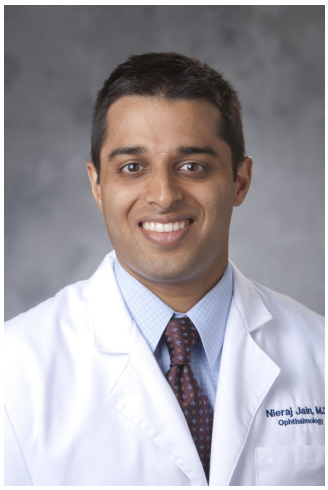
10/9/2021 1:10PM

Pentosan Polysulfate Maculopathy: Prospective Observational Study



- Nieraj Jain, MD
- Aaron Tippett Lindeke-Myers, BA
- Riley J Lyons, MD

OBJECTIVE What happens to eyes with pentosan polysulfate (PPS) maculopathy after drug discontinuation?

PURPOSE Recent studies have demonstrated an association between long term PPS use and a vision-threatening maculopathy. Given that this interstitial cystitis medication has been widely prescribed since its 1996 FDA approval, thousands of patients are at risk. Prospective data are needed regarding the long term visual impact of this condition to guide treatment decisions.

METHODS Thirteen patients with PPS maculopathy were followed prospectively with multimodal assessments of retinal structure and function. Functional testing endpoints included: ETDRS best corrected visual acuity (BCVA), and microperimetry (MP) mean and percent reduced thresholds. Structural endpoints included: subfoveal choroidal thickness (SFCT), central subfield retinal thickness (CST), and geographic atrophy area (defined as complete retinal and outer retinal atrophy). Baseline and Year 1 outcomes were compared using a Wilcoxon signed rank test. Mean results were computed for the two eyes for each subject to account for inter-eye correlation.

RESULTS Eleven participants (22 eyes) completed the Year 1 visit. Ten (91%) were female, and the median age was 63 (range 38-77). Patients stopped PPS use a median of 9.9 months (IQR 5.6 – 20.5) prior to baseline. Median change in ETDRS BCVA during the study period was -3 letters (IQR -4.75 – 1.5) [Baseline: 81.5 letters (IQR 79 – 86.3); Year 1: 78.5 letters (IQR 74.5 – 86.8) (p = 0.07)]. Four (18%) eyes, each with progressive atrophy, lost ≥ 10

letters. Median MP average thresholds declined from 25.7 dB (IQR 17.8 – 26.7) to 25.2 dB (IQR 16.5 – 27.6) (p = 0.18). Median MP percent reduced thresholds increased from median 23.0% (IQR 9.5% – 54.1%) to 25.2% (IQR 14.2% – 28.6%) (p = 0.88). Fifteen eyes (68%) had atrophy at baseline, exhibiting a median linearized increase in atrophy of 0.21 mm (IQR 0.08 – 0.39) per eye. Median CST decreased from 278 µm (IQR 243 – 287) to 267 µm (IQR 238 – 290) (p = 0.08). Median SFCT decreased from 268 µm (IQR 159 – 324) to 261 µm (IQR 161 - 334) (p = 0.47).

CONCLUSION This prospective study demonstrates continued evolution of PPS maculopathy even after drug cessation. Geographic atrophy enlarged in all eyes that manifested atrophy at baseline. Retina specialists screening patients for PPS maculopathy should be aware of the potential long term visual impact of this condition.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/9/2021 1:14PM

Evaluating Pentosan Polysulfate Sodium-Associated Retinopathy Risk Factors and Grading Criteria

- S. Krishna Mukkamala, MD
- Ella H Leung, MD
- Sahana Sharma
- Ana Levie-Sprick
- Gregory D Lee, MD
- Hyung Cho, MD

OBJECTIVE To determine the risk factors and assess the current diagnostic criteria for categorizing patients with pentosan polysulfate sodium-associated retinopathy.

PURPOSE To evaluate the risk factors and assess the grading criteria for patients with potential pentosan polysulfate sodium (PPS)-associated retinopathy

METHODS A retrospective chart review was performed of patients who had taken PPS (Elmiron, Janssen Pharmaceuticals, Inc) and underwent a dilated fundus examination from 2018-2021. Using previously published grading criterias and observations from prior retrospective studies, the multimodal images were evaluated by retina specialists masked to the patients' medical histories and the dosages and durations of PPS.

