Real World Rates of Suspected Endophthalmitis Following Anti-VEGF and Steroid Intravitreal Injections in the United States

- Dilsher S. Dhoot, MD
- John D. Pitcher, MD

OBJECTIVE To evaluate real world rates of suspected endophthalmitis following intravitreal injections of aflibercept, bevacizumab, ranbizumab, dexamethasone implant, and triamcinolone.

PURPOSE To compare real world rates of suspected endophthalmitis following intravitreal injection of aflibercept, bevacizumab, ranbizumab (both pre-filled and conventional preparation), dexamethasone implant, and triamcinolone.

METHODS Retrospective study of aggregated, longitudinal electronic medical records obtained from Vestrum Health Retina Database, a geographically diverse sample of US retina providers. Inclusion criteria were a diagnosis of endophthalmitis based on billing codes between January 2013 and March of 2018. Primary outcome was the rate of acute endophthalmitis post intravitreal injection. Secondary outcomes included visual acuity change. Statistical comparisons between groups were performed using Chi-Square testing. A total of 358,824 unique patients were included in this analysis.

RESULTS The total number of injections performed, suspected endophthalmitis cases, and rate for each of the intravitreal medications in the defined study period were: Aflibercept 915,786 injections, 420 cases, 0.046%; Bevacizumab 1,002,405 injections, 236 suspected cases, 0.024%;

Ranibizumab conventional 728,865 injections, 193 cases, 0.026%, Ranibizumab pre-filled 128,075 injections, 26 cases, 0.02%; Dexamethasone 28,188 injections, 15 cases, 0.053%; Triamcinolone 56,194 injections, 64 cases, 0.114%. The rates of suspected endophthalmitis were statistically lower for both bevacizumab and ranibiuzumab (conventional and pre-filled) compared to aflibercept, dexamethasone, and triamcinolone ($P < 0.05$). Triamcinolone had a statistically higher rate of suspected endophthalmitis compared to all of the other medications ($p < 0.05$). No statistical difference in rates of endophthalmitis were seen between bevacizumab, ranibizumab conventional, and ranibizumab pre-filled medications.

CONCLUSION In this large retrospective review of real world rates of endophthalmitis, intravitreal anti-VEGF rates of suspected endophthalmitis were between 0.02 and 0.046%, similar to reported rates in anti-VEGF clinical trials. Rates of suspected endophthalmitis in steroids trended higher, with significantly higher rates seen with triamcinolone injection.

HUMAN RESEARCH Yes: Exempt from approval

Vitreoretinal Findings in a Large Cohort of Ebola Survivors

- Duncan E. Berry, MD
- Jessica Shantha, MD
- Steven Yeh, MD

OBJECTIVE The aim of this study is to describe the baseline vitreoretinal findings and visual acuity (VA) from a large cohort of Ebola survivors.

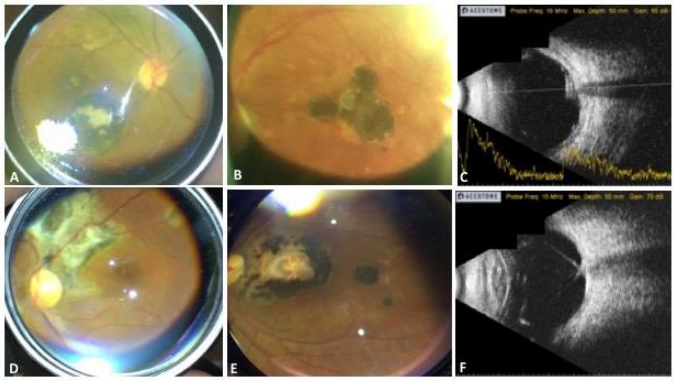
PURPOSE The largest Ebola virus disease (EVD) outbreak occurred from 2013 – 2016 in West Africa and consequently resulted in the largest cohort of EVD survivors to date. While anterior uveitis is the most common ocular finding, vitreoretinal involvement may also be present and result in significant VA impairment.

METHODS The Ebola Virus Persistence in Ocular Tissues and Fluids (EVICT) study screened a large cohort of EVD survivors and demonstrated that cataract surgery can be safely performed in EVD survivors. Patients with cataract, active uveitis, uveitis recurrence or medical indication for ocular fluid sampling (aqueous humor or vitreous humor) were screened for the EVICT study. Demographic and medical information were collected at baseline. Complete baseline ophthalmologic examination including VA, visual fields, slit lamp examination, dilated funduscopic examination were performed. B-scan ultrasound was performed in patients where an incomplete view of the posterior segment was noted.

