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Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid

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Purpose: To compare the effect of intravitreal aflibercept or ranibizumab drug type and frequency on visual acuity outcomes in eyes with neovascular age-related macular degeneration (NVAMD) and early persistent retinal fluid after 3 initial monthly injections.

Design: A post hoc analysis of eyes enrolled in VIEW 1 and VIEW 2, 2 similarly designed, randomized, phase 3 trials.

Participants: A total of 1815 eyes with NVAMD from VIEW 1 and VIEW 2.

Methods: Analyses included patients with known fluid status at baseline and weeks 4, 8, and 12 in 3 treatment groups: ranibizumab 0.5 mg every 4 weeks (Rq4) (n = 595), intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4) (n = 613), and IAI 2 mg every 8 weeks (2q8) after 3 monthly injections (n = 607).

Main Outcome Measures: Mean best-corrected visual acuity (BCVA) change from baseline over weeks 16 to 52 and the proportion of eyes that gained ≥15 letters or lost ≥5 letters were evaluated in eyes with and without persistent fluid (cystic intraretinal or subretinal fluid at all 4 initial visits). Visual outcomes also were assessed in eyes with persistent fluid by fluid type (intraretinal and subretinal fluid).

Results: The proportions of eyes with persistent fluid were 29.4%, 18.8%, and 20.3% in the Rq4, 2q4, and 2q8 groups, respectively. In these eyes, mean BCVA gain from baseline to week 52 was greater with 2q4 compared with Rq4 ($P < 0.01$) and 2q8 ($P < 0.05$), whereas it was similar with Rq4 and 2q8 ($P = 0.294$). At week 52, similar proportions of eyes gained ≥15 letters (31.5%−35.2%), whereas fewer eyes lost ≥5 letters with 2q4 compared with Rq4 and 2q8 (6.5% vs. 16.6% and 16.2%). The pattern of visual outcomes was similar regardless of fluid type. In eyes without persistent fluid, BCVA changes were similar across treatment groups.

Conclusions: In patients with early persistent fluid, 2q4 may provide additional clinical benefit over 2q8 or Rq4. *Ophthalmology 2016;123:1856-1864 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Aflibercept is a soluble human fusion protein. It acts as a decoy receptor for vascular endothelial growth factor (VEGF) and placental growth factor, and has potent anti-VEGF activity.[1] In 2 pivotal phase 3 trials, VIEW 1 and VIEW 2, in patients with neovascular age-related macular degeneration (NVAMD), outcomes were similar for the primary and secondary visual acuity end points when 2 mg of intravitreal aflibercept injection (IAI) was given every 4 weeks (2q4) or every 8 weeks (2q8) after 3 initial monthly injections, or when 0.5 mg ranibizumab was given every 4 weeks (Rq4) at week 52.[2] These data led to an approval by the United States Food and Drug Administration (FDA) in 2011 of IAI to treat NVAMD in the United States monthly or every 2 months after 3 initial doses.

In VIEW 1 and VIEW 2, as well as the Comparison of Age-related Macular Degeneration Treatment Trials (CATT), there was a rapid reduction of macular fluid, as measured by optical coherence tomography (OCT), in the majority of treated eyes during the first several weeks of therapy.[2,3] However, a subgroup of eyes had residual fluid on OCT despite injections with anti-VEGF drugs.[2,3] In the CATT, at each study visit, eyes with residual intraretinal fluid had worse visual acuity than those without intraretinal fluid, whereas eyes with subretinal fluid had better visual acuity than eyes without fluid in that location. These findings were particularly prominent when the fluid affected the fovea and were independent of drug or treatment regimen.[4]

In multiple randomized trials, on average, eyes that are given fixed-dosing anti-VEGF treatments had better visual acuity at 1 and 2 years than those given less frequent treatments.[2,3,5–9] Furthermore, when patients were given monthly treatment for 1 year and then switched to a pro re nata (PRN) regimen, the visual acuity decreased to a level similar to that of patients given PRN treatment all along.[10] Despite these findings, in the United States, the majority of patients with NVAMD are given fewer than monthly intravitreal

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anti-VEGF injections and are treated using according to a PRN or "treat-and-extend" strategy.[11] Treatment decisions often are driven by the presence of fluid seen on OCT.[11] However, the factors that determine the needed anti-VEGF treatment frequency in any individual patient are not well understood.

