JAMA Ophthalmology | Original Investigation

Association of Acute Endophthalmitis With Intravitreal Injections of Corticosteroids or Anti–Vascular Growth Factor Agents in a Nationwide Study in France

Florian Baudin, MD; Eric Benzenine, MSc; Anne-Sophie Mariet, MD; Alain M. Bron, MD; Vincent Daien, MD, PhD; Jean François Korobelnik, MD, PhD; Catherine Quantin, MD, PhD; Catherine Creuzot-Garcher, MD, PhD

IMPORTANCE The number of patients affected by retinal diseases treated with intravitreal injections (IVTs) has resulted in a rapidly growing number of procedures. One of the worst complications after these injections is endophthalmitis.

OBJECTIVE To evaluate the incidence of acute endophthalmitis after IVTs of corticosteroids or anti–vascular endothelial growth factor (anti-VEGF) agents.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study included patients undergoing IVTs from January 1, 2012, through December 31, 2015, in France. Data were acquired from the French medical-administrative database (Système National d'Information Inter-Régime de l'Assurance Maladie), which collects hospitalization discharge abstracts and out-of-hospital care information for the whole country. Data were analyzed from March through July 2017.

EXPOSURES Intravitreal injections of corticosteroid or anti-VEGF agents.

MAIN OUTCOMES AND MEASURES Incidence of acute endophthalmitis within 6 weeks after IVT by means of billing codes from a national database.

RESULTS During the study period, 1 811 977 IVTs of corticosteroids or anti-VEGF agents performed on 254 927 patients (60.4% female; median age, 79 years [interquartile range, 70-85 years]) were analyzed. A total of 444 acute endophthalmitis cases (crude incidence, 0.0245%) were recorded. In multivariable analysis, which did not include adjustment for when the endophthalmitis occurred during the study period, the risk of endophthalmitis was lower in male patients (incidence rate ratio [IRR], 0.78; 95% CI, 0.63-0.96; $P = .02$), higher for corticosteroids than for anti-VEGF agents (IRR, 3.21; 95% CI, 2.33-4.44; $P < .001$), and higher for nonprefilled syringes of anti-VEGF medications than prefilled syringes for ranibizumab (IRR, 1.63; 95% CI, 1.15-2.30) and aflibercept (IRR, 1.82; 95% CI, 1.25-2.66; $P < .001$).

CONCLUSIONS AND RELEVANCE The findings from this study of a nationwide database appear to have confirmed the low incidence rate of acute endophthalmitis after IVTs of corticosteroids or anti-VEGF agents. Although an association may not necessarily indicate a cause and effect, the risk for acute endophthalmitis after IVTs appeared to be higher for corticosteroids compared with anti-VEGF agents, while a lower risk of endophthalmitis appeared to be found with prefilled syringes of anti-VEGF medications.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Catherine Creuzot-Garcher, MD, PhD, Department of Ophthalmology, Dijon University Hospital, 14 rue Paul Gaffarel, 21000 Dijon, France (catherine.creuzot-garcher@chu-dijon.fr).

JAMA Ophthalmol. 2018;136(12):1352-1358. doi:10.1001/jamaophthalmol.2018.3939
Published online September 13, 2018.

The number of patients affected by retinal diseases, the efficacy of anti-vascular endothelial growth factor (anti-VEGF) agents or corticosteroids, and their expanding indications have resulted in a rapidly growing number of intravitreal injections (IVTs).[1] Ranibizumab (0.5 mg/0.05 mL [Lucentis; Novartis Pharma SAS]), bevacizumab (1.25 mg/0.05 mL [Avastin; Roche]), and aflibercept (2 mg/0.05 mL [Eylea; Bayer HealthCare]) have been used for the treatment of several retinal diseases, including exudative age-related macular degeneration, diabetic macular edema, and retinal vein occlusion.[2,3] Triamcinolone acetonide (4 mg/0.1 mL [Kenacort; Bristol-Myers Squibb]) and dexamethasone implant (0.7 mg [Ozurdex; Allergan SAS]) are the 2 corticosteroid agents used in France for the treatment of diabetic macular edema,[4] retinal vein occlusion edema,[5] and noninfectious intermediate or posterior uveitis.[6]

Acute endophthalmitis is one of the worst sight-threatening complications after IVTs. Its incidence is low, ranging from 0.02% to 0.08%.[7-10] Among factors influencing endophthalmitis occurrence, previous studies suggested associations with the class of medication,[11] topical antibiotic prophylaxis,[12,13] and types 1 and 2 diabetes.[11,14] However, owing to the low rate of endophthalmitis, even large observational studies are not sufficiently powered to analyze factors associated with this complication.[8,10,15] Medical-administrative databases (collecting all reimbursement claims, including hospital and out-of-hospital care) could overcome these limitations, providing more events to collect. The use of this type of database provides information at the scale of an entire country and, used with caution, could help decipher the associations between different events.[16-18] In the present study, we aimed to assess the incidence and factors associated with acute endophthalmitis after IVTs of corticosteroids or anti-VEGF agents in France from 2012 to 2015.

