Endophthalmitis After Intravitreal Injections: Incidence, Presentation, Management, and Visual Outcome

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• PURPOSE: To report the incidence and characteristics of endophthalmitis after intravitreal injections of anti–vascular endothelial growth factor agents or corticosteroids and to describe the clinical and bacteriologic characteristics, management, and outcome of these eyes with acute endophthalmitis in France.

• DESIGN: Retrospective, nationwide multicenter case series.

• METHODS: From January 2, 2008 to June 30, 2013, a total of 316 576 intravitreal injections from 25 French ophthalmic centers were included. For each center, the number of intravitreal injections was determined using billing codes and the injection protocol was recorded. A registry and hospital records were reviewed to identify patients treated for endophthalmitis after injection during the same time period. The main outcome measures were the incidence of clinical endophthalmitis and visual acuity of endophthalmitis cases.

• RESULTS: During the study period, 65 cases of presumed endophthalmitis were found, giving an overall incidence of 0.021% (2.1 in 10 000 injections) (95% confidence interval [CI], 0.016%–0.026%). The median number of days from injection to presentation was 4 [1–26] days. The most common symptom was vision loss. Bacterial identification was achieved in 43.4%. The most frequent pathogens were gram-positive bacteria (91.3%), including coagulase-negative *Staphylococcus* in 78.3%. Neither the interval between injection and presentation for endophthalmitis nor the clinical signs differentiated culture-positive from culture-negative cases. In multivariate analysis, the use of a disposable conjunctival mould assist device and the use of prophylaxis with an antibiotic or antiseptic were significantly associated with an increased incidence of endophthalmitis (P .001). The majority of patients had worse visual acuity after 3 months of follow-up when compared with acuity before endophthalmitis.

• CONCLUSIONS: The incidence of presumed endophthalmitis after intravitreal injections of anti–vascular endothelial growth factors or corticosteroids was low and the prognosis poor. Prevention and management remain challenging. It remains to be determined whether the findings of this study are relevant for other countries using different techniques for intravitreal injections. (Am J Ophthalmol 2015;160(1):17–25. © 2015 by Elsevier Inc. All rights reserved.)

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THE NUMBER OF INTRAVITREAL (IVT) INJECTIONS HAS dramatically increased over the last 10 years owing to the efficacy of corticosteroids and anti vascular endothelial growth factor (anti-VEGF) agents for various posterior segment diseases such as age-related macular degeneration (AMD), diabetic macular edema (DME), macular edema secondary to retinal vein occlusion, and uveitis. More than 1 million IVT injections were performed in the United States in 2009.[1] IVT injections may induce complications, including endophthalmitis, retinal detachment, and cataract.[2] Infectious endophthalmitis is one of the most feared complications after IVT injections because of its poor prognosis. In the literature, the incidence of endophthalmitis after IVT injections can vary from 0 to 0.092%.[3,4] Recently 2 meta-analyses reported 0.056% and 0.049% incidence of infection following 350 535 and 105 536 IVT injections, respectively.[5,6] Although the risk is low, infectious endophthalmitis after IVT injections remains the most preoccupying complication. Indeed, the treatment of these macular pathologies usually requires repeated IVT injections. Each injection carries a small risk of endophthalmitis, leading to a cumulative risk of more than 1% after 2 years.[7]

Many studies have identified modifiable risk factors to prevent endophthalmitis following IVT injections, and guidelines based on current best evidence and practices have been published in different countries.[8,9] However, while some recommendations have been applied in current clinical practice, such as a dedicated setting for IVT injections, debate continues on the intraoperative and postoperative environment, such as the use of a surgical mask and prophylactic anti-infectious treatment.

The purpose of this study was, first, to report the incidence of presumed endophthalmitis after IVT injections

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performed in 25 nationwide ophthalmic centers throughout France and, second, to describe the prophylactic measures, the clinical and microbiological spectrum, the management, and the outcome of endophthalmitis following IVT injections.

