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The Systemic Safety of Ranibizumab in Patients 85 Years and Older with Neovascular Age-Related Macular Degeneration

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Objective: Ranibizumab safety is well established for treatment of neovascular age-related macular degeneration (nAMD), but less is known about the risk of systemic serious adverse events (SAEs), specifically among patients with heightened baseline risk due to age (≥85 years). This analysis examines whether patients ≥85 years of age versus those <85 years experience an increased risk of key systemic SAEs during intravitreal ranibizumab treatment for nAMD.

Design: Retrospective, pooled analysis of safety data from 5 phase III/IIIb multicenter randomized clinical trials in patients with nAMD: ANCHOR, MARINA, PIER, SAILOR, and HARBOR.

Participants: Patients with nAMD receiving ranibizumab (n = 4347) or control (sham/verteporfin photodynamic therapy, n = 441) treatment included in the safety-evaluable set of the 5 trials.

Methods: The incidence of nonocular SAEs was analyzed stratified by age (<85 years [n = 3795] vs ≥85 years [n = 993]), treatment (control, ranibizumab 0.3 mg, ranibizumab 0.5 mg, ranibizumab 2.0 mg), and injection frequency (monthly, as needed [PRN]).

Main Outcome Measures: Incidence of key systemic SAEs, defined as total nonocular SAEs, deaths, cardiovascular events, cerebrovascular (CBV) events, and Antiplatelet Trialists' Collaboration events.

Results: The MARINA and ANCHOR trials had greater rates of key SAEs for patients ≥85 years versus those <85 years. Ranibizumab exposure did not increase the risk of most SAEs in elderly patients; for CBV events and death, the effect of ranibizumab versus control treatment for age ≥85 years was not interpretable due to small number of events (CBV: n = 2, 2, 5 for control, ranibizumab 0.3 mg, and ranibizumab 0.5 mg, respectively; death: n = 2, 4, 5, respectively). Across all 5 trials, an increased risk was found for age ≥85 years versus <85 years for the marketed dose of ranibizumab 0.5 mg. In the HARBOR trial, increased rates of key SAEs (excluding total nonocular SAEs) for age ≥85 years versus <85 years were observed with monthly dosing but not with PRN dosing; event rates were similar for 2.0 mg versus 0.5 mg.

Conclusions: Consistent with general trends, the risk of key systemic SAEs was associated with age ≥85 years versus <85 years, but not with ranibizumab drug exposure. The difference between monthly versus PRN was inconclusive. There was no evidence of a dose effect. Interpretation of this retrospective analysis is limited because it was not prospectively powered for statistically definitive conclusions. *Ophthalmology Retina 2018;■:1–9* © *2018 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/).*

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Intraocular inhibition of vascular endothelial growth factor (VEGF) with ranibizumab can prevent vision loss and improve visual acuity in many patients with neovascular age-related macular degeneration (nAMD).[1,2] However, although the systemic safety profile of ranibizumab is well characterized,[1–4] there is ongoing discussion regarding the potential for systemic serious adverse events (SAEs) among patients with a heightened baseline risk for arterial thromboembolic events (ATEs).

In particular, the risk of ATEs with intraocular VEGF inhibitor therapy in the elderly is a recognized gap in our understanding of the safety risks of this class of drugs.[5–8] Defined by the National Institutes of Health as the "oldest old," patients aged ≥85 years old are the most vulnerable to safety risks.[9] Compared with patients aged <85 years, those aged ≥85 years have an already heightened risk of cardiovascular (CV) and cerebrovascular (CBV) events[10–15] and are often underrepresented in clinical trial populations due to relatively lower rates of recruitment and retention.[16–18]

VEGF, in addition to promoting angiogenesis, regulates vasodilation by stimulating the production of nitric oxide by vascular endothelial cells.[19–21] Inhibition of VEGF leads to vasoconstriction, which can ultimately result in hypertension,[22] an established risk factor for ATEs, including stroke and myocardial infarction (MI).[11,21,23] Systemic suppression of VEGF for the treatment of metastatic colorectal cancer is associated with treatment-emergent SAEs,

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including hypertension, stroke, and wound-healing complications[21,24–29]; however, these effects are observed with intravenous doses ~100 times higher than those used for ocular indications. Despite the low dosage and local administration, intraocular injection of VEGF inhibitors has been shown to decrease systemic VEGF levels for varying durations depending on the drug evaluated.[30–35] It is unclear whether this measured suppression of systemic VEGF with intraocular administration is sufficient to induce the treatment-emergent SAEs observed with systemic administration for oncologic indications.

A recent report by the European Medicines Agency found that elderly patients (defined by the National Institutes of Health as ≥85 years old)[9] had higher rates of SAEs, including ATEs, compared with patients <85 years following treatment with the anti-VEGF agents aflibercept (Eylea) or ranibizumab (Lucentis), based on data from the VIEW 1 and 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) studies.[5] The rate of SAEs over 1 year increased sharply for patients aged ≥85 years (n = 370): the average rates were 10.9%, 14.9%, and 23.6% for patients aged ≥65 to <75, ≥75 to <85, and ≥85 years, respectively. The observation in patients aged ≥85 years led to this review of the larger ranibizumab dataset to better understand the potential risks of ranibizumab treatment in this more vulnerable population.

