INCREASED INCIDENCE OF STERILE ENDOPHTHALMITIS AFTER INTRAVITREAL TRIAMCINOLONE ACETONIDE IN SPRING 2006

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Purpose: To compare the incidence of sterile endophthalmitis after intravitreal triamcinolone acetonide injections during a 6 month period in 2006 to the same period in 2005 and determine the incidence after switching to intravitreal preservative-free triamcinolone acetonide.

Methods: Retrospective multicenter interventional case series in which patients receiving intravitreal triamcinolone acetonide at three institutions from March 2005 to August 2005 and from March 2006 to August 2006 and intravitreal preservative-free triamcinolone acetonide from late summer 2006 through February 2007 were reviewed for the development of sterile endophthalmitis.

Results: From March 2005 to August 2005, the rate of sterile endophthalmitis was 0% at all institutions. From March 2006 to August 2006, a statistically significant increase in sterile endophthalmitis was seen at all institutions with frequencies of 3.5% to 6.3% ($P < 0.001$). With transition to preservative-free triamcinolone acetonide, sterile endophthalmitis over the next 6 months decreased to 0% at two sites and to 2.5% (from 5.5%) at the third institution ($P < 0.009$).

Conclusions: A statistically significant increase in the rate of sterile endophthalmitis after intravitreal triamcinolone acetonide was seen in a 6 month period in 2006 when compared with the same period in 2005. Transition to preservative-free triamcinolone acetonide produced a frequency of sterile endophthalmitis similar to 2005.

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Intravitreal triamcinolone acetonide (TA) is routinely used in the treatment of macular edema from various conditions including venous occlusive disease, refractory diabetic macular edema, uveitis, and cystoid macular edema.[1–4] Additionally, intravitreal TA is used as an adjunctive therapy in the treatment of proliferative diabetic retinopathy and age-related macular degeneration.[5,6] Increased intraocular pressure and cataract progression are the most common adverse effects associated with intravitreal TA.[7] Other rarer complications include retinal detachment, vitreous hemorrhage, pseudohypopyon, and endophthalmitis.

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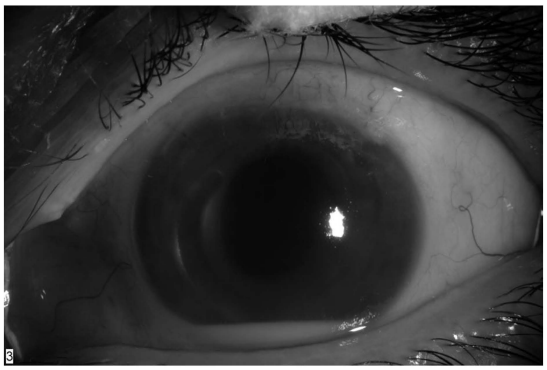


Fig. 1. Sixty-eight year old female presenting with sterile endophthalmitis 48 hours after an intravitreal injection of triamcinolone acetonide. Vision had decreased to hand motions from 20/300. A vitreous tap with injection of intravitreal antibiotics was preformed. Cultures were negative. Vision returned to baseline 5 days after initial injection.

Noninfectious or sterile endophthalmitis has been reported after intravitreal TA.[8–13] Patients present with an acute inflammatory reaction shortly after injection (Figure 1). In most cases, visual acuity is significantly decreased but patients rarely complain of pain or discomfort. Cultures, if taken, are negative and most patients improve quickly with good visual prognosis. Whether sterile endophthalmitis is an inflammatory reaction to the drug or its vehicle or if it represents a true infection with negative cultures remains unclear. Rates of sterile endophthalmitis have been reported from 0.87% to 7.3%.[8,9]

In the spring of 2006, the authors noted an increasing occurrence of sterile endophthalmitis in their practices and switched to intravitreal compounded preservative-free triamcinolone acetonide (PFTA) towards the end of summer of 2006. Herein, we determined the incidence of sterile endophthalmitis after intravitreal TA during a 6 month period in 2006 to the same time period in 2005. Additionally, we examined the incidence of sterile endophthalmitis after switching to intravitreal PFTA.