METHODS

ALL PATIENTS SIGNED INFORMED CONSENT BEFORE THE injections. The protocol was in accordance with the tenets of the Declaration of Helsinki. The local Ethics Committee ruled that approval was not required for this retrospective study. This was a large multicenter retrospective study of endophthalmitis after intravitreal injections given from January 2, 2008, to June 30, 2013. Public and private practice retina ophthalmologists were contacted through the 2 main French retina societies (Fédération Française de la Macula and Club Francophone des Spécialistes de la Rétine) and were included in a group called FRenCh Retina specialists, the FRCR net, to participate in the study. For each participating center, both the number of IVT injections collected through billing codes for IVT injection and the setting in which IVT injections were performed were recorded. The treatments used in this study were ranibizumab (0.5 mg/0.05 mL; Lucentis; Novartis Pharma SAS, Basel, Switzerland), bevacizumab (1.25 mg/0.05 mL; Avastin; Roche, Basel, Switzerland), triamcinolone acetonide (4 mg/0.1 mL; Kenacort; Bristol-Myers Squibb, New York, New York, USA), and the dexamethasone implant (0.7 mg; Ozurdex; Allergan SAS, Irvine, CA, USA). Indications for injections consisted of macular edema secondary to retinal vein occlusion and diabetes, neovascularization occurring in AMD and degenerative myopia, and miscellaneous causes.

Presumed endophthalmitis was defined as any acute intraocular inflammation occurring within 4 weeks after IVT injection and requiring intravitreal antibiotics. In each center, the cases of endophthalmitis during the same time period were identified by searching the operative code for endophthalmitis in registry or hospital records. Case-related data included patient demographics; Snellen visual acuity (VA) before infection, at presentation, and after 3 months; the number of days from injection to presentation; the number of injections preceding endophthalmitis; and the reason for performing IVT injection. Finally, the management of the endophthalmitis, namely intravitreal antibiotic injection, pars plana vitrectomy, bacterial culture and sensitivity results, and complications such as retinal detachment or phthisis, were reported.

• **INTRAVITREAL INJECTION TECHNIQUE:** All eyes were prepared using a standardized procedure according to the recommendations of the French Agency for the Safety of Health Products (Agence Nationale de Sécurité du Médicament), with minor variations between centers.[9] Briefly, before injection, local anesthesia was applied with 1 drop of tetracaine (Tetracaïne Faure unidose 1%; Novartis, Basel, Switzerland). Five percent periocular and conjunctival povidone-iodine (Bétadine; MEDA Pharma, Paris, France) was applied for 2 minutes and then a fenestrated self-adhesive sterile drape large enough to mask the patient's nose and mouth was used. In all centers a lid speculum or a disposable conjunctival mould assist device (InVitria; FCI Ophthalmics, Pembroke, Massachusetts, USA) without a lid speculum was used. Each ophthalmologist administered anti-VEGF agents or steroids through the pars plana 3.5 4 mm from the limbus without any displacement of the conjunctiva. A 30 gauge needle was used to inject anti-VEGF agents while a 27 gauge needle was used for corticosteroids, except for the dexamethasone implant, where the device provided by the manufacturer was used. All ophthalmologists wore a face mask, a surgical hat, sterile gloves, and a surgical gown. All ophthalmologists were assisted for the injections. Assistants wore a disposable cap, a face mask, and a surgical gown. All patients wore a disposable cap. At the end of the procedure, the ability of the patient to see light was assessed in all cases. Oral and written information with a list of telephone numbers to contact in case of emergency were given, and written consent was obtained before IVT injection. The parameters studied are listed in Table 1.

When antibiotic prophylaxis was used, topical 1.5% azithromycin (Azyter; Thea, Clermont-Ferrand, France) was given for 3 days either before or after IVT injection. Centers employing antiseptics used topical 0.05% picloxydine (Vitabact; Thea) 3 days before and 3 days after IVT injection in every case.

• **VISUAL OUTCOME:** Visual acuity was measured with Snellen charts and secondarily converted to the logarithm of the minimal angle of resolution (logMAR) values for statistical analysis. According to Holladay, VA equal to count fingers (CF) and hand motion (HM) corresponds to logMAR 2 and logMAR 3, respectively.[10] Baseline VA was defined as VA measured at presentation with endophthalmitis, and final VA was measured 3 months later.

