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Aflibercept-Related Sterile Inflammation

Within the first 3 months after approval of aflibercept (Eylea; Regeneron, Inc., Tarrytown, NY) by the US Food and Drug Administration on November 18, 2011, a cluster of injection-related sterile intraocular inflammation was reported, raising safety concerns. The American Society of Retina Specialists formed a Therapeutic Surveillance Subcommittee as an independent taskforce to monitor and report such events to the greater ophthalmology community.

The Therapeutic Surveillance Subcommittee surveyed retina specialists regarding event details (Tables 1–3; available at <http://www.aaojournal.org>). The survey, collected from February 2012 until the end of March 2012, identified 15 cases of presumed sterile inflammation after intravitreal aflibercept injection. All but 1 case occurred in patients treated for neovascular age-related macular degeneration, its only US Food and Drug Administration-approved indication during that time. Consistent with this demographic, the majority of patients were elderly, Caucasian, and pseudophakic. One patient had a history of postoperative uveitis in the fellow eye after vitrectomy. No other patients had a history of uveitis, which may be associated with injection-related sterile inflammation.¹

All injections were performed with standard techniques based on survey responses. Povidone-iodine 5% was applied before injection in all cases. Thirteen of 15 eyes were administered topical anesthesia, and 2 eyes were given subconjunctival lidocaine. All eyes were injected with the Becton Dickinson (Franklin Lakes, NJ) 1-ml Luer-Lok syringe included in the aflibercept packaging. The majority of eyes were injected in the superotemporal quadrant (12 of 15 eyes) and with a 32-G needle (13 of 15 eyes), while the remainder were injected in the inferotemporal quadrant (3 of 15 eyes) and with a 30-G needle (2 of 15 eyes). These differences likely represent individual practice pattern differences and are not an implication of these techniques.

Five physicians practicing in the Northeast, the Southeast, and the Southern United States reported cases of sterile inflammation. Three physicians practiced in the same retina group, and 9 of 15 cases (60%) were reported by a single retina specialist in this practice, consistent with a clustering pattern previously reported with other intravitreal therapies.² All cases were attributed to 5 separate drug lots, with 3 lots accounting for 13 of 15 cases. All but 1 patient experienced symptoms within 3 days. Visual acuity generally recovered to baseline levels with nearly identical mean visual acuities at baseline (0.4 logarithm of the minimum angle of resolution) and after resolution (0.32 logarithm of the minimum angle of resolution) and a mean time to resolution of 30 days. No patient lost >1 Snellen line of visual acuity.

In contrast with previous reports associating sterile inflammation from other intravitreal therapies with painless loss of vision,³ 9 of these 15 aflibercept-related cases (60%) presented with pain. Redness was noted only in eyes presenting with pain and in 6 of these 9 painful cases. It is possible that aflibercept-related sterile inflammation may be associated with higher rates of pain than previously reported. Alternatively, this difference may reflect differences in the treatment cohorts. Distinguishing between infectious and sterile endophthalmitis was at the discretion of the treating physician. Although all reported cases were culture negative, some of the cases treated with intravitreal antibiotics may have represented culture-negative infectious endophthalmitis, which is associated with increased pain, and not true sterile inflammation. However, 5 of 9 cases associated with pain were treated with vitreous tap and intravitreal antibiotic injection, and the remaining 4 cases were treated with topical steroids only, suggesting that potential misclassification of these symptoms is not fully responsible for this difference. It is likely that patients presenting with more pain were biased toward an initial diagnosis of infectious endophthalmitis (treated with tap/antibiotic injection) compared with those patients managed with topical steroids alone.

Small sample size, clinical variation, and the limitations of voluntary reporting preclude definitive conclusions. Subgroup analysis did not detect any variables significantly affecting visual outcome or number of days to resolution (Tables 4 and 5; available at <http://www.aaojournal.org>). This letter serves as a descriptive case series to better understand the clinical characteristics of a cluster of aflibercept-related sterile inflammation. The manufacturer reports that approximately 30 000 injections had been administered during the reporting period, corresponding with a sterile inflammation rate of approximately 0.05%. Although there may certainly be additional, nonreported cases resulting in a higher actual rate, this frequency lies within the range documented by pivotal, prospective trials with aflibercept and other intravitreal agents and by retrospective analyses (Tables 6 and 7; available at <http://www.aaojournal.org>). The manufacturer continued to closely observe without public recalls or testing, and use of aflibercept has continued without persistent reports of unexpected rates of complications. The American Society of Retina Specialists Therapeutic Surveillance Subcommittee strongly urges practitioners to actively participate in postmarket surveillance of drug- and device-associated adverse events.

