
Predominantly classic	25 (20.8)	27 (22.9)	21 (18.3)	73 (20.7)
Minimally classic	50 (41.7)	46 (39.0)	46 (40.0)	142 (40.2)
Occult (no classic)	45 (37.5)	45 (38.1)	48 (41.7)	138 (39.1)
Retinal thickness at central point (μm)[§]				
n	100	100	95	295
Mean (SD)	313.6 (85.05)	324.5 (115.94)	320.6 (118.55)	319.5 (107.13)
Retinal thickness at central subfield (μm)				
Mean (SD)	321.4 (86.80)	331.9 (105.74)	326.6 (99.44)	326.6 (97.38)

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
*Measured using ETDRS-like charts at a distance of 4 m.
[§]Measured using optical coherence tomography.

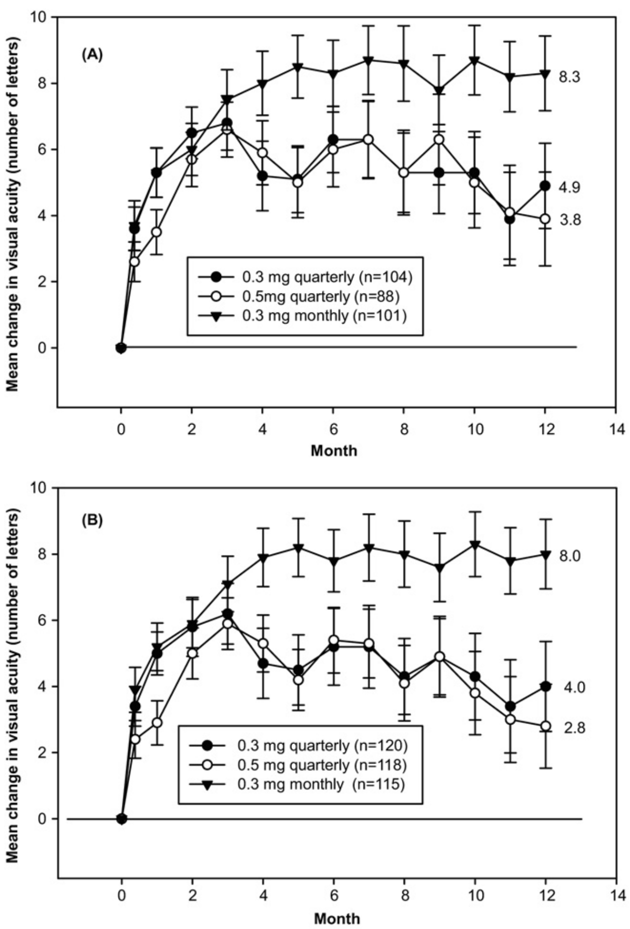

Figure 2. Mean change in best-corrected visual acuity score from baseline over time in the (**A**) per-protocol population (study visit) and (**B**) intent-to-treat population (last observation carried forward [LOCF]) of EXCITE. Vertical bars represent standard error of the mean.

the mean BCVA increase from baseline to month 12 (primary end point) was 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively. In all the 3 treatment arms, the mean BCVA increased from baseline to month 3 (monthly dosing phase for all treatment arms) by 6.8, 6.6, and 7.5 letters, in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively. However, between months 3 and 12 (maintenance phase), patients in the quarterly treatment groups lost 1.8 (0.3 mg quarterly) and 2.8 (0.5 mg quarterly) letters, whereas patients in the monthly treatment group gained 0.8 letters on average. Up to month 3, there was no notable difference between the treatment arms. The first notable difference was observed at month 4, that is, 2 months after the last loading dose (Fig 2A). Although this study was designed to test noninferiority of the quarterly treatment regimen versus monthly treatment regimen, this was not achieved for the 0.5 mg quarterly regimen, as evidenced by the lower CI limits for the corresponding treatment difference being below the noninferiority threshold of −6.8 letters (95% CI, −7.9 to −0.7; 97.5% CI, −8.4 to −0.2; $P = 0.0867$). For the comparison of 0.3 mg quarterly versus 0.3 mg monthly treatment groups (from months 3 to 12), the lower CI limit (97.5% CI, −5.6 to 0.22; $P = 0.0008$), however, indicates a theoretical noninferiority, also driven by the smaller variability in the end point 'change from months 3 to 12' compared with 'change from baseline to month 12.' However, given that the 97.5% CI barely includes 0, it can be interpreted that 0.3 mg quarterly treatment is numerically inferior to the 0.3 mg monthly treatment regimen.

