Pentosan Polysulfate Maculopathy Versus Age-Related Macular Degeneration: Comparative Assessment With Multimodal Imaging

- Joseph S Christiansen, MD
- Alexander C Barnes, MD
- Duncan E Berry, MD
- Nieraj Jain, MD

OBJECTIVE Does pentosan polysulfate maculopathy manifest distinctive imaging features that can be differentiated from those found in age-related macular degeneration?

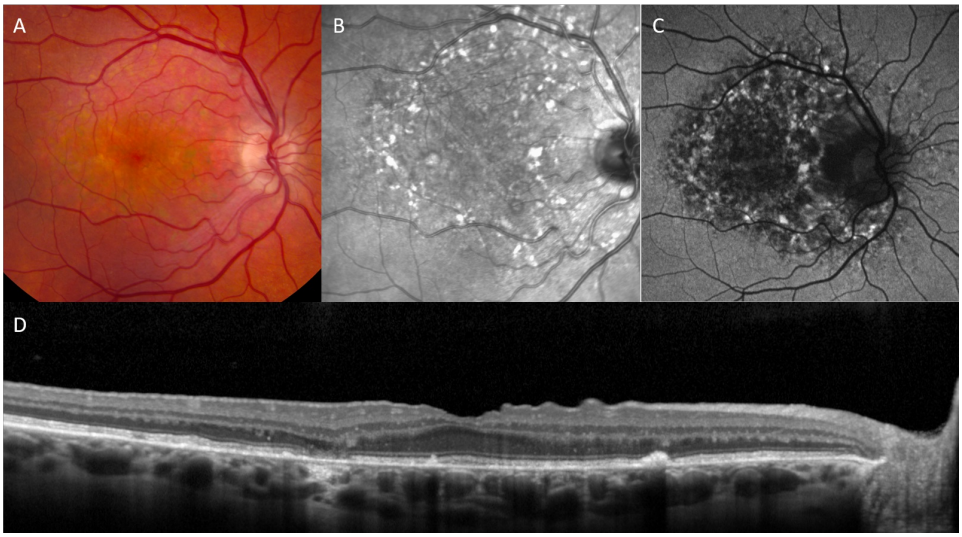
PURPOSE Many patients with pentosan polysulfate maculopathy are incorrectly diagnosed with age-related macular degeneration due to the similarities in demographic characteristics and fundus manifestations seen in these conditions. These similarities may present clinicians with diagnostic challenges. The goal of the present study is to investigate the hypothesis that PPS maculopathy manifests distinctive imaging features that can be differentiated from those found in AMD.

METHODS In this restropective review, local databases were queried to identify patients with a diagnosis of interstitial cystitis who were seen at the Emory Eye Center between May 2014 and January 2019. Fundus images were reviewed for each patient to determine which subjects had adequate imaging that would allow for further categorization. Ninety subjects met these eligibility criteria. Masked graders reviewed all available fundus images and categorized subjects as follows: Category 1 – pentosan polysulfate maculopathy; Category 2 – AMD or drusen; Category 3 – neither; Category 4 – unsure. Pentosan polysulfate exposure characteristics were compared among groups.

RESULTS Of the ninety subjects evaluated, 79 (88%) were female and the median age was 61.5 years (range, 30 - 89). There were 17 subjects placed in Category 1, 25 subjects in Category 2, 47 subjects in Category 3, and 1 subject in Category 4. There were 17 (100%) subjects exposed to pentosan polysulfate in Category 1, 15 (60%) in Category 2, 28 (60%) in Category 3, and 0 in Category 4. Mean cumulative exposure to pentosan polysulfate across categories 1-4 was 2.1 kg, 0.36 kg, and 0.34 kg, and 0 kg, respectively ($p<0.00001$). Eyes with pentosan polysulfate maculopathy did not have typical drusen in the macula.

CONCLUSION Although pentosan polysulfate maculopathy is similar to some aspects of AMD, the two conditions can be differentiated with the use of multimodal fundus imaging.