RESULTS During the screening phase for EVICT, 137 patients were screened, of which 125 had eye exam data sufficient for analysis. 250 eyes of 125 patients were thus included in this study. Median patient age was 28 years (range 4 – 70). The median VA was 20/30 (range 20/20 – LP). The presence of vitreoretinal findings was documented in 26 of 250 eyes (10.4%) with the most common finding being chorioretinal scarring which was present in 18 of 231 eyes (7.8%) where fundus examination was not precluded due to media opacity. Other vitreoretinal findings

included choroidal thickening detected by ultrasound in 8 eyes, retinal detachment (RD) in 5 eyes and macular pucker in 1 eye. The presence of vitreoretinal findings was significantly associated with worse VA (p=0.002). Evidence of active or inactive uveitis was present in 85 eyes (34.0%) and was also significantly associated with worse VA (p<0.001). Visually significant cataract was present in 56 eyes (22.4%).

CONCLUSION There is a high incidence of visually-significant vitreoretinal pathology in EVD survivors. Surgical intervention for the treatment of vitreoretinal disease may be indicated in select cases. While the safety of cataract surgery was established by the EVICT study, further investigation is needed to determine the safety of vitreoretinal surgery in these patients.



Vitreoretinal findings in EVD survivors. Chorioretinal scarring (A, B, D and E); vitreoretinal traction with a peripapillary TRD (C); and incomplete posterior vitreous detachment with vitreoretinal traction (F)

Table 1. Summary of Ocular Findings in Ebola Survivors

	All, N=250 eyes
Visual Acuity, median (range)	20/30 (20/20 – LP)
Uveitis, N (%)	85 (34.0%)
Visually Significant Cataract, N (%)	56 (22,4%)
Vitreoretinal Disease, N (%)	26 (10.4%)
Chorioretinal Scarring, N (%)	18 (7.8%)
Retinal Detachment, N (%)	5 (2.4%)

HUMAN RESEARCH Yes: Approved by institutional review board

Best Corrected Visual Acuity at 36 Months in Study of Fluocinolone Acetonide Intravitreal (FAi) Insert for Noninfectious Posterior Uveitis (NIPU)

- Sumit Sharma, MD

OBJECTIVE To report 36-month BCVA data and examine the effects of baseline characteristics on BCVA outcomes with a sustained-release 0.18 mg FAi insert in eyes with chronic NIPU.

PURPOSE Preservation of visual acuity is an important goal in the treatment of chronic NIPU. Compared to other forms of uveitis, posterior uveitis accounts for a greater proportion of vision loss, particularly due to retinal damage and macular edema. In this study, visual acuity outcomes with a single, sustained-release FAi insert are compared with sham injection through 36 months.

METHODS In this prospective, randomized, double-masked, 36-month phase 3 clinical trial, subjects with a history of chronic NIPU (≥ 1 year), who had experienced at least two separate recurrences requiring ≥ 3 months of systemic therapy or ≥ 2 intra- or periocular steroid injections, were randomized to receive an FAi (n=87) or sham injection (n=42). Mean and categorical change in BCVA (ETDRS letter score) from baseline to month 36 were calculated for subjects treated with the FAi insert and sham injection. Change in BCVA was also compared for subgroups, according to lens status, use of intraocular pressure (IOP)-lowering medications or surgery, and degree of baseline vitreous haze and macular edema.

RESULTS Through month 36, mean (SD) change from baseline BCVA was 9.1 (13.02) letters for the FAi group vs 2.5 (14.20) letters for the sham group. A greater proportion of eyes in the FAi group gained ≥ 15 letters: 24/72 (33.3%) vs 5/34 (14.7%) with sham. Categorical BCVA improvements were highest for eyes with lower baseline BCVA. For those receiving IOP-

lowering medication, 12/37 (32.4%) in the FAi group gained ≥ 15 letters vs 4/23 (17.4%) in the sham group. For those requiring IOP-lowering surgery, BCVA data at 36 months was only available for 2/5 in the FAi group, for whom mean gain was 12.5 (13.44) letters, vs a mean loss of 2.8 (27.29) letters for the 5 sham-treated subjects. For patients who were phakic at baseline, more in the FAi group gained ≥ 15 letters: 13/35 (37.1%) vs 1/15 (6.7%) for sham. Likewise, for pseudophakes, 11/37 (29.7%) FAi-treated and 4/19 (21.1%) sham-treated gained ≥ 15 letters. BCVA data according to baseline vitreous haze and macular edema will also be presented.

