Extended (Every 12 Weeks or Longer) Dosing Interval With Intravitreal Aflibercept and Ranibizumab in Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of VIEW Trials

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• PURPOSE: To evaluate outcomes and disease characteristics in eyes with neovascular age-related macular degeneration that received intravitreal aflibercept injection (IAI) and ranibizumab every 12 weeks or longer (≥q12 weeks) or less than every 12 weeks (<q12 weeks) during year 2 of VIEW studies.

• DESIGN: Post hoc analysis of randomized clinical trial data.

• METHODS: In year 1, eyes received ranibizumab q4 weeks (Rq4), IAI 2 mg q4 weeks (2q4), or IAI 2 mg q8 weeks after 3 monthly injections (2q8). In year 2, eyes received pro re nata treatment, with mandatory treatment at least q12 weeks.

• RESULTS: At week 96, 218 (42.5%), 284 (53.9%), and 245 (47.9%) eyes treated with Rq4, 2q4, and 2q8, respectively, received treatment at ≥q12-week intervals and 295 (57.5%), 243 (46.1%), and 266 (52.1%) eyes at <12q-week intervals during the second year. Baseline occult-type choroidal neovascularization (CNV) ($P = .0156$) and retinal fluid ($P < .0001$) and leakage ($P < .0001$) at week 52 were associated with <q12-week dosing. Mean best-corrected visual acuity gains from baseline with Rq4, 2q4, and 2q8 at ≥q12-week interval were 8.7, 9.9, and 9.7 letters at week 52 and 8.5, 8.8, and 9.2 letters at week 96, respectively. The corresponding gains with <q12-week dosing were 10.3, 9.7, and 8.9 letters at week 52 and 9.1, 7.7, and 8.1 letters at week 96.

• CONCLUSIONS: Baseline CNV type other than occult and absence of retinal fluid and leakage at week 52 were significantly associated with ≥q12-week dosing. Vision improvements at week 52 following a year of fixed dosing with ranibizumab and IAI were maintained at week 96 in eyes that received treatment ≥q12 weeks and <q12 weeks. (Am J Ophthalmol 2019;200: 161–168. © 2019 Elsevier Inc. All rights reserved.)

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) is an important mediator of angiogenesis and vascular permeability.[1,2] Increased levels of VEGF result in the development of choroidal neovascularization (CNV) and vascular leakage, hallmarks of neovascular age-related macular degeneration (nAMD).[3] As such, targeting VEGF to reverse these pathologic events has become the current standard of treatment for nAMD.[4]

The VIEW studies, which evaluated the efficacy and safety of intravitreal ranibizumab (Lucentis; Genentech, Inc., South San Francisco, California, USA) and intravitreal aflibercept injection (IAI; Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA), were the first studies to include 2 fixed dosing regimens of IAI (every 4 weeks and every 8 weeks after 3 initial monthly injections) during the first year of treatment,[5] providing physicians options to individualize treatment for their patients with nAMD. In the second year of these studies, patients could be treated with ranibizumab and IAI every 4, 8, or 12 weeks based on protocol-defined re-treatment criteria. The minimum number of treatments patients could have received after week 52 was 3 injections, as the exploratory phase of the VIEW studies had 3 distinct 12-week intervals through week 96 (fewer than 3 injections occurred in a few patients as a protocol violation). Overall, 43% to 54% of patients received the minimum number of treatments (≤3 injections) across treatment groups during their second year of follow-up.[6] This subgroup of patients largely maintained their visual and anatomic outcomes at the end of the second year.[6]

To further put these findings into perspective, we performed a comprehensive evaluation of subgroups of

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patients who received a minimum number of treatments (at least every 12 weeks) or those who received treatment more frequently (less than every 12 weeks) in the second year of the VIEW studies, including an examination of disease characteristics associated with treatment frequency, which are important to patient management.

METHODS

• **STUDY DESIGN:** VIEW 1 and VIEW 2 (registered at www.clinicaltrials.gov; NCT00509795 and NCT00637377, respectively) were 2 similarly designed, double-masked, randomized, active-controlled, multicenter, parallel-group, 96-week phase 3 trials that compared the efficacy and safety of repeated doses of IAI with intravitreal injections of ranibizumab in patients with nAMD.[5] The VIEW 1 trial was conducted in the United States and Canada, and the VIEW 2 trial was conducted in Europe, the Middle East, the Asia-Pacific region, and Latin America, at a total of 326 sites for both trials. Each institutional review board or ethics committee approved the study protocol. All patients signed a written consent form before initiation of the study-specific procedures. The VIEW 1 and 2 trials were conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki.