The goal of this study was to determine whether patients aged ≥85 years versus <85 years experienced an increased risk of key systemic SAEs during intravitreal ranibizumab treatment for nAMD. Safety data, stratified by age, were retrospectively examined from 5 phase III trials of ranibizumab for nAMD—namely MARINA,[2] ANCHOR,[1] PIER,[4] SAILOR,[36] and HARBOR.[37] The rates of key systemic SAEs in patients <85 versus ≥85 years were compared to identify potential interactions by treatment (ranibizumab versus sham/verteporfin photodynamic therapy [PDT]) and treatment regimen (monthly versus as needed [pro re nata, PRN]; 0.5 mg versus 2.0 mg) on SAE incidence.

Methods

This study was an exploratory, post hoc analysis of 5 phase III randomized, multicenter clinical trials: ANCHOR [NCT00061594], MARINA [NCT00056836], PIER [NCT00090623], SAILOR [NCT00251459], and HARBOR [NCT00891735] (clinical trial registration is publicly available at ClinicalTrials.gov). These studies evaluated the efficacy and safety of intravitreal ranibizumab treatment for nAMD in patients aged ≥50 years. The study designs and primary outcomes of these trials were published previously.[1,2,4,36,37] Patients provided written informed consent for study participation. Each study was performed in compliance with the Health Insurance Portability and Accountability Act, was approved by the institutional review boards of their respective participating clinical centers, and adhered to the tenets of the Declaration of Helsinki.

MARINA[2] and ANCHOR[1,3] were double-blind 24-month studies that compared monthly administration of ranibizumab 0.3 mg and ranibizumab 0.5 mg with control treatment (MARINA, sham injections; ANCHOR, PDT) in treatment-naive patients with predominantly classic (ANCHOR) or minimally classic or occult (MARINA) lesions secondary to nAMD. Patients with preexisting CV, CBV, or peripheral vascular conditions were not excluded from the MARINA and ANCHOR studies. Patients who crossed over from sham to ranibizumab treatment were not included in this analysis after time of the crossover (MARINA, n = 12, median time of crossover 23 months; ANCHOR, n = 50, median time of crossover 21 months).

PIER[4,38] was a 24-month double-blind study that compared ranibizumab 0.3 mg, ranibizumab 0.5 mg, and sham injections, administered as 3 consecutive monthly loading doses followed by quarterly (every 3 months) administration in treatment-naive patients with or without a classic lesion secondary to nAMD. After year 1, sham-group patients crossed over to receive ranibizumab 0.5 mg. Patients with CV, CBV, or peripheral vascular conditions were not excluded from the PIER study.

SAILOR[36] cohort 1 was a 12-month single-blind study that compared ranibizumab 0.3 mg and ranibizumab 0.5 mg in treatment-naive and previously treated patients with choroidal neovascularization secondary to nAMD. Treatment was administered as 3 consecutive monthly loading doses followed by PRN retreatment based on time-domain OCT and visual acuity criteria. Cohort 2, a nonrandomized, single-dose cohort trial, was not included in this analysis; hereafter, SAILOR refers to SAILOR cohort 1. Patients with controlled CV disease were not excluded from the SAILOR study.

HARBOR[37,39] was a 24-month double-blind study that compared ranibizumab 0.5 mg and ranibizumab 2.0 mg, administered as 3 consecutive monthly loading doses followed by monthly or PRN retreatment based on strict spectral-domain OCT and visual acuity criteria in treatment-naive patients with subfoveal nAMD. Patients with uncontrolled blood pressure; atrial fibrillation not managed by the patient's primary care physician or cardiologist within 3 months of the screening visit; or a history of stroke within 3 months of the screening visit were excluded from the HARBOR study.

Study Populations and Analysis of Systemic Safety

Analyses are reported on 3 populations to assess the effect of treatment versus no treatment, injection frequency, and dose on the risk of key systemic SAEs. For population 1, safety events in ranibizumab 0.3 mg, ranibizumab 0.5 mg, and the control (sham injection or verteporfin PDT) groups of the MARINA and ANCHOR studies were pooled to assess the effect of ranibizumab treatment in patients aged ≥85 years versus those aged <85 years. For population 2, safety events in all patients treated with ranibizumab 0.5 mg in the MARINA, ANCHOR, PIER, SAILOR, and HARBOR studies were pooled to assess the effect of age when treated with the marketed dose of ranibizumab. Finally, for population 3, safety events of HARBOR were used to assess the effect of dose (ranibizumab 0.5 mg and 2.0 mg) and regimen (monthly versus PRN) to assess the effects of injection frequency and dose on SAE risk.

End Points

The key systemic safety end points selected were total nonocular SAEs and 5 subcategories of SAEs: ATEs, deaths, CV events, CBV events, and Antiplatelet Trialists' Collaboration (APTC) events (including vascular deaths, deaths of unknown cause, nonfatal MIs, and nonfatal CBV events). These end points were selected to be consistent with existing Standardised Medical Dictionary for Regulatory Activities Query definitions and those described in the European Medicines Agency's Public Assessment Report (EPAR) for aflibercept.[5] Secondary systemic safety end points of interest included MIs, strokes, transient ischemic attacks (TIAs), and strokes plus TIAs. The end point definitions