CONCLUSION The beneficial effect of the FAi insert on BCVA letters gained was observed through 36 months, even when taking into account baseline characteristics and the need for IOP-lowering treatment. These results suggest that for chronic NIPU, a sustained-release treatment can limit the cumulative damage resulting from recurrent episodes of inflammation that characterize the disease.

HUMAN RESEARCH Yes: Approved by institutional review board

Cumulative Recurrences With the Fluocinolone Acetonide Intravitreal (FAi) Insert for Noninfectious Posterior Uveitis (NIPU): 36-Month

- David Callanan, MD

OBJECTIVE To report 36-month data on cumulative recurrences of uveitis and the use of adjunctive medications with a sustained-release 0.18 mg FAi insert in eyes with chronic NIPU.

PURPOSE Repeated episodes of inflammation can lead to cumulative, vision-threatening damage in chronic NIPU, highlighting a need for long-acting therapy that limits recurrences of inflammation. The number of recurrences of uveitis over 3 years was compared between eyes treated with a single, sustained-release 0.18 mg FAi insert and those treated with a sham injection.

METHODS This was a prospective, randomized, double-masked, 36-month phase 3 clinical trial for subjects with a history of chronic NIPU (≥ 1 year) who had experienced at least two separate recurrences requiring ≥ 3 months of systemic therapy or ≥ 2 intra-/periocular corticosteroid injections in the last year. Subjects were randomized to intravitreal FAi (n=87) or sham injection (n=42). Cumulative recurrences of uveitis were defined as ≥ 2 step increase in vitreous haze or ≥ 15-letter loss of VA; or were imputed in the case of rescue treatment for ocular inflammation or missing data. The number of recurrences as well as the nature of any rescue treatments given were compared through 36 months.

RESULTS Through 36 months, the rate of recurrence in eyes randomized to FAi, 49/87 (56.3%) was significantly lower than in eyes randomized to sham, 39/42 (92.9%) ($P < 0.001$). A total of 103 recurrences were reported in FAi-treated eyes (mean 1.2±2.00/eye) versus 166 recurrences in sham-treated eyes (mean 4.0±3.29/eye). Multiple (>1) recurrences were observed in 21.8%

(19/87) of the FAi-treated eyes and 73.8% (31/42) of the sham-treated eyes. Intra/peri-ocular corticosteroid injections were used to control inflammation in 19.5% (17/87) for FAi-treated and 69.0% (29/42) of sham-treated eyes, while systemic steroid or immunosuppressive treatments were given to 34.5% (30/87) and 50.0% (21/42), respectively. Adverse events included cataract and intraocular pressure increase.

CONCLUSION Treatment with a single, sustained-release FAi insert resulted in a reduced rate of recurrence, fewer cumulative episodes of recurrence, and consequently, lower exposure to adjunctive anti-inflammatory medications over the full 36-month study period.

HUMAN RESEARCH Yes: Approved by institutional review board

Suprachoroidal CLS-TA Improves Patient Outcomes in Uveitis of All Anatomic Subtypes: Results of the Phase 3 PEACHTREE Study

- Christopher R. Henry, MD

OBJECTIVE To determine if patients with macular edema associated with uveitis would benefit from suprachoridally injected CLS-TA treatment irrespective of the anatomic location of uveitis.

PURPOSE To evaluate the efficacy of suprachoroidal injection of CLS-TA, a proprietary triamcinolone acetonide (TA) injectable suspension, in subjects with macular edema associated with uveitis from all anatomic subtypes: anterior, intermediate, posterior, and panuveitis.

METHODS In PEACHTREE, a double-masked, prospective, multicenter study, 160 subjects with macular edema associated with noninfectious uveitis of any anatomic subtype were randomized 3:2 to receive suprachoroidal injections of CLS-TA (4.0 mg; n=96) or a sham procedure (n=64) administered at Day 0 and at Week 12. Evaluations were every 4 weeks through Week 24. Mean change from baseline in BCVA and central subfield thickness (CST) were evaluated at Week 24 for each anatomic subtype: anterior, intermediate, posterior, and panuveitis.

