Anatomic and Visual Outcomes of Noninfectious Endophthalmitis after Intravitreal Triamcinolone

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• PURPOSE: To describe the anatomic and visual outcomes of patients in whom noninfectious endophthalmitis developed after injection of intravitreal triamcinolone acetonide.
• DESIGN: Retrospective case series.
• METHODS: Ophthalmologic evaluations of patients in whom noninfectious endophthalmitis developed after intravitreal triamcinolone took place on the day of injection, at the time of presentation of noninfectious endophthalmitis, at the time of clearance of inflammation, and on follow-up examination. Seventeen eyes of 17 patients were identified from 2 institutions. Noninfectious endophthalmitis was identified based on history of visual loss immediately or soon after injection, lack of ocular pain, hypopyon, anterior or vitreous inflammation, and triamcinolone crystals present in the anterior or posterior chambers. Main outcome measures were Snellen visual acuity (VA) and mean foveal thickness by optical coherence tomography.
• RESULTS: Mean VA and mean foveal thickness on the day of injection of intravitreal triamcinolone were 20/132 (logarithm of the minimum angle of resolution [logMAR], 0.82 ± 0.45) and 432 ± 118 μm, respectively. Mean VA at time of noninfectious endophthalmitis (mean, 1.9 days after injection) was 20/4444 (logMAR, 2.35 ± 0.98). At last follow-up (mean, 57.6 days), VA and mean foveal thickness were 20/56 (logMAR, 0.44 ± 0.30) and 301 ± 71 μm, respectively.
• CONCLUSIONS: VA and mean foveal thickness in all patients with noninfectious endophthalmitis after intravitreal triamcinolone improved to better than preinjection levels in this series. At last follow-up, no patient had sustained visual loss from noninfectious endophthalmitis. Noninfectious endophthalmitis after intravitreal triamcinolone may not exclude good visual and anatomic prognoses. (Am J Ophthalmol 2009;147:1031–1036.

SINCE THE INTRODUCTION OF INTRAVITREAL TRIAMcinolone in 2002 by Martidis and associates and Greenberg and associates, its use has become widespread by retinal specialists for a variety of intraocular inflammatory, neovascular, and edematous diseases, such as chronic uveitis, refractory diabetic macular edema (DME), proliferative vitreoretinopathy, branch retinal vein occlusion, and pseudophakic cystoid macular edema (CME).[1–4] Corticosteroids inhibit leukotriene and prostaglandin synthesis creating an anti-inflammatory effect and also have been shown to stabilize the blood-retinal barrier and reverse capillary permeability.[5,6] The therapeutic spectrum of intravitreal triamcinolone continues to widen as clinical studies validate its efficacy.

Well-known complications associated with intraocular corticosteroids include ocular hypertension and the progression of cataracts.[7] Infectious endophthalmitis is a rare but potentially devastating outcome of any intravitreal injection, and the added immunosuppressive effects of intraocular corticosteroids warrants increased concern. Acute infectious endophthalmitis after intravitreal triamcinolone injection has been reported with an incidence of 0.10% to 0.87%[8,9] per injection. An endophthalmitis-like noninfectious intraocular inflammatory reaction has also been reported and has been termed *sterile endophthalmitis*. This entity is thought to represent a sterile inflammatory response against a component of the drug formulation.[10,11] *Pseudoendophthalmitis* is a term that indicates the dispersion of triamcinolone crystals in the anterior chamber (AC), and *pseudohypopyon* is a term used to describe the layering of triamcinolone crystals in the inferior AC angle. In this study, we grouped these entities together as *noninfectious endophthalmitis*. Herein, we describe the short-term anatomic and visual outcomes after the clearance of noninfectious endophthalmitis after intravitreal triamcinolone.

METHODS

THE RECORDS OF PATIENTS RECEIVING INTRAVITREAL TRIamcinolone acetonide (Kenalog; Bristol-Myers Squibb, Princeton, New Jersey, USA) injections from 6 retinal specialists at the New England Eye Center, Boston, Massachusetts, and Lahey Clinic, Burlington, Massachusetts, were reviewed. From January 2002 through June 2007 approximately 1,600 intravitreal triamcinolone injections were administered between the 2 institutions. The risks and benefits of the procedure were discussed, and written informed consent was obtained from each patient before injection. Standard sterile technique was used with a sterile lid speculum, calipers, sterile gloves, 5% povidone–

Accepted for publication Dec 29, 2008.
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TABLE 1. Cause of Cystoid Macular Edema in Patients in Whom Noninfectious Endophthalmitis Developed after Intravitreal Triamcinolone Administration

