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Intraocular Pressure in Patients with Neovascular Age-Related Macular Degeneration Receiving Intravitreal Aflibercept or Ranibizumab

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Purpose: To assess change in intraocular pressure (IOP) in patients with neovascular age-related macular degeneration (NVAMD) receiving intravitreal aflibercept injection (IAI) or ranibizumab in VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and 2 studies.

Design: Analyses from 2 randomized, active-controlled, phase III trials.

Participants: A total of 2457 patients with NVAMD.

Methods: Patients received IAI 2 mg every (q) 4 weeks (2q4), 0.5 mg q4 weeks (0.5q4), 2 mg q8 weeks (after 3 monthly doses; 2q8), or ranibizumab 0.5 mg q4 weeks (Rq4) for 52 weeks. At week 52, patients were switched to a variable regimen requiring at least quarterly dosing and allowing interim injections based on anatomic and visual assessment.

Main Outcome Measures: Pre-injection IOP was analyzed in study and uninjected fellow eyes from baseline to week 96. Prespecified end points included mean change in IOP from baseline and prevalence of a >21 mmHg and >10 mmHg increase in IOP from baseline. Cumulative incidence of sustained (at 2 consecutive visits) IOP >21 mmHg, a single event of IOP >25 mmHg, and sustained IOP increase from baseline (≥5 mmHg) was also evaluated.

Results: Mean IOP change from baseline over 96 weeks in all IAI groups was consistently lower than in the Rq4 group, and this finding was replicated in both trials. In an analysis integrating both studies, the proportion of study eyes with IOP >21 mmHg at week 96 was 20.2%, 14.2%, 12.1%, and 12.5% in Rq4, 2q4, 2q8, and 0.5q4, respectively. Reduction in risk, relative to Rq4, of having sustained IOP >21 mmHg over 96 weeks was 62% (95% confidence interval [CI], 36%−78%), 50% (95% CI, 19%−70%), and 69% (95% CI, 45%−84%) for 2q4, 2q8, and 0.5q4, respectively. Risk reduction in the IAI groups for a sustained IOP increase ≥5 mmHg was 31% (95% CI, 8%−48%), 38% (95% CI, 17%−54%), and 47% (95% CI, 27%−61%), respectively. In uninjected fellow eyes, only sustained IOP >21 mmHg events were higher in the Rq4 group compared with all IAI groups.

Conclusions: Incidence of elevated IOP in eyes with NVAMD was lower in all IAI groups than in the ranibizumab group. *Ophthalmology 2015;122:1802-1810 © 2015 by the American Academy of Ophthalmology*

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Intravitreal anti−vascular endothelial growth factor (VEGF) agents, including ranibizumab (Lucentis; Genentech, San Francisco, CA), bevacizumab (Avastin; Genentech), and aflibercept (Eylea, also referred to as "VEGF Trap-Eye"; Regeneron Pharmaceuticals, Inc., Tarrytown, NY), are frequently used to treat choroidal neovascularization and retinal vascular disorders.[1−4] With the addition of fluid into the vitreous cavity, it is not surprising that intraocular pressure (IOP) increases occur transiently after intravitreal injections.[5−8] Recent reports suggest sustained ocular hypertension can occur after intravitreal ranibizumab or bevacizumab.[9−18] A post hoc analysis of the 24-month data from the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) trials by Bakri et al[18] showed more eyes treated with intravitreal ranibizumab had 1 or more pre-injection IOP increases from baseline of ≥6 or ≥8 mmHg, with concurrent highest IOPs of ≥21 and ≥25 mmHg, versus eyes receiving sham injections. Also, a recent report demonstrated that in 207 patients with neovascular age-related macular degeneration (NVAMD) who received unilateral ranibizumab and/or bevacizumab intravitreal injections, 11.6% of injected versus 5.3% of contralateral, uninjected control eyes experienced an IOP elevation of ≥6 mmHg on ≥2 consecutive visits.[17] In a larger study of 449 eyes of 328 patients with NVAMD, a greater number of intravitreal injections of ranibizumab and bevacizumab was shown to be associated with an increased risk for sustained IOP elevation in eyes when controlling for the confounder (prior intravitreal steroid injection).[16]

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and 2 studies have

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demonstrated that intravitreal aflibercept injection (IAI), also referred to as "VEGF Trap-Eye," given monthly or every 2 months after 3 initial doses is noninferior and clinically equivalent to monthly ranibizumab for maintaining vision of patients with NVAMD at week 52.[4] All IAI groups and ranibizumab were also equally effective in improving visual acuity and preventing visual acuity loss at week 96.[19]

We evaluate changes in IOP in patients with NVAMD receiving IAI or ranibizumab for 96 weeks in the VIEW 1 and 2 studies. Analyses were conducted to determine whether elevated IOPs before injection, relative to baseline, were related to treatment group assignment or other baseline characteristics in the study eye. In addition, IOP events in uninjected fellow eyes were evaluated to investigate whether they were related to similar events in the study eyes.

