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Postinjection Endophthalmitis in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)

*Travis A. Meredith, MD,[1] Colin A. McCannel, MD,[2] Charles Barr, MD,[3] Bernard H. Doft, MD,[4] Ellen Peskin, MA,[5] Maureen G. Maguire, PhD,[5] Daniel F. Martin, MD,[6] Jonathan L. Prenner, MD,[7] for the Comparison of Age-Related Macular Degeneration Treatments Trials Research Group**

Objective: To describe the incidence and outcomes of endophthalmitis after intravitreal injections of anti–vascular endothelial growth factor agents in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and to assess the effect of prophylactic topical antimicrobials on incidence.

Design: Cohort study within a randomized clinical trial.

Participants: Patients enrolled in CATT.

Methods: Patients with neovascular age-related macular degeneration received intravitreal injections of ranibizumab or bevacizumab under 1 of 3 dosing regimens. The study protocol specified preinjection preparation to include use of a sterile lid speculum and povidone iodine (5%). Use of preinjection and postinjection antibiotics was at the discretion of the treating ophthalmologist. Patients were followed up monthly for 2 years.

Main Outcome Measures: Development of endophthalmitis and visual acuity.

Results: Endophthalmitis developed after 11 of 18 509 injections (1 per 1700 [0.06%]; 95% confidence interval, 0.03%–0.11%), and in 11 of 1185 patients (0.93%; 95% confidence interval, 0.52–1.66). Incidence of endophthalmitis was 0.15% among injections with no antibiotic use, 0.08% among injections with preinjection antibiotics only, 0.06% among injections with postinjection antibiotics only, and 0.04% among injections with preinjection and postinjection antibiotics ($P = 0.20$). All eyes were treated with intravitreal antibiotics and 4 underwent vitrectomy. Among the 11 affected eyes, the final study visual acuity was 20/40 or better in 4 eyes (36%), 20/50 to 20/80 in 2 eyes (18%), 20/100 to 20/160 in 3 eyes (27%), and worse than 20/800 in 2 eyes (18%). The final visual acuity was within 2 lines of the visual acuity before endophthalmitis in 5 eyes (45%).

Conclusions: Rates of endophthalmitis were low and similar to those in other large-scale studies. Use of topical antibiotics either before or after injection does not seem to reduce the risk for endophthalmitis. *Ophthalmology 2015;122:817-821 © 2015 by the American Academy of Ophthalmology.*

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Intravitreal injections of anti–vascular endothelial growth factor (anti-VEGF) drugs have become one of the most commonly performed procedures in ophthalmology, with an estimate of more than 3 million per year for the Medicare population.[1] Although infrequent, endophthalmitis is the complication of greatest concern because of poor functional outcomes in some patients even with prompt treatment.

The rate of endophthalmitis after intravitreal injections varies in the literature. In large prospective, randomized trials, the endophthalmitis rate ranges from 6 (0.02%) among an estimated 26 300 injections to 3 (0.10%) among 3125 injections.[2–4] In retrospective case series, in which generally 1 or a small number of institutions or practices report their findings, the rates vary more widely.[3,4] The largest meta-analysis performed to date analyzed 43 published articles and found an endophthalmitis incidence of 197 (0.056%) in 350 535 injections.[4]

The few generally agreed on preventive strategies include the use of povidone iodine on the ocular surface immediately before the injection and the use of a lid speculum.[5] Other precautions, such as the use of gloves,[5] and strategies to minimize droplet contamination, such as the use of a mask or minimizing talking during injection, remain controversial.[6–8]

The administration of prophylactic preinjection or postinjection topical antibiotics has been required in many clinical trials and is practiced routinely by many ophthalmologists. Recommendations for antibiotic use recently have been called into question by reports of lower endophthalmitis rates among those patients who did not receive preinjection or postinjection antibiotics in some Diabetic Retinopathy Clinical Research Network studies.[6] Additionally, the use of prophylactic topical antibiotics has been demonstrated to cause rapid development of

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Table 1. Incidence of Endophthalmitis by Use of Antibiotics

Antibiotic Use	No. of Injections	No. of Cases	Rate (%)	95% Confidence Interval
None	2000	3	0.15	0.05%–0.44%
Preinjection only	1301	1	0.08	0.01%–0.43%
Postinjection only	5247	3	0.06	0.05%–0.25%
Preinjection and postinjection	9961	4	0.04	0.02%–0.10%
Total	18 509	11	0.06	0.03%–0.11%

antibiotic-resistant virulent bacteria on the ocular surface and displacement of commensal flora with more virulent species.[9–11]

We report the rate of endophthalmitis in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), a multicenter, randomized clinical trial, and describe the impact of endophthalmitis on visual acuity. We also examine the effect of preinjection or postinjection use of antibiotics on the endophthalmitis rates in this large cohort.