The study design and patient eligibility of the VIEW trials have been described previously.[5] In brief, patients 50 years of age and older with active, subfoveal CNV lesions (including juxtafoveal lesions affecting the fovea) secondary to nAMD were eligible for enrollment if CNV made up at least 50% of the total lesion size and best-corrected visual acuity (BCVA) was between 25 and 73 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/320 to 20/40 Snellen equivalent). Only 1 eye from each patient was enrolled in the study.

Eyes were randomized in a 1:1:1:1 ratio to receive 1 of the following 4 regimens in the study eye for the first 52 weeks: (1) intravitreal ranibizumab 0.5 mg every 4 weeks (Rq4), (2) IAI 2 mg every 4 weeks (IAI 2q4), (3) IAI 0.5 mg every 4 weeks (IAI 0.5q4), and (4) IAI 2 mg every 8 weeks after 3 initial monthly injections (IAI 2q8). Starting at week 52 through week 96 (year 2), patients received the same study medication and dosage strength as in the first 52 weeks, but were re-treated if at least 1 of the following prespecified re-treatment criteria was met, as assessed by the investigator: (1) new or persistent fluid (presence of any new or unchanged cystic retinal edema and/or subretinal fluid) on time-domain optical coherence tomography (TD-OCT), (2) increase in central (optical coherence tomography [OCT]) subfield thickness (CST) ≥100 μm (presence of cystic retinal edema and/or subretinal fluid meeting a specific quantitative thickening threshold) compared with the lowest previous value, (3) loss of ≥5 ETDRS letters from the best previous score in conjunction with recurrent fluid on TD-OCT, (4) new-onset classic neovascularization, (5) new or persistent leak on fluorescein angiography (FA), (6) new macular hemorrhage, or (7) time lapse of at least 12 weeks since the previous injection. Based on these criteria, patients could be treated every 4, 8, or 12 weeks. Patients who were treated only every 12 weeks would receive a maximum of 3 re-treatments (weeks 60, 72, and 84). Re-treatment decisions were made at the monthly (28 ± 3 days) follow-up visits.

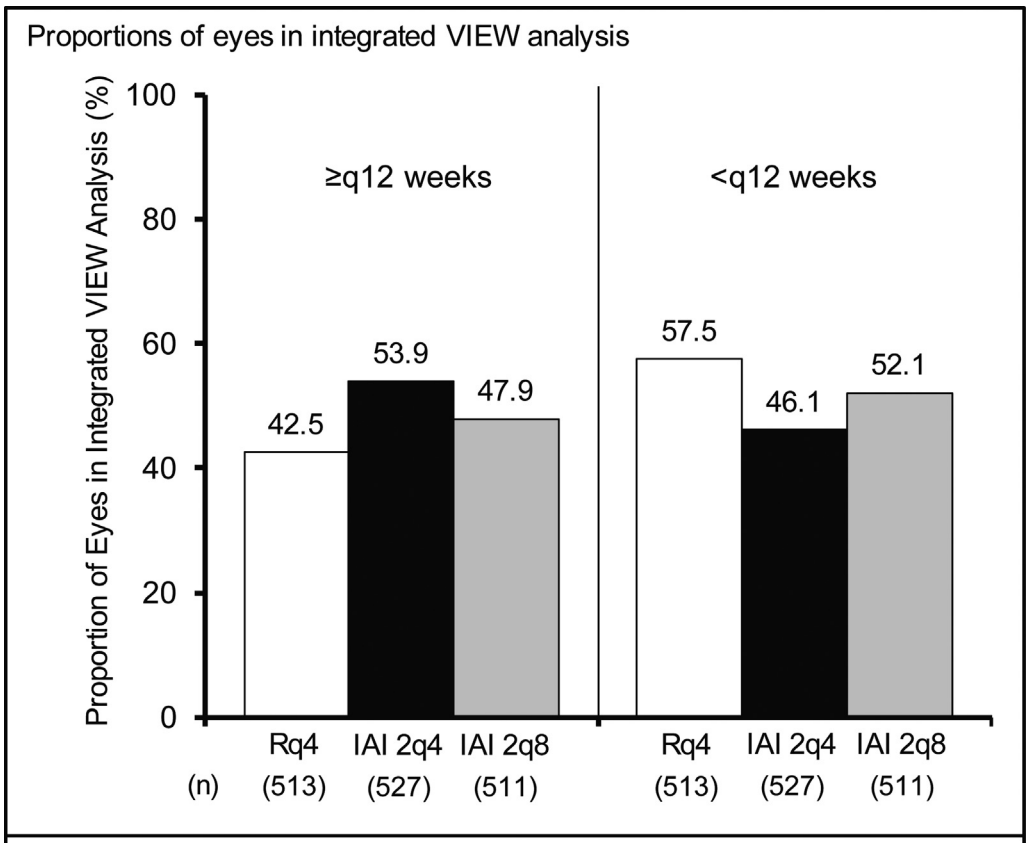
• **OUTCOME MEASURES:** The primary efficacy endpoint of the VIEW 1 and VIEW 2 trials was noninferiority of the IAI regimens to ranibizumab in the proportion of patients maintaining BCVA (losing <15 ETDRS letters) at week 52.[5] The primary, secondary, and exploratory efficacy outcomes at weeks 52 and 96 have been reported previously.[5,7] This post hoc analysis evaluated the efficacy in 2 subgroups of patients: (1) those who always received study treatment during year 2 at intervals of 12 weeks or more (≥q12-week interval), and (2) those who received study treatment, at least once during year 2, at a 4- or 8-week interval (<q12-week interval). Approximately 4% of patients were dosed out of the visit window, resulting in an interval >12 weeks. Of the 2457 patients randomized into the VIEW 1 and VIEW 2 trials, a total of 1551 patients were included in this post hoc analysis.