RESULTS A total of 123 patients were included, of whom 95 patients were deemed not to have PPS-associated retinopathy, 28 had PPS-associated retinopathy. The mean age was 59.2 years old, and the follow-up was 11.5 months. The characteristic findings of PPS-associated retinopathy included densely packed hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelial atrophy centered on the fovea. PPS-associated retinopathy was associated with a higher mean cumulative dose (730,000mg vs. 1,587,750mg, P=0.0044), longer duration of PPS use (7.00 vs. 13.75 years, P=0.0039), and longer duration of interstitial cystitis (11.75 vs. 16 years, P=0.0312). There was no difference based on the dosage per day for the weight (P=0.90), body mass index (P= 0.56),

body surface area (P=0.98), lean body weight (P=0.81), history of kidney disease (P>0.999), or history of liver disease (P=0.39).

CONCLUSION In patients with interstitial cystitis who had taken PPS, a longer duration of PPS use, higher cumulative dose, and a longer duration of interstitial cystitis were all associated with an increased risk of developing maculopathy.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/9/2021 1:20PM

Suprachoroidal Delivery of Small Molecule Suspensions: Pre-Clinical Results Correlate to Clinical Trial Outcomes

- James C. Major, MD, PhD FACS FASRS
- Viral Kansara
- Thomas A. Ciulla, MD, MBA, FASRS

OBJECTIVE The objective of this research is to characterize performance of various small molecule suspensions in the suprachoroidal space in preclinical studies and clinical trials.

PURPOSE The small molecule suspension triamcinolone acetonide delivered via suprachoroidal injection has demonstrated potential signs of efficacy and safety in preclinical models. Those results were corroborated in Phase 3 clinical trials for noninfectious uveitis. This study evaluated the suprachoroidal space (SCS) as a delivery pathway for other small molecule suspensions.

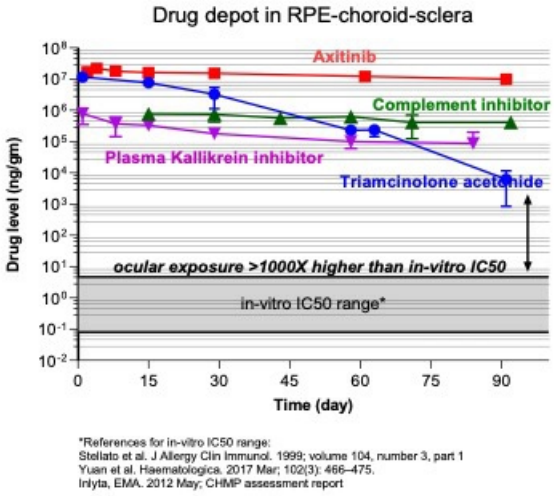
METHODS Suprachoroidal delivery of various small molecule therapeutic agents was evaluated for pharmacokinetic (PK) and ocular distribution, including compartmentalization and durability after a single bilateral injection to rabbits. Agents tested included suspensions of tyrosine kinase inhibitor axitinib, complement factor D inhibitor A01017, and plasma kallikrein inhibitor BCX4161. Drug levels were assessed in retinal pigment epithelium (RPE)/choroid/sclera (RCS), retina, vitreous humor, aqueous humor and plasma over a period of 3 months.

RESULTS Suprachoroidal delivery of small molecule suspensions of axitinib, A01017, and BCX4161 demonstrated greater concentration of those agents in the posterior segment tissues than in anterior segment tissues, vitreous humor or plasma. At 3 months, drug depot levels in the RCS remained above IC50 levels. Axitinib preclinical studies demonstrate signs of potential efficacy in neovascularization models. BCX4161 was detected in the central retina and central RCS near the optic nerve. SCH delivery of small molecule suspensions may provide safe and efficacious delivery to the RPE, choroid and retina while minimizing

exposure to the lens and aqueous humor. These attributes correlated to outcomes for triamcinolone acetonide, as demonstrated across multiple clinical trials.