Methods

A detailed discussion of the methodology for the CATT has been published previously.[12–14] From February 2008 through December 2009, 1185 patients from 43 clinical centers in the United States were enrolled into the trial. Eyes were eligible for the study if they had active choroidal neovascularization secondary to age-related macular degeneration, no previous treatment, and visual acuity between 20/25 and 20/320. Patients were randomized to intravitreal injections of either ranibizumab or bevacizumab administered monthly or pro re nata (PRN) for 2 years or monthly for 1 year followed by PRN for 1 year. Bevacizumab was prepared centrally by an aseptic filling facility and was distributed in small glass vials. Ranibizumab was obtained by each clinic through their normal commercial sources. Ophthalmologists were masked to the identity of the drug at the time of treatment and throughout follow-up. The study was approved by an institutional review board associated with each center. All patients provided written informed consent.

Patients were evaluated every 28 days and treated with intravitreal injections according to their assigned treatment. The CATT protocol for intravitreal injection required application of 5% povidone iodine and use of a sterile eyelid speculum. Use of topical antibiotic medications either before or after the injection was at the discretion of the treating ophthalmologist.

Study ophthalmologists examined patients as soon as possible after a report of symptoms of endophthalmitis. The diagnosis of presumed endophthalmitis was made by the examining ophthalmologist on the basis of clinical examination. Signs of endophthalmitis included the presence of pain, decreased visual acuity, conjunctival injection, corneal edema, anterior chamber cell and flare, hypopyon, vitreitis, and intraretinal hemorrhage. Study ophthalmologists initiated treatment with intravitreal antimicrobial medications and, in some instances, vitrectomy on making the diagnosis of presumed endophthalmitis.

All reported cases of presumed endophthalmitis, that is, those treated with intravitreal antibiotics, in the CATT were identified and reviewed in detail. Cases with positive culture results were classified as endophthalmitis. Cases with negative or no culture results and no later episodes of inflammation after additional anti-VEGF treatment also were classified as endophthalmitis. However, cases with negative culture results that had a subsequent episode of severe inflammation after intravitreal injection of the assigned study drug that completely resolved with topical steroids only were classified as severe noninfectious inflammation, and not as endophthalmitis.

Incidence rates and associated 95% confidence intervals were calculated on a per-injection basis and a per-patient basis.[15] Comparisons of rates were evaluated by chi-square tests with exact calculations of P values.

Results

Eleven eyes demonstrated endophthalmitis after 18 509 injections in 1185 patients (Table 1). The incidence rate per injection was 0.06% (95% confidence interval, 0.03%–0.11%) or 1 per 1700 injections. The incidence rate per patient was 0.93% (95% confidence interval, 0.52%–1.66%). Of the 11 eyes with endophthalmitis, 4 were treated with ranibizumab and 7 with bevacizumab.

Incidence rates of endophthalmitis for 4 groups defined by use of topical antibiotics before and after injection are displayed in Table 1. Antibiotics were used both before and after injection for 9961 (54%) injections and were not used at either time for 2000 (11%) injections. The rate of endophthalmitis was highest in the group with no antibiotic use (0.15%) and lowest in the group with antibiotics administered both before and after (0.04%); however, the differences in incidence rates among the 4 groups were not statistically significant ($P = 0.20$). Povidone iodine was used per protocol for 18 332 (99.04%) of the 18 509 injections. Among the 11 injections resulting in endophthalmitis, povidone iodine was used for 10 and not used for 1 (Table 2, week 56) because the patient had an allergy to shellfish.

Of the 11 endophthalmitis patients, 1 patient had no culture results, 1 had a specimen obtained at primary vitrectomy, 2 had anterior chamber tap alone, and 7 had vitreous tap. Of the 10 cultures, 3 demonstrated negative results, 3 demonstrated positive results for *Staphylococcus epidermidis*, 1 demonstrated positive results for *Staphylococcus aureus*, and 3 demonstrated positive results for *Streptococcal* species (Table 2). Three patients underwent a vitrectomy between 5 days and 2 months after the initial treatment for endophthalmitis.