For each subgroup, BCVA as measured by ETDRS, central OCT subfield thickness by TD-OCT, and retinal fluid status were measured from baseline through week 96. Methodology for assessing these outcomes has been reported previously.[5]

• **STATISTICAL ANALYSES:** The full analysis set (FAS) included all randomized patients who received any study medication and had a baseline BCVA measurement and at least 1 BCVA assessment after baseline. This post hoc analysis was carried out in the subset of FAS eyes that completed year 2 of the study (year 2 medication and study completers). Patients treated with IAI 0.5q4 were not included in the analysis, as IAI 2 mg is the only available Food and Drug Administration-approved dose. This analysis integrated the VIEW 1 and VIEW 2 studies.

Continuous variables were analyzed descriptively by sample statistics and categorical variables were analyzed by frequency tables. Missing values were imputed using the last observation carried forward (LOCF) method, except for the analysis of proportions of patients without fluid at week 96, which was based on the observed values. All outcome measures at week 96 were analyzed in an exploratory manner, and *P* values reported herein are considered nominal.

Univariate and multivariate logistic regression analyses combining all treatment groups were conducted post hoc to explore whether select disease characteristics were associated with ≥q12-week and <q12-week dosing. Stepwise selection was used to identify the covariates in the final



Proportions of Eyes in VIEW 1 and VIEW 2

	VIEW 1		VIEW 2	
	≥q12 weeks	<q12 weeks	≥q12 weeks	<q12 weeks
Rq4, n (%)	118/257 (45.9)	139/257 (54.1)	100/256 (39.1)	156/256 (60.9)
2q4, n (%)	137/273 (50.2)	136/273 (49.8)	147/254 (57.9)	107/254 (42.1)
2q8, n (%)	106/249 (42.6)	143/249 (57.4)	139/262 (53.1)	123/262 (46.9)

FIGURE 1. Proportion of study eyes receiving injections at ≥q12-week intervals or <q12-week intervals in year 2. (Top) Integrated VIEW analysis. (Bottom) VIEW 1 and VIEW 2. Full analysis set, year 2 medication completers. <q12-week intervals = less-than-every-12-week intervals during year 2; ≥q12-week intervals = every-12-week intervals or longer during year 2; IAI 2q4 = intravitreal aflibercept injection 2 mg every 4 weeks; IAI 2q8 = intravitreal aflibercept injection 2 mg every 8 weeks after 3 initial monthly doses; Rq4 = ranibizumab 0.5 mg every 4 weeks.

multivariate model. In addition, as a sensitivity analysis, univariate and multivariate logistic regression analyses stratified by the treatment groups were performed to compare the disease characteristic associations within each treatment group. Only within-treatment group analyses contributed to the overall odds ratios. Select disease characteristics included CNV type assessed at baseline and BCVA, CST, CNV size, total lesion size, retinal fluid status, and leakage status by FA assessed at week 52.

Safety was assessed on the safety analysis set, which included all randomized patients who received any study treatment.

RESULTS

IN THE INTEGRATED ANALYSIS OF DATA FROM VIEW 1 AND VIEW 2, 42.5% to 53.9% of eyes received injections at ≥q12-week intervals, while 46.1% to 57.5% of eyes received injections at <q12-week intervals (Figure 1). The mean (standard deviation) number of injections with Rq4, IAI 2q4, and IAI 2q8 during year 2 were 3.0 (0.2), 3.0 (0.2), and 3.0 (0.2) in the subgroup of eyes receiving injections at ≥q12-week intervals, and 6.0 (2.2), 5.4 (2.0), and 5.3 (1.8) in the subgroup of patients receiving injections at <q12-week intervals, respectively.