Because most patients with NVAMD receive fewer than monthly injections based on PRN and treat-and-extend dosing approaches,[5] it would be desirable to identify during initiation of therapy those treatment-naïve patients who will benefit most if they are given monthly anti-VEGF injections. However, there are few data available to guide the clinician in this regard, even from the primary data from the VIEW studies. The design of the VIEW studies afforded us the opportunity to study outcomes based on fluid status. We began by evaluating the fluid status over time and treatment effect on fluid status. This analysis subsequently led us to focus on the fluid status in the initial phase of therapy. Data from this on-treatment analysis have the potential to provide valuable information to the clinician. Specifically, from VIEW 1 and VIEW 2, we determined (1) the degree of retinal fluid fluctuation, (2) the time to absence of retinal fluid, and (3) whether the presence of persistent retinal fluid observed after 3 initial monthly intravitreal injections, as seen on time-domain OCT, predicted longer-term outcomes and visual acuity, and whether these visual acuity changes depended on the treatment regimen. We also assessed whether the visual acuity outcomes observed throughout the study would differ on the basis of fluid type (subretinal or intraretinal). If so, this information could help to inform the clinician about injection frequency strategy in eyes with NVAMD.

Methods

VIEW 1 and VIEW 2 Study Designs

The VIEW 1 and VIEW 2 studies were 2 similarly designed, randomized, double-masked, active-controlled, multicenter, 96-week, phase 3 trials comparing the efficacy and safety of IAI and ranibizumab in treatment-naïve eyes with NVAMD. The design of the VIEW studies has been described.[2,12] Each clinical site's respective institutional review board/ethics committee approved the study. All patients provided written informed consent. Participants were randomized in a 1:1:1:1 ratio to 1 of the following 4 regimens for the first 52 weeks: (1) 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), (2) 2 mg IAI every 4 weeks (2q4), (3) 0.5 mg IAI every 4 weeks, and (4) 2 mg IAI every 8 weeks (2q8) after 3 initial monthly injections. From week 52 to week 96, patients were treated with the same dose as the first 52 weeks at least every 12 weeks, with monthly evaluations for additional injections.[12] Analyses presented in this article were limited to data through week 52 because the dosing regimen in all treatment arms changed to PRN from week 52 to week 96, and thus this period is not included in our analysis.

Outcome Measures

Independent masked readers at 2 central reading centers, Duke Reading Center (VIEW 1) and Vienna Reading Center (VIEW 2), determined the presence (termed "wet") or absence (denoted "dry") of retinal fluid. The OCT image grading was harmonized between the Duke and Vienna OCT reading centers. This process included conference calls and joint grading exercises on representative image samples to ensure that the same grading procedure was followed at the 2 institutions.

Retinal fluid was defined as the presence of intraretinal (cystic) fluid or subretinal fluid on time-domain OCT images at baseline and then monthly through week 52. The time to a single absence of retinal fluid and sustained absence of retinal fluid (fluid absent on $\geq$2 consecutive visits) was determined. Eyes that were not dry by week 12 were then further evaluated. Because retinal fluid can fluctuate depending on anti-VEGF treatment, we defined an "early persistent fluid" group as one that had retinal fluid as defined earlier on all initial 4 visits (baseline and weeks 4, 8, and 12). This period included all 3 visits during the initial loading dose period when all eyes were treated every 4 weeks, as well as 4 weeks after the third treatment. Specific baseline characteristics were evaluated to determine the influence on persistent fluid status. The mean change from baseline best-corrected visual acuity (BCVA), as measured by Early Treatment Diabetic Retinopathy Study letters over week 52, and the proportion of eyes gaining $\geq$15 letters and losing $\geq$5 letters in eyes with early persistent fluid were compared with those without early persistent fluid. In addition, we determined whether the fluid type, intraretinal or subretinal, influenced visual outcomes for those eyes with and those without early persistent fluid.