• **ENDOPHTHALMITIS MANAGEMENT:** All eyes in which presumed infectious endophthalmitis developed were treated in either the center where they were injected or a nearby reference center. All patients benefited from bacteriologic samples (vitreous and/or aqueous tap). All patients received antibiotic IVT injections of vancomycin (1 mg/0.1 mL) (Vancomycin; Mylan, Canonsburg, Pennsylvania, USA) associated with ceftazidime (2.25 mg/0.1 mL) (Fortum; GlaxoSmithKline, Brentford, UK). All patients received a systemic broad-spectrum antibiotic regimen, intravenous imipenem (Tienam; MSD, Courbevoie, France) 1.5 g daily combined with oral ciprofloxacin (Ciflox; Bayer Sante, Loos, France) 1 g daily, and dexamethasone phosphate

TABLE 1. Factors Influencing the Incidence of Endophthalmitis After Intravitreal Injections of Corticosteroids or Anti–Vascular Endothelial Growth Factor Agents in 25 French Centers

	Centers, Number (%)	Univariate Analysis, *P*	Multivariate Analysis, *P*
1. Room			
Dedicated room	24 (96.0)	.242	ND
Filtration airflow	10 (40.0)	.079	ND
2. Operator			
Surgical sterile smock changed for each patient	4 (16.0)	.412	ND
3. Patient			
Disposable smock	22 (88.0)	.174	ND
4. Technique for intravitreal injection			
Disposable conjunctival fixed mould assist device	4 (16.0)	.011	.001
Intravitreal injections never done in superior hemisphere	3 (12.0)	.548	ND
Intravitreal injections never done in inferior hemisphere	7 (28.0)	.180	ND
5. Prophylaxis			
Topical antibiotic started before intravitreal injections	10 (40.0)	.844	ND
Topical antibiotic started after intravitreal injections	11 (44.0)	.645	ND
Topical antiseptic	2 (8.0)	.534	ND
No prophylaxis with antibiotic or antiseptic	2 (8.0)	.021	.001

ND = not done.
A negative binomial regression model was used when the data did not fit the Poisson model satisfactorily.
Multivariate analysis included variables with $P < .05$ in univariate analysis.

sodium (Dexafree; Thea, Clermont-Ferrand, France) eye drops for 8 days. The parameters studied are listed in Table 2.

• **STATISTICAL ANALYSIS:** All analyses were conducted using STATA software version 12.0 (STATACORP, College Station, Texas, USA) and R software version 3, "meta" and "metaphor" packages (R Foundation for Statistical Computing, Vienna, Austria).

The distribution of quantitative variables was determined using histograms followed by normality tests based on Ladder of Power (logarithmic and powers). They are given as median (range). Qualitative variables were described using percentages. Ninety-five percent confidence intervals (95% CI) were estimated using the binomial exact method. Qualitative variables were compared using the χ^2 or Fisher exact test. Continuous variables were compared using nonparametric tests. Logistic regression was also performed. Variance of beta coefficients was assessed using bootstrap or robust variance (Hubert/White/Sandwich).

A meta-analysis of the incidence of endophthalmitis was performed using the inverse variance method and a Freeman-Tukey double-arcsine transformation to stabilize the variance of proportions. The Sidik-Jonkman method for random effects meta-analysis was used in the presence of heterogeneity.[11] An influential analysis of the random-effects model was performed. The Clopper-Pearson confidence interval was used for individual studies and a funnel plot was performed to assess center bias. The number of endophthalmitis cases was modeled using univariate or multivariate negative binomial regression with the number of injections as the exposure variable. Statistical significance was set at $P < .05$ and the tests were 2-tailed.

RESULTS

TWENTY-FIVE CENTERS INCLUDING 16 PUBLIC AND 9 PRIvate practices throughout France participated in the study. The median (range) number of IVT injections in each center was 8390 (680 39 857), for a total of 316 576 IVT injections. Over the time period studied, a total of 65 presumed infections were observed. Therefore, the overall incidence of presumed endophthalmitis was 0.021% (2.1 in 10 000 injections) (95% CI, 0.016% 0.026%). The median number of presumed cases of endophthalmitis

TABLE 2. Demographics, Management, Bacteriology and Visual Outcome of Suspected Endophthalmitis Cases (N 60) After Intravitreal Injections, in 25 French Centers