TABLE. Baseline Disease Characteristics of Study Eyes That Received Year 2 Study Medication at Intervals Every 12 Weeks or Longer or Less Than Every 12 Weeks

	≥q12 Weeks (N = 747)			<q12 Weeks (N = 804)		
	Rq4 (N = 218, 29.2%)	IAI 2q4 (N = 284, 38.0%)	IAI 2q8 (N = 245, 32.8%)	Rq4 (N = 295, 36.7%)	IAI 2q4 (N = 243, 30.2%)	IAI 2q8 (N = 266, 33.1%)
BCVA						
n	218	284	245	295	243	266
Mean (SD), ETDRS letters	52.6 (13.4)	54.0 (13.4)	53.5 (13.7)	55.2 (13.1)	54.7 (13.6)	54.3 (13.0)
CST						
n	209	279	240	286	231	258
Mean (SD), μm	317.5 (105.5)	322.2 (111.5)	331.3 (120.6)	322.3 (109.5)	327.2 (119.4)	333.6 (114.0)
CNV area						
n	216	283	244	294	242	266
Mean (SD), mm^2	6.7 (5.4)	7.4 (5.3)	7.0 (5.3)	7.3 (5.4)	7.2 (5.6)	7.2 (5.3)
Total lesion size						
n	215	282	244	294	242	266
Mean (SD), mm^2	7.0 (5.8)	7.8 (5.8)	7.4 (5.5)	7.8 (5.8)	7.6 (5.8)	7.5 (5.5)
≤4 DA (≤10.16 mm^2), n (%)	162 (74.3)	209 (73.6)	175 (71.4)	211 (71.5)	181 (74.5)	194 (72.9)
>4 DA (>10.16 mm^2), n (%)	53 (24.3)	73 (25.7)	69 (28.2)	83 (28.1)	61 (25.1)	72 (27.1)
Missing	3	2	1	1	1	0
Type of CNV, n (%)						
n	218	284	245	295	243	266
Occult	69 (31.7)	98 (34.5)	88 (35.9)	125 (42.4)	98 (40.3)	110 (41.4)
Minimally classic	81 (37.2)	122 (43.0)	80 (32.7)	95 (32.2)	68 (28.0)	97 (36.5)
Predominantly classic	65 (29.8)	62 (21.8)	76 (31.0)	74 (25.1)	76 (31.3)	58 (21.8)
Missing	3	2	1	1	1	1

≥q12-week intervals = every 12-week intervals or longer during year 2; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CST = central (optical coherence tomography) subfield thickness; DA = disc areas; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI 2q4 = intravitreal aflibercept injection 2 mg every 4 weeks; IAI 2q8 = intravitreal aflibercept injection 2 mg every 8 weeks after 3 initial monthly doses; Rq4 = ranibizumab 0.5 mg every 4 weeks.

Full analysis set, year 2 medication completers.

Approximately 4% of patients were dosed out of the visit window, resulting in an interval >12 weeks.

The Table presents baseline disease characteristics of the study eyes of patients in the 2 dosing subgroups. For both dosing interval subgroups, all baseline characteristics of the study eye appeared similar among the 3 treatment groups. In the subgroup of eyes with ≥q12-week dosing interval, mean BCVA was 52.6 letters (approximate Snellen equivalent of 20/100) to 54.0 letters (approximate Snellen equivalent of 20/80), mean CST was 317.5 μm to 331.3 μm, and mean total lesion size ranged from 7.0 mm^2 to 7.8 mm^2 (Table). In the subgroup of eyes with <q12-week dosing interval, mean BCVA was 54.3 letters to 55.2 letters, mean CST was 322.3 μm to 333.6 μm, and mean total lesion size ranged from 7.5 mm^2 to 7.8 mm^2 (Table).

• **ASSOCIATION WITH KEY DISEASE CHARACTERISTICS:** A univariate analysis showed baseline occult CNV type and anatomic features at week 52 of thicker CST, greater CNV size, larger total lesion size, presence of retinal fluid, and presence of retinal leakage significantly associated with the <q12-week dosing interval (Figure 2, Top). A multivariate analysis revealed 3 disease characteristics that were significantly associated with <q12-week dosing interval: baseline occult-type CNV (odds ratio 95% confidence interval [CI]): (0.762 [0.612, 0.950]; $P = .0156$) and the presence of retinal fluid (odds ratio [95% CI]: 0.353 [0.277, 0.449]; $P < .0001$) and presence of retinal leakage (odds ratio [95% CI]: 0.494 [0.393, 0.621]; $P < .0001$) at week 52 (Figure 2, Bottom).