Cause of Macular Edema	% of Patients
Diabetes	41% (7)
Pseudophakia	18% (3)
Epiretinal membrane	18% (3)
Branch retinal vein occlusion	12% (2)
Uveitis	6% (1)
Cancer-associated retinopathy	6% (1)

TABLE 2. Prior Ocular History in Patients in Whom Noninfectious Endophthalmitis Developed after Intravitreal Triamcinolone Administration

Ocular History	% of Patients
Prior intraocular surgery	82% (14)
Pseudophakia	71% (12)
Pars plana vitrectomy	53% (9)
Open posterior capsule	17% (3)
Prior intravitreal triamcinolone injection	53% (9)

iodine, topical tobramycin or ofloxacin, and topical tetracaine for anesthesia. A pars plana injection was performed with previously unopened bottles of intravitreal triamcinolone acetonide (4 mg/0.1 ml) using 27- or 30-gauge needles. Topical antibiotics then were used 4 times daily for 3 to 5 days. Follow-up appointments were made 4 to 6 weeks after the injection. Patients were asked to call if decreased vision developed after the injection, and a nurse called each patient 1 to 2 days after the injection to verify that no difficulties were encountered after the intravitreal injection.

Snellen visual acuity (VA) and mean foveal thickness with optical coherence tomography were measured on the day of injection, on presentation of noninfectious endophthalmitis, at a time when clearance of inflammation was observed, and on follow-up examination. Eyes were identified as having noninfectious endophthalmitis based on history of decreased vision within 24 to 48 hours of injection without pain, and characteristic findings such as hypopyon, AC and vitreous cell, vitreous haze, and triamcinolone crystals identified by slit-lamp biomicroscopy and indirect ophthalmoscopy. B-scan ultrasonography was performed if no view to the posterior segment was appreciated. Patients underwent vitreous culture and intravitreal injection of antibiotics at the discretion of the attending physician. Any patient whose gram-stain, aqueous, or vitreous culture results were positive was excluded from this study. Patients then were followed up closely at regular intervals at the physician's discretion.

RESULTS

SEVENTEEN EYES OF 17 PATIENTS WERE IDENTIFIED AS HAVing noninfectious endophthalmitis after intravitreal triamcinolone injection. Clinical characteristics of involved eyes are summarized in Tables 1 and 2. Intravitreal triamcinolone was used to treat DME in 7 patients (41%), pseudophakic CME in 3 patients (18%), CME associated with an epiretinal membrane in 3 patients (18%), CME associated with branch retinal vein occlusion in 2 patients (12%), CME associated with uveitis in 1 patient (6%), and CME associated with cancer-associated retinopathy in 1 patient (6%).

Nine (53%) of the patients had received at least 1 prior intravitreal triamcinolone injection before presentation of noninfectious endophthalmitis. None of these 9 eyes were diagnosed with any untoward inflammation previously. Nine patients (53%) had prior pars plana vitrectomies performed in the affected eye. Twelve (71%) of the patients were pseudophakic, and only 3 of these patients had an open posterior capsule. Fourteen (82%) of the 17 patients had some type of prior intraocular surgery performed.

The average time to presentation after injection was 1.9 days (range, 1 to 3 days). All patients had decreased vision in the affected eye at presentation. No patients reported ocular pain. However, 5 patients reported periorbital soreness, and 1 patient reported photophobia.

All patients demonstrated AC and vitreous cellular reaction at the time of presentation of noninfectious endophthalmitis. Eleven patients had a visible pseudohypopyon (Figure 1, Top left and right), and all patients demonstrated various degrees of vitreous haze. Triamcinolone crystals were visible in the AC and vitreous in 9 (53%) of the 17 patients, and it was identified on B-scan ultrasonography when no view to the posterior segment was appreciated (Figure 2, right). The presumed triamcinolone particles seemed to be larger and more crystalline in character than typical inflammatory white blood cells (Figure 1, Bottom left; Figure 2, right). Fibrin was identified in the AC in 3 of the patients (18%). Eight patients underwent vitreous cultures and injections of intravitreal antibiotics. One patient with light perception vision at the time of presentation underwent vitrectomy with intravitreal antibiotics. No growth of any organisms was identified on gram-stain, aqueous, or vitreous cultures of these patients.