CONCLUSION Suprachoroidal delivery of small molecule suspensions demonstrate prolonged therapeutic levels with potential for sustained release and high bioavailability, while showing compartmentalization to ocular posterior tissues. A Phase 1/2a clinical study evaluating suprachoroidal administration of axitinib (CLS-AX) for the treatment of nAMD is currently ongoing.

IRB APPROVAL Not applicable — I responded "No" to previous question regarding human subjects.



Drug Depot in RPE-Choroid-Sclera

10/9/2021 1:32PM

Comparison of Hypochlorous Acid vs. Povidone Iodine Use Prior to Intravitreal Injection: A Randomized Prospective Trial (PAVE Study)

- Robert L. Avery, MD
- Georgia Avery
- Gabe Gordon
- Rebecca Carron

OBJECTIVE To compare the pain and disinfection induced by applying hypoclorous acid vs. providone iodine to the ocular surface of patients undergoing intravitreal injections.

PURPOSE Povidone iodine (PI) is the standard disinfectant before intravitreal injection (IVT) despite frequently causing patient discomfort. Hypochlorous acid (HA), a broad-spectrum disinfectant approved for blepharitis treatment, is a potential alternative candidate for ocular disinfection prior to IVT. We assessed pain and disinfection status after instillation of PI or HA in patients undergoing IVT.

METHODS This was a randomized, prospective clinical trial of patients undergoing bilateral IVT. This study enrolled 124 eyes of 62 patients. Patients were treated with PI and HA in opposite eyes prior to IVI. Pain scores (0-10) were measured just after disinfectant instillation, the injection, and 1-2 hours after IVT. Disinfection levels were assessed by swabbing the conjunctiva before and after disinfection; cultures were plated on chocolate and blood agar and assessed as either positive or negative for microbial growth.

RESULTS Pain scores recorded immediately after disinfectant application, after the injection, and 1-2 hours after injection for PI vs. HA were: 1.15 vs. 0.11 ($p<0.001$), 1.02 vs. 0.78 ($p=.19$), and 3.0 vs. 0.47 ($p<0.001$), respectively. PI and HA administration both significantly increased the culture negativity of the conjunctiva, $p =0.001$ and $p = 0.009$, respectively. There was a trend for PI to more completely disinfect a culture positive conjunctiva than HA, 67% vs. 44%, $p=0.067$, respectively. No patient developed endophthalmitis in this relatively small study.

CONCLUSION Most discomfort from IVT occurs several hours after the injection and is

dramatically reduced by using HA instead of PI. Both disinfectants significantly reduce conjunctival culture positivity, and given the level of discomfort some patients experience with PI, further study of HA as an alternative in sensitive patients is indicated.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/9/2021 1:36PM

A Phase 1 Single Dose Study of RZ402: A Novel Orally Administered Plasma Kallikrein Inhibitor to target Diabetic Macular Edema

- Robert B. Bhisitkul, MD, PhD
- Quan Dong Nguyen, MD, MSc, FARVO, FASRS
- Brian Roberts, MD
- Rajat Agrawal, MD MS

OBJECTIVE A first-in-human Phase 1 study was conducted to assess the safety and pharmacokinetics of RZ402, a novel oral plasma kallikrein inhibitor under development for the treatment of diabetic macular edema.

PURPOSE The plasma kallikrein-kinin system (PKK) is implicated in diseases of vascular inflammation and leakage, offering a novel pathway for the treatment of retinal diseases. RZ402 is a novel orally administered plasma kallikrein inhibitor (PKI). A phase 1, controlled trial was conducted to assess the safety and pharmacokinetics of oral RZ402 in a clinical development program for the treatment of DME.

METHODS A phase 1 randomized, double-masked, placebo-controlled, single ascending dose study of RZ402 oral solution in 30 healthy adult male and female subjects was conducted. Three sequential ascending dose cohorts of 10 subjects each were enrolled, with each cohort receiving single oral doses of RZ402 (or matched placebo in 8:2 fashion) at dose levels of 25-mg, 100-mg, and 250-mg. Safety assessments included systemic and ophthalmic evaluations. Serial plasma RZ402 concentrations by LC/MS/MS supported the pharmacokinetic evaluation.