Characteristics	
Sex (F/M)	43/17
Age (y)	81 (42 96)
Diabetes	12 (20.0)
Indications	
Age related macular degeneration	42 (70.0)
Diabetic macular edema	6 (10.0)
Vein occlusion	6 (10.0)
High myopia	1 (1.7)
Miscellaneous causes	5 (8.3)
Agents	
Ranibizumab	41 (68.3)
Bevacizumab	9 (15.0)
Triamcinolone acetonide	6 (10.0)
Dexamethasone implant	4 (6.7)
Number of intravitreal injections before endophthalmitis	7 (1 28)
Initial Presentation	
Days to presentation	4 (1 26)
Vision loss	57 (95.0)
Pain	53 (88.3)
Redness	59 (98.3)
Tyndall	60 (100.0)
Hypopyon	40 (66.7)
Vitritis	59 (98.3)
Management	
Second intravitreal injection of antibiotics[a]	36 (60.0)
Intravitreal injection of betamethasone	17 (28.3)
Third intravitreal injection of antibiotics[a]	3 (5.0)
Topical fortified antibiotics	19 (31.7)
Systemic corticosteroids	22 (36.7)
Subconjunctival injections of betamethasone	39 (65.0)
Early pars plana vitrectomy	8 (13.3)
Delayed vitrectomy	3 (5.0)
Bacteriology	
Aqueous sampling (n = 53)[b]	37 (69.8)
Positivity rate	11 (29.7)
Vitreous sampling (n = 53)	21 (39.6)
Positivity rate	17 (81.0)
Bacterial identification (culture positive)	23 (43.4)
Coagulase negative staphylococci	18 (78.3)
Staphylococcus aureus	2 (8.7)
Streptococcus sp	1 (4.3)
Pseudomonas aeruginosa	2 (8.7)
Visual Outcome (logMAR)[c]	
Visual acuity before endophthalmitis	0.5 (0.4 0.7)
Baseline visual acuity	3.0 (2.0 3.0)
Limited to light perception (n/%)	14 (23.3)
Visual acuity, 8 days after endophthalmitis	2.0 (0.9 3.0)
Visual acuity, 1 month after endophthalmitis	0.7 (0.6 1.3)
Visual acuity, 3 months after endophthalmitis	0.7 (0.4 1.0)

LogMAR = logarithm of the minimal angle of resolution.

Values are displayed as median (range) for continuous variables and number (%) for categorical variables.

[a]Vancomycin 1 mg and ceftazidime 2.25 mg.

[b]Five patients had both aqueous and vitreous sampling.

[c]For visual outcome, values are displayed as median (25th percentile 75th percentile).

in each center was 1 (0 12). Taking into account the great heterogeneity of the number of injections among participating centers, a complementary analysis that stabilized the variance of proportions was performed as detailed above, providing a corrected incidence of endophthalmitis of 0.011% (95% CI, 0.005% 0.019%). A funnel plot was made to confirm the absence of bias attributable to the heterogeneity between centers (data not shown). Of the 65 cases of presumed endophthalmitis, we collected complete data at 3 months for 60 of them (Table 2).

• **INTRAVITREAL INJECTION PROCEDURE:** The details of the IVT injection procedures between the 25 centers are shown in Table 1. In univariate analysis, use of a disposable conjunctival fixed mould and prophylaxis with an antibiotic or antiseptic were statistically associated with an increased incidence of endophthalmitis ($P = .011$ and $P = .021$, respectively). In multivariate analysis, use of a disposable conjunctival fixed mould remained positively associated with the incidence of endophthalmitis (incidence rate ratio [IRR] = 2.38) (95% CI, 1.64 3.47) ($P = .001$). Prophylaxis with an antibiotic or antiseptic remained statistically associated with an increased incidence of endophthalmitis (IRR = 2.77) (95% CI, 1.54 5.00) ($P = .001$).

• **ENDOPHTHALMITIS MANAGEMENT:** The characteristics of endophthalmitis management are displayed in Table 2. The first intravitreal antibiotic injection (vancomycin and ceftazidime) was performed in the emergency setting on presentation immediately after bacterial sampling, or the following day at the latest in 3 cases. The second intravitreal antibiotic injection was performed 2 (1 8) days after the first antibiotic IVT injection. When needed, the third intravitreal antibiotic injection was performed 4 (3 13) days after the first antibiotic IVT injection. Systemic administration of corticosteroids was started after a median delay of

TABLE 3. Univariate Analysis of Factors Influencing Visual Acuity Recovery at 3 Months in Patients With Endophthalmitis After Intravitreal Injections