As a sensitivity analysis, when comparisons were made within each treatment group, the univariate regression model stratified by the treatment group detected the same disease characteristics as the univariate regression model combining all treatment groups. The stratified multivariate analysis revealed the same 3 disease characteristics that were significantly associated with <q12-week dosing interval: baseline occult-type CNV (odds ratio [95% CI]: 0.761 [0.610, 0.948]; $P = .0148$) and the presence of retinal fluid (odds ratio [95% CI]: 0.362 [0.284, 0.461]; $P < .0001$) and presence of retinal leakage (odds ratio [95% CI]: 0.501 [0.398, 0.630]; $P < .0001$) at week 52.

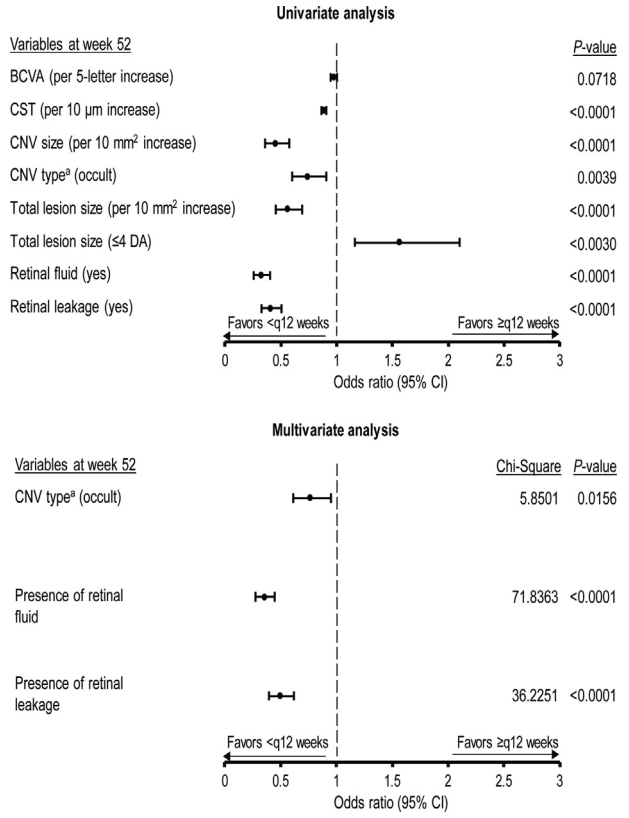


FIGURE 2. Forest plot of week 52 variables associated with anti–vascular endothelial growth factor dosing interval in year 2 of the VIEW Studies. (Top) Univariate analysis. (Bottom) Multivariate analysis. Full analysis set, year 2 medication and study completers; last observation carried forward. <q12-week intervals = less-than-every-12-week intervals during year 2; ≥q12-week intervals = every-12-week intervals or longer during year 2; BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; CST = central (optical coherence tomography) subfield thickness; DA = disc areas. [a]At baseline.