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Transiency of Fleischer's Rings in Forme-Fruste Keratoconus

Keratoconus has characteristic biomicroscopic signs that increase in prevalence as the disease progresses. Vögt striae and Fleischer's ring are considered pathognomonic¹; however, no comment has been made regarding their relative permanency. This report describes the bilateral disappearance of Fleischer's rings in a patient with forme-fruste keratoconus after orthokeratology.

In June 2010, a 26-year-old woman came to our clinic for an orthokeratology assessment. Ocular history was negative for allergy, trauma, and surgery. General health was excellent; she did not take any medications. There was no family history of ocular disease. Refraction and best-corrected visual acuities (BCVAs) had remained stable for 10 years: Right eye, $-1.00/-0.25 \times 75$ (20/15); left eye, $-1.00/-0.25 \times 130$ (20/15). Slit-lamp biomicroscopy revealed bilateral, inferonasal, paracentral corneal iron lines, consistent with Fleischer's rings (Fig 1A, B, available at <http://aaojournal.org>). There were no other signs of keratoconus; retinoscopy revealed the absence of scissoring reflexes in both eyes.

Baseline corneal topography demonstrated subtle inferior-superior axial power asymmetry (Fig 1C, D, available at <http://aaojournal.org>); the corneal apices were decentered inferonasally, consistent with the location of Fleischer's rings (both eyes). Videokeratographic indices were used to quantify baseline corneal asymmetry (Table 1, available at <http://aaojournal.org>); 1 index was beyond normative ranges in the right eye and 4 parameters were outside expected levels in the left eye. Central-corneal thicknesses were: right eye, 535 μm ; left eye, 512 μm .

Given these corneal findings, a corneal specialist assessed the patient's suitability for orthokeratology. Ophthalmologic opinion was that given the long-term refractive stability and excellent BCVAs, forme-fruste keratoconus did not contraindicate orthokeratology.

In July 2010, the patient commenced overnight-wear of Paragon CRT (Paragon Vision Sciences; Mesa, AZ) orthokeratology lenses. The corneal area inclusive of the Fleischer's rings was overlaid by the lens optic zone (Fig 1E, F, available at <http://aaojournal.org>). After 3 months, unaided vision was 20/10 in the right eye and 20/10 in the left. Videokeratographic maps demonstrated large treatment zones with mild inferior displacement. Fleischer's rings were absent; each cornea had a normal biomicroscopic appearance (Fig 2, available at <http://aaojournal.org>). This patient has been successfully undertaking orthokeratology without adverse event for more than 2 years; the Fleischer's rings have not reappeared.

Superficial corneal iron lines develop in physiologic and pathologic contexts. The Hudson-Stähli line occurs in the aging cornea. Refractive procedures including radial keratotomy, intrastromal corneal ring, and LASIK can induce corneal iron lines. Ocular disease also produces characteristic pigmented corneal arcs; Stocker's line for pterygia, Ferry's line at filtering blebs, and Fleischer's ring in keratoconus. Although the emergence of 'new' iron lines is well-documented, this is the first report describing the loss of a Fleischer's ring.

Fleischer's rings consist of ferritin deposits within basal corneal epithelial cells that form at sites of local discontinuity in curvature.² Although the reported prevalence of the rings in keratoconus is 87%,³ their pathogenesis remains unclear.

Orthokeratology involves using reverse-geometry, rigid, gas-permeable contact lenses to reduce manifest refractive error.⁴ In myopic orthokeratology, the central zone of the lens imparts a positive hydraulic pressure to induce corneal flattening; the epithelium is compressed such that basal cells assume a rounded configuration compared with their normally elongated morphology. Both the decentered corneal apices and region possessing Fleischer's rings were therefore remodeled to a flatter curvature. Although only a low myopic correction, this degree of remodeling was sufficient to induce the necessary, and presently poorly understood, epithelial changes to reverse the iron deposition.

Should the disappearance of a Fleischer's ring be specifically related to a reduction in corneal apical power, similar effects would be expected after corneal cross-linking for keratoconus; there are currently no published reports to this effect. A further possibility is that orthokeratology alters basal epithelial cell turnover. This hypothesis is supported by evidence that orthokeratology increases epithelial cell proliferation rates.⁵ Further work is required to elucidate the mechanism underlying the observation.