Key Points

Question What are the risk factors of acute endophthalmitis after intravitreal injections of corticosteroids or anti–vascular endothelial growth factor agents?

Findings In this population-based study that included 254 927 patients, the risk of endophthalmitis was higher for patients who received corticosteroid injections than for those who received anti–vascular endothelial growth factor agents (incidence rate ratio, 3.21) and higher for those who received nonprefilled syringes of anti–vascular endothelial growth factor medications than prefilled syringes (incidence rate ratios, 1.63 for ranibizumab and 1.82 for aflibercept).

Meaning Although an association may not indicate cause and effect, these data suggest the use of prefilled anti–vascular endothelial growth factor syringes could lower the already very low risk of acute endophthalmitis.

Methods

Data Source

This study is part of the French Epidemiology and Safety collaborative program designed to assess the epidemiology and safety of interventions in ophthalmology.[19] The French medical-administrative database (Système National d'Information Interrégime de l'Assurance Maladie [SNIIRAM]) collects data for the whole country (ie, 66 million inhabitants). Briefly, this database contains the full coverage of health expenditures, including hospitalization discharge abstracts (with medical diagnoses) and out-of-hospital care (visits, procedures, and drugs). The SNIIRAM was created to link all interscheme and hospital outpatient claim reimbursements of the French population with the national hospital discharge abstract database. After 2007, data were linked over time to allow for longitudinal analyses. The high quality of this database has previously been evaluated and has been used in several epidemiologic studies.[16,18,20,21] This study adhered to the tenets of the Declaration of Helsinki.[22] The present study was approved by the French Institute of Health Data and by the French data protection authority, which did not require informed consent for the use of registry data.

Data Extraction

The data set available for this study included all patients in the database who received at least 1 IVT from January 1, 2012, through December 31, 2015. Data were not included when a look-back period or a follow-up of 42 days was not available or when the patient died within the 42-day follow-up period. As a result, only index dates from February 12, 2012, through November 19, 2015, were considered. Intravitreal injections were tracked with the billing code for IVT (BGLB001). The date of the injection was used as the index date. A diagnosis of endophthalmitis was identified with the billing codes H440 or H441 from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, within 42 days after the injection index date.[23] Data from injections that were related to surgical procedures with an occurrence of endophthalmitis within 6 weeks were censored and were not included in the analysis. All cases of endophthalmitis occurring within 6 weeks after an ocular operation were excluded from the analysis. The type of injected medication (corticosteroid or anti-VEGF agent), the type of packaging, and topical antibiotic prescriptions were obtained from the records of medications delivered and identified through the database. Patients having any hospital discharge code mentioning diabetes as the main or associated diagnosis, repeated deliveries of the antidiabetic drug for more than 3 months, or a diabetes-related long-term disease reimbursement code were identified as having diabetes.[17] Insulin-treated diabetes was determined by entries concerning continuous insulin deliveries.

Statistical Analysis

Data were analyzed from March through July 2017. Most of the continuous variables did not follow a normal distribution according to a Kolmogorov-Smirnov normality test. Therefore, median (interquartile range [IQR]) was provided for continuous variables, and nonparametric tests were used for comparison. For categorical variables, numbers (percentage) were provided and the χ^2 test was performed to compare percentages. We estimated incidence rates as the number of events per 100

injection procedures. Incidence rate ratios (IRRs) were estimated using a Poisson regression. We analyzed first the associations between the variables studied and endophthalmitis using a univariate Poisson regression. Multivariable Poisson regressions were then performed, adjusting for potential confounders that included sex, age, diabetes, drug, drug preparation, and topical antibiotic prophylaxis. Analyses were based on repeated-measures Poisson regression models accounting for dependencies between repeated observations on the same study patient. In these models, the association between the variables studied and the outcome was estimated using IRRs and the corresponding 95% CIs. Statistical significance was set at $P < .05$ (2-tailed tests). All data processing and statistical analyses were performed using the SAS statistical analysis software package (version 9.4; SAS Institute, Inc).

Results

From 2012 to 2015, 1 959 462 IVTs were performed. A total of 1 811 977 IVTs from 254 927 patients (60.4% female and 39.6% male; median age, 79 years [IQR, 70-85 years]) were retained for analysis after excluding IVTs with an insufficient lookback period or lacking 42 days of follow-up and those IVTs concomitant with ocular surgery (**Table 1**). Most IVTs were anti-VEGF injections, accounting for 92.7% of all procedures, 3.7% were corticosteroids, and 3.6% were not identified in the database. The most frequently injected agent was ranibizumab (70.9% of all injections), followed by aflibercept (21.6%). Patients receiving IVTs with corticosteroids were younger than those receiving anti-VEGF agents (median age, 73 years [IQR, 64-80 years] vs 80 years [IQR, 72-85 years]; $P < .001$) and were more likely to have diabetes (34.6% [n = 22 326] vs 25.1% [n = 421 858]; $P < .001$). Topical antibiotic prophylaxis was given in 73.6% of all injections, the most prescribed antibiotic class being macrolides (63.2% [n = 843 484]), followed by fluoroquinolones (18.2% [n = 242 098]) and aminoglycosides (13.9% [n = 185 066]). Combination medications with a corticosteroid and antibiotic were administered to 4.4% of the patients (n = 58 444).