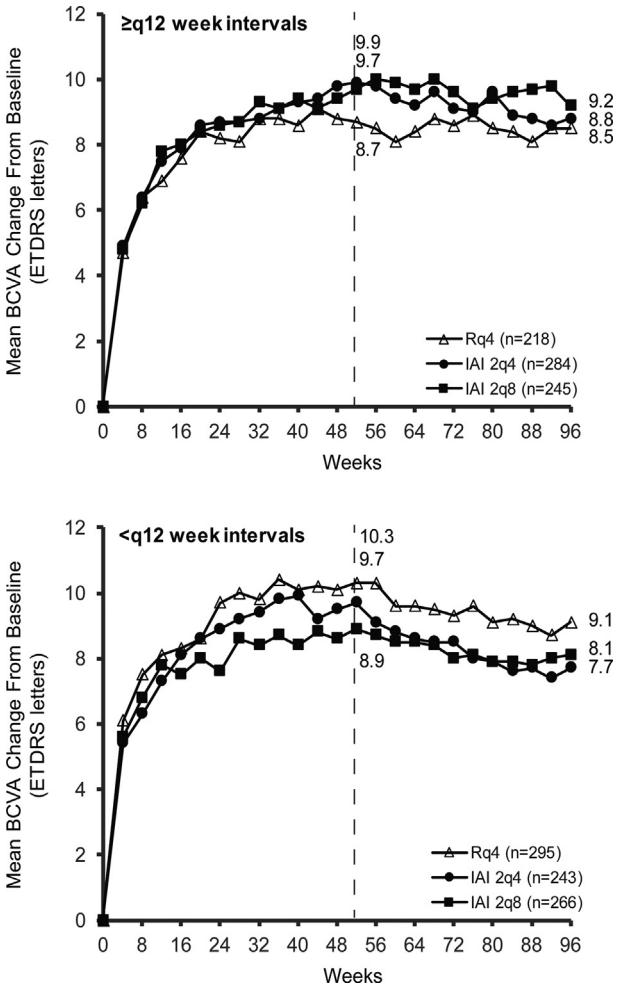


FIGURE 3. Mean best-corrected visual acuity (BCVA) gains from baseline through week 96 by anti–vascular endothelial growth factor dosing interval in year 2 of the VIEW studies. (Top) ≥q12-week intervals. (Bottom) <q12-week intervals. Full analysis set, year 2 medication and study completers; last observation carried forward. <q12-week intervals = less-than-every-12-week intervals during year 2; ≥q12-week intervals = every-12-week intervals or longer during year 2; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI 2q4 = intravitreal aflibercept injection 2 mg every 4 weeks; IAI 2q8 = intravitreal aflibercept injection 2 mg every 8 weeks after 3 initial monthly doses; Rq4 = ranibizumab 0.5 mg every 4 weeks.

• **VISUAL ACUITY OUTCOMES:** Among study eyes with ≥q12-week dosing interval, the mean BCVA gains from baseline at week 52 were 8.7, 9.9, and 9.7 letters in the Rq4, IAI 2q4, and IAI 2q8 groups, respectively. All 3 treatment groups maintained week 52 gains from baseline in mean BCVA through year 2, with the Rq4, IAI 2q4, and IAI 2q8 groups showing 8.5, 8.8, and 9.2 letters improvement from baseline at week 96 (Figure 3, Top). Among study eyes with <q12-week dosing interval, the mean BCVA gains from baseline at week 52 were 10.3, 9.7, and 8.9 letters in the Rq4, IAI 2q4, and IAI 2q8 groups, respectively. These gains were also largely maintained through the second year for all 3 treatment groups (Figure 3, Bottom), with the Rq4, IAI 2q4, and IAI 2q8 groups showing 9.1, 7.7, and 8.1 letters improvement from baseline at week 96.

• **ANATOMIC OUTCOMES:** Among study eyes with ≥q12-week dosing interval, the mean CST reductions from baseline at week 52 were 141.5, 148.5, and 153.1 µm in the Rq4, IAI 2q4, and IAI 2q8 groups, respectively. All 3 treatment groups maintained week 52 reductions from baseline through year 2, with the Rq4, IAI 2q4, and IAI 2q8 groups showing 130.6, 139.8, and 153.3 µm reductions from baseline at week 96 (Figure 4, Top). Among study eyes with <q12-week dosing interval,

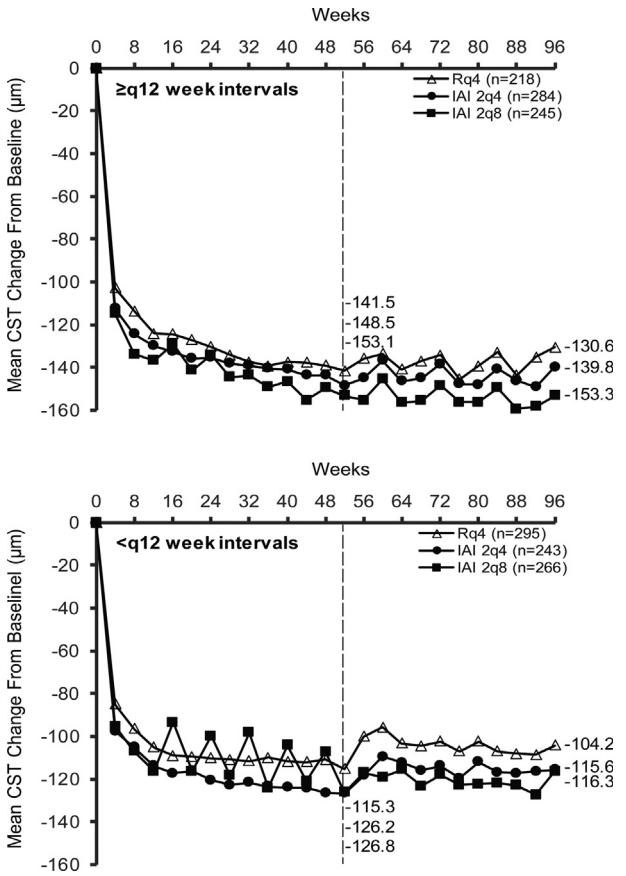


FIGURE 4. Mean central (optical coherence tomography) subfield thickness (CST) reductions from baseline through week 96 by anti–vascular endothelial growth factor dosing interval in year 2 of the VIEW studies. (Top) ≥q12-week intervals. (Bottom) <q12-week intervals. Full analysis set, year 2 medication and study completers; last observation carried forward. <q12-week intervals = less-than-every-12-week intervals during year 2; ≥q12-week intervals = every-12-week intervals or longer during year 2; IAI 2q4 = intravitreal aflibercept injection 2 mg every 4 weeks; IAI 2q8 = intravitreal aflibercept injection 2 mg every 8 weeks after 3 initial monthly doses; Rq4 = ranibizumab 0.5 mg every 4 weeks.