The mean preinjection Snellen VA was 20/132 (logarithm of the minimum angle of resolution [logMAR], 0.82 ± 0.45) and mean central foveal thickness of 432 ± 118 μm. At the time of presentation of noninfectious endophthalmitis, mean VA was 20/4444 (logMAR, 2.35 ± 0.98). At the time of clearance of inflammation (mean, 15.1 days), mean VA was 20/99 (logMAR, 0.70 ± 0.41). Of the 11 of 17 patients undergoing optical coherence tomography examination at that time, the mean central foveal thickness measured 30 2 ± 66 μm, and the decrease in foveal thickness averaged 109 μm. On short-term follow-up (mean, 57.6 days), mean VA was 20/56 (logMAR, 0.44 ± 0.30), and mean central foveal

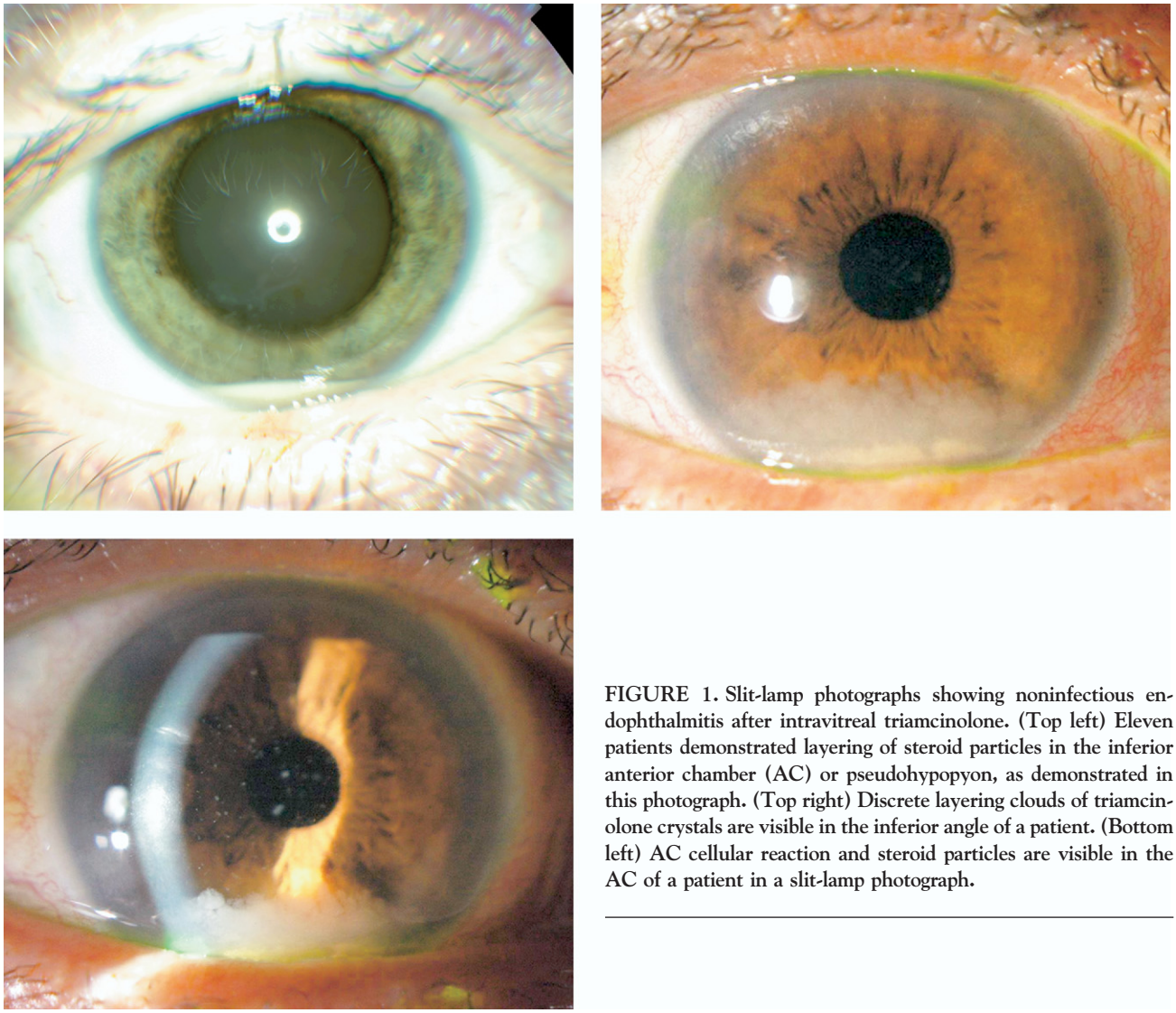

FIGURE 1. Slit-lamp photographs showing noninfectious endophthalmitis after intravitreal triamcinolone. (Top left) Eleven patients demonstrated layering of steroid particles in the inferior anterior chamber (AC) or pseudohypopyon, as demonstrated in this photograph. (Top right) Discrete layering clouds of triamcinolone crystals are visible in the inferior angle of a patient. (Bottom left) AC cellular reaction and steroid particles are visible in the AC of a patient in a slit-lamp photograph.