HUMAN RESEARCH Yes: Approved by institutional review board



Fundus imaging of the right eye from a representative case of PPS maculopathy in a 63-year-old female with 2.48 kg cumulative exposure to PPS. This patient has characteristic macular pigment clumps (A) amidst a background of pale yellow deposits. Near infrared reflectance imaging (B) and autofluorescence imaging (C) demonstrate the extent of involved tissue, with a fairly dense arrangement of signal abnormalities. Macular pigment clumps are associated with corresponding hyperreflective nodules at the RPE (D).

Role of Metabolomics in Age-Related Macular Degeneration

- Deeba Husain, MD
- Ines Lains, MD, MSc
- John B. Miller, MD
- Demetrios Vavvas, MD, PhD
- Ivana K. Kim, MD
- Joan W. Miller, MD

OBJECTIVE Metabolomics could point to novel biomarkers of AMD and help better understand disease mechanism.

PURPOSE This study aims to compare the plasma metabolomic profiles of AMD patients and controls in two distinct cohorts. This was done to assess and validate plasma metabolomic profiles in patients with age-related macular degeneration (AMD) and to better understand AMD pathogenesis.

METHODS Prospective, cross-sectional study at two sites, (Boston, US and Coimbra, Portugal) including subjects with AMD and controls. Detailed history, eye exam, color fundus photographs (AMD graded using AREDS classification) and SD-OCT were performed. Fasting blood samples were analyzed by Metabolon Inc., using ultra-performance liquid chromatography (UPLC) and high-resolution mass spectrometry (MS). Multivariate analysis including partial-least square discriminant analysis was performed to assess clustering between AMD and controls. Meta-analysis based on the Liptak-Stouffer weighted Z-method was performed. Biological relevance of significant metabolites was assessed using Metaboanalyst 4.0.

RESULTS A total of 491 subjects-149 patients with AMD and 47 controls from Boston, United States, and 242 patients with AMD and 53 controls from Coimbra, Portugal, were included in the study. After excluding 61 exogenous metabolites, analyses were performed

on 544 metabolites. Meta-analysis identified 69 significantly different metabolites ($p<0.05$) between patients with AMD and controls, with 28 metabolites reaching a statistically significant false discovery rates(q value). Most of the significant metabolites (q value) were lipids (m=10; 35.7%), followed by amino acids (m=8; 28.6%), nucelotides (m=6; 21.4%), carbohydrates (m=2; 7.1%), cofactors and vitamins (m=1; 3.6%), and peptides (m=1; 3.6%). Pathway analysis of the 28 significant metabolites revealed a significant enrichment for purine (p=7.2x10-4), sphingolipid (p=0.0010), glycerophospholipid (p=0.0037), and nitrogen metabolites (p=0.0404).

CONCLUSION Patients with AMD have a distinct plasma metabolomic profile compared to controls. Metabolomics may provide easily accessible AMD biomarkers, that can be combined with imaging and genomic profile to identify AMD subtypes. These metabolites could provide insight into disease pathogenesis and be the basis for a precision medicine approach leading to effective therapies for early and intermediate AMD.

HUMAN RESEARCH Yes: Approved by institutional review board

Phase 1 Safety Study of Intravitreal (ITV) Anti-High Temperature Requirement A1 (aHtrA1), a Novel Serine Protease Inhibitor, in Patients With GA

- William Z. Bridges, MD
- Arshad M. Khanani, MD
- Erich C Strauss, MD
- Hao Chen, PhD
- Flavia Brunstein
- Ling Ma, PhD
- Lee Honiberg, PhD
- Katherine Maass
- Phil Lai, MD

OBJECTIVE To investigate the safety, tolerability and pharmacokinetics of ITV aHtrA1, an antigen-binding fragment, following single and multiple doses in patients with geographic atrophy (GA) secondary to AMD.