The BCVA time course in the ITT population (last observation carried forward method) was consistent with that of the PP population, with a mean change in BCVA from baseline to month 12 of 4.0, 2.8, and 8.0 letters for the ranibizumab 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively ($P = 0.0751$ [95% CI, −7.7 to −0.9] for the 0.3 mg quarterly and $P = 0.1678$ [95% CI, −8.6 to −1.7] for the 0.5 mg quarterly, both compared with the 0.3 mg monthly group). In the monthly treatment regimen, the initially gained mean BCVA remained stable during the treatment period, whereas it gradually decreased in the quarterly treatment regimens with a pattern reflecting the impact of the quarterly injections (Fig 2B). The BCVA values at baseline and the change from baseline at month 12 are given in Table 3 for both the PP and the ITT populations.

The proportion of patients who lost <15 letters from baseline to month 12 was similar across the treatment groups (ITT population) with 93.3%, 91.5%, and 94.8% in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly ranibizumab groups, respectively (Fig 3A). The proportion of patients who had a VA gain of ≥15 letters from baseline to month 12 was 14.2% in the ranibizumab 0.3 mg quarterly group, 17.8% in the ranibizumab 0.5 mg quarterly group, and 28.7% in the ranibizumab 0.3 mg monthly group (Fig 3B). The proportion of patients with a gain of ≥0 letters of VA were 71.7% (86/120; 0.3 mg quarterly), 66.9% (79/118; 0.5 mg quarterly), and 82.6% (95/115; 0.3 mg monthly) at month 12.

The percentage of patients, at month 12, with a VA Snellen equivalent of ≤20/200 (BCVA = 34 letters) was greater in the quarterly dosing regimen (7.5% for 0.3 mg and 6.8% for 0.5 mg) compared with the 0.3 mg monthly dosing regimen (2.6%). Severe vision loss (≥30 letters) at the end of this study was observed in 2 patients (1.7%) of each of the quarterly treatment groups and in none of the 0.3 mg monthly treatment group.

Anatomically, the overall reduction in CRT of the study eye from baseline to month 3 and to month 12 was similar between the 3 treatment groups in the ITT population. However, although the mean CRT decreased similarly from baseline to month 3 in all 3 treatment groups, thereafter it remained more or less stable at the monthly dosing regimen but was variable in the quarterly dosing groups (mean CRT decrease 1 month after each treatment and increase thereafter until next treatment visit at months 5, 8, and 11; Fig 4). The mean change in CRT from baseline to month 12 was similar between the 0.5 mg quarterly group (−105.6 μm) and the 0.3 mg monthly group (−105.3 μm). For the 0.3 mg quarterly group, the mean CRT change was −96.0 μm. The overall retinal thickness at the central subfield of the study eye at baseline and months 3 and 12 was also similar between the treatment groups.

On the basis of angiographic data, the mean decrease in CNV lesion area from baseline to month 12 was numerically higher in the 0.5 mg quarterly treatment group compared with the other treatment groups; however, this difference was not significant (−2.28 mm^2 in the 0.3 mg quarterly, −3.49 mm^2 in the 0.5 mg quarterly, and −2.63 mm^2 in the 0.3 mg monthly dosing regimen; Table 4). The mean change (decrease) from baseline to month 12 in the total area of leakage and total lesion area are shown in Table 4.

Contrast sensitivity analysis (ITT population; last observation carried forward method) at month 6 showed a mean change of 0.071 log units from baseline in the 0.3 mg quarterly group (100 patients), 0.107 log units in the 0.5 mg group quarterly group (98 patients), and 0.123 log units in the 0.3 mg monthly treatment group (98 patients). In the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly treatment groups, the mean change from baseline to month 12 showed an overall improvement by 0.085, 0.081, and 0.131 log units, respectively.

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