Statistical Analysis

Of the 2457 eyes randomized into the VIEW studies, 2412 patients received study medication and had a baseline and at least 1 postbaseline BCVA assessment (full analysis set). The 597 eyes treated with 0.5 mg IAI every 4 weeks were not included in the analysis because IAI 2 mg is the Food and Drug Administration–approved dose, and the only dose currently available to clinicians in the United States. Thus, a total of 1815 eyes (Rq4, n = 595; 2q4, n = 613; and 2q8, n = 607) were included in these analyses. There were 91 eyes (34 eyes in the Rq4 group, 29 eyes in the 2q4 group, and 28 eyes in the 2q8 group) with missing observations in at least one visit during baseline to week 12. These eyes were classified as wet if the preceding and the following visits were classified as wet.

Time to absence of retinal fluid was evaluated by the Kaplan–Meier method and a proportional hazard analysis. These approaches provided a means to estimate the cumulative incidence and accounts for eyes that did not have complete follow-up. The log-rank test was used to test the difference between the cumulative incidence curves of the treatment groups. The relative risks (or relative hazards) comparing the various IAI treatment groups with the Rq4 group were estimated by the proportional hazards analysis. Time at risk for each patient is the minimum from the time at randomization to the first of any of the following: (1) the date of discontinuation, (2) the first episode of dryness, or (3) the end of the study. Time at risk is expressed as person-years at risk, and the rate is the number of events/person-years at risk. The relative risk (or hazard) is determined as the ratio of the rate in the ranibizumab group to the rate in the IAI group. The relative risk analyses were stratified by study (VIEW 1 vs. VIEW 2). Only within-stratum analyses contributed to the overall relative risks. Logistic regression was used to determine baseline factors that were useful to predict eyes that had persistent retinal fluid. Repeated-measures methodology was used to evaluate the differences in the means of groups defined by on-treatment variables. On-treatment variables are those that are evaluated after randomization. Analysis of covariance was used to assess differences in BCVA between the treatment groups. The covariates used in the model are baseline characteristics listed in Table 1. Least-squares means are reported and implicitly corrected for sample size imbalances among the treatment groups.

Table 1. Baseline Characteristics of Patients with and without Persistent Retinal Fluid* by Treatment Groups

	Rq4 (N = 595)		IAI 2q4 (N = 613)		IAI 2q8 (N = 607)	
	Not Persistent	*Persistent*	*Not Persistent*	*Persistent*	*Not Persistent*	*Persistent*
Patients (n)	420	175	498	115	484	123
BCVA (ETDRS letters), mean ± SD	53.6 (13.4)	54.5 (13.5)	54.1 (13.8)	53.3 (12.7)	53.9 (13.4)	52.4 (13.7)
CST (μm), mean ± SD	289.8 (122.1)	311.0 (123.5)	292.1 (127.3)	325.9 (118.9)	292.8 (126.4)	357.2 (149.3)
CNV lesion size, n (%)						
≤10.16 mm^2	324 (77.1)	123 (70.3)	373 (74.9)	82 (71.3)	349 (72.1)	99 (80.5)
>10.16 mm^2	91 (21.7)	51 (29.1)	124 (24.9)	31 (27.0)	134 (27.7)	23 (18.7)
Missing	5 (1.2)	1 (0.6)	1 (0.2)	2 (1.7)	1 (0.2)	1 (0.8)
CNV lesion type, n (%)						
Occult	163 (38.8)	68 (38.9)	194 (39.0)	39 (33.9)	191 (39.5)	38 (30.9)
MC	145 (34.5)	60 (34.3)	187 (37.6)	30 (26.1)	180 (37.2)	36 (29.3)
PC	106 (25.2)	46 (26.3)	115 (23.1)	44 (38.3)	111 (22.9)	48 (39.0)
Missing	6 (1.4)	1 (0.6)	2 (0.4)	2 (1.7)	2 (0.4)	1 (0.8)

Full analysis set.
BCVA = best-corrected visual acuity; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection; MC = minimally classic; PC = predominantly classic; Rq4 = 0.5 mg intravitreal ranibizumab every 4 weeks; SD = standard deviation; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks.
*Persistent fluid was defined as the presence of intraretinal or subretinal fluid on all initial 4 visits (baseline and weeks 4, 8, and 12).

