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 88150 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 88150 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 (3/54776, 0.005%; $P = 0.005$) and aflibercept (0/23425; $P = 0.016$), 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 2018;125:66-74 © 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.
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...
Infectious endophthalmitis developed in both eyes and were recorded on the same day. The number of patients lost to follow-up after developing endophthalmitis were 2/18 and 2/11 of the infectious and noninfectious cases, respectively. These did not have at least the 3 months of follow-up required to be included in the VA outcomes analysis, but they were included in calculation of the rate of incidence of endophthalmitis. Questionnaires for infectious and noninfectious endophthalmitis were obtained for 14/18 and 9/11 cases, respectively. Eight eyes (57%) had a microbiological confirmation of infectious endophthalmitis.

Incidence and Cumulative Rate of Infectious Endophthalmitis

Infectious endophthalmitis developed in 18 cases of 88 150 injections (1 per 4897 injections [0.020%]; 95% CI, 0.012%–0.032). The incidence of infectious endophthalmitis for ranibizumab, aflibercept, and bevacizumab was 0.020%, 0.021%, and 0.020%, respectively, with no difference between drugs (P = 0.896). The cumulative rate of infectious endophthalmitis per eye increased from 0.055% after 10 injections to 0.183%, 0.360%, 0.360%, 0.555% and 0.843% after 20, 30, 40, 50, and 60 injections, respectively (Table 1 and Fig 1A). The risk of infectious endophthalmitis did not increase significantly with each successive injection (P = 0.202). The median (interquartile range) number of injections until infectious endophthalmitis developed was 14 (6–22).

Incidence and Cumulative Rate of Noninfectious Endophthalmitis

Noninfectious endophthalmitis developed in 11 cases of 88 150 injections (1 per 8014 injections [0.012%]; 95% CI, 0.006%–0.022). The cumulative rate of noninfectious endophthalmitis per patient increased to 0.087% and 0.228% after 10 and 20 injections, respectively (Table 1 and Fig 1C). Of note, no cases of noninfectious endophthalmitis were recorded in eyes after the 20th injection (Table 1 and Fig 1C). The risk of noninfectious endophthalmitis did not increase significantly with each successive injection (P = 0.203). The median (interquartile range) number of injections until noninfectious endophthalmitis was 10 (3–15).

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); no differences were observed between ranibizumab and aflibercept (P = 1.0). Note that the number of eyes receiving ranibizumab was more than twice that of those receiving aflibercept.

Outcomes of Endophthalmitis

Baseline characteristics of age, gender, baseline VA, and lesion size were not significantly different among cases of infectious endophthalmitis, noninfectious endophthalmitis, and eyes with no endophthalmitis (Table 2).

Mean VA change (95% CI) from before infectious endophthalmitis was −5.9 (−17.8, 6.0; P = 0.304) letters at 3 months and −7.4 (−19.4, 4.6; P = 0.206) letters at 12 months after infectious endophthalmitis (Table 2 and Fig 2). The 12-month VA was within ±2 lines of the VA before infectious endophthalmitis in 53% of eyes and 31% of eyes lost >10 letters (2 lines) (Table 2).

Eyes with noninfectious endophthalmitis lost −10.7 (−17.2, −4.2; P = 0.005) letters at 3 months and −6.4 (−12.7, −0.1; P = 0.048) letters after 12 months relative to

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Table 1. Incidence and Cumulative Rate of Infectious and Noninfectious Endophthalmitis

<table>
<thead>
<tr>
<th></th>
<th>Infectious Endophthalmitis*</th>
<th>Noninfectious Endophthalmitis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>No. of injections along the study period</td>
<td>88 150</td>
<td>88 150</td>
</tr>
<tr>
<td>Incidence of endophthalmitis per injection, % (95% CI)</td>
<td>0.020% (0.012–0.032)</td>
<td>0.012% (0.006–0.022)</td>
</tr>
<tr>
<td>Cases and incidence by injection type, cases/injections (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>11/54 776 (0.020%)</td>
<td>3/54 776 (0.005%)</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>5/23 425 (0.021%)</td>
<td>0/23 425 (-)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2/9931 (0.020%)</td>
<td>8/9931 (0.081%)</td>
</tr>
<tr>
<td>No. of patients along the study period</td>
<td>4564</td>
<td>4564</td>
</tr>
<tr>
<td>Cumulative rate per patient following‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10th injection</td>
<td>0.055%</td>
<td>0.087%</td>
</tr>
<tr>
<td>20th injection</td>
<td>0.183%</td>
<td>0.228%</td>
</tr>
<tr>
<td>30th injection</td>
<td>0.360%</td>
<td>0.228%</td>
</tr>
<tr>
<td>40th injection</td>
<td>0.360%</td>
<td>0.228%</td>
</tr>
<tr>
<td>50th injection</td>
<td>0.556%</td>
<td>0.228%</td>
</tr>
<tr>
<td>60th injection</td>
<td>0.843%</td>
<td>0.228%</td>
</tr>
<tr>
<td>Time (days) to endophthalmitis, median (IQR)</td>
<td>870 (481–1143)</td>
<td>448 (149–686)</td>
</tr>
<tr>
<td>Injections until endophthalmitis, median (IQR)</td>
<td>14 (6–22)</td>
<td>10 (3–15)</td>
</tr>
</tbody>
</table>