Methods

This multicenter retrospective review was carried out at three clinical centers (Bascom Palmer Eye Institute, University of Miami, Miami, FL; Duke University Eye Center, Duke University Medical Center, Durham, NC; Retina Health Center, Fort Myers, FL) after receiving Institutional Review Board approval. The sites were selected because of large volume of intravitreal TA done by multiple physicians at these locations, increasing sample size and reducing bias. Charts of all patients who received intravitreal TA between March to August 2005 and March to August 2006 as identified by ICD-9 codes were reviewed. Additionally, charts of all patients who received intravitreal PFTA from August or early September 2006 through February 2007 were reviewed. Patients who received intravitreal TA as an adjunct to a surgical procedure or who had undergone a surgical procedure within the 30 days preceding injection were excluded from the study.

Patients were included in the study if they experienced symptoms of sterile endophthalmitis within 7 days of injection. Sterile endophthalmitis was defined as presence of inflammation in the anterior chamber and/or vitreous cavity within 7 days after intravitreal TA or PFTA with the absence of organisms on gram stain and negative intraocular cultures, if obtained. If cultures were not obtained, patients were defined as having sterile endophthalmitis if there was clearance of inflammation and improvement in vision with no treatment or with only topical medication treatment within the next 30 days. Clinical exam findings, ocular history, indication for intravitreal TA or PFTA, time to presentation and treatment were recorded.

Injections of intravitreal TA or PFTA were performed by multiple physicians at all sites. Injections were performed according to accepted techniques[14] and included topical or subconjunctival anesthesia under aseptic technique, disinfection by instillation of 5% povidone–iodine in the conjunctival sac, and a sterile lid speculum. Four milligrams of TA in 0.1 mL was injected into the vitreous cavity 3.5 to 4 mm posterior to the limbus. In the spring of 2005 and 2006, single-use vials of Kenalog-40 (Bristol-Myers Squibb, Princeton, NJ) were used at all three sites. Kenalog-40 contains 0.99% benzyl alcohol, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80 for buffering and isotonicity. Supernatant was neither routinely removed from the TA, nor was the TA filtered. Perfusion and intraocular pressure were monitored after injection. Patients were instructed to use a topical antibiotic 3 to 4 days after the procedure at all three sites.

PFTA (New England Compounding Pharmacy, Framingham, MA) was injected in an identical manner after summer 2006 at two sites (BPEI and Duke). One site (Retinal Health Center) removed supernatant from the PFTA before injection. Crystals of PFTA were allowed to precipitate out in the syringe against the plunger and clearer supernatant was discarded before injection. This was done to reduce the amount of any other substance other than triamcinolone from the injection.

Upon presentation with signs of sterile endophthalmitis, patients were treated according to the discretion of their physician. Patients were either closely observed with or without topical corticosteroid and/or

Table 1. Sterile Endophthalmitis After Intravitreal Triamcinolone Acetonide (March 2006–August 2006) Patient Characteristics

Patient No.	Age (yrs)	Lens Status	Indication For IVTA	Time to Presentation (h)	Hypopyon	Treatment	Past Ocular History	Return to Initial VA
1	72	PCIOL	cme	12–24	Yes	gtts	trauma	Yes
2	68	ACIOL	cme	48–72	Yes	tap & inj	pseudophakic cme	Yes
3	67	PCIOL	cme/dme	12–24	Yes	tap & inj	dme/cme	Lost to F/U
4	79	PCIOL	dme	72–96	Yes	gtts	dme	Yes
5	NR	PCIOL	cme	24–48	Yes	gtts	rd repair retinoschisis	Yes
6	78	PCIOL	cme/amd	48–72	No	gtts	amd	Yes
7	77	PCIOL	cme	24–48	Yes	gtts	nvg, crvo	Yes
8	76	PCIOL	cme	24–48	Yes	gtts	coag pseudophakic cme	Yes
9	59	PCIOL	hypotony	24–48	Yes	gtts	trauma, rd repair	No
10	NR	PCIOL	cme	24–48	No	ppv-scheduled	sickle cell retinopathy	Yes
11	55	PCIOL	uveitic cme	12–24	Yes	tap & inj	uveitic cme	No
12	76	Phakic	cme	12–24	No	gtts	post op ppv	No
13	48	PCIOL	cme	24–48	Yes	gtts	trauma, rd repair	Yes
14	47	Phakic	cme	48–72	Yes	gtts	post op ppv	Yes
15	NR	Phakic	dme	24–48	No	gtts	dme	Yes
16	NR	Phakic	uveitic cme	12–24	No	gtts	uveitic cme	Yes
17	58	PCIOL	cme	12–24	Yes	gtts	rd repair	Yes
18	57	PCIOL	cme	12–24	Yes	tap & inj	rd repair	No
19	91	PCIOL	brvo	>96	No	gtts	brvo	Yes
20	100	PCIOL	amd	24–48	No	tap & inj	amd	Yes
21	74	PCIOL	erm	72–96	No	gtts	erm	Yes
22	57	PCIOL	cme	24–48	Yes	tap & inj	post op cme	No
23	54	PCIOL	cme	12–24	Yes	tap & inj	macular translocation surgery, POHS	Yes
24	46	PCIOL	uveitic cme, hypotony	>96	No	gtts	uveitis, hypotony	Yes
25	58	PCIOL	cme	24–48	Yes	tap & inj	coag, post op trab	Yes
26	NR	PCIOL	cme	48–72	No	diamox	retinal degeneration, cme	Yes
27	51	Phakic	uveitic cme	12–24	Yes	gtts	uveitis	Lost to F/U