Results

Retinal Fluid Status over Time

Retinal fluid status based on the presence or absence of retinal fluid was first determined at each study visit for each treatment group. During the 52 weeks of follow-up, the retinal fluid status as defined earlier fluctuated in all treatment groups, although greater fluctuation over time was noted in the 2q8 group. Specifically, the average proportions of visits without retinal fluid were 57.4%, 75.1%, and 57.9% in the Rq4, 2q4, and 2q8 groups, respectively. Figure 1 shows the proportion of eyes without retinal fluid by visit and treatment assignment.

Time to Absence of Retinal Fluid

Time to retinal fluid absence ("dryness") was compared among the 3 treatment groups (Fig 2A). By week 52, there were 512, 571, and 548 study eyes with retinal fluid absent on at least 1 study visit, with resultant cumulative incidences of 86.9%, 93.9%, and 91.9% in the Rq4, 2q4, and 2q8 groups, respectively. The IAI groups were more likely than the Rq4 group to have an episode of absent retinal fluid: 1.5 (2q4) and 1.4 (2q8) times, respectively. The overall rates (calculated as the number of events per 100 person-years at risk of dryness) between the 2q4 and 2q8 groups were similar. The separation between the IAI and Rq4 groups was seen early and was maintained through 52 weeks. As expected, the 2q4 and 2q8 cumulative incidence curves were almost identical until week 16. Thereafter, there was a slight separation between the 2 IAI groups. In both the 2q4 and 2q8 groups, more than 50% of the study eyes had the first episode of retinal fluid absence by week 4. At week 12, more than 75% of the eyes treated with 2q4 or 2q8 were dry on at least 1 visit. The 75% cumulative incidence of a dry retina on at least 1 visit for eyes treated with Rq4 was reached at week 20.

The proportion of eyes with sustained dryness, defined as absent fluid on at least 2 consecutive visits, and the time to sustained dryness were then assessed for each of the 3 treatment groups (Fig 2B). There

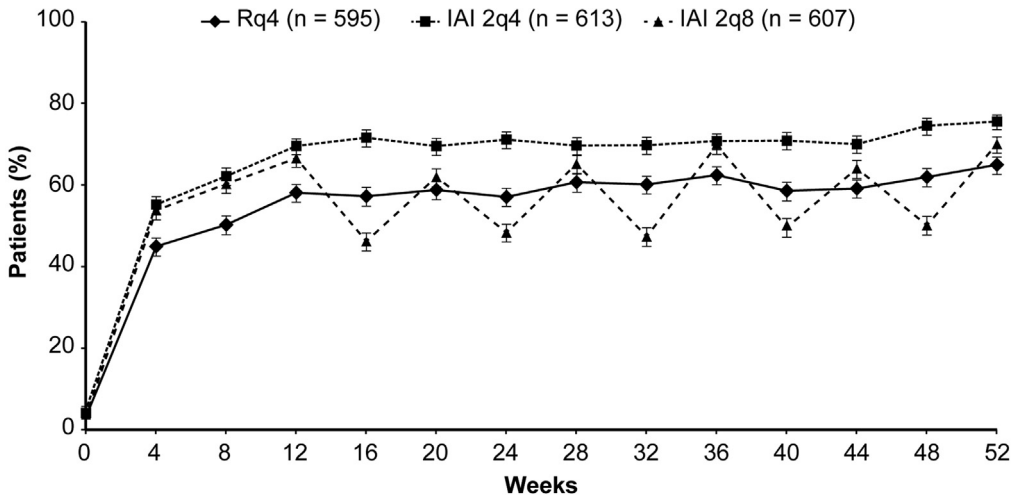

Figure 1. Proportion of patients without retinal fluid over 52 weeks of study. IAI = intravitreal aflibercept injection; Rq4 = 0.5 mg intravitreal ranibizumab every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 3 initial monthly injections.