CI = confidence interval; IQR = interquartile range.

*Infectious endophthalmitis, P value among the 3 drugs = 0.896.

†Noninfectious endophthalmitis: bevacizumab versus ranibizumab, P = 0.005; bevacizumab versus aflibercept, P = 0.016; ranibizumab versus aflibercept (P = 1.0).

‡Injection received before diagnosis of endophthalmitis.

§The risk of infectious endophthalmitis did not increase with each successive injection (P = 0.202).
their VA before endophthalmitis. The 12-month VA was within ±2 lines of the VA before infectious endophthalmitis in 75% of eyes, and 25% of eyes lost >2 lines (Table 2). Anti-VEGF treatment was continued in 83% of eyes after developing infectious endophthalmitis and in 73% after developing noninfectious endophthalmitis.

The mean number of anti-VEGF IVT performed in the 12 months after the onset of infectious endophthalmitis was similar to the control group (7.3 vs. 7.1 injections; P = 0.869). The mean number of IVT was lower in noninfectious endophthalmitis compared with controls (4.6 vs. 6.3), although this was not statistically significant (P = 0.111) (Table 2).

Discussion

The FRB! observational database allowed us to assess the incidence of infectious and noninfectious endophthalmitis and VA outcomes over a long period of time. Incidences of infectious endophthalmitis and noninfectious endophthalmitis “per injection” were in the range of previous studies. The prospective design of FRB! registry allowed us to report the median number of IVT before the occurrence of endophthalmitis and the cumulative rate of endophthalmitis “per patient,” which increased over time and the number of injections. However, we found that the risk of infectious endophthalmitis did not increase significantly with each successive injection, which is reassuring for clinical practice. Our results also suggest a difference in rates of noninfectious endophthalmitis between anti-VEGF medications.

The large variation in the incidence of infectious endophthalmitis after IVT in the literature may be due to many factors, including the conditions under which the injections were given. Aerosolized droplets containing oral contaminants from the patient or providers are a potential

Figure 1. Cumulative rate of infectious (A, B) and noninfectious (C, D) endophthalmitis by number of injections received and length of follow-up. The cumulative rate of infectious endophthalmitis per patient was 0.055%, 0.183%, 0.360%, 0.360%, 0.556%, and 0.843% after 10, 20, 30, 40, 50, and 60 intravitreal injections (IVTs), respectively. The “risk” of infectious endophthalmitis did not increase significantly with each successive injection (P = 0.202). 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.
Table 2. Visual Acuity Outcomes at 3 and 12 Months after Endophthalmitis Compared With a Control Group Without Endophthalmitis

