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Incidence and Outcomes of Infectious and Noninfectious Endophthalmitis after Intravitreal Injections for Age-Related Macular Degeneration

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Purpose: To assess the incidence, cumulative rate, and long-term outcomes of infectious and noninfectious endophthalmitis after intravitreal injections (IVTs) of anti-vascular endothelial growth factor (VEGF) agents.

Design: Database study, prospectively designed.

Participants: Treatment-naïve eyes with neovascular age-related macular degeneration (nAMD) tracked by the Fight Retinal Blindness! (FRB!) registry that commenced anti-VEGF therapy between January 1, 2006, and November 30, 2016.

Methods: Cumulative rate of endophthalmitis and survival curves were measured using Cox-proportional hazards models. Locally weighted scatterplot smoothing curves were used to display visual acuity (VA).

Main Outcome Measures: Incidence and cumulative rate of endophthalmitis, and change in VA 12 months after endophthalmitis.

Results: Infectious endophthalmitis developed in 18 of 88 150 injections (1/4897 injections [0.020%]; 95% confidence interval [CI], 0.012−0.032) with no difference found between types of anti-VEGF medications ($P = 0.896$). The cumulative rate of infectious endophthalmitis per patient was 0.055%, 0.183%, 0.360%, 0.360%, 0.555%, and 0.843% after 10, 20, 30, 40, 50, and 60 IVTs, respectively. However, the "risk" of infectious endophthalmitis did not increase with each successive injection ($P = 0.202$). Noninfectious endophthalmitis developed in 11 of 88 150 injections (1/8013 injections [0.012%]; 95% CI, 0.006−0.022). The cumulative rate of noninfectious endophthalmitis per patient was 0.087% and 0.228% after 10 and 20 IVTs, respectively, and then remained stable up to 60 IVTs. The incidence of noninfectious endophthalmitis was higher for bevacizumab (8/9931, 0.081%) compared with ranibizumab (3/54 776, 0.005%; $P = 0.005$) and aflibercept (0/23 425; $P = 0.016$), and no differences were observed between ranibizumab and aflibercept ($P = 1.0$). The 12-month VA in infectious and noninfectious endophthalmitis was within ±2 lines of before endophthalmitis in 53% and 75% of eyes, respectively; a loss >2 lines was observed in 31% and 25% of eyes, respectively.

Conclusions: The incidences of infectious and noninfectious endophthalmitis after IVT were low, and the risk did not increase with each successive injection. We found higher rates of noninfectious endophthalmitis with bevacizumab compared with ranibizumab or aflibercept. Three quarters of cases with infectious and two thirds of cases with noninfectious endophthalmitis retained vision within 10 letters of the pre-endophthalmitis level. *Ophthalmology 2017;■:1−9 © 2017 by the American Academy of Ophthalmology*

Intravitreal injections (IVTs) are currently the fastest growing procedure in ophthalmology because of the aging population and expanding indications.[1] Intravitreal injections are considered to be relatively safe, but serious complications can occur, including rhegmatogenous retinal detachment, cataract formation, retinal artery occlusion, and endophthalmitis.[2]

Endophthalmitis after IVT of anti-vascular endothelial growth factor (VEGF) agents may be infectious or noninfectious. The incidence of infectious endophthalmitis has been estimated to be between 0.008% and 0.092% by previous meta-analyses and large population-based studies.[3−15] Variations in its incidence may be related to the differences in performing IVT.[12,16] Although the cause of infectious endophthalmitis is well understood, the pathophysiology of noninfectious endophthalmitis, also referred to as "sterile intraocular inflammation" or "noninfectious vitritis," after anti-VEGF treatment has not been completely determined and could involve an immune reaction to the drug itself or impurities gathered in manufacture, storage, or preparation of the agent.[17−24] Reports of the incidence of noninfectious endophthalmitis have varied, ranging from 0.09% and 0.37%.[17−24] This may be explained by differences in the populations studied or the lack of standardization in assessment of noninfectious endophthalmitis.

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Most of the previous studies of endophthalmitis were retrospective chart surveys. They reported the incidence of endophthalmitis "per IVT" by dividing the total number of endophthalmitis by the total number of IVT. However, most of the patients with neovascular age-related macular degeneration (nAMD) receive many injections.[25,26] The individual risk of endophthalmitis likely increases over time with repeated IVT. To report the risk of IVT in nAMD, it may be appropriate to report both endophthalmitis incidence "per IVT" and cumulative rate "per patient." Visual acuity (VA) outcomes reported by previous studies had short-term follow-up and did not include control groups.[4,8,14,15]

In the present study, we aimed to assess the incidence and the long-term cumulative rate of infectious and noninfectious endophthalmitis. The secondary objective was to assess the long-term VA outcomes of infectious and noninfectious endophthalmitis compared with control groups.

