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Real-world Outcomes of Anti Vascular Endothelial Growth Factor Therapy in Neovascular Age-Related Macular Degeneration in the United States

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Purpose: Real-world visual outcomes of anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (nAMD) have been reported in cohorts outside of the United States. This study sought to assess the relationship between presenting visual acuity (VA) and visual outcomes, as well as the potential impact of loss to follow-up, in real-world anti-VEGF-treated nAMD patients from the United States.

Design: Retrospective study of aggregated, longitudinal electronic medical records obtained from a geographically diverse sample of US retina specialists and included in the Vestrum Health Retina Database.

Participants: Inclusion criteria were a diagnosis of nAMD, no previous treatment, and ≥3 monthly anti-VEGF injections in the first 4 months from diagnosis in patients diagnosed between January 2011 and July 2013.

Methods: To model loss to follow-up, mutually exclusive cohorts of nAMD patients with loss to follow-up after specific time points of 6 and 12 months (i.e., no follow-up beyond) were compared with a separate cohort of patients who completed 24 months of follow-up ending prior to July 2015 (n = 2213).

Main Outcome Measure: VA outcomes were assessed on each cohort as a whole, with additional stratification by baseline VA.

Results: The 6-, 12-, and 24-month cohorts received means of 5.4, 7.3, and 12.1 injections and showed no change, no change, and a mean change of +3.1 letters from baseline (95% confidence interval 1.8-4.4 letters, $P < 0.01$), respectively. When stratified by baseline VA, nearly all groups lose VA at their respective follow-up periods, except for those with baseline VA of 20/200 or worse.

Conclusions: Real-world nAMD patients in the United States receive fewer anti-VEGF injections and experience worse visual outcomes compared with patients in randomized clinical trials, consistent with non-US studies. Patients with better VA at presentation tend to be particularly vulnerable to vision loss. Compared with other patients, those ultimately lost to follow-up have worse visual outcomes at, or prior to, their final visit, suggesting that loss to follow-up may lead to overestimation of visual outcomes in clinical studies of nAMD.

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Timing of Povidone Iodine Application to Reduce the Risk of Endophthalmitis after Intravitreal Injections

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Purpose: To analyze comparatively the effect of different intravitreal injection (IVI) protocols on the incidence of endophthalmitis occurring after injection.

Design: Retrospective case-control series.

Participants: Twenty-seven retina specialists in a large vitreoretinal practice performed 37 646 IVIs.

Methods: Multivariate analysis was used to identify risk factors for development of endophthalmitis occurring after injection. Before all injections, a technician applied 5% povidone-iodine (PI) to the eyelids and conjunctiva. There were 4 distinct aseptic protocols with regard to reapplication of PI by physicians: physicians who did not reapply PI, reapplication of PI without the use of a lid speculum, reapplication of PI before speculum placement, and reapplication of PI after speculum placement. Other analyzed variables included the use of gloves, a caliper to mark the injection site, and the class of medication (steroid vs. anti-vascular endothelial growth factor).

Main Outcome Measures: Cases of presumed infectious endophthalmitis.

Results: Thirty-three cases of presumed infectious endophthalmitis occurred after 37 646 injections (0.088%). The method of PI application was found to be a statistically significant predictor of the incidence of endophthalmitis ($P = 0.031$). When compared with the incidence of endophthalmitis for physicians who did not reapply PI (0.124% [20/16 155]), there was no statistical difference for reapplication of PI without the use of a speculum (0.110% [6/5472]; $P = 0.584$) or reapplication before speculum insertion (0.122% [5/4067]; $P = 0.863$). However, reapplication of PI after insertion of the lid speculum was associated with a significantly decreased incidence of endophthalmitis (0.017% [2/11 952]; $P = 0.004$; odds ratio, 0.113). Use of gloves ($P = 0.119$) or a caliper to mark the injection site ($P = 0.496$) and the class of medication ($P = 0.740$) were not found to be statistically significant risk factors for endophthalmitis development.

Conclusions: The application of PI after placement of the lid speculum reduced the incidence of endophthalmitis occurring after injection approximately 7-fold compared with other aseptic protocols. Preventing the eyelid from contacting the injection site after the final application of PI is an important step in improving the safety of intravitreal injections.

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Fluorescein Angiography Does Not Alter the Initial Clinical Management of Choroidal Neovascularization in Age-Related Macular Degeneration

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Purpose: Fundus fluorescein angiography (FFA) is the standard modality to diagnose and manage choroidal neovascularization (CNV). However, FFA is costly and has considerable morbidity from allergic reactions and a mortality of 1 per 220 000. Since the advent of anti-vascular endothelial growth factor (VEGF) therapy for CNV, OCT has been used extensively to manage CNV, but FFA is still widely used. One recent study found the sensitivity and specificity of OCT compared with FFA in diagnosis of CNV were 100% and 80.8%, respectively. We hypothesize that FFA does not affect the management of patients initially suspected of having CNV to a clinically significant degree.

Design: Evaluation of diagnostic test using vignettes.

Participants: A total of 99 patients (99 eyes) who had an initial presentation of later confirmed CNV.

Methods: We retrospectively extracted in de-identified form the FFA, OCT, and clinical histories of the subjects. Vignettes were created with a standard narrative clinical history, posterior-pole color fundus image, central B-scan OCT of the initial visit, and early, mid, and late FFA of the affected eye. Four masked retinal specialists reviewed, in randomized order, these vignettes without FFA images (FFA- arm) and answered a forced choice management question: observation, 3 consecutive anti-VEGF injections, or other. After re-randomization, experts again reviewed the vignettes with the addition of the FFA images (FFA+ arm).

Main Outcome Measures: Intraobserver and interobserver concordance and reliability statistics within and between specialists.

Results: Among our retina specialists, intraobserver concordances were 89.7%, 88.7%, 88.7%, and 95.9% (average 90.7%, 95% confidence interval [CI], 83.7-97.6). The average interobserver concordance for the FFA- arm was 84.0% (95% CI, 72.6-95.4), and for the FFA+ arm, 81.8% (95% CI, 68.5-95.2); paired t testing demonstrated no significant difference between the FFA- and FFA+ arms: $t = 0.6$, $P = 0.55$.

Conclusions: Our data suggest a high degree of agreement in clinical decision making whether FFA was used or not. There was a similar level of agreement among specialists in the FFA- and FFA+ groups, albeit at higher, not statistically significant, variability. We believe these findings further support deferring the use of FFA in the initial management of CNV in AMD, except in treatment failures and nonstandard cases.

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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.

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Impact of Baseline Characteristics on Treatment Response to Intravitreal Aflibercept Injection for Wet Age-Related Macular Degeneration

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Purpose: To determine whether wet age-related macular degeneration (AMD) treatment outcomes within prespecified patient subgroups were consistent with overall study results.