	Visual Acuity Loss (N 36)	Visual Acuity Recovery (N 24)	*P*
Age (y)	80 (42 96)	79 (72 86)	.131
Diabetes	7 (19.4)	5 (20.8)	.999
Indication, AMD	27 (75.0)	15 (62.5)	.391
Agent, anti VEGF	31 (86.1)	19 (79.2)	.501
Number of intravitreal injections before endophthalmitis	8 (1 25)	6 (1 28)	.279
Days to presentation	3 (1 26)	4 (1 8)	.957
Vision loss	36 (100.0)	21 (87.5)	.059
Pain	33 (91.7)	20 (83.3)	.422
Redness	35 (97.2)	24 (100.0)	.999
Hypopyon	25 (69.4)	15 (62.5)	.590
Vitritis	36 (100.0)	23 (95.8)	.400
Second intravitreal injection of antibiotics	21 (58.3)	15 (62.5)	.793
Intravitreal injection of betamethasone	11 (30.6)	6 (25.0)	.773
Topical fortified antibiotics	13 (36.1)	6 (25.0)	.410
Systemic corticosteroids	13 (36.1)	9 (37.5)	.999
Subconjunctival injections of betamethasone	24 (66.7)	15 (62.5)	.788
Early pars plana vitrectomy	3 (8.3)	5 (20.8)	.247
Bacterial identification (culture positive)[a]	11 (34.4)	12 (57.1)	.157
Baseline visual acuity limited to light perception	9 (25.0)	5 (20.8)	.765

AMD = age related macular degeneration; anti VEGF = anti vascular endothelial growth factor.

Values are displayed as median (range) for continuous variables and percentage for categorical variables.

Comparisons were made with the Fisher exact test for dichotomous data. A nonparametric Mann Whitney test was used for continuous variables; the level of statistical significance was set at $P < .05$.

[a]Done in 53 patients.

2 (0 4) days after initial presentation for a median period of 3 (1 30) days. Subconjunctival injections of betamethasone were started after a median delay of 2.5 (1 9) days after initial presentation, for a median period of 3.5 (1 7) days.

Median baseline logMAR VA in patients undergoing early vitrectomy was significantly worse than in patients who did not undergo early vitrectomy ($P = .032$), but this difference was no longer statistically significant at 3 months ($P = .332$). Among the 14 patients with a baseline VA limited to light perception (LP), 5 patients underwent a pars plana vitrectomy. The VA of these patients did not reach statistical significance when compared to those who did not benefit from an early vitrectomy: 0.7 (0.4 3.0) vs 0.9 (0.3 2.0) ($P = .919$).

• **BACTERIOLOGY:** The bacteriologic results are shown in Table 2. The median time from IVT injection to sampling in culture-positive endophthalmitis was not significantly different from that of culture-negative endophthalmitis: 4 (1 26) days vs 3 (1 14) days, $P = .122$. The clinical characteristics on admission and recovery of initial VA were not significantly different between culture-positive and culture-negative patients, *P* ranging from .249 to .999 and $P = .157$, respectively. The median number of IVT injections before endophthalmitis was not statistically different between culture-positive and culture-negative cases: 3 (1 33) vs 8 (1 28) ($P = .114$). Aqueous or vitreous samples were not taken in 7 patients.

• **VISUAL OUTCOME:** The visual outcome is summarized in Table 2. After a 3-month follow-up, VA was significantly better than baseline VA ($P < .001$) but still less than the VA found before infection occurred ($P < .001$). The majority of patients (39/60, 65.0%) had worse VA after the 3-month follow-up when compared with VA just before endophthalmitis. At 3 months, 6 of 60 patients (10%) ended up with nonambulating vision: 4 with count-fingers visual acuity and 2 with light perception. We did not have patients with hand motion visual acuity or non light perception.

Risk factors influencing visual acuity at the 3-month follow-up visit were not identified in univariate or multivariate analysis (Table 3; only univariate analysis is displayed). During the follow-up, 1 case of phthisis occurred 105 days after the presentation with endophthalmitis. After endophthalmitis, corticosteroid or anti-VEGF IVT injections to treat initial macular disease were restarted in 37 of 60 patients (61.7%) after a median time of 113 (25 770) days.

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