RESULTS In the overall cohort, patients in the CLS-TA arm gained significantly more letters than control at week 24 (13.8 vs 3.0 ETDRS letters, $p < 0.001$) and also experienced significant reductions in CST (-152.6 microns vs -17.9 microns, $p < 0.001$). CLS-TA significantly increased BCVA relative to the control arm in all four anatomic subtypes (Figure 1). CLS-TA also significantly reduced CST in all anatomic subtypes except for patients with anterior uveitis (Figure 2).

CONCLUSION In a pivotal, 6-month, phase 3 trial in subjects with macular edema associated with noninfectious uveitis, suprachoroidal injection of CLS-TA significantly improved patient outcomes irrespective of the anatomic location of uveitis.

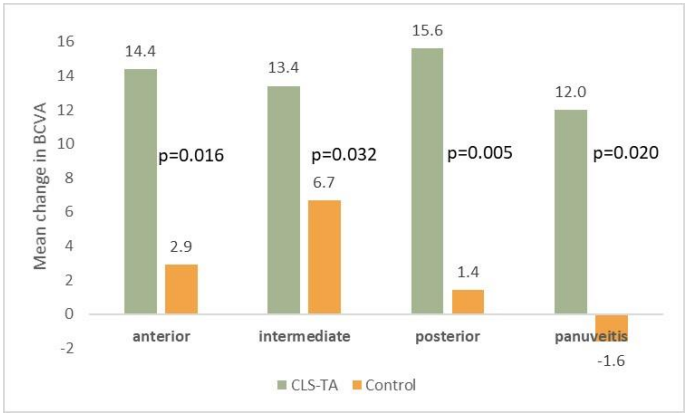


Figure 1: Mean Change From Baseline in BCVA by Anatomic Location

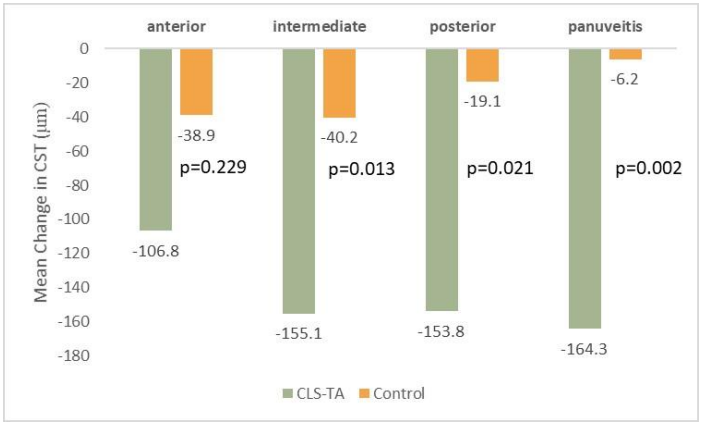


Figure 2: Mean Change from Baseline in CST by Anatomic Location

HUMAN RESEARCH Yes: Approved by institutional review board

Suprachoroidally Injected CLS-TA in Uveitis Maintains Efficacy Outcomes Through 48 Weeks: Results of the MAGNOLIA Phase 3 Extension Study

- Pauline T. Merrill, MD

OBJECTIVE To determine if patients who were treated with suprachoroidally injected triamcinolone acetonide CLS-TA at Baseline & Week 12 (W12) in the PEACHTREE study could maintain efficacy outcomes through W48.

PURPOSE To characterize the continued clinical benefit of the suprachoroidally injected triamcinolone acetonide suspension CLS-TA through 48 weeks in subjects with macular edema (ME) associated with uveitis.

METHODS Subjects with ME associated with uveitis of any anatomic subtype (anterior, intermediate, posterior, or panuveitis) treated with CLS-TA at baseline and W12 in the PEACHTREE study were followed for an additional 24 weeks in MAGNOLIA, a prospective, non-interventional, masked, observational, extension trial. The total evaluation period was 48 weeks. Subjects who completed PEACHTREE and did not receive rescue medication were eligible for MAGNOLIA. The primary outcome in MAGNOLIA was the time to rescue therapy relative to Day 0 of PEACHTREE. Secondary outcomes included incidence of adverse events grouped by organ system. No further injections of CLS-TA were administered after PEACHTREE W12.