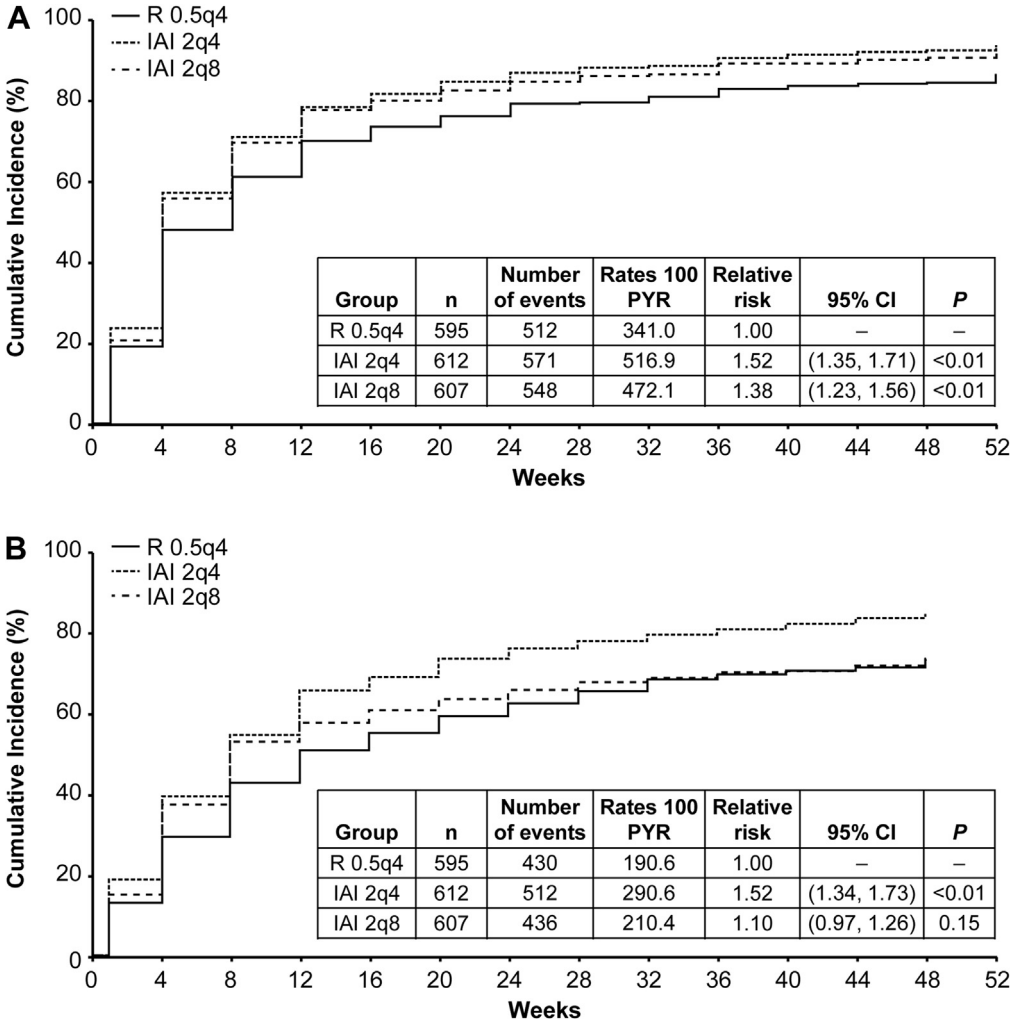

Figure 2. Cumulative incidence of (**A**) single and (**B**) sustained absence of retinal fluid. Sustained absence refers to absent retinal fluid on 2 or more consecutive visits. Full analysis set. CI = confidence interval; IAI = intravitreal aflibercept injection; PYR = person-years; R 0.5q4 = 0.5 mg intravitreal ranibizumab every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks.

were 430, 512, and 436 study eyes with retinal fluid absent on 2 or more consecutive study visits by week 52 that resulted in cumulative incidences of 73.7%, 84.8%, and 73.8% in the Rq4, 2q4, and 2q8 groups, respectively. The rates of the events are provided in the table within Fig 2B. On the basis of the relative hazard ratio for sustained dryness, eyes treated 2q4 were approximately 1.5 times more likely than those treated Rq4 and 2q8 to achieve sustained dryness. During the first 12 weeks, the cumulative incidence of sustained dryness in the 2q4 and 2q8 groups was similar, but from week 16 onward, the cumulative incidence of sustained dryness in the 2q8 group was lower than that observed in the 2q4 group. The separation for the cumulative incidence curves between 2q4 and Rq4 was seen early, at approximately week 4. The 50th percentile for the cumulative incidence of sustained dryness was achieved at week 8 in both of the IAI groups. The 75th percentile was achieved at week 24 for the 2q4 group but was never achieved for the 2q8 or Rq4 groups.