<table>
<thead>
<tr>
<th></th>
<th>Infectious Endophthalmitis</th>
<th>Matched Control (Infectious)*</th>
<th>Noninfectious Endophthalmitis</th>
<th>Matched Control (Noninfectious)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-mo completers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of eyes</td>
<td>16</td>
<td>48</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline (SD)</td>
<td>55 (21)</td>
<td>55 (19)</td>
<td>61 (12.0)</td>
<td>61 (11.5)</td>
</tr>
<tr>
<td>Before endophthalmitis (SD)</td>
<td>61 (20)</td>
<td>61 (18)</td>
<td>62 (13.3)</td>
<td>63 (12.3)</td>
</tr>
<tr>
<td>At endophthalmitis (SD)</td>
<td>39 (30)</td>
<td>-</td>
<td>40 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Change due to endophthalmitis (95% CI)</td>
<td>-21 (--39, -4)</td>
<td>-</td>
<td>-22.0 (--41.3, -2.7)</td>
<td></td>
</tr>
<tr>
<td>3 mos after endophthalmitis (SD)</td>
<td>55 (19)</td>
<td>62 (17)</td>
<td>52 (15.3)</td>
<td>67 (11.5)</td>
</tr>
<tr>
<td>≤35 letters, %</td>
<td>19%</td>
<td>13%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>36–69 letters, %</td>
<td>63%</td>
<td>48%</td>
<td>67%</td>
<td>41%</td>
</tr>
<tr>
<td>&gt;70 letters, %</td>
<td>19%</td>
<td>40%</td>
<td>22%</td>
<td>56%</td>
</tr>
<tr>
<td>Change from before endophthalmitis at 3 mos (95% CI)</td>
<td>-5.9 (--17.8 to 6)</td>
<td>1.5 (--1.1 to 4)</td>
<td>-10.7 (--17.2 to -4.2)</td>
<td>4 (--0.5 to 8.6)</td>
</tr>
<tr>
<td>Loss &gt;10 letters (2 lines), %</td>
<td>44%</td>
<td>6%</td>
<td>56%</td>
<td>11%</td>
</tr>
<tr>
<td>Loss between 1 and 9 letters (&lt;2 lines), %</td>
<td>19%</td>
<td>29%</td>
<td>33%</td>
<td>22%</td>
</tr>
<tr>
<td>Improvement between 0 and 9 letters (&lt;2 lines), %</td>
<td>19%</td>
<td>48%</td>
<td>11%</td>
<td>41%</td>
</tr>
<tr>
<td>Improvement &gt;10 letters (2 lines), %</td>
<td>19%</td>
<td>17%</td>
<td>0%</td>
<td>26%</td>
</tr>
<tr>
<td>Injections 3 mos after endophthalmitis (SD)</td>
<td>1.6 (1.0)</td>
<td>2.0 (1.0)</td>
<td>1.0 (1.0)</td>
<td>2.2 (0.7)</td>
</tr>
<tr>
<td><strong>12-mo completers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of eyes</td>
<td>13</td>
<td>39</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline (SD)</td>
<td>57.9 (17.0)</td>
<td>57.6 (16.4)</td>
<td>59.5 (11.4)</td>
<td>59.7 (11.0)</td>
</tr>
<tr>
<td>Before endophthalmitis (SD)</td>
<td>63.0 (18.2)</td>
<td>62.5 (17.2)</td>
<td>61.2 (13.9)</td>
<td>61.7 (12.8)</td>
</tr>
<tr>
<td>At endophthalmitis (SD)</td>
<td>38.9 (32.8)</td>
<td>44.9 (33.8)</td>
<td>-16.4 (--32.9 to 0.2)</td>
<td>-</td>
</tr>
<tr>
<td>Change due to endophthalmitis (95% CI)</td>
<td>-24.1 (--44.2 to -4.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>At 12 mos after endophthalmitis (SD)</td>
<td>55.6 (19.5)</td>
<td>62.6 (16.9)</td>
<td>54.9 (16.2)</td>
<td>67.2 (13.4)</td>
</tr>
<tr>
<td>≤35 letters, %</td>
<td>8%</td>
<td>10%</td>
<td>25%</td>
<td>4%</td>
</tr>
<tr>
<td>36–69 letters, %</td>
<td>62%</td>
<td>49%</td>
<td>50%</td>
<td>38%</td>
</tr>
<tr>
<td>&gt;70 letters, %</td>
<td>31%</td>
<td>41%</td>
<td>25%</td>
<td>58%</td>
</tr>
<tr>
<td>Change from before endophthalmitis at 12 mos (95% CI)</td>
<td>-7.4 (--19.4 to 4.6)</td>
<td>0.1 (--2.9 to 3)</td>
<td>-6.4 (--12.7 to -0.1)</td>
<td>5.5 (--0.7 to 11.6)</td>
</tr>
<tr>
<td>Loss &gt;10 letters (2 lines), %</td>
<td>31%</td>
<td>13%</td>
<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>Loss between 1 and 9 letters (&lt;2 lines), %</td>
<td>31%</td>
<td>31%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Recovery between 0 and 9 letters (&lt;2 lines), %</td>
<td>23%</td>
<td>41%</td>
<td>13%</td>
<td>38%</td>
</tr>
<tr>
<td>Recovery &gt;10 letters (2 lines), %</td>
<td>15%</td>
<td>15%</td>
<td>0%</td>
<td>29%</td>
</tr>
<tr>
<td>Injections 12 mos after endophthalmitis (SD)</td>
<td>7.3 (3.6)</td>
<td>7.1 (3.2)</td>
<td>4.6 (2.7)</td>
<td>6.3 (2)</td>
</tr>
</tbody>
</table>

CI = confidence interval; SD = standard deviation; VA = visual acuity.