Among 11 affected eyes, the final study visual acuity was 20/40 or better in 4 eyes (36%), 20/50 to 20/80 in 2 eyes (18%), 20/100 to 20/160 in 3 eyes (27%), and worse than 20/800 in 2 eyes (18%; Table 2). The final visual acuity was within 2 lines of the visual acuity before endophthalmitis in 5 eyes (45%).

In addition to the 11 eyes in which endophthalmitis developed, 3 (0.25%) of the 1185 eyes (95% confidence interval, 0.08%–0.74%) demonstrated severe noninfectious inflammation. For 2 of the patients, the postinjection inflammation initially was presumed to be the result of endophthalmitis and treated with intravitreal antibiotics. Vitreous samples showed negative results for bacteria or fungus. Each patient subsequently demonstrated severe inflammation similar to the original episode immediately after the next challenge with the same drug (ranibizumab in 1 case and bevacizumab in 1 case), and in each case, the inflammation resolved

Table 2. Summary of Eyes with Endophthalmitis or Severe Noninfectious Inflammation

Injection Week	Previous Injections	Topical Antibiotics		Days to Presentation	Intravitreal Antibiotics	Vitrectomy	Culture Results	Visual Acuity	
		Before	*After*					*Before*	*Final*
Endophthalmitis									
0	0	No	Yes	2	Yes	Yes	*Streptococcus*	20/32	20/25
4	1	No	Yes	3	Yes	Yes	Negative	20/32	20/63
8	2	Yes	Yes	1	Yes	No	*Staphylococcus*	20/40	20/63
24	5	No	No	1	Yes	No	*Streptococcus*	20/40	<20/800*
48	10	No	No	11	Yes	No	Negative	20/25	20/32
52	12	Yes	Yes	2	Yes	Yes	*Streptococcus*	20/32	20/160
56	14	Yes	Yes	2	Yes	No	*Staphylococcus*	20/32	20/32
60	14	Yes	Yes	1	Yes	No	Not done	20/63	<20/800†
76	13	No	Yes	4	Yes	No	*Staphylococcus*	20/32	20/32
84	21	Yes	No	1	Yes	Yes	*Staphylococcus*	20/32	20/100
100	21	No	No	2	Yes	No	Negative	20/25	20/160
Severe noninfectious inflammation									
12	3	Yes	Yes	4	No	No	Not done	20/40	20/40
72	12	Yes	Yes	17	Yes	No	Negative	20/40	20/160
76	18	Yes	Yes	2	Yes	No	Negative	20/16	20/16

*Last study visit at week 32.
†Visual acuity returned to 20/63 before a retinal hemorrhage and choroidal detachment at week 80.

with topical steroids only and no antibiotics. One additional patient, treated with ranibizumab, demonstrated severe postinjection inflammation considered by the treating ophthalmologist to be an immune phenomenon, and the episode resolved promptly with topical steroid therapy.

Discussion

The rates of endophthalmitis in CATT (0.06% per injection, 0.93% per patient) are consistent with the results of other large clinical trials of intraocular injections of anti-VEGF agents.[16–21] The ratio of culture-negative cases to culture-positive cases was similar to postoperative endophthalmitis after cataract surgery, and visual acuity outcomes after treatment were consistent with large series of endophthalmitis cases occurring after cataract surgery.[22–24]

The rate of infection did not seem to be influenced by the use of topical antibiotic medication before or after the injection. Although most practitioners agree on the use of topical povidone iodine and a lid speculum for intravitreal injections, the use of antibiotics in conjunction with intravitreal injections has changed substantially over the last 10 years. Because anti-VEGF injection became common clinical practice in 2005, preinjection or postinjection topical antibiotics have been used in the vast majority of cases. In the CATT, investigators elected to use preinjection or postinjection antibiotics in 90% of the intravitreal injections given during the period of study between February 2008 and December 2011. The practice was supported by clinical conjunctival culture data demonstrating significant reduction in positive conjunctival cultures after antibiotic instillation.[25,26]

More recently, several studies demonstrating increased antibiotic resistance in conjunctival bacteria because of repeated topical antibiotic exposure and an apparent lack of efficacy in preventing endophthalmitis have resulted in a dramatic decline of topical antibiotic use.[9–11,27,28] Bhavsar et al[6,29] reported the rate of endophthalmitis in 4 Diabetic Retinopathy Clinical Research Network studies among patients using and not using topical prophylactic antibiotics. The endophthalmitis rate was higher among those using prophylactic topical antibiotics than those not using antibiotics (0.13% vs. 0.03%; $P = 0.25$). Similarly, Bhatt et al[16] found no difference in endophthalmitis rates between 2287 patients who received topical antibiotics and 2480 patients who did not. Cheung et al[30] found the lowest rate of endophthalmitis among more than 15 000 injections in eyes that did not receive any prophylactic antibiotics.