VA, visual acuity; PCIOL, posterior chamber intraocular lens; ACIOL, anterior chamber intraocular lens; NR, not recorded; cme, cystoid macular edema; dme, diabetic macular edema; amd, age-related macular edema; rd, retinal detachment; nvg, neovacular glaucoma; brvo, branch retinal vein occlusion; crvo, central retinal vein occlusion; trab, trabeculectomy; erm, epiretinal membrane; POHS, presumed ocular histoplasmosis; coag, chronic open angle glaucoma; ppv, pars plana vitrectomy; gtts, topical medication drops; tap & inj, tap and injection; F/U, follow-up.

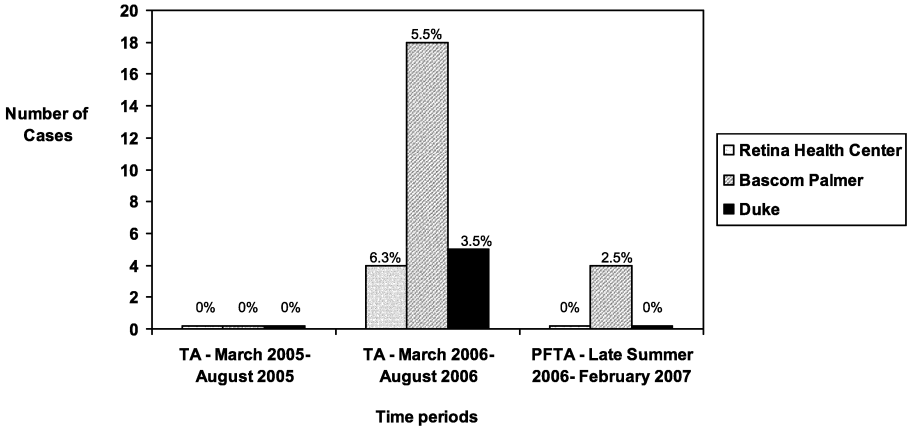
antibiotic drops or underwent a vitreous tap with intravitreal antibiotics. In one case, a patient underwent a pars plana vitrectomy; however, this procedure was previously scheduled before the injection as a result of other retinal pathology. Patients were then followed at intervals determined by their treating physician.

A vial of Kenalog-40 from the same lot as a vial known to cause a case of sterile endophthalmitis in a patient in this study was forwarded to Arjun Srinivasan, MD, at the Centers for Disease Control and Prevention, Atlanta, GA and tested for the presence of endotoxin. Statistical analysis was performed with the exact Mantel–Haenszel chi-square test, stratifying by clinic.

Results

In the 6 month period between March 2005 and August 2005, 445 injections of intravitreal TA were performed and no cases of sterile endophthalmitis were identified. From March 2006 to August 2006, 532 injections were performed and 27 cases of sterile endophthalmitis occurred. Use of PFTA began in late August–early September 2006 at all three sites. A total of 308 intravitreal PFTA injections were administered through February 2007 and four cases of sterile endophthalmitis were found.