RESULTS Of the 61 potential subjects from PEACHTREE from sites where the MAGNOLIA extension study was offered, 33 qualified and participated. Of the 28 subjects from the

PEACHTREE CLS-TA arm, 14 patients (50%) completed MAGNOLIA without receiving any additional medication through W48 (36 weeks after the last treatment in PEACHTREE in W12). Mean time to rescue therapy in MAGNOLIA was 344 days (Figure 1). Patients gained a mean of 16 letters through W24 and 12 letters through W48 (Figure 2). No SAEs related to study treatment were observed; all safety events including new reports of IOP elevations and cataract progression will be reported.

CONCLUSION CLS-TA-treated patients were able to maintain efficacy outcomes through week 48 in the MAGNOLIA extension study. Half of patients did not require additional treatment 36 weeks after their last injection of CLS-TA.

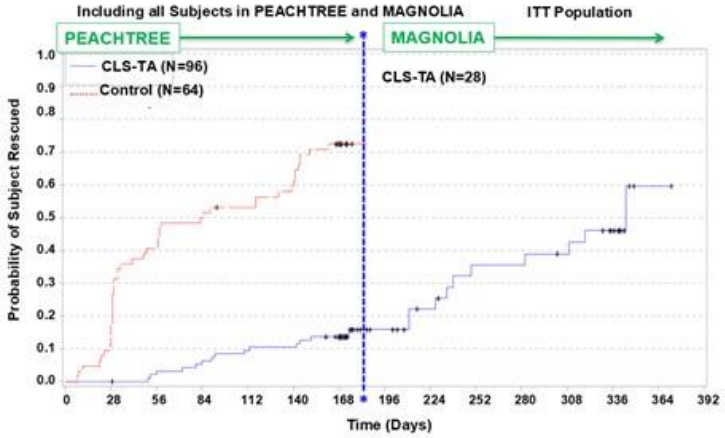


Figure 1. Kaplan-Meier plot of time to first rescue in PEACHTREE and MAGNOLIA

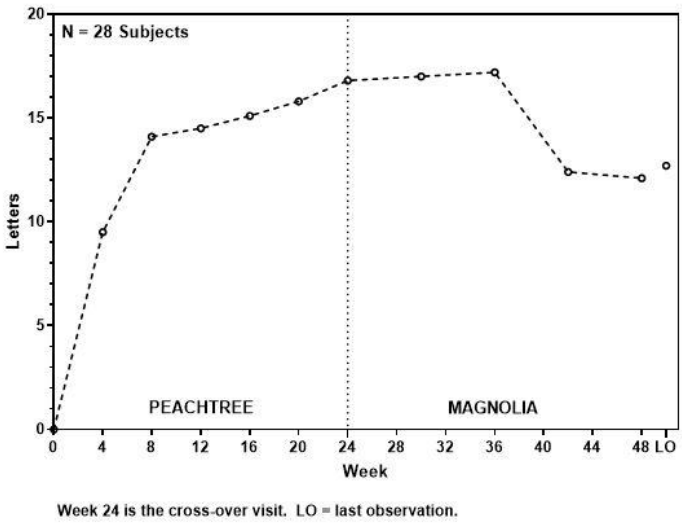


Figure 2. Mean change in BCVA from baseline through week 48 in PEACHTREE and MAGNOLIA

HUMAN RESEARCH Yes: Approved by institutional review board

Toxic Posterior Segment Syndrome: Clinical Characteristics of 48 Eyes

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- Lori E. Coors, MD
- Deborah Yeh Chong, MD
- Timothy S. Fuller, MD
- Dwain G. Fuller, MD, JD
- Gary Edd Fish, MD, JD, MBA, LLM
- Robert C. Wang, MD