Methods

This study followed the STROBE checklist items for reporting observational study data.[27]

Study Design

Database study, prospectively designed.

Setting

Data were obtained from the Fight Retinal Blindness! (FRB!) database. The study design has been published.[28] Countries participating in this analysis were Australia, New Zealand, and Switzerland. Ethics approval was obtained from the Human Research Ethics Committees of the Royal Victorian Eye and Ear Hospital, the Royal Australian and New Zealand College of Ophthalmologists, the University of Sydney, and the Cantonal Ethics Committee Zurich, Switzerland. The FRB! study conformed to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

Data Sources/Measurements

The FRB! system collects data from each clinical visit, including the number of letters read on a logarithm of the minimum angle of resolution (logMAR) VA chart (best uncorrected, corrected, or pinhole); treatment given, if any; and ocular adverse events.[28] At baseline only, lesion size and type and prior treatment were recorded. Treatment decisions, including choice of drug and visit schedules, were entirely at the discretion of the practitioner in consultation with the patient, thereby reflecting real-world practice.

Documentation of endophthalmitis was recorded as follows at the discretion of the ophthalmologist. Infectious endophthalmitis included all cases of suspected infectious endophthalmitis, whether culture-proven (i.e., positive culture) or those with a negative culture that behaved clinically like infection (e.g., responsive to antibiotic treatment). Noninfectious endophthalmitis excluded all cases of suspected infectious endophthalmitis as defined earlier. An audit on the rate of microbiologic confirmation in infectious endophthalmitis was performed by sending a questionnaire to ophthalmologists. We also asked them to report the symptoms of patients classified as noninfectious endophthalmitis.

The VA at endophthalmitis was defined as the VA during the visit endophthalmitis was recorded while the VA before endophthalmitis was defined as the VA in the visit immediately before the endophthalmitis visit. The VA loss (change) resulting from endophthalmitis was the VA before endophthalmitis minus VA at endophthalmitis.

Outcomes

The primary outcome was the incidence and cumulative rate of infectious and noninfectious endophthalmitis. Secondary outcomes were the change in VA and number of IVTs received at 3 and 12 months after the diagnosis of endophthalmitis, including a comparison between cases and their matched controls.

Participants

Treatment-naïve eyes with nAMD tracked by the FRB! outcome registry that commenced anti-VEGF therapy between January 1, 2006, and November 30, 2016, were considered for the analysis.

To study the primary outcome, all cases of endophthalmitis were recorded regardless of their follow-up. To study the secondary outcome, cases with at least 3 months of follow-up were used. We used a matched cohort consisting of 3 controls per case matched with their respective cases on the following characteristics: baseline VA, time duration before endophthalmitis, last VA recorded before endophthalmitis, and the number of IVT before endophthalmitis.

Statistical Analysis

Descriptive data included the mean (standard deviation), median (interquartile range), and percentages where appropriate. Analysis of variance and Kruskal–Wallis tests were used to compare baseline characteristics among eyes with no endophthalmitis, infectious endophthalmitis, and noninfectious endophthalmitis. The Bonferroni correction was used in all pairwise comparisons between the baseline characteristics and the incidence rate of endophthalmitis. Cumulative rate of endophthalmitis and the corresponding survival curves were measured using Cox-proportional hazards models adjusted for baseline VA, baseline age, lesion size, and lesion type. Survival analyses were used to take into account of varying lengths of follow-up and patient dropouts in our estimation of the risk of developing endophthalmitis.

Logistic regression was used to assess whether cumulative number of injections received increased the risk of endophthalmitis. Comparison of VA and IVT at 12 months between endophthalmitis and their respective controls was performed using mixed-effects and Poisson regression models with an identifier variable to indicate matched patients as a random effect. Poisson regression models also included log days follow-up as an offset variable.

All analyses were performed using R V.3.3.1 with the *survival* package (V.2.40-1) for Cox-proportional hazards survival analysis, the *MatchIt* package (V.2.4-21) for identifying matched controls and the *lme4* package (V.1.1-12) for mixed-effects models.[29–31]

Results

Study Population

This study included 4564 patients collectively receiving 88 150 IVTs over 10 years between January 2006 and November 2016. Fifty-three percent of the 4564 patients completed at least 5 years of follow-up, and 8% went on to complete at least 10 years of follow-up. The average number of visits per patient was 22. During the study period, we recorded 18 infectious endophthalmitis and 11 noninfectious endophthalmitis. Two patients