RESULTS All 30 subjects completed the study with no discontinuations . RZ402 was generally safe and well tolerated across all dose levels. Overall, 13 subjects (54%) who received RZ402 experienced a total of 18 adverse events (AEs), compared to 2 subjects

(33%; 5 AEs) who received placebo. Only 3 AEs (diarrhea, nausea and headache; all grade 1/mild) in 3 subjects were judged as possibly drug-related. There was no grade 2 (moderate) or higher AEs nor any serious AEs (SAEs). No clinically meaningful changes in laboratory values, vital signs, or ECG results were observed, and ophthalmic examinations were unremarkable. There were no observed dose-limiting toxicities. Dose-dependent increases in RZ402 blood concentrations had peak levels at 3 to 4 hours after dose with an elimination half-life at 20.2 to 25.6 hours across the dose groups. Durable and pharmacologically relevant concentrations of RZ402 were observed throughout the intended 24-hour dosing interval.

CONCLUSION RZ402, a novel, orally administered PKI was demonstrated to have a good systemic and ocular safety profile and produced effective serum levels over 24 hours that support a once-a-day oral regimen as a potential treatment for patients with DME.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/9/2021 1:42PM

Efficacy and Safety of 'Dropless Vitrectomy Surgery' and Comparison of Outcomes to Standard of Care Topical Therapy

- K. V. Chalam, MD, PhD, MBA, FRCS(C), FASRS
- Moises Enghelberg, DO, MSc
- Suzie Gasparian, MD

OBJECTIVE Single introoperative (trimoxi) triamcinoloneacetonide–moxifloxacin injection without postoperative drops effectively controlinflammation after vitreous surgery and comparable to standard droptherapy

PURPOSE To compare the effectiveness of intravitreal injection of triamcinolone acetonide–moxifloxacin (Tri-Moxi) to a standard eyedrop regimen in controlling postoperative inflammation, visual acuity, and the rate of high intraocular pressure (IOP) among patients undergoing vitrectomy surgery for a variety of retinal disorders in an academic setting.

METHODS In this retrospective longitudinal comparative study, the electronic medical records of patients who under- went vitrectomy surgery using single intravitreal injection of triamcinolone acetonide–moxifloxacin injection (Imprimis) at the end of surgery were reviewed (Group 1)and compared with patients who received a standard topical regimen of tapering doses of steroid-antibiotic (Tobradex) eye drops (Group 2) in terms of degree of intraocular inflammation, corneal edema, visual acuity, and the rate of high IOP. Postoperative observations were made at days 1, 42 (6 weeks) and 90 (three months). Anterior chamber cell reaction and corneal edema were graded on a scale of 0 -4.

RESULTS A total of 162 consecutive eyes (Group 1 [81 eyes], Group 2 [81 eyes]) of 156 patients were included in the study. The anterior chamber cell reaction severity decreased by 24.0%, and 25.0% at 6 weeks and 90 days, respectively, after surgery following triamcinolone acetonide–moxifloxacin injection (Group 1) compared with standard eyedrop therapy ($P < .001$ and $P < .02$, respectively). The best corrected visual acuity improved about 2 lines on average in both groups 90 days after surgery compared with the

preoperative values (P < .001). Group 1 was associated with increased severity of corneal edema (odds ratio, 1.24; P < .001) on postoperative day 1, with no statistically significant difference at 6 weeks and 90 days postoperatively (P <0 .22 and P < 0.38, respectively). There was no statistically significant difference in the rate of high IOP between the two groups at different time points postoperatively. High intraocular pressure was defined as IOP higher than 24 mm hg

CONCLUSION Attainment of good outcomes in vitrectomy surgery depend in part on patient compliance. Triamcinolone acetonide–moxifloxacin injection is an effective method to control intraocular inflammation after vitrectomy surgery and not inferior to standard postoperative topical therapy. It is a promising substitute for standard eyedrop therapy, especially for patients non compliant with eyedrop usage

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.