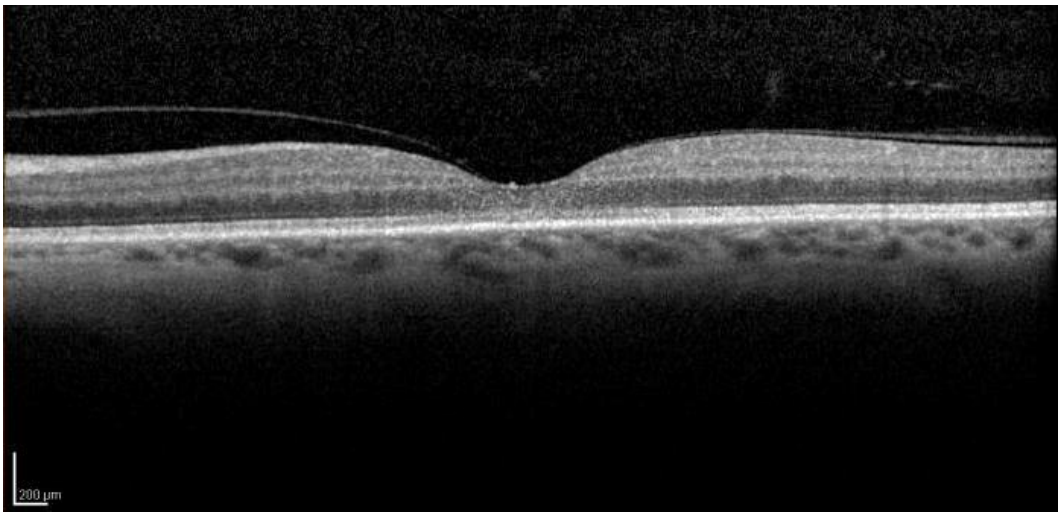
OBJECTIVE To describe the clinical features of toxic posterior segment syndrome (TPSS), a toxic maculopathy that may occur after an intraocular injection of compounded triamcinolone and moxifloxacin.

PURPOSE "Dropless cataract surgery" with an intraocular injection of compounded triamcinolone and moxifloxacin at the time of surgery has become an increasingly popular surgical trend. Recently, a cohort of patients experienced adverse events after exposure to this injection. We aim to describe the clinical features of a unique toxic maculopathy (TPSS) seen in these patients.

METHODS This retrospective case series included 48 eyes of 47 patients. Patients were identified by query of the electronic medical record system. All patients received the same batch of compounded triamcinolone and moxifloxacin from a local compounding pharmacy during their cataract surgery. The findings on presentation, clinical course, and outcomes were reviewed for a comprehensive analysis. Main outcome measures included best-corrected visual acuity (BCVA), subjective nature of the visual disturbance, qualitative examination and imaging features, treatment regimens, and final visual and anatomic outcomes.

RESULTS Characteristic findings of TPSS include unremarkable postoperative day 1 examination; delayed-onset painless central vision loss within the first week, often followed by continued deterioration of central vision for one to two months; varying degrees of subfoveal blurring and disruption of the outer retinal layers on OCT; electroretinogram with reduced rod and cone responses; and varying degrees of optic disc pallor. All eyes received the same batch of compounded intraocular triamcinolone and moxifloxacin via intracameral bolus, transzonular injection into the vitreous, or pars plana intravitreal injection. Patients were referred to our practice 14 to 35 days after surgery. Follow-up period ranged from one to 12 months. The majority of patients (85%) were treated with oral and topical corticosteroids. Visual outcomes were variable, ranging from hand movements to 20/25, with minimal to no improvement over time. In all patients, outer retinal disruption improved gradually over time.

CONCLUSION TPSS is a rare, visually debilitating condition that can develop after an intraocular injection of compounded triamcinolone and moxifloxacin during cataract surgery. Disease course and findings suggest that TPSS is a progressive toxic maculopathy. With extended follow up, subfoveal outer retinal disruption improves; however, despite treatment with corticosteroids, vision does not tend to improve.



This OCT demonstrates blurring and disruption of the subfoveal outer retinal layers one month after an intraocular injection of compounded triamcinolone and moxifloxacin during cataract surgery.

HUMAN RESEARCH Yes: Approved by institutional review board

Expanded Clinical Spectrum of Pentosan Polysulfate Sodium Associated Maculopathy

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- Stanford C. Taylor, MD
- Stephen Armenti, MD, PhD
- Rachel Shah, MD
- Austin D. Igelman
- Mark E. Pennesi, MD, PhD
- Kanishka T. Jayasundera, MD, FRANZCO
- Paul Yang, MD, PhD
- Thomas S. Hwang, MD
- Christina Joy Flaxel, MD
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- Joshua D Stein, MD, MS

OBJECTIVE What are the exposure characteristics and key clinical features of pentosan polysulfate sodium (PPS) associated maculopathy?