This case highlights that Fleischer's rings can occur with mild topographic asymmetry, average central corneal thickness, stable refraction, normal BCVA, normal retinoscopic reflexes, and without other signs of keratoconus. This report also demonstrates that Fleischer's rings are not permanent. Practitioners should be aware of the apparent transiency of this important diagnostic sign, in their evaluation of patients with the condition.

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Reports

Table 1. Baseline Demographic Characteristics

Pt ID	Age	Gender	Race	Disease Treated	Eye Treated	Preinject VA	Prior Anti-VEGF?	# Prior Eylea	Lens Status	Medical Conditions	Ocular Comorbidities	Fellow Eye VA
1	69	F	Caucasian	NVAMD	OS	20/80 +2	Yes	0	Phakic	HTN, chol, afib	None	HM
2	83	M	Caucasian	NVAMD	OS	20/40 -2	Yes	0	Pseudo	DM, HTN, chol	POAG	20/50 +2
3	79	F	Caucasian	NVAMD	OS	20/20 -2	Yes	0	Pseudo	HTN, chol, COPD	None	20/20
4	88	M	Caucasian	NVAMD	OS	20/50 +2	Yes	0	Pseudo	HTN	None	CF 1 ft
5	76	F	Caucasian	NVAMD	OS	20/40 -2	Yes	0	Pseudo	HTN	POAG	20/30 +1
6	88	M	Caucasian	NVAMD	OS	20/70	Yes	0	Pseudo	HTN, CAD	None	20/25
7	79	F	Caucasian	NVAMD	OD	20/25	Yes	0	Phakic	DM, afib, COPD	POAG	20/40
8	80	F	Caucasian	NVAMD	OD	20/40	Yes	0	Pseudo	NIDDM, HTN	PVD	20/40
9	85	F	Caucasian	NVAMD	OS	20/40	Yes	0	Pseudo	Chol, HTN	None	20/30 +2
10	81	M	Caucasian	NVAMD	OD	20/50 -2	Yes	1	Pseudo	Afib, HTN, chol	None	20/40 +1
11	82	F	Caucasian	NVAMD	OD	20/25	Yes	0	Pseudo	NIDDM, HTN	PVD, lattice	20/63
12	75	M	Caucasian	NVAMD	OD	CF 2 ft	Yes	2	Pseudo	Chol, HTN, CAD	None	20/40 +2
13	80	M	Caucasian	NVAMD	OD	20/50 -2	Yes	2	Pseudo	HTN, chol	None	20/25
14	85	M	Caucasian	NVAMD	OD	20/30 +2	Yes	1	Pseudo	Hypothyroid, BPH	None	20/25 -2
15	46	M	Middle Eastern	Myopic CNV	OS	20/25 -3	Yes	2	Phakic	None	High myopia; lattice; h/o RD OD s/p repair 2009; h/o postop iritis OD	20/200

afib = atrial fibrillation; BPH = benign prostate hypertrophy; CAD = coronary artery disease; CF = count fingers; chol = hypercholesterolemia; CNV = choroidal neovascularization; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HM = hand motion; HTN = hypertension; NIDDM = non-insulin-dependent diabetes mellitus; NVAMD = neovascular age-related macular degeneration; OD = right eye; OS = left eye; POAG = primary open angle glaucoma; pseudo = pseudophakic; RD = retinal detachment; VA = visual acuity.

Table 2. Injection Characteristics

Pt ID	Injection Date	Physician	Lot #	Anesthetic Delivery	Prep	Syringe Model	Needle Gauge	Quadrant Injected
1	12/1/11	A	1	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
2	12/6/11	A	2	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
3	12/6/11	B	2	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Inferotemporal
4	12/12/11	A	2	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
5	12/16/11	A	3	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
6	12/28/11	C	3	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Inferotemporal
7	1/3/12	A	2	topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
8	1/11/12	D	3	Subconjunctival	Povidone-iodine	BD 1 mL Luer-Lok	30G	Superotemporal
9	1/13/12	A	2	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
10	1/13/12	A	3	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
11	1/19/12	D	4	Subconjunctival	Povidone-iodine	BD 1 mL Luer-Lok	30G	Superotemporal
12	2/1/12	A	1	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
13	2/1/12	A	1	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal
14	2/2/12	B	1	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Inferotemporal
15	3/23/12	E	5	Topical	Povidone-iodine	BD 1 mL Luer-Lok	32G	Superotemporal

Lot #: 1 = 8073400005A; 2 = 8073400005; 3 = 8073400006; 4 = 73400006; 5 = 8073400014

BD = Becton Dickinson.