After the reports of emerging resistance and limited effectiveness, there has been a dramatic shift away from using topical antibiotics in the peri-injection setting. In annual surveys by the American Society of Retina Specialists, the proportion of members reporting use of topical antibiotics decreased from approximately 90% in 2008 to 20% in 2013.[31,32] The totality of the published evidence at this point, combined with the findings in CATT, do not support a clinically important benefit of prophylactic topical antibiotics in reducing the risk of endophthalmitis after intravitreal injections.

Among the CATT culture-positive endophthalmitis cases, 3 (42%) of 7 were a *Streptococcus* species. Higher rates of *Streptococcus* species after intravitreal injections than after intraocular surgery have been reported previously.[33,34] Wen et al[7] have suggested that oropharyngeal droplet contamination may be responsible. Although still controversial, recommendations for reducing the risk of *Streptococcal* endophthalmitis include controlling droplet contamination with such measures as minimizing speaking during the injection or wearing a face mask.

There were 3 cases of severe noninfectious inflammation after injection in CATT that were of particular interest. In each case, there was convincing evidence that the inflammation was not because of infection. All culture results were

negative, but negative culture results have been reported in several studies of endophthalmitis when it was highly likely that an infectious organism was present.[21,35] Instead, what was unique in these 3 cases was that the inflammation either completely resolved with topical steroids alone and no antibiotic (1 case after a ranibizumab injection), or the patient experienced a recurrent episode of severe inflammation similar to the original event with subsequent injection of the same anti-VEGF injection (1 case with ranibizumab and 1 with bevacizumab), and the inflammation resolved with topical steroids and no antibiotics. These cases highlight the fact that not all cases of severe inflammation after injection are infectious and that there is a clinical distinction between severe noninfectious inflammation and infectious endophthalmitis. Severe noninfectious inflammation is used to denote a transient, self-limited inflammatory reaction that occurs after intravitreal injection. This is distinguished from infectious endophthalmitis where the source of inflammation is an intraocular microbe.[4]

Eyes with severe noninfectious inflammation, also referred to in the literature as noninfectious endophthalmitis, have a typical clinical presentation. Patients usually have symptoms of decreased vision and minimal pain soon after the intravitreal injection (i.e., days 0−2). Patients demonstrate marked anterior chamber reaction with cell and flare, but often will not have hypopyon or fibrin. Posteriorly, patients have a pseudogranulomatous appearance, with large cellular aggregates and moderate vitreous haze.[36] This contrasts with the presentation of infectious endophthalmitis, where findings of pain, decreased visual acuity, conjunctival injection, corneal edema, anterior chamber cell and flare, hypopyon, fibrin, vitreitis, and intraretinal hemorrhage typically occur 2 days or more after injection, when the microinoculum of bacteria has had time to cause a consequential cellular reaction.

In summary, the rate (0.06%, or 1 per 1700) of endophthalmitis in the CATT per injection was similar to rates in other large clinical trials evaluating anti-VEGF drugs for neovascular age-related macular degeneration. Topical antibiotics used before or after injection did not result in a statistically or clinically significant reduction in the risk for endophthalmitis ($P = 0.20$). Patients who demonstrate endophthalmitis were treated with intravitreal antibiotics and, in 4 cases (36%), vitrectomy. The final study visual acuity was within 2 lines of the visual acuity before endophthalmitis in 5 (45%) of 11 eyes. Three patients demonstrated severe noninfectious inflammation that resolved with topical steroids.

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[1] Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina.

[2] Department of Ophthalmology, University of California, Los Angeles, California.

[3] Department of Ophthalmology, University of Louisville, Louisville, Kentucky.

[4] Retina Vitreous Consultants, Pittsburgh, Pennsylvania.

[5] Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania.

[6] Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

[7] Retina Vitreous Center, New Brunswick, New Jersey.

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Abbreviations and Acronyms:
CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; **VEGF** = vascular endothelial growth factor.

Correspondence:
Maureen G. Maguire, PhD, Department of Ophthalmology, University of Pennsylvania, 3535 Market Street, Suite 700, Philadelphia, PA 19104. E-mail: maguirem@mail.med.upenne.edu.