*Control groups are matched for VA at baseline, VA before endophthalmitis, and injections received before endophthalmitis.
source of infection. Very low risk incidence of endophthalmitis of 0.007% to 0.008% was reported when IVTs were performed in an operating room. A survey on IVT techniques used by US retinal specialists found that 88% of them did not use a sterile drape, and only 33% of them wore sterile gloves. The rate of infectious endophthalmitis from US Medicare Claims data was 0.09%. In the present study from the FRB! database with participants in Australia, New Zealand, and Switzerland, the endophthalmitis rate per injection was 0.020%. Injections in Switzerland were performed in an operating room, which may have contributed to the low incidence rate of endophthalmitis observed in the present study.

The median number of IVT before the development of infectious endophthalmitis reported by Lyall et al and Dossarp et al was 5.2 to 9.0, respectively. In this study, the median number of IVT before infectious endophthalmitis was 14.

We believe it is important to report a “per patient” risk of endophthalmitis in IVT. Some patients have been treated for up to 10 years and have received up to 60 IVTs. In other circumstances, in which only 1 intervention is necessary, such as cataract surgery, it may be adequate just to report endophthalmitis rates “per patient.” An incidence of infectious endophthalmitis after IVT of 0.05% was reported in the MARINA trial, whereas the endophthalmitis rate “per patient” was 1.0% over a 2-year period. In this study, the incidence of infectious endophthalmitis “per IVT” was 0.020, whereas the rate “per patient” increased over the number of injections from 0.055% after 10 IVTs to 0.843% after 60 IVTs. However, we did not detect a clinically relevant increase in the risk per injection over the number of injections (P = 0.202). This means that the risk of endophthalmitis was linear and not exponential. A P value < 0.05 by this analysis would suggest that the risk of endophthalmitis increased at each successive injection.

Comparison of the incidence of noninfectious endophthalmitis between studies is difficult because of variations in the definitions of this condition. In the MARINA trial, the incidence of uveitis was 0.057% but was not differentiated into anterior and posterior inflammation. In the VIEW trials, adverse events were listed as vitreous floaters or endophthalmitis but not specifically as noninfectious endophthalmitis. According to Williams et al, the signs of noninfectious endophthalmitis include absence of hypopyon, absence of fibrin in the anterior chamber, moderate visual disturbance, and lack of pain. In a retrospective case series including 100 588 IVTs performed between 2006 and 2013, the incidence of noninfectious endophthalmitis was 0.08% per IVT with variations according to the drug injected: 0.10% for bevacizumab, 0.02% for ranibizumab, and 0.16% for aflibercept. The off-label use of bevacizumab may be associated with lesser oversight for compounding pharmacies, shipping, and storage. In the present study, the overall incidence of noninfectious endophthalmitis was lower (0.012%), but we also observed a higher incidence of noninfection endophthalmitis with bevacizumab compared with ranibizumab or aflibercept. The technique of preparing bevacizumab was not documented in the registry. It was prepared by the pharmacy of the hospital or by a compounding pharmacy. Potential reasons for a higher rate of noninfectious endophthalmitis using bevacizumab were irregularities in preparation by compounding pharmacies, shipping, or storage.

Reported levels of VA after endophthalmitis have varied somewhat. The VA 3 months after infectious endophthalmitis in a study that included 316 576 IVTs between 2008 and 2013 was 50 logMAR letters. Final VA after noninfectious endophthalmitis was 60 logMAR letters in the study conducted by Williams et al. In this study, VA at 3 months after infectious and noninfectious endophthalmitis was 55 and 51 logMAR letters, respectively. In the CATT endophthalmitis study, the final VA was within ±2 lines of the VA before infectious endophthalmitis in 45% of eyes. In this study, the 12-month VA was within ±2 lines of

![Figure 2](image-url)
before endophthalmitis in 53% and a loss >2 lines was observed in 31% of eyes.