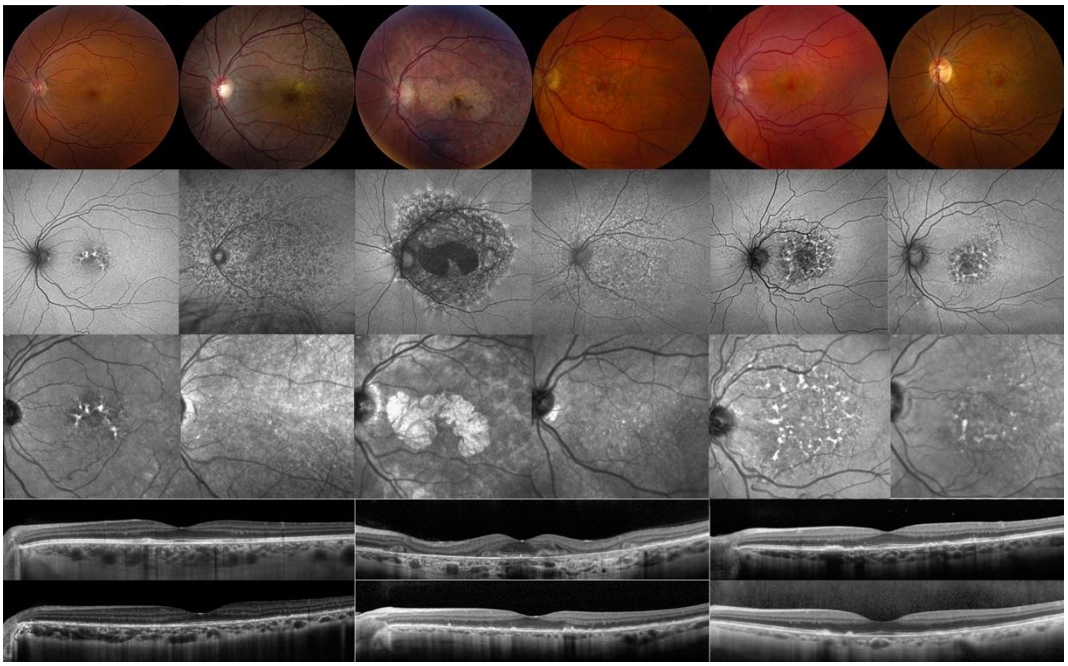
PURPOSE We recently described a pigmentary maculopathy in 6 patients with chronic exposure to PPS. Many thousands of patients have taken this drug since its 1996 FDA approval for interstitial cystitis. Clinicians will benefit from further information regarding exposure thresholds and clinical characteristics to screen and diagnose patients at risk for this condition.

METHODS This is a retrospective case series across 4 institutions (Emory Eye Center, Casey Eye Institute, Kellogg Eye Center, and Northern California Retina Vitreous Associates). Patients with a history of PPS exposure were identified at each site. Retinal imaging records were reviewed to identify cases resembling the recently described PPS-associated maculopathy. A total of 62 eyes of 31 patients of the characteristic maculopathy were identified. Medical charts were reviewed for demographics, clinical characteristics, and imaging features. Exposure history to PPS and other medications were recorded.

RESULTS Thirty (96.8%) patients were female, with median age at the time of diagnosis of 60 years (range, 38-79). The most common presenting diagnoses were macular or pattern dystrophy (n = 15, 48.4%) and age related macular degeneration (n=9, 29.0%). Patients reported a median (range) cumulative PPS exposure of 1.6 kg (0.33 - 4.31), over a median duration of 14.0 years (3.0 - 21.9). The most common chief complaints were difficulty reading (n = 16, 51.6%) and subjectively prolonged dark adaptation (n = 13, 41.9%).Median logMAR visual

acuity in both the right and left eyes was 0.10 (OD range 0 - 1.18, OS range -0.12 - 1.30). Macular hyperpigmented spots were present in 58.9% of eyes, more commonly in less extensive disease, and RPE atrophy in 37.5% of eyes. Fundus autofluorescence imaging typically demonstrated a confluent array of hyper- and hypoautofluorescent spots centered on and involving the fovea. There was no correlation between disease severity and extent of PPS exposure.

CONCLUSION PPS-associated maculopathy manifests in the setting of chronic exposure. Fundus findings are subtle, yet posterior segment imaging reveals a distinctive appearance characterized by signal abnormality centered on and involving the fovea. Thousands of patients are at risk for this condition, which may masquerade as AMD or pattern dystrophy. We recommend drug cessation in affected patients.



Spectrum of clinical phenotypes in pentosan polysulfate sodium-associated maculopathy. Although findings are subtle on color fundus photography (Row 1), multimodal imaging, in particular fundus autofluorescence (Row 2) and near infrared reflectance imaging (Row 3), demonstrate striking abnormalities.

HUMAN RESEARCH Yes: Approved by institutional review board