Evaluation of Early Persistent Fluid

We next determined how frequently retinal fluid persisted over each of the first 4 study visits (including baseline) through week 12 (termed "early persistent fluid") and whether the specific anti-VEGF treatment affected fluid persistence. For this analysis, eyes were determined to have early persistent fluid if the presence of fluid was confirmed at all initial 4 visits: baseline, week 4, week 8, and week 12. Those that did not meet this criterion were determined not to have early persistent fluid. Most eyes (1402 [77.2%]) did not have early persistent fluid over the first 4 visits through week 12: 420 eyes (70.6%), 498 eyes (81.2%), and 484 eyes (79.7%) in the Rq4, 2q4, and 2q8 treatment groups, respectively. Overall, 413 eyes (22.8%) had early persistent retinal fluid during the first 4 visits. The proportion of eyes with early persistent fluid was similar in the IAI arms (2q4:18.8%, 115/613; 2q8: 20.3%, 123/607; combined 19.5%, 238/1220), as expected since both were dosed monthly during the loading phase, while eyes treated with Rq4 were 51% more likely (95% confidence interval [CI]: 27%, 78%) to have early persistent fluid (Rq4: 29.4%; 175/595). Eyes with and without early persistent fluid through week 12 had similar baseline visual acuity, lesion size, and lesion type across treatment groups (Table 1). However, eyes with early persistent fluid had greater baseline central subfield thickness on OCT across treatment groups compared with eyes without early persistent fluid.