Note. Physician names arbitrarily assigned letter designation (A-E).

Table 3. Characteristics of Sterile Inflammation

Pt ID	Presenting Signs/Symptoms	Days after Injection	Management	Culture Obtained?	Organism	Days to Resolution	Final VA
1	Large floater, looking thru wax paper	1	Tap/inject	Y	NG	14	20/70 -2
2	Hazy vision	3	Tap/inject	Y	NG	30	20/40 -2
3	Blurry vision, heavy eye, floaters	2	Topical steroid	N	—	35	20/20
4	Curtain over vision, foggy	1	Tap/inject	Y	NG	35	20/50 -2
5	Pain, floaters, irritation, decrease vision	30	Topical steroid	N	—	14	20/50 +1
6	Blurry vision, pain, redness, floaters	3	Tap/inject	Y	NG	75	20/100
7	Cloud over eye, pain, redness	1	Tap/inject	Y	NG	30	20/30
8	Pain, decreased vision	2	Tap/inject	Y	NG	30	20/40
9	Pain, watery eyes, blurry vision, redness	1	Topical steroid	N	—	17	20/40 -2
10	Fog with decreased vision, pain, redness	3	Topical steroid	N	—	14	20/70 +2
11	Loss of vision, no pain	2	Topical steroid	N	—	14	20/32
12	Redness, light sensitive, sore eye	1	Tap/inject	Y	NG	28	20/40 -1
13	Cobwebs, decrease vision, floater, white blur	3	Topical steroid	N	—	28	20/40 -1
14	Pain, red eye, tear	1	Topical steroid	N	—	56	20/30
15	Floaters, decreased vision, mild ache	1	Tap/inject	Y	NG	Ongoing	20/25 -3

NG = no growth.

Table 4. Subgroup Analysis on Change in Visual Acuity

	N	Mean Δ VA (SD)	Min/Median/Max
Age (yrs)			
≤80	8	-0.21 (0.61)	-1.7/0/0.1
>80	7	0.06 (0.07)	0/0/0.15
P			0.088
Days to resolution			
≤28	7	-0.21 (0.66)	-1.7/0/0.15
>28	7	0.03 (0.06)	0/0/0.15
P			0.595
Lens status			
Phakic	3	0.01 (0.07)	-0.06/0/0.08
Pseudophakic	12	-0.11 (0.51)	-1.7/0/0.15
P			0.648
Prior aflibercept injections			
No	10	0.04 (0.07)	-0.06/0/0.15
Yes	5	-0.33 (0.77)	-1.7/0/0.15
P			0.245
Management			
Tap/inject	8	-0.19 (0.61)	-1.7/0/0.15
Topical steroids	7	0.04 (0.08)	-0.1/0/0.15
P			0.464

P value based on Wilcoxon test of difference between medians.

max = maximum; min = minimum; SD = standard deviation.

Table 5. Subgroup Analysis on Time to Resolution

	N	Mean Days (SD)	Min/Median/Max
Age (yrs)			
≤80	7	25.57 (8.24)	14/28/35
>80	7	34.43 (23.34)	14/30/75
P			0.515
Lens status			
Phakic	2	22.00 (11.31)	14/22/30
Pseudophakic	12	31.33 (18.28)	14/29/75
P			0.515
Prior aflibercept injections			
No	10	29.4 (18.28)	14/30/75
Yes	4	31.5 (17.62)	14/28/56
P			0.829
Management			
Tap/inject	7	34.57 (18.99)	14/30/75
Topical steroids	7	25.43 (15.79)	14/17/56
P			0.242

P value based on Wilcoxon test of difference between medians.

max = maximum; min = minimum; SD = standard deviation.