thickness was 301 ± 71 μm, with a mean change of 131 μm. The data is summarized in Table 3 and Figures 3 and 4.

DISCUSSION

NONINFECTIOUS ENDOPHTHALMITIS AFTER INTRAVITREAL triamcinolone has become a recognized entity with the increased use of intravitreal triamcinolone for refractory macular edema. The incidence of noninfectious endophthalmitis after intravitreal triamcinolone has been reported to range from 0.2% to 1.6% in various series,[10–13] and our approximate incidence was 1.06% of injections at The New England Eye Center and Lahey Clinic. Previously reported case reports of noninfectious endophthalmitis describe painless visual loss immediately or soon after the injection. Other clinical characteristics in reports include a layering of steroid particles in the inferior AC angle simulating a hypopyon, vitreous haze, and white crystalline opacities in the aqueous humor and vitreous. This entity may represent the dispersion of triamcinolone crystals in the AC and a distinct sterile inflammatory response against a component of the drug. These patients typically have no ocular pain and are reported to recover rapidly within days to preinjection levels of VA without intervention.

It has been suggested that noninfectious endophthalmitis may be caused by an acute toxic reaction to the triamcinolone acetonide particle or the vehicle of the drug suspension.[10,12] Experimental studies found that the vehicle used in intravitreal triamcinolone was nontoxic to the rabbit retina[14] and also nontoxic to the human retina based on electrophysiologic analysis.[15] The vehicle of the commercial formulation of triamcinolone includes 6.9 mg sodium chloride, 15 mg benzyl alcohol, 7.5 mg carmellose sodium, and 0.4 mg polysorbate 80. The benzyl alcohol preservative in the preparation has been speculated to be a stimulus for the inflammatory reaction. Studies with filtered or preservative-free triamcinolone acetonide to improve the potential toxicity of the suspension thus far have been inconclusive.[13]

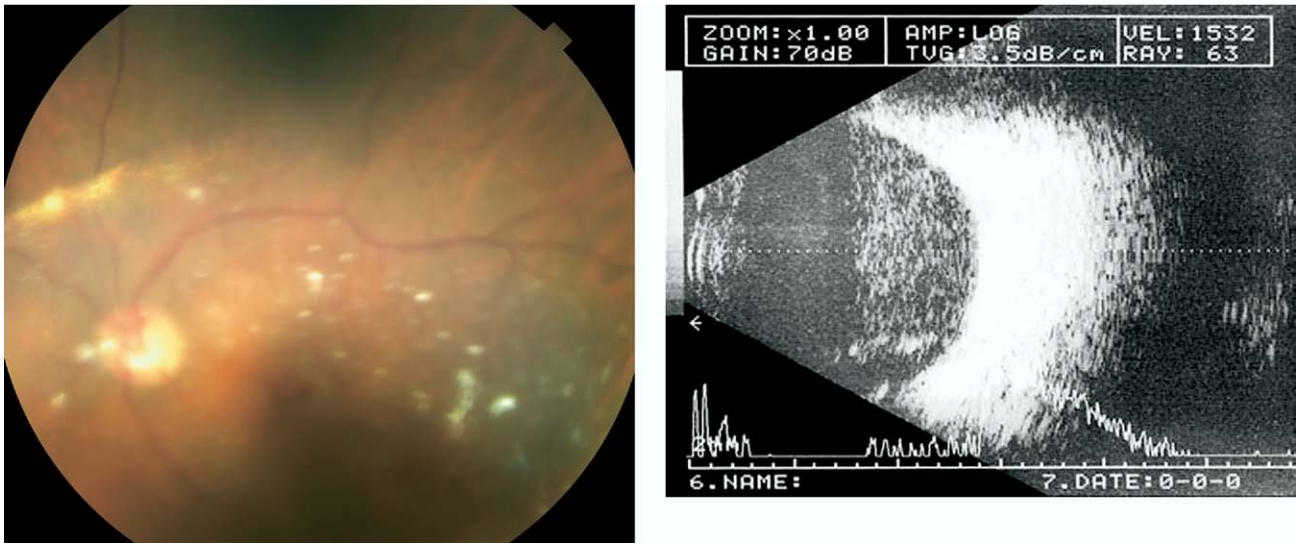

FIGURE 2. Images showing noninfectious endophthalmitis after intravitreal triamcinolone. (Left) Fundus photograph showing vitreous haze and triamcinolone crystals in a patient. (Right) B-scan ultrasonography image showing intravitreal triamcinolone crystals of a patient when no view to the posterior segment was appreciated.