Relatively good VA outcomes in the present study were probably related to the treatment intensity after endophthalmitis. A similar treatment frequency in the year after was observed between endophthalmitis or noninfectious endophthalmitis than controls (7.3 vs. 7.1, \( P = 0.869 \) and 4.6 vs. 6.3, \( P = 0.111 \), respectively).

Patients can have endophthalmitis more than once. Therefore, we did not censor patients with a history of endophthalmitis in the Cox model. We did not observe any eyes that had a second episode of endophthalmitis in the FRB! registry. However, this analysis was not large enough to assess the increased risk of recurrence of endophthalmitis in eyes with a history of endophthalmitis.

**Study Strengths and Limitations**

This study has several strengths and some weaknesses. Strengths included the use of the FRB! database that collect a prospectively endophthalmitis (infectious vs. noninfec-
tious) diagnostics for up to 10 years. Additional information from questionnaires sent to ophthalmologists was obtained for 14 of 18 cases of infectious endophthalmitis. Another original feature of the present analysis was to report both the incidence of endophthalmitis “per injection” and the cumulative rate “per-patient” over a long period of time. The VA outcomes were presented up to 12 months and were compared with matched controls, and we reported the influence of endophthalmitis on anti-VEGF treatment course.

Fifty-seven percent of infectious endophthalmitis were culture positive. This was within the range of other series reporting identification between 30% and 60%. The remaining 43% were “presumed” infectious endophthalmitis. The FRB! database specifically distinguishes between infectious and noninfectious endophthalmitis. We cannot exclude the possibility that some cases non-
infectious endophthalmitis were culture-negative infectious endophthalmitis.

A weakness of the present analysis was a possible under-
estimation of the incidence of endophthalmitis for 2 reasons: Cases had to be self-reported, and mild endoph-
thalmitis may have been not recognized by the physician.

We also acknowledge the lack of information on IVT techniques and conditions. Injections were performed by ophthalmologists (not nurses) by FRB! practitioners. Because this is an observational study, we are unable to report individual practitioner techniques. We can only speculate that injections were performed in accordance with recommendations. In Switzerland, injections were performed in the operative room with the use of sterile gloves, surgical masks, Betadine, and a speculum. In Australia and New Zealand, injections were performed in the clinic. The techniques were probably mixed and thus reflect real-world clinical practice. Thus, we were unable to assess the risk factors for endophthalmitis in this study.

There are 2 potential reasons that we have overestimated VA outcomes: The complete case analysis strategy to deal with missing outcomes and the possibility that culture-negative infectious endophthalmitis were classified as noninfectious.

The incidences of infectious and noninfectious endoph-
thalmitis after IVT were low and similar to those in other large-scale studies, but the cumulative rate increased as treatment progressed. We found higher rates of noninfectious endophthalmitis with bevacizumab compared with ranibizumab or afilbercept. However, we found that the risk of infectious endophthalmitis did not increase significantly with each successive injection, which is reassuring for clinical practice. Three quarters of cases with infectious and two thirds of cases with noninfectious endophthalmitis retained vision within 10 letters of the pre-endophthalmitis level 12 months later.