Table 6. Rates of Inflammation after Intravitreal Injection (inj) of Anti-VEGF Pharmacotherapy

Study	Study Design	#Cases/#Inj	Rate (per inj)	Intravitreal Agent	Outcome/Notes
MARINA 2006 ¹	Prospective	6–10/10 443	0.06–0.10%	Ranibizumab	6 cases uveitis; 4 cases culture-negative endophthalmitis
ANCHOR 2009 ²	Prospective	1–3/5921	0.02–0.05%	Ranibizumab	1 case uveitis; 1 case culture-negative endophthalmitis; 1 case inflammation
CATT 2011 ³	Prospective	1/5449	0.02%	Anti-VEGF	1 case pseudoendophthalmitis after ranibizumab administration
	Retrospective ×36 mos	1/3839	0.03%	Ranibizumab	Mild AC reaction; resolved without treatment
Chong et al 2010 ⁴	Retrospective ×36 mos	44/16 166	0.27%	Bevacizumab	19 separate cases (0.12%) culture-negative endophthalmitis; clustering of cases noted
Wu et al (PACORES) 2007 ⁵	Retrospective ×12 mos	4/4304	0.09%	Bevacizumab	Uveitis
Shima et al 2008 ⁶	Retrospective	2/1300	0.15%	Bevacizumab	injection-related inflammation
Ness et al 2010 ⁷	Retrospective ×12 mos	10–11/3357	0.29%	Anti-VEGF + TA	sterile endophthalmitis
Georgopoulos et al 2009 ⁸	Retrospective ×18 mos	8/2500	0.32%	Bevacizumab	severe intraocular inflammation
Johnson et al 2010 ⁹	Retrospective ×21 mos	4–9/693	0.58–1.3%	Bevacizumab	4 cases sterile inflammation; 5 cases culture-negative endophthalmitis; clustering of cases noted
Wickremasinghe et al 2008 ¹⁰	Retrospective ×12 mos	14/1278	1.10%	Bevacizumab	acute ocular inflammation
Ladas et al 2009 ¹¹	Retrospective ×24 mos	38/2000	1.90%	Anti-VEGF	anterior intraocular inflammation
Kay et al 2011 ¹²	Retrospective ×4 mos	7/978	7.20%	Bevacizumab	Uveitis; clustering of cases noted
Kay et al 2011 ¹²	Retrospective ×4 mos	0/338	0%	Ranibizumab	uveitis
Day et al 2011 ¹³	Retrospective Medicare database analysis ×84 mos	45/40 903	0.11%	Anti-VEGF	Medicare database analysis, not based on clinical information
Fung et al 2006 ¹⁴	International internet survey	10/7113	0.14%	Bevacizumab	inflammation

TA = triamcinolone acetate; VEGF = vascular endothelial growth factor.

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Table 7. Rates of Inflammation after Intravitreal Injection (inj) of Triamcinolone Acetonide

Study	Study Design	#Cases/#Inj	Rate (per inj)	Intravitreal Agent	Outcome/Notes
SCORE 2009 ¹	Prospective	0/1500	0%	PFTA	Noninfectious endophthalmitis; PFTA (Trivaris; Allergan, Inc.)
Roth et al 2008 ²	Retrospective ×36 mos	6/929	0.60%	TA	Culture-negative inflammation
Moshfeghi et al 2005 ³	Retrospective ×17 mos	8/922	0.87%	TA	Sterile endophthalmitis; 2 cases treated with topical steroids/PO abx; 6 s/p tap&inject
Nelson et al 2003 ⁴	Retrospective ×23 mos	6/440	1.60%	TA	Noninfectious endophthalmitis
Taban et al 2007 ⁵	Retrospective ×9 mos	6/310	1.90%	TA	Culture-negative endophthalmitis
Jonisch et al 2008 ⁶	Retrospective ×18 mos	11/554	1.90%	TA	Culture-negative endophthalmitis; clustering of cases noted
Roth et al 2003 ⁷	Retrospective ×13 mos	7/104	6.70%	TA	Culture-negative endophthalmitis; clustering of cases: all cases arose within 1 month period
Maia et al 2007 ⁸	Retrospective ×50 mos	5/69	7.30%	TA	Inflammation (painful)
Maia et al 2007 ⁸	Retrospective ×50 mos	7/577	1.20%	PFTA	Inflammation (painless); PFTA (Ophthalmos Laboratories, San Paolo, Brazil)
Stepien et al 2009 ⁹	Retrospective ×6 mos (2005)	0/445	0%	TA	Sterile endophthalmitis
Stepien et al 2009 ⁹	Retrospective ×6 mos (2006)	27/532	5.10%	TA	Sterile endophthalmitis; clustering of cases noted
Stepien et al 2009 ⁹	Retrospective ×6 mos (2007)	4/308	1.30%	PFTA	Sterile endophthalmitis; PFTA (New England Compounding Pharmacy, Framingham, MA)

abx = antibiotics; PFTA = preservative-free TA; TA = triamcinolone acetonide (Kenalog; Bristol-Myers Squibb).

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