Twenty-seven eyes of 27 patients developed sterile endophthalmitis after an intravitreal injection of TA during the period of March to August 2006 (Table 1). The rate of sterile endophthalmitis after intravitreal TA was 6.3% at Retinal Health Center, 5.5% at Bascom Palmer Eye Institute, and 3.5% at Duke University Eye Center. This increase was found to be statistically significant when compared with the same time period 1 year previous ($P < 0.001$) (Figure 2). The rate of sterile endophthalmitis with data combined from all three sites was 5.1%, which was statistically



TA – Triamcinolone Acetonide, PFTA – Preservative-free Triamcinolone Acetonide

Fig. 2. Incidence of sterile endophthalmitis by site.

significant ($P < 0.001$). Ages ranged from 46 to 100 years old and there were 13 males and 14 females. One patient had an anterior chamber intraocular lens, 21 patients had a posterior chamber intraocular lens and 5 were phakic. Treatment with intravitreal TA was given for cystoid macular edema in 19 patients, four of whom had uveitic cystoid macular edema, for diabetic macular edema in three patients, for age-related macular degeneration in two patients, and for an epiretinal membrane, a branch retinal vein occlusion and hypotony in one patient each. Hypopyons were present in 17 eyes at presentation. Anterior chamber inflammation could be seen in 26 eyes and greater than 1+ vitreous haze was noted in 26 eyes.

Seventeen eyes were treated with close observation and topical medications, eight patients underwent vitreous tap with intravitreal antibiotic injection, one patient was treated with topical medications and then underwent a pars plana vitrectomy with epiretinal membrane removal 4 days after injection as was previously scheduled before the injection, and one patient with retinal degeneration was followed with close observation and continuation of oral acetazolamide. All gram stains and cultures obtained were negative. Twenty of the patients returned to at least preinjection visual acuity, five patients did not return to preinjection vision and two patients were lost to follow-up. In those five patients whom preinjection vision was not obtained, their poorer vision was thought to be due to their underlying ocular pathology and not inflammatory causes.

One vial of Kenalog-40 from the same lot as a vial that had caused a sterile endophthalmitis reaction in a patient in our study was forwarded to the Centers for Disease Control and Prevention and tested by Dr. Arjun Srinivasan for presence of an endotoxin. Levels in the sample were found to be negative to less than 2 EU/mL which is the lowest level that can be detected in a solution of TA. The Food and Drug Association has set a limit of 0.5 EU/mL for endotoxins in injectable solutions. However, because of its opacities, the solution of TA can only be analyzed accurately for the presence of endotoxins to levels of 2 EU/mL. (Arjun Srinivasan, personal communication).

In late August 2006 or early September 2006, all three sites began using PFTA. Two of the three sites had no further cases of sterile endophthalmitis during the next 6 month period. One site had four cases of sterile endophthalmitis in 4 eyes of 4 patients or a rate of 2.5% at this institution (Table 2). This site preformed 53% of the reviewed injections with PFTA

Table 2. Sterile Endophthalmitis After Preservative-Free Triamcinolone Acetonide Patient Characteristics

Patient No.	Age (yrs)	Lens Status	Indication For IVTA	Time to Presentation (h)	Hypopyon	Treatment	Past Ocular History	Return to Initial VA
28	77	PCIOL	cme	48–72	No	gtts	coag brvo	Yes
29	58	PCIOL	cme	24–48	Yes	gtts	angioma, rd repair	No
30	73	PCIOL	cme	24–48	No	gtts	rd repair	No
31	71	PCIOL	cme	24–48	Yes	gtts	rd repair	Yes

PCIOL, posterior chamber intraocular lens; cme, cystoid macular edema; gtts, topical medication drops; coag, chronic open angle glaucoma; brvo, branch retinal vein occlusion; rd, retinal detachment; IVTA, intravitreal triamcinolone acetonide; VA, visual acuity.

and did not remove supernatant before injection with PFTA. The reduction in sterile endophthalmitis was statistically significant ($P = 0.009$) when compared with the previous 6 month period from March 2006 to August 2006. When compared with the March to August 2005 time period, this increase with PFTA was statistically significant ($P = 0.013$). Ages ranged from 58 to 77 years and there were two males and two females. All patients had posterior chamber intraocular lens and all had received treatment for cystoid macular edema. All presented within 24 to 72 hours after injection with symptoms. Hypopyons were present in two of the patients. Three of four patients had anterior chamber cell and significant vitreous haze was present in three of the four patients. All were followed with close observation and topical medications. Half regained preinjection vision. All four patients had undergone previous intraocular surgery with three having retinal detachment repair and one with recent glaucoma surgery.