the mean CST reductions from baseline at week 52 were 115.3, 126.8, and 126.2 µm in the Rq4, IAI 2q4, and IAI 2q8 groups, respectively. These reductions at week 52 were also largely maintained for all 3 treatment groups (Figure 4, Bottom), with the Rq4, IAI 2q4, and IAI 2q8 groups showing 104.2, 115.6, and 116.3 µm reductions from baseline at week 96.

Proportions of Rq4, IAI 2q4, and IAI 2q8 eyes without retinal fluid at week 96 (observed cases) were 61.9% (133 of 215 eyes), 62.1% (175 of 282 eyes), and 60.5% (147 of 243 eyes) among eyes with ≥q12-week dosing interval, and 33.4% (97 of 290 eyes), 45.6% (109 of 239 eyes), and 40.4% (105 of 260 eyes) among eyes with <q12-week dosing interval.

• **SAFETY:** Safety from the VIEW 1 and VIEW 2 trials through year 2 has previously been reported.[5,7] In brief, ocular adverse events occurring in 10% or more of patients across treatment groups were conjunctival hemorrhage, retinal hemorrhage, reduced visual acuity, eye pain, vitreous detachment, and increased intraocular pressure from baseline to week 96. Serious ocular adverse events were infrequent and occurred with a similar rate across all treatment groups (3.6% to 4.4%). The incidence of arterial thromboembolic events as defined by the Antiplatelet Trialists' Collaboration criteria was similar among treatment groups (2.4% to 3.6%).

DISCUSSION

THIS POST HOC ANALYSIS FROM THE VIEW STUDIES DEMONstrated that approximately 40% to 50% of patients with nAMD received treatment with ranibizumab or IAI every 12 weeks during their second year of follow-up. Re-treatment decisions were made monthly based on prespecified treatment criteria, including both visual and anatomic parameters. On average, vision and anatomic improvements at week 52 following a year of fixed dosing regimen with ranibizumab or IAI were maintained in both subgroups of patients who received treatment at least every 12 weeks and those who received treatment at a more frequent interval at least 1 time during the study.

As confirmed by the multivariate regression analysis, the absence of retinal fluid on TD-OCT and absence of leakage on FA at the end of 1 year were significantly associated with the ability to extend treatment to every 12 weeks. Consistent with the multivariate analysis findings, new or persistent fluid as indicated by TD-OCT was cited as a top reason for criteria-based injections as determined by treating physician in the overall VIEW study population from week 52 through week 96 (data on file). This is not unexpected, as a survey of 689 retinal specialists showed that 83% of U.S. retinal specialists believe fluid recurrence on OCT is the most important factor indicating recurrent nAMD disease activity in the maintenance phase of anti-VEGF treatment.[8] In addition, the multivariate analysis confirmed that patients who had been determined to have occult lesions at baseline were more likely to require treatment more frequently than every 12 weeks.

It should be noted that patients treated with either ranibizumab or IAI maintained their visual outcomes through the end of the study in both dosing subgroups. This supports the notion that clinical presentation of nAMD is variable across patients, resulting in the need for an individualized consistent dosing schedule to maintain visual gains. While there are patients who, following a period of intensive dosing, present with no disease activity and hence can be treated every 12 weeks or more, there are others who need to continue on a more frequent treatment schedule, as

observed in this post hoc analysis. Quarterly dosing following specified criteria in the VIEW studies is not necessarily the same as a 12-week "disease-free" interval, which is terminology often used when describing treatment intervals within a treat-and-extend dosing approach. Variability across patient populations was also observed in another post hoc analysis from the VIEW studies. Jaffe and associates demonstrated that in patients with persistent retinal fluid following 3 initial injections, monthly treatment with IAI 2q4 resulted in significantly better visual acuity when compared with IAI 2q8 or monthly ranibizumab.[9] In patients without initial persistent retinal fluid, visual acuity results were similar across all treatment groups at 52 weeks.[9]

The VIEW study design allowed a 12-week treatment interval following a period of fixed dosing. However, clinicians may determine whether an individual patient may be extended based on their visual and anatomic response earlier in the course of therapy. Supportive studies evaluating treatment interval as determined by criteria-based dosing demonstrated that 42% to 50% of patients treated with IAI (depending on every 2- or 4-week extension of dosing interval following an initial mandatory treatment phase) in the ALTAIR study[10] were able to achieve an injection-free interval of ≥12 weeks, and 41% of patients in the CAPELLA study (data on file; Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA) went at least 12 weeks prior to receiving their first as-needed injection during the first year of treatment with IAI 2 mg.