Table 1. Baseline Demographics of Patients With IVTs of Corticosteroids or Anti-VEGF Agents From 2012 to 2015

Characteristic	Patient Data (n = 254 927)
Age, median (IQR), y	79 (70-85)
Female, No. (%)	153 976 (60.4)
No. of injections, median (IQR)	5 (3-10)
Follow-up, median (IQR), d	302 (63-277)
Diabetes, No. (%)	
All	68 604 (26.9)
Type 1	31 512 (45.9)

Abbreviations: IQR, interquartile range; IVT, intravitreal injection; VEGF, vascular endothelial growth factor.

During the study period, we recorded 444 endophthalmitis cases of 1 811 977 IVTs (1 of 4082 injections; crude incidence, 0.0245%) (**Table 2**). The incidence of endophthalmitis after anti-VEGF and corticosteroid injections was 0.0204% and 0.0667%, respectively. Patients with endophthalmitis after corticosteroid IVTs were younger than those infected after anti-VEGF IVTs (median age, 73 years [IQR, 65-80 years] vs 79 years [IQR, 71-84 years]; $P < .001$). No statistical differences were found for age, sex, and diabetes when considering IVTs with or without endophthalmitis. In univariate analysis, acute post-IVT endophthalmitis was more likely to occur in younger patients. An injection performed among patients older than 85 years was associated with a decreased IRR of endophthalmitis compared with patients younger than 70 years (IRR, 0.64; 95% CI, 0.48-0.84). Associations were also found for patients receiving corticosteroid IVTs (IRR, 3.26; 95% CI, 2.38-4.48) and those with nonprefilled anti-VEGF syringes (vs prefilled ranibizumab) (IRR for nonprefilled ranibizumab, 1.60 [95% CI, 1.14-2.25]; IRR for aflibercept, 1.80 [95% CI, 1.24-2.61]) and, at the beginning of the study period, injections performed in 2013 and 2014 were at higher risk than in 2012 (IRRs, 1.43-1.67; $P < .01$) (**Table 3**). In multivariable analysis, acute endophthal-

Table 2. Acute Endophthalmitis Incidence After IVTs of Corticosteroids or Anti-VEGF Agents from 2012 to 2015

Variable	No. of Intravitreal Injections		Crude Incidence, %
	Without Endophthalmitis	With Endophthalmitis	
Agent			
Aflibercept (2.00 mg/0.05 mL)	392 082	94	0.0240
Bevacizumab (1.25 mg/0.05 mL)	2 592	0	0
Ranibizumab (0.50 mg/0.05 mL)	1 284 785	249	0.0194
Nonprefilled	969 790	207	0.0213
Prefilled	314 995	42	0.0133
Dexamethasone implant	60 689	41	0.0676
Triamcinolone acetonide	3747	2	0.0533
Unknown	67 638	58	0.0858
Year			
2012	266 313	47	0.0176
2013	473 544	139	0.0293
2014	543 432	137	0.0252
2015	528 244	121	0.0229

Abbreviations: IVT, intravitreal injection; VEGF, vascular endothelial growth factor.

mitis after IVTs was more likely to occur in female patients (IRR, 1.28; 95% CI, 1.04-1.59), those who received corticosteroids (IRR, 3.21; 95% CI 2.33-4.44), and those who received nonprefilled syringes of anti-VEGF agents, regardless of the drug injected (IRR for ranibizumab, 1.63 [95% CI 1.15-2.30]; IRR for aflibercept, 1.82 [95% CI, 1.25-2.66]) (**Table 4**).

Discussion

In this study examining a large sample of IVTs, we observed a postinjection endophthalmitis rate of 0.0245% (1 of 4082 injections). This rate agrees with those of other reports in which rates range from 0.02% to 0.08%.[7-10] After adjusting for agent class or type, preparation of the drug (prefilled vs nonprefilled syringes), sex, age, use of topical antibiotic prophylaxis, and diabetes, an association between endophthalmitis incidence and the type of drug injected was found.