Discussion

Intravitreal TA is used to treat retinal pathology of many etiologies.[1–6] Endophthalmitis is a potential complication of intravitreal TA and has been described in three forms; infectious endophthalmitis, noninfectious or sterile endophthalmitis, and pseudoendophthalmitis. Patients with acute infectious endophthalmitis present with decreased vision and pain at a median of 7.5 days after intravitreal TA.[15] This devastating complication usually has a prolonged recovery time, poorer visual outcomes and is estimated to occur at an incidence of 0.43% to 0.87%.[11,15] In contrast, pseudoendophthalmitis is caused by migration of TA crystals into the anterior chamber, not infection. Patients present with no pain, minimal visual symptoms and are more likely to be pseudophakic or aphakic with a peripheral iridotomy. Symptoms resolve without treatment and within a few days.[16,17]

Patients with noninfectious or sterile endophthalmitis present with an acute inflammatory reaction shortly after injection of intravitreal TA or PFTA. Visual acuity is usually significantly decreased but patients rarely complain of pain or discomfort. Cultures, if taken, are negative. Patients improve quickly with good visual prognosis. Sterile endophthalmitis rates have been reported from 0.87% to as high as 7.3% as reported by Maia et al.[8,9] It should be noted that patients in the study reported by Maia et al received intravitreal TA from two different manufacturers, Ophthalmos Laboratories, San Paulo, Brazil and Bristol–Myers Squibb, Princeton, NY.[9] Patients in this study were treated with intravitreal TA from Bristol–Myers Squibb only.

There are several possible explanations for the inflammatory changes associated with sterile endophthalmitis we observed in the present study. The commercially prepared TA, Kenalog-40, has 0.99% benzyl alcohol, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80 in its suspension and is buffered with sodium hydroxide or hydrochloric acid to a pH of 5.0 to 7.5. Benzyl alcohol is a bacteriostatic preservative that has been theorized to be a potential cause of an inflammatory response, prompting some providers to decant supernatant or filter the TA before injection.[18,19] Sterile endophthalmitis can still occur, however, as Carrero et al recently reported sterile endophthalmitis cases despite removal of 90% of benzyl alcohol by filtration before injection.[20] The role of pH of the intravitreal solution is uncertain. Although the range of pH in Kenalog-40 is broad, nonphysiologic pH is present in some approved intravitreal medications such as ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) which has a pH of 5.5.[21]

The preservative-free formulation of triamcinolone uses United States Pharmacopeia micronized triamcinolone suspended in a buffered polyethylene glycol solution. Although cases of sterile endophthalmitis still occurred in our study after treatment with preservative free triamcinolone, rates were lower. Sterile endophthalmitis has also been reported after PFTA by Maia et al.[9] As sterile endophthalmitis can occur despite removal of almost all benzyl alcohol[20] or in preservative-free formulations,[9] it is unlikely that the preservative is the sole cause of sterile endophthalmitis.

Sterile solutions can contain bacterial endotoxins that may incite an inflammatory response. An epidemic outbreak of diffuse lamellar keratitis after LASIK was found to be caused by endotoxins released by gram negative biofilms in a sterilizer.[22] A bacterial endotoxin contaminant could persist in the vehicle or vial of a drug and induce an inflammatory response, despite preparation of the drug under sterile conditions. One vial of Kenalog-40 from the same lot as a vial that had caused a sterile endophthalmitis reaction in a patient in our study was forwarded to the Centers for Disease Control and Prevention and was found to be negative for endotoxin to the extent of detection in an opaque solution; however, this level is still higher than the limit set by the Food and Drug Association for injectable solutions (Arjun Srinivasan, personal communication). If endotoxins were the cause of sterile endophthalmitis, one would expect cases to be clustered nearer to each other as medications from the same lots or lots produced close together were used. As all three centers were located in the southeast, it is

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