Methods

Analyses were conducted in patients enrolled in 2 large, multicenter, controlled trials (VIEW 1 and 2) comparing IAI with intravitreal ranibizumab. Each study center's review board or ethics committee approved the study protocols. Both trials were registered with ClinicalTrials.gov (identifier no. NCT00509795 and NCT00637377), and all patients signed a written consent form before initiation of the study-specific procedures. The VIEW 1 and 2 studies were conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

VIEW 1 and 2 Study Designs

The VIEW 1 and 2 studies were 2 similarly designed, randomized, double-masked, active-controlled, multicenter, 96-week, phase III trials comparing the efficacy and safety of IAI and ranibizumab in patients with NVAMD. The design of the VIEW studies has been described by Heier et al.[4] Patients were randomized in a 1:1:1:1 ratio to 1 of the following 4 regimens for the first 52 weeks: (a) 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), (b) 2 mg IAI every 4 weeks (2q4), (c) 0.5 mg IAI every 4 weeks (0.5q4), and (d) 2 mg IAI every 8 weeks (2q8) after 3 initial monthly injections. From week 52 to 96, patients were treated with the same dose as the first 52 weeks at least every 12 weeks, with monthly evaluations for interim injections based on assessment of anatomic and visual outcomes. Patients could receive intravitreal ranibizumab in the fellow eye if there was evidence of NVAMD that required treatment. For these analyses, only fellow eyes that were not injected were used for IOP assessments.

Intraocular Pressure Measurements

Intraocular pressure was measured using applanation tonometry (Goldmann [Haag-Streit Diagnostics, Koeniz, Switzerland] or Tono-Pen [Reichert Technologies, Depew, NY]). The same method of IOP measurement had to be used in each patient throughout the study. Unmasked study personnel measured IOP at every visit in both eyes before injection and in the study eye 30 to 60 minutes after the intravitreal injection. Only 1 IOP measurement for both eyes was recorded before injection at every visit as required by the study protocol.

Statistical Analysis

Of the 2457 patients randomized into the VIEW studies, 2419 were included in the safety data set. Simple proportions were used to describe the various binary events through weeks 52 and 96. Least-squares means were used to compare continuous variables (e.g., observed IOP at each visit) between treatment groups. Time-to-event methodology was used to assess the key outcomes: reaching IOPs >21 or ≥ 25 mmHg and changes from baseline of ≥ 5 mmHg. Cumulative incidence, which is the proportion of an event that occurs before a given time, was computed for each of the preceding events. For all time-to-event analyses (except the threshold of 25 mmHg), the outcome of interest had to be sustained for at least 2 consecutive visits. Event rates are presented as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure to Rq4 or to the different dosing regimens of IAI. The Kaplan–Meier method was used to estimate the cumulative incidence. This provides a means to estimate the cumulative incidence and accounts for eyes not having 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 comparing the various IAI treatment groups with the Rq4 group were estimated by the proportional-hazards analysis. The relative risk analyses were stratified by study (VIEW 1 vs. VIEW 2). Only within-stratum analyses contributed to the overall relative risks. This was done iteratively. PROC Means, PROC LIFETEST, and PROC GENMOD were used in the analyses.

Outcome Measures

Intraocular pressure was assessed before injection at each visit in both study and fellow eyes. Prespecified IOP measurements that were evaluated included (a) mean change in IOP from baseline through week 96, (b) prevalence of IOP >21 mmHg through week 96, and (c) prevalence of IOP change from baseline of ≥ 10 mmHg through week 96.

Cumulative incidence of sustained IOP >21 mmHg, cumulative incidence of IOP ≥ 25 mmHg, and cumulative incidence of sustained IOP changes from baseline of ≥ 5 mmHg were evaluated in both the study and uninjected fellow eyes. A sustained event was defined as changes from baseline or IOP exceeding a specific threshold for at least 2 consecutive visits. This definition of a sustained event was chosen because of its reproducibility and because it represented a measure of clinically important elevation of IOP. Single events for IOP ≥ 25 mmHg were evaluated because too few patients had sustained IOP ≥ 25 mmHg for reliable conclusions to be drawn from a time-to-event analysis.

Results

Baseline Characteristics

There were no meaningful differences in pre-injection IOPs among the 4 dosing regimens at baseline (Table 1). Slightly fewer patients in the 2q4 group had a history of preexisting glaucoma or used glaucoma medication compared with the Rq4, 2q8, and 0.5q4 groups.

Outcomes

Overall, a small decrease in mean change in IOP in the study eye of patients in all IAI groups from baseline over the 96 weeks of follow-up, was observed. The mean change in IOP was consistently higher in the Rq4 group than in all IAI groups, and this higher mean change in IOP in the Rq4 group was observed in both VIEW studies (Fig 1A, B). Because of the similar results with regard to mean IOP in both VIEW studies, an integrated perspective combining the VIEW 1 and 2 studies is used for