Corticosteroids, and more specifically the dexamethasone implant, were associated with more than 3 times more endophthalmitis cases than anti-VEGF agents. This finding is in line with that of a previous study[24] in which a 3-fold higher risk of endophthalmitis after triamcinolone injection occurred compared with anti-VEGF administration and a medical-administrative study (national US medical claims database) that found a 7-fold higher risk.[11] Several reasons have been postulated to explain this difference. First, owing to their immunosuppressive properties,[25,26] corticosteroids could lead to greater susceptibility to bacterial endophthalmitis.[27] Second, the gauge of the needle of the dexamethasone implant is larger than that of anti-VEGF agents (22-gauge vs 30- or 32-gauge), inducing a larger scleral wound, which could lead to a greater risk of bacterial penetration in the vitreous.[28,29]

One finding in this study, not previously reported to our knowledge, was the difference in the risk of postinjection endophthalmitis owing to the preparation type. The prefilled syringe—available only for ranibizumab—had decreased the rate of endophthalmitis after IVTs, specifically by 40% compared with room preparation of nonprefilled ranibizumab and by 46% for aflibercept, only available as a nonprefilled medication. Although a ready-to-use material prepared by a pharmaceutical company vs a homemade preparation has been demonstrated to decrease endophthalmitis incidence after cataract surgery,[16] to the best of our knowledge, this is the first time that the relative risk of the anti-VEGF agent preparation type for endophthalmitis after IVTs has been identified, although it had been previously hypothesized.[30] The main reason could lie in fewer manipulations and the professional preparation in a controlled environment, leading to better safety and accuracy. This reason is in line with previous descriptions of endophthalmitis outbreak associated with repackaged bevacizumab.[31,32] This association, however, does not indicate a cause and effect. Although numerous potential confounders were adjusted in the analyses, other confounding factors could contribute in part or completely to the results, which also were associated with the use of prefilled syringes. For example, the year of injection was not included in the multivariable analysis, but more cases of endophthalmitis occurred in the earlier years, before prefilled syringes were available. Thus, confounding factors, such as greater attention to use of antiseptics over the injection site or greater overall experience with injections in the latter years when prefilled syringes became available, might have accounted for the decreased rate. Also, the absolute rate of endophthalmitis without prefilled syringes was quite low, which could influence the cost-effectiveness of prefilled syringes.

In univariate analysis, we found a significant association between the early years of the study and endophthalmitis. This period effect is a consequence of the change in the presentation of the ranibizumab syringe. Indeed, the year of injection

Table 3. Univariate Analysis of Factors Associated With Acute Endophthalmitis After IVTs of Corticosteroids or Anti-VEGF Agents From 2012 to 2015

Variable	Univariate Poisson Regression	
	IRR (95% CI)	*P* Value
Age category, y		
<70	1 [Reference]	.01
70-79	0.84 (0.65-1.07)	
80-84	0.80 (0.61-1.04)	
≥85	0.64 (0.48-0.84)	
Sex		
Female	1 [Reference]	.16
Male	0.87 (0.71-1.06)	
Diabetes		
None	1 [Reference]	.46
Diabetes	1.08 (0.88-1.34)	
Insulin dependence		
Type 2 diabetes	1 [Reference]	.82
Type 1 diabetes	1.04 (0.73-1.50)	
Topical antibiotic prophylaxis		
None	1 [Reference]	.26
All	0.88 (0.72-1.09)	
Type of antibiotic prophylaxis		
Antibiotic alone	1 [Reference]	.06
Topical antibiotic-corticosteroid combination	1.67 (1.08-2.58)	
Agent class[a]		
Anti-VEGF agent	1 [Reference]	<.001
Corticosteroid	3.26 (2.38-4.48)	
Agent preparation[a,b]		
Prefilled ranibizumab (0.50 mg/0.05 mL)	1 [Reference]	<.001
Nonprefilled ranibizumab (0.50 mg/ 0.05 mL)	1.60 (1.14-2.25)	
Aflibercept (2.00 mg/0.05 mL)	1.80 (1.24-2.61)	
Dexamethasone implant	5.06 (3.27-7.83)	
Triamcinolone acetonide	4.00 (0.96-16.57)	
Year		
2012	1 [Reference]	.01
2013	1.67 (1.20-2.32)	
2014	1.43 (1.03-1.99)	
2015	1.30 (0.93-1.82)	

Abbreviations: IRR, incidence rate ratio; IVT, intravitreal injection; VEGF, vascular endothelial growth factor.

[a] Data were missing for 67 657 injections.

[b] Because no endophthalmitis occurred after bevacizumab IVTs, these 2592 injections were not considered for the by-agent analysis.

Table 4. Multivariable Analysis of Factors Associated With Acute Endophthalmitis After IVTs of Corticosteroids or Anti-VEGF Agents From 2012 to 2015