TABLE 3. Snellen Visual Acuity and Central Foveal Thickness Measurements on the Day of Injection, Presentation, Clearance, and Follow-up for Patients in Whom Noninfectious Endophthalmitis Developed after Intravitreal Triamcinolone Administration

		Day of Injection		Presentation		Clearance			Follow-up		
Case No.	Cause	VA	CFT (μm)	Day	VA	Day	VA	CFT (μm)[a]	Day	VA	CFT (μm)
1	Diabetes	20/60	403	3	20/20000	30	20/50	413	44	20/30	334
2	Diabetes	20/100	276	1	20/2000	15	20/80	—	36	20/60	203
3	BRVO	20/400	552	3	20/2000	14	20/200	368	35	20/125	277
4	CAR	20/40	453	2	20/60	23	20/60	237	63	20/30	198
5	ERM	20/2000	546	2	20/20000	21	20/2000	364	39	20/400	413
6	Diabetes	20/100	312	1	20/2000	19	20/80	237	61	20/60	255
7	Pseudophakia	20/50	506	3	20/2000	8	20/60	—	28	20/50	380
8	Pseudophakia	20/160	593	1	20/20000	9	20/160	302	44	20/60	256
9	Diabetes	20/60	590	2	20/200	5	20/50	—	20	20/30	338
10	ERM	20/400	366	3	20/20000	21	20/40	347	40	20/30	360
11	Diabetes	20/400	390	2	20/20000	12	20/100	308	33	20/70	262
12	Uveitis	20/200	376	1	20/20000	7	20/100	222	189	20/100	275
13	Diabetes	20/100	362	2	20/20000	13	20/200	—	91	20/60	266
14	ERM	20/60	322	1	20/20000	14	20/60	308	117	20/50	310
15	BRVO	20/50	214	2	20/60	14	20/30	221	57	20/20	201
16	Pseudophakia	20/80	550	1	20/200000	22	20/200	—	52	20/40	386
17	Diabetes	20/80	530	3	20/2000	10	20/80	—	31	20/60	404
Average values		20/132	432	1.9	20/4444	15.1	20/99	302	57.6	20/56	301
Standard deviations		0.82 ± 0.45 (logMAR)	± 118		2.35 ± 0.98 (logMAR)		0.70 ± 0.41 (logMAR)	± 66		0.44 ± 0.30 (logMAR)	± 71

BRVO = branch retinal vein occlusion; CAR = cancer-associated retinopathy; CFT = central foveal thickness; ERM = epiretinal membrane; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.

[a]Not all patients underwent optical coherence tomography at the clearance visit. The mean decrease in foveal thickness of the 11 of 17 patients measured 109 μm less than that of the initial scan.

A recent report compared the incidence of noninfectious endophthalmitis after injection with commercially available triamcinolone acetonide vs preservative-free triamcinolone (sodium chloride, monobasic, and dibasic sodium phosphate, 0.04% polysorbate 80, water).[16] The incidence of noninfectious endophthalmitis in the preservative-free group was

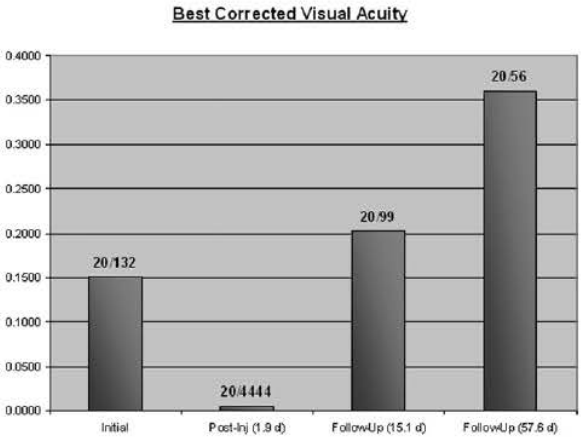

FIGURE 3. Bar graph showing mean best-corrected visual acuity (Snellen acuity and logarithm of the minimum angle of resolution units) on the day of injection, presentation, clearance, and follow-up for patients in whom noninfectious endophthalmitis developed after intravitreal triamcinolone administration.