Interpretation of these data from the VIEW studies is limited by the post hoc nature of the analysis. Though prespecified and exploratory, the original studies were not designed to prospectively determine outcomes based on these dosing subgroups. In addition, the last injection of year 1 was given at week 48, but disease characteristics were evaluated at week 52. In the current study, week 52 was selected as the starting time point as FA assessments were performed at week 52, the primary endpoint of the study, and not at week 48. It should be emphasized that other disease characteristics evaluated at week 48 demonstrated consistency with those at week 52. Of note, morphologic factors that may influence re-treatment of patients with nAMD in current clinical practice (eg, foveal intraretinal fluid associating with worse visual outcomes[11,12]) may have evolved further since the time of the VIEW studies.

The strength of the post hoc analysis lies in the dataset acquired from 2 large, prospective, randomized clinical trials. The outcome of mean change in BCVA was based on measurements conducted by personnel masked to treatment assignments, and grading of the anatomic parameters was conducted by masked reading centers. In addition, the study design included monthly treatment evaluation, allowing for re-treatment to be given at any demonstration of disease recurrence.

In conclusion, this post hoc analysis provides clinically relevant information regarding management of patients with nAMD with ranibizumab or IAI. Ongoing physician assessment of an individual patient's visual and anatomic response to IAI treatment can inform treatment decisions leading to every-4-week, every-8-week, or every-12-week dosing regimens. When determining an appropriate dosing approach, the goal of management should be to attain maximal vision gains and maintain these gains with consistent anti-VEGF dosing, as demonstrated in long-term AMD studies.[13,14] Although management of nAMD may include extended dosing in some patients, any benefit of an interval extension should not come at the expense of vision loss. Precision dosing with anti-VEGF agents may best achieve the opportunity for vision improvement and maintenance of vision gains.

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REFERENCES

1. Yancopoulos GD. Clinical application of therapies targeting VEGF. *Cell* 2010;143(1):13–16.
2. Ferrara N. VEGF-A: a critical regulator of blood vessel growth. *Eur Cytokine Netw* 2009;20(4):158–163.
3. Miller JW, Le Couter J, Strauss EC, Ferrara N. Vascular endothelial growth factor a in intraocular vascular disease. *Ophthalmology* 2013;120(1):106–114.
4. Eandi CM, Alovisi C, De Sanctis U, Grignolo FM. Treatment for neovascular age related macular degeneration: the state of the art. *Eur J Pharmacol* 2016;787:78–83.

5. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119(12):2537–2548.
6. Richard G, Mones J, Wolf S, et al. Scheduled versus pro re nata dosing in the VIEW Trials. *Ophthalmology* 2015; 122(12):2497–2503.
7. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014;121(1):193–201.
8. The ASRS PAT Survey 2016. Ameican Society of Retina Specialists. Available at: https://www.asrs.org/content/documents/2016_global_trends_in_retina_survey_highlights_for_website_2.pdf. Accessed July 9, 2018.
9. Jaffe GJ, Kaiser PK, Thompson D, et al. Differential response to anti-VEGF regimens in age-related macular degeneration patients with early persistent retinal fluid. *Ophthalmology* 2016;123(9):1856–1864.
10. Ohji M, Okada AA, Takahashi K, Kobayashi M, Terano Y. Two different treat and extend dosing regimens of intravitreal aflibercept for wAMD in Japanese patients: 52-week results of the ALTAIR study. Presented at the European Society of Retina Specialists [EURETINA]. September 7-10, 2017; Barcelona, Spain.
11. Jaffe GJ, Martin DF, Toth CA, et al. Macular morphology and visual acuity in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2013;120(9): 1860–1870.
12. Jaffe GJ, Ying GS, Toth CA, et al. Macular morphology and visual acuity in year five of the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2019; 126(2):252–260.
13. Kaiser PK, Singer MA, Tolentino M, et al. Long-term safety and visual outcome of intravitreal aflibercept in neovascular age-related macular degeneration: VIEW 1 extension study. *Ophthalmol Retina* 2017;1:304–313.
14. Peden MC, Suner IJ, Hammer ME, Grizzard WS. Long-term outcomes in eyes receiving fixed-interval dosing of anti-vascular endothelial growth factor agents for wet age-related macular degeneration. *Ophthalmology* 2015;122(4):803–808.