	Multivariable Poisson Regression			
	Model 1		Model 2	
Covariate	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Model 1[a]				
Agent class				
Anti-VEGF agent	1 [Reference]	<.001	NA	NA
Corticosteroids	3.21 (2.33-4.44)		NA	NA
Model 2[b]				
Agent preparation				
Prefilled ranibizumab (0.50 mg/0.05 mL)	NA	NA	1 [Reference]	<.001
Nonprefilled ranibizumab (0.50 mg/ 0.05 mL)	NA	NA	1.63 (1.15-2.30)	
Aflibercept (2.00 mg/0.05 mL)	NA	NA	1.82 (1.25-2.66)	
Dexamethasone implant	NA	NA	5.04 (3.23-7.86)	
Triamcinolone acetonide	NA	NA	3.98 (0.96-16.45)	
Both Models				
Sex				
Female	1 [Reference]	.02	1 [Reference]	.02
Male	0.78 (0.63-0.96)		0.78 (0.63-0.96)	
Age category, y				
<70	1 [Reference]	.27	1 [Reference]	.28
70-79	1.00 (0.75-1.32)		0.97 (0.74-1.29)	
80-84	0.97 (0.71-1.31)		0.95 (0.70-1.28)	
≥85	0.78 (0.57-1.07)		0.77 (0.56-1.05)	
Diabetes				
None	1 [Reference]	.72	1 [Reference]	.60
All	1.04 (0.83-1.32)		1.06 (0.84-1.34)	
Topical antibiotic prophylaxis				
None	1 [Reference]	.49	1 [Reference]	.34
All	0.92 (0.73-1.16)		0.89 (0.71-1.12)	

Abbreviations: IRR, incidence rate ratio; IVT, intravitreal injection; NA, not available; VEGF, vascular endothelial growth factor.

[a] Includes 1744 201 injections.

[b] Includes 1 741 609 injections. Because no endophthalmitis occurred after bevacizumab IVTs, these 2592 injections were not considered for the by-agent analysis.

and the type of drug were highly correlated. Therefore, this variable was not included in the multivariable analysis. The variable age did not remain significant in multivariable analyses, probably because the agent injected significantly depended on the patient's age.

Women were at greater risk of developing endophthalmitis. Few studies on endophthalmitis after IVTs report the patients' sex. Moshfeghi et al[14] found a sex ratio for endophthalmitis of 6 female to 2 male patients, and in a case series, Irigoyen et al[33] found 12 female and 8 male cases.

Our study showed no significant association between endophthalmitis and diabetes. This finding contradicts the controversial hypothesis that, because of relative immune suppression, patients with diabetes were at higher risk for endophthalmitis,[8,9] but supports previous findings reported by VanderBeek et al,[11] where diabetes was not associated with endophthalmitis risk after IVTs.

Similarly, no significant association between endophthalmitis after IVTs and the use of topical antibiotic prophylaxis was found in our cohort. Topical antibiotics applied before or after the injection have been the standard clinical practice for many years. However, several reports on large series and systematic reviews[34,35] have led to the conclusion that antibiotic prophylaxis for IVTs is no longer recommended. The guidelines on the perioperative strategy to minimize the risk of post-IVT endophthalmitis have been updated, and in France a topical antibiotic is no longer recommended after anti-VEGF IVTs.[36] We would probably need a longer observational period to measure the influence of this change in recommendations in France.

Strengths and Limitations

The strength of this study is the large collection of IVTs registered in a single administrative database. The subgroup size is large enough to detect a statistically significant difference between exposure groups. Moreover, the French medical-administrative database includes all patients, especially those who are usually excluded from clinical trials (eg, older patients with comorbidities) or from Medicare studies (eg, younger patients with diabetes),[37] who could be at different risk for endophthalmitis.

We also acknowledge several limitations to this study. First, post-IVT endophthalmitis was diagnosed based on clinical findings and not bacteriologic identification. This distinction could lead to misclassification if sterile endophthalmitis or uveitis were clinically diagnosed as endophthalmitis. However, this rate is very close to what was found in a previous study examining 310 000 IVTs with data collected from 25 centers in France.[10] Furthermore, sterile endophthalmitis is mostly associated with triam-

cinolone injections, which account for only 0.2% of the IVTs collected in the present study.[38] A recent database study[39] reported an incidence of 0.012% of noninfectious endophthalmitis after IVTs. Furthermore, the same caveat was found in other studies.[11] Biological confirmation is missing in 40% of post-IVT endophthalmitis cases, as reported by Lyall et al.[40]

Second, given that the definition of diabetes was based on an algorithm, we could not fully ascertain that all patients were classified in the proper group. To avoid this uncertainty, we used a validated algorithm, based on long-term disease and hospital diagnostic codes as well as the drugs used.[17]

Third, we limited our main outcome measures to infectious events occurring after 42 days, as defined by the Endophthalmitis Vitrectomy Study Group.[23] However, we support previous findings that most acute endophthalmitis cases occur within the first 2 weeks. In our study, 90% of endophthalmitis cases occurred within this time frame. When considering only acute endophthalmitis after IVT occurring within 15 days, we drew the same conclusion in the univariate and multivariable analyses, except for the increased risk in female patients in the univariate analysis.

Fourth, the agent injected was unknown in 3.6% of the IVTs; other studies have reported this weakness in as many as 10% of cases.[11] The results did not change after including them as a specific agent category in the statistical analysis.