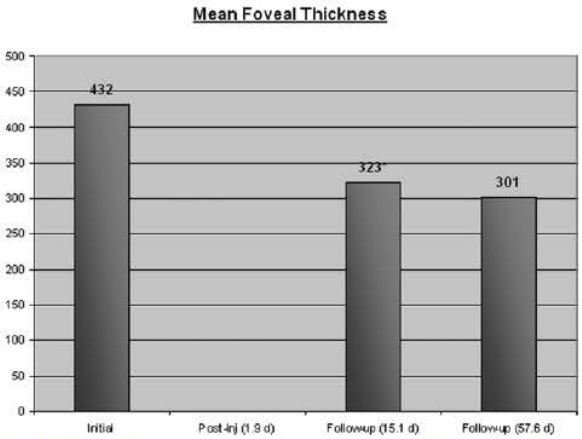

FIGURE 4. Bar graph showing mean central foveal thickness (in micrometers) on the day of injection, presentation, clearance, and follow-up for patients in whom noninfectious endophthalmitis developed after intravitreal triamcinolone.

1.9% (n = 646 injections) vs 7.3% (n = 69 injections) in the commercially available triamcinolone. The incidence of noninfectious endophthalmitis occurring with preservative-free triamcinolone in this study demonstrates that this entity still occurs despite the removal of the benzyl alcohol, and at a rate similar to that of previously published reports with commercially available triamcinolone. The very high incidence of noninfectious endophthalmitis in the commercially available triamcinolone group in this retrospective series is curious and may be related to the disparity of the number of injections between the 2 groups (n = 646 vs n = 69). Prospective studies comparing preservative-free triamcinolone vs commercially available triamcinolone would elucidate further the effect of benzyl alcohol on noninfectious endophthalmitis.

In 4 of the 17 patients during the 5.5-year span of the study, noninfectious endophthalmitis developed within a period of 7 weeks. These 4 patients were administered injections of intravitreal triamcinolone from the same lot number. The cluster of cases is suspicious, and there have been previous reports with similar experiences; Nelson and associates reported 7 cases in a span of 5 weeks.[12] This leads us to speculate that the triamcinolone formulation in these particular lots created an inflammatory reaction, potentially related to an unknown additive in the solution or an unidentified bacterial endotoxin remaining despite sterilization.[12]

One patient in this series was reinjected with intravitreal triamcinolone on 3 separate occasions to the same eye after the episode of noninfectious endophthalmitis. No inflammatory reaction or dispersion of triamcinolone crystals was observed in the subsequent injections, which may lead us to believe the triamcinolone formulation in that bottle or lot, may be more responsible for the inflammatory reaction than the individual's immune response.

Another suggested mechanism of noninfectious endophthalmitis is thought to be the result of the impaction of the drug into the barrel of a 30-gauge needle, resulting in high-velocity dispersion into a vitreous suspension at time of injection into the eye.[10] Microscopy of vitreous samples in reports reveal a dense collection of triamcinolone crystals with no cells, suggesting that clinical signs were a result of dispersed triamcinolone particles.[13,17] However, in this and other studies, noninfectious endophthalmitis occurred in patients with the use of both 27- and 30-gauge needles for injection.

The diagnosis of noninfectious endophthalmitis is a critical judgment by the clinician that may avoid unnecessary invasive treatments. Nine patients in this study received treatment for presumed infectious endophthalmitis in this study based on the severity of clinical findings at presentation. The gram stains and cultures of these 9 patients had negative results, and these were presumed to be noninfectious cases in hindsight after rapid recovery of vision and inflammation. The lack of growth in these cultures does not exclude the possibility of infectious endophthalmitis, because 18% of vitreous samples from the Endophthalmitis Vitrectomy Study had culture-negative results.[18] The treatment with intravitreal antibiotics in our series occurred earlier in the study, and if these cases presented today, very close observation may have been determined based on our clinical experience with noninfectious endophthalmitis. It is notable that 2 patients (0.13%) of the approximately 1,600 injections of intravitreal triamcinolone were reported by the physicians to have developed infectious endophthalmitis after intravitreal triamcinolone. These patients had a distinct presentation and clinical course, with a later onset, presence of ocular pain, and a slow visual recovery. However, if a case is questionable, it is

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