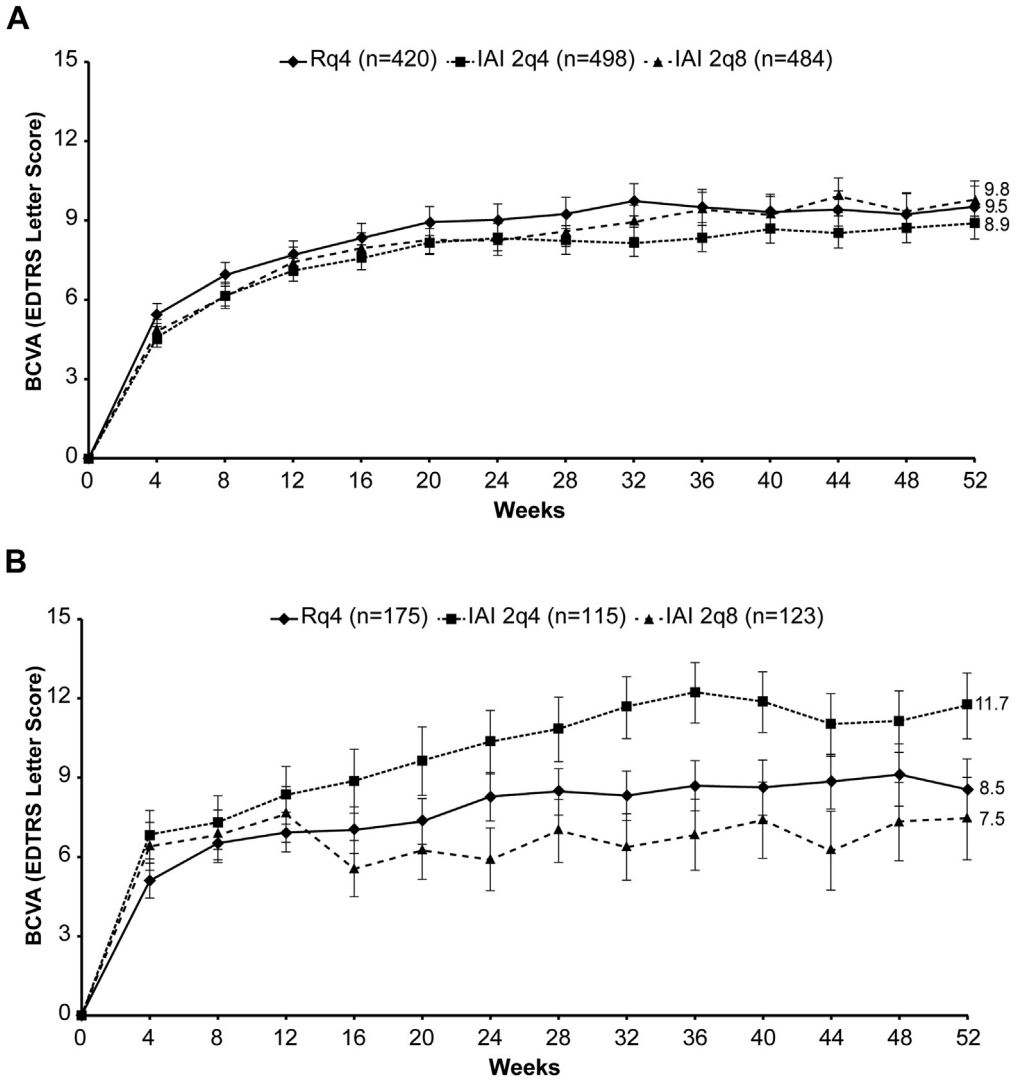

Figure 3. Least square mean change in best-corrected visual acuity (BCVA) from baseline through week 52 in eyes (**A**) without and (**B**) with persistent retinal fluid through week 12. ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection; Rq4 = 0.5 mg intravitreal ranibizumab every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks.

Relationships between Early Persistent Fluid and Visual Acuity

For eyes without early persistent retinal fluid (from baseline through week 12), there were no differences among the treatment groups in mean BCVA change from baseline over the interval beginning at week 16 and spanning through week 52 (Fig 3A). An examination of the means and error bars at each visit suggests no differences between the treatment groups at any visit.

In contrast, in eyes with early persistent fluid from baseline through week 12, the mean BCVA gains from baseline over the interval spanning weeks 16 to 52 were observed as early as week 16 for the 2q4 group and were consistently greater than those for the 2q8 and Rq4 groups. An analysis of covariance using covariates from Table 1 confirms and quantifies these suggestions at week 52. A test of the equality of the means among the treatment groups was rejected ($P = 0.006$). Pairwise treatment group comparisons yield the following: 2q4 versus 2q8 and 2q4 versus Rq4 are $P = 0.006$ and $P = 0.049$, respectively, and the P value for Rq4 versus 2Q8 is 0.294. The adjusted mean changes from baseline at week 52 were 11.7, 8.5, and 7.5 letters for the 2q4, Rq4, and 2q8 groups, respectively (Fig 4). These mean changes correspond to difference of 3.2 letters for 2q4 versus Rq4, 4.2 letters for 2q4 versus 2q8 and 1.0 letters for Rq4 versus 2q8.

At week 52, the percentages of study eyes that gained ≥15 letters were similar among the 3 study groups: 33.7% (95% CI, 26.5−41.0), 35.2% (95% CI, 26.2−44.2), and 31.5% (95% CI, 22.9−40.2) for Rq4, 2q4, and 2q8, respectively (Fig 5A). However, a lower percentage of eyes in the 2q4 group lost ≥5 letters compared with eyes in the Rq4 and 2q8 groups (6.5% [95% CI, 1.8−11.1] vs. 16.6% [95% CI, 10.9−22.3] and 16.2% [95% CI, 9.4−23.1]) (Fig 5B).

The described analysis in eyes with early persistent fluid through week 12 was repeated separately for persistent fluid subtypes: 52 eyes (8.7%), 43 eyes (7%), and 45 eyes (7.4%) with early persistent intraretinal fluid, and 113 eyes (19.0%), 57 eyes (9.3%), and 76 eyes (12.5%) with early persistent subretinal fluid in the Rq4, 2q4, and 2q8 treatment groups, respectively. However, the numbers of eyes available for these analyses were small. In

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