Fifth, our findings cannot fully extend to another country; French guidelines for IVTs are somewhat different from US guidelines, for example.[41,42] In France, performing IVTs in a dedicated room wearing sterile gloves is recommended. By contrast, similar recommendations in both countries include topical povidone-iodine use, surgical mask wear, and no topical antibiotics.[38]

Sixth, certain variables such as the number of IVTs before endophthalmitis could not be reliably analyzed because some patients may have been treated with bilateral injections. However, a recent study did not identify an increased risk of endophthalmitis with each successive IVT.[39]

Seventh, the conclusions drawn from big data always need to be interpreted cautiously due to their limitations, as has already been pointed out in the ophthalmic literature.[43] Indeed, an association does not necessarily indicate a cause and effect, and although numerous potential confounders were adjusted in the analyses, other confounders not included or studied could be associated with the risk of endophthalmitis.

Conclusions

This study supports previous findings on the higher incidence of post-IVT endophthalmitis with corticosteroids vs anti-VEGF agents. It also demonstrates a nearly halved rate of endophthalmitis after IVTs with a prefilled anti-VEGF agent syringe, although this association does not necessarily indicate a cause and effect relationship between prefilled syringes and decreased rate of endophthalmitis.

ARTICLE INFORMATION

Accepted for Publication: June 26, 2018.

Published Online: September 13, 2018. doi:10.1001/jamaophthalmol.2018.3939

Author Affiliations: Department of Ophthalmology, Dijon University Hospital, Dijon, France (Baudin, Bron, Creuzot-Garcher); Department of Biostatistics and Bioinformatics, Dijon University Hospital, Franche-Comté University, Dijon, France (Benzenine, Mariet, Quantin); Institut National de la Santé et de la Recherche Medicale (INSERM), Centre d'Investigation Clinique 1432, Dijon, France (Mariet, Quantin); Clinical Investigation Center, Clinical Epidemiology/Clinical Trials Unit, Dijon University Hospital, Dijon, France (Mariet, Quantin); Department of Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases, INSERM, Université de Versailles Saint-Quentin-en-Yvelines, Institut Pasteur, Université Paris-Saclay, Paris, France (Mariet, Quantin); Eye and Nutrition Research Group, Bourgogne Franche-Comté University, Dijon, France (Bron, Creuzot-Garcher); Department of Ophthalmology, University Hospital of Montpellier, Montpellier, France (Daien); INSERM U1061, University of Montpellier, Montpellier, France (Daien); Department of Ophthalmology, University Hospital of Bordeaux, Bordeaux, France (Korobelnik); INSERM U1219, Population Health Research Center, Bordeaux, France (Korobelnik).

Author Contributions: Drs Quantin and Creuzot-Garcher had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Baudin, Bron, Korobelnik, Creuzot-Garcher.
Acquisition, analysis, or interpretation of data: Baudin, Benzenine, Mariet, Daien, Korobelnik, Quantin.
Drafting of the manuscript: Baudin, Benzenine, Mariet.
Critical revision of the manuscript for important intellectual content: Baudin, Benzenine, Bron, Daien, Korobelnik, Quantin, Creuzot-Garcher.
Statistical analysis: Baudin, Benzenine, Mariet, Bron, Quantin.
Obtained funding: Baudin, Creuzot-Garcher.
Administrative, technical, or material support: Baudin, Benzenine, Korobelnik, Creuzot-Garcher.
Supervision: Baudin, Daien, Korobelnik, Creuzot-Garcher.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Bron reported consulting for Aerie, Allergan SAS, Bausch & Lomb, Carl Zeiss Meditec, Horus Pharma, and Théa. Dr Daien reported consulting for Bayer HealthCare, Horus Pharma, Novartis Pharma SAS, and Théa. Dr Korobelnik reported consulting for Alcon, Alimera, Bayer HealthCare, Carl Zeiss Meditec, Novartis Pharma SAS, Roche, and Théa. Dr Creuzot-Garcher reported consulting for Allergan SAS, Bayer HealthCare, Horus Pharma, Novartis Pharma SAS, Roche, and Théa. No other disclosures were reported.

Funding/Support: This study was supported by an institutional grant from Dijon-Bourgogne University Hospital and the University of Dijon.

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Ip MS, Scott IU, Brown GC, et al; American Academy of Ophthalmology. Anti-vascular endothelial growth factor pharmacotherapy for age-related macular degeneration: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2008;115(10):1837-1846. doi:10.1016/j.ophtha.2008.08.012

2. Maguire MG, Martin DF, Ying GS, et al; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-Related Macular Degeneration Treatments trials. *Ophthalmology*. 2016;123(8):1751-1761. doi:10.1016/j.ophtha.2016.03.045

3. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-1203. doi:10.1056/NEJMoa1414264

4. Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904-1914. doi:10.1016/j.ophtha.2014.04.024

5. Haller JA, Bandello F, Belfort R Jr, et al; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to

retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146.e3. doi:10.1016/j.ophtha.2010.03.032

6. Lowder C, Belfort R Jr, Lightman S, et al; Ozurdex HURON Study Group. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011;129(5):545-553. doi:10.1001/archophthalmol.2010.339