**Acknowledgments.** The Fight Retinal Blindness! Investigati-
gators: Eye Associates, Sydney, NSW (Prof M. Gillies, Dr. Adrian Hunt); Canberra Hospital, Garran, ACT (Dr. R. Essex; Dr. C. Dayajeeewa); Retina Associates, Chatswood, NSW (Prof A. Hunyor, A/Prof. S. Fraser-Bell, Dr. C. Younan, Dr. A. Fung); Centre for Eye Research Australia, East Melbourne, VIC (Prof R. Guymer, Dr. D. Louis); Marsden Eye Specialists, Parramatta, NSW (Dr. J. Arnold, Dr. D. Chan, Dr. H. Cass); Victoria Parade Eye Consultants, Fitzroy, VIC (Prof R. Guymer, Dr. A. Harper, Dr. J. O’Day, Dr. M. Danielli); Cairns Eye and Laser Clinic, Manoora, QLD (Dr. A. Field); Doncaster Eye Centre, VIC (Dr. L. P. Chow); University Hospital Zurich, University of Zurich, Zurich Switzerland (Dr. D. Barthelmes); Specialist Eye Group, Glen Waverly, VIC (Dr. L. P. Chow; Dr. A. Cohn); Gladstone Eye Specialists, Gladstone, NSW (Dr. S. Young); Hornsby Eye Specialists, Hornsby, NSW (Dr. S. Lal); Gosford Eye Surgeons, Gosford, NSW (Dr. S. Young, Dr. R. Ferrier); Retina Specialist Auckland, NZ (Dr. R. Barnes, Dr. A. Thompson, Dr. A. Vincent); Les Manning Practice, Brisbane, QLD (Dr. L. Manning); Eye-
medics, Adelaid e, SA (Dr. S. Lake; Dr. R. Phillips, Dr. M. Perks, Dr. J. Y. Chen, Dr. J. Landers, Dr. Niladri); Nepean Valley Eye Surgeons, Penrith, NSW (Dr. Gayatri Banerjee); Southeastern Eye Care, Miranda, NSW (Dr. B. Swamy); Dr. Phillip Windle’s Practice, Rockville QLD (Dr. P. Windle); Care Foresight, Hamil-
ton, NSW (Dr. A. Dunlop); Park Street Eye Clinic Tauranga, Tauranga, NZ (Dr. A. Thompson); Midwest Ophthalmology, Orange, NSW (Dr. K. C. Tang); Victorian Eye Surgeons, Foot-
sray, VIC (Dr. A. Cohn); Armadale Eye Clinic, Armadale, VIC (Dr. A. Cohn); Bundaberg Eye Clinic, Bundaberg, QLD (Dr. I. McLean); Dr. Alex Amini’s Practice, Mount Waverley, VIC (Dr. A. Amini); Eye Surgeons Miranda, Miranda, NSW (Dr. Adrian Hunt); Dr. Clarks Practice, Lismore, NSW (Dr. G. Clark); Lions Eye Institute, N e r l a, WA (Prof I. McAllister, Prof F. Chen); A D H B, Auckland, NZ (Dr. D. Squirrel); Caulfield Eye Clinic, Caulfield, VIC (Dr. C. Ng); Southeastern Eye Care, Miranda, NSW (Dr. D. Louis); Sydney Eye Hospital, Sydney, NSW (Prof M. Gillies); Tamworth Eye Centre, Tamworth, NSW (Dr. P. Hinchcliff e); Bunbury and Busselton Eye Doctors, South Bun-
bury, WA (Dr. R. Barry); Cheltenham Eye Centre, Cheltenham, VIC (Dr. D. Louis); Crest Eye Associates, Palmerston North, NZ (Dr. J. Ah-Chan); Dorset Consultant Center, Boronia, VIC (Dr. H. Steiner); Hawthorn Eye Clinic, Kew, VIC (Dr. L. P. Chow); Melbourne Retina Associates, Melbourne, VIC (Dr. A. Cohn); New England Eye Centre, Armidale, NSW (Dr. M. Morgan); Northern Rivers Eye Surgeons, Lismore, NSW (Dr. G. Clark); Orange Practice, Orange, NSW (Dr. B. Swamy); Port Macquarie Eye Centre, Port Macquarie, NSW (Dr. C. Thompson, Dr. J. Game); Retina Consultants, Hurstville, NSW (Dr. S. Young); Rotorua Eye Clinic, Rotorua, NZ (Dr. N. Murray).
References


**Footnotes and Financial Disclosures**

Originally received: March 9, 2017.
Final revision: June 19, 2017.
Accepted: July 6, 2017.
Available online: August 8, 2017.

Manuscript no. 2017-568.

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Financial Disclosure(s):
The author(s) made the following disclosures: V.D.: Research grant of the French Society of Ophthalmology.

M.C.G.: Sydney Medical Foundation Fellow; Support — National Health and Medical Research Council practitioner fellowship.


Supported by grants from the Royal Australian NZ College of Ophthalmologists Eye Foundation (2007-2009), the National Health and Medical Research Council, Australia (2010-2012), and the Macular Disease Foundation, Australia. Funding was provided by Novartis and Bayer. These supporting organizations had no role in the design or conduct of the research.

Author Contributions:
Conception and design: Daien, Nguyen, Essex, Gillies
Data collection: Daien, Morlet, Barthelmes, Gillies
Analysis and interpretation: Daien, Nguyen, Essex
Obtained funding: Not applicable
Overall responsibility: Daien, Nguyen, Essex, Morlet, Barthelmes, Gillies

Abbreviations and Acronyms:
CI = confidence interval; FRB! = Fight Retinal Blindness!;
IVT = intravitreal injection; logMAR = logarithm of the minimum angle of resolution; nAMD = neovascular age-related macular degeneration;
VA = visual acuity; VEGF = vascular endothelial growth factor.

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