7. Fileta JB, Scott IU, Flynn HW Jr. Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45(2):143-149. doi:10.3928/23258160-20140306-08

8. Rayess N, Rahimy E, Shah CP, et al. Incidence and clinical features of post-injection endophthalmitis according to diagnosis. *Br J Ophthalmol*. 2016;100(8):1058-1061. doi:10.1136/bjophthalmol-2015-307707

9. Shah CP, Garg SJ, Vander JF, Brown GC, Kaiser RS, Haller JA; Post-Injection Endophthalmitis (PIE) Study Team. Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti–vascular endothelial growth factor agents. *Ophthalmology*. 2011;118(10):2028-2034. doi:10.1016/j.ophtha.2011.02.034

10. Dossarps D, Bron AM, Koehrer P, Aho-Glele LS, Creuzot-Garcher C. Endophthalmitis after intravitreal injections: incidence, presentation, management, and visual outcome. *Am J Ophthalmol*. 2015;160(1):17-25.e1. doi:10.1016/j.ajo.2015.04.013

11. VanderBeek BL, Bonaffini SG, Ma L. The association between intravitreal steroids and post-injection endophthalmitis rates. *Ophthalmology*. 2015;122(11):2311-2315.e1. doi:10.1016/j.ophtha.2015.07.005

12. Yin VT, Weisbrod DJ, Eng KT, et al. Antibiotic resistance of ocular surface flora with repeated use of a topical antibiotic after intravitreal injection. *JAMA Ophthalmol*. 2013;131(4):456-461. doi:10.1001/jamaophthalmol.2013.2379

13. Bhavsar AR, Sandler DR, Gentile RC. Intravitreal injections, antibiotics and endophthalmitis. *Eye (Lond)*. 2013;27(12):1426-1427. doi:10.1038/eye.2013.225

14. Moshfeghi DM, Kaiser PK, Scott IU, et al. Acute endophthalmitis following intravitreal triamcinolone acetonide injection. *Am J Ophthalmol*. 2003;136(5):791-796. doi:10.1016/S0002-9394(03)00483-5

15. Rayess N, Rahimy E, Storey P, et al. Postinjection endophthalmitis rates and characteristics following intravitreal bevacizumab, ranibizumab, and aflibercept. *Am J Ophthalmol*. 2016;165:88-93. doi:10.1016/j.ajo.2016.02.028

16. Creuzot-Garcher C, Benzenine E, Mariet AS, et al. Incidence of acute postoperative endophthalmitis after cataract surgery: a nationwide study in France from 2005 to 2014. *Ophthalmology*. 2016;123(7):1414-1420. doi:10.1016/j.ophtha.2016.02.019

17. Goueslard K, Cottenet J, Mariet AS, et al. Early cardiovascular events in women with a history of gestational diabetes mellitus. *Cardiovasc Diabetol*. 2016;15:15. doi:10.1186/s12933-016-0338-0

18. Lainay C, Benzenine E, Durier J, et al. Hospitalization within the first year after stroke: the Dijon Stroke Registry. *Stroke*. 2015;46(1):190-196. doi:10.1161/STROKEAHA.114.007429

19. Daien V, Korobelnik JF, Delcourt C, et al. French Medical-Administrative Database for Epidemiology and Safety in Ophthalmology (EPISAFE): the EPISAFE Collaboration Program in Cataract Surgery [published online April 4, 2017]. *Ophthalmic Res*. doi:10.1159/000456721

20. Lorgis L, Cottenet J, Molins G, et al. Outcomes after acute myocardial infarction in HIV-infected patients: analysis of data from a French nationwide hospital medical information database. *Circulation*. 2013;127(17):1767-1774. doi:10.1161/CIRCULATIONAHA.113.001874

21. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2017;26(8):954-962. doi:10.1002/pds.4233

22. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

23. Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study: a randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. *Arch Ophthalmol*. 1995;113(12):1479-1496. doi:10.1001/archopht.1995.01100120009001

24. Mishra C, Lalitha P, Rameshkumar G, et al. Incidence of endophthalmitis after intravitreal injections: risk factors, microbiology profile, and clinical outcomes. *Ocul Immunol Inflamm*. 2018;26(4):559-568.

25. Cheung CS, Wong AW, Lui A, Kertes PJ, Devenyi RG, Lam WC. Incidence of endophthalmitis and use of antibiotic prophylaxis after intravitreal injections. *Ophthalmology*. 2012;119(8):1609-1614. doi:10.1016/j.ophtha.2012.02.014

26. Pastor JC, Del Nozal MJ, Zamarron E, García M. Solubility of triamcinolone acetonide and other anti-inflammatory drugs in silicone oil: implications for therapeutic efficacy. *Retina*. 2008;28(9):1247-1250. doi:10.1097/IAE.0b013e31817d5bf6

27. Bucher RS, Hall E, Reed DM, Richards JE, Johnson MW, Zacks DN. Effect of intravitreal triamcinolone acetonide on susceptibility to experimental bacterial endophthalmitis and subsequent response to treatment. *Arch Ophthalmol*. 2005;123(5):649-653. doi:10.1001/archopht.123.5.649

28. Czajka MP, Byhr E, Olivestedt G, Olofsson EM. Endophthalmitis after small-gauge vitrectomy: a retrospective case series from Sweden. *Acta Ophthalmol*. 2016;94(8):829-835. doi:10.1111/aos.13121

29. Gupta OP, Maguire JI, Eagle RC Jr, Garg SJ, Gonye GE. The competency of pars plana vitrectomy incisions: a comparative histologic and spectrophotometric analysis. *Am J Ophthalmol*. 2009;147(2):243-250.e1. doi:10.1016/j.ajo.2008.08.025

30. VanderBeek BL, Bonaffini SG, Ma L. Association of compounded bevacizumab with postinjection endophthalmitis. *JAMA Ophthalmol*. 2015;133(10):1159-1164. doi:10.1001/jamaophthalmol.2015.2556

31. Sheyman AT, Cohen BZ, Friedman AH, Ackert JM. An outbreak of fungal endophthalmitis after intravitreal injection of compounded combined bevacizumab and triamcinolone. *JAMA Ophthalmol*. 2013;131(7):864-869. doi:10.1001/jamaophthalmol.2013.88

32. Edison LS, Dishman HO, Tobin-D'Angelo MJ, Allen CR, Guh AY, Drenzek CL. Endophthalmitis outbreak associated with repackaged bevacizumab. *Emerg Infect Dis*. 2015;21(1):171-173. doi:10.3201/eid2101.141040

33. Irigoyen C, Ziahosseini K, Morphis G, Stappler T, Heimann H. Endophthalmitis following intravitreal injections. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(4):499-505. doi:10.1007/s00417-011-1851-1

34. Benoist d'Azy C, Pereira B, Naughton G, Chiambaretta F, Dutheil F. Antibioprophylaxis in prevention of endophthalmitis in intravitreal injection: a systematic review and meta-analysis. *PLoS One*. 2016;11(6):e0156431. doi:10.1371/journal.pone.0156431

35. Bhavsar AR, Stockdale CR, Ferris FL III, Brucker AJ, Bressler NM, Glassman AR; Diabetic Retinopathy Clinical Research Network. Update on risk of endophthalmitis after intravitreal drug injections and potential impact of elimination of topical antibiotics. *Arch Ophthalmol*. 2012;130(6):809-810. doi:10.1001/archophthalmol.2012.227

36. Creuzot C, Bron A, Cochereau I, Labetoulle M, Bodaghi B. Indication of antibiotic prophylaxis during intravitreal injections. http://www.sfo.asso.fr/files/files//FICHE-INFO-MEDECIN/Indication%20of%20antibiotic%20prophylaxis%20during%20intravitreal%20injections.pdf. 2014. Accessed November 13, 2017.

37. Fung V, Brand RJ, Newhouse JP, Hsu J. Using Medicare data for comparative effectiveness research: opportunities and challenges. *Am J Manag Care*. 2011;17(7):488-496.

38. Jonisch J, Lai JC, Deramo VA, Flug AJ, Fastenberg DM. Increased incidence of sterile endophthalmitis following intravitreal preserved triamcinolone acetonide. *Br J Ophthalmol*. 2008;92(8):1051-1054. doi:10.1136/bjo.2007.136069

39. Daien V, Nguyen V, Essex RW, Morlet N, Barthelmes D, Gillies MC; Fight Retinal Blindness! Study Group. Incidence and outcomes of infectious and noninfectious endophthalmitis after intravitreal injections for age-related macular degeneration. *Ophthalmology*. 2018;125(1):66-74. doi:10.1016/j.ophtha.2017.07.005

40. Lyall DA, Tey A, Foot B, et al. Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: incidence, features, risk factors, and outcomes. *Eye (Lond)*. 2012;26(12):1517-1526. doi:10.1038/eye.2012.199

41. Avery RL, Bakri SJ, Blumenkranz MS, et al. Intravitreal injection technique and monitoring: updated guidelines of an expert panel. *Retina*. 2014;34(suppl 12):S1-S18. doi:10.1097/IAE.0000000000000399

42. Bodaghi B, Korobelnik JF, Cochereau I, Hajjar J, Goebel F, Dumarcet N; AFSSAPS (Association Francaise de Securite Sanitaire des Produits de Sante). Intravitreal injections: AFSSAPS guide to good practice [in French]. *J Fr Ophtalmol*. 2012;35(1):69-71. doi:10.1016/j.jfo.2011.11.005

43. Coleman AL. How big data informs us about cataract surgery: the LXXII Edward Jackson Memorial Lecture. *Am J Ophthalmol*. 2015;160(6):1091-1103.e3. doi:10.1016/j.ajo.2015.09.028