PURPOSE The secreted protease HtrA1 is active in the retina and can potentially degrade extracellular matrix proteins and proteins involved in the visual cycle. Inhibiting HtrA1 is hypothesized to slow progression of GA lesion growth. The Phase 1 study investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics (PD) of ITV aHtrA1 following single and multiple doses in patients with GA.

METHODS In the single ascending dose stage (SAD), a single ITV injection of aHtrA1 was given in 5 dose-escalation cohorts ranging from 1 mg to 20 mg, with patients followed for 12 weeks (n=15). The second stage evaluated the maximum tested dose of 20 mg administered every 4 weeks (q4w) for 3 doses, with patients followed until week 20 (n=13). The primary outcome measures were safety and tolerability of ITV aHtrA1. Exploratory outcome measures included aqueous and serum pharmacokinetics as well as assessment of the pharmacodynamic (PD) effect of aHtrA1 in aqueous humor as measured by inhibition of cleavage of Dickkopf-related protein 3 (DKK3), an HtrA1 substrate.

RESULTS ITV aHtrA1 was well tolerated at single doses up to 20 mg ITV and multiple doses of 20 mg q4w X 3 in patients with GA. No dose-limiting toxicities were observed at any dose level. No ocular serious adverse events (AEs), or systemic or ocular AEs, were reported related to ITV aHtrA1. Based on serum and aqueous humor PK data, the half-life for vitreal elimination of aHtrA1 was 4.8 days, as estimated by a population PK model. Dose-dependent inhibition of DKK3 cleavage by aHtrA1 was observed in the SAD cohorts. Higher doses of aHtrA1 yielded longer duration of HtrA1 inhibition; at the 20 mg dose, inhibition of DKK3 cleavage was sustained for at least 8 weeks after a single ITV administration. In the multiple dose stage, DKK3 cleavage remained inhibited throughout the treatment period with aHtrA1. Following the last dose at Week 8, inhibition was maintained through Day 112 (8 weeks after the last dose), with an upward trend towards

baseline levels by Day 133 (11 weeks after the last dose).

CONCLUSION ITV aHtrA1 was well tolerated with an acceptable safety profile at the maximum tested dose of 20 mg q4w for 3 doses. Furthermore, a sustained PD effect suggesting potential for ≥ 8 weeks of target inhibition with the 20mg dose was observed in the aqueous humor as measured by inhibition of cleavage of DKK3. A Phase 2 study evaluating the efficacy of ITV aHtrA1 is currently in progress.

HUMAN RESEARCH Yes: Approved by institutional review board

Pentosan Polysulfate Maculopathy: Disease Course After Drug Cessation

- Rachel Shah, MD
- Riley Lyons, BA
- Joseph M Simonett, MD
- Mark E Pennesi, MD/PhD
- Rajesh C. Rao, MD
- Nieraj Jain, MD

OBJECTIVE Does pentosan polysulfate (PPS) maculopathy evolve after drug cessation?

PURPOSE Recent studies have linked a vision-threatening maculopathy with long-term use of pentosan polysulfate sodium (PPS). Little is known about what occurs after drug cessation. This study aims to evaluate long-term outcomes after drug cessation in subjects with PPS maculopathy.

METHODS This retrospective study across three institutions (Emory Eye Center, Casey Eye Institute, and Kellogg Eye Center) evaluated subjects with PPS maculopathy who had reported discontinuation of PPS use. Patients with at least 6 months of follow-up and at least two visits while off the medication were included. Twenty-four eyes of 12 patients were included in the study. Expert image reviewers assessed retinal imaging characteristics to assess for evolution of structural changes. Change in subjective visual function and visual acuity was also evaluated.

RESULTS Twelve subjects, all female with a median age of 57 years (range, 37 - 74 years), met the eligibility criteria. Participants had a baseline visit at a median of 2.5 months (range, 0 - 480 months) after drug cessation, and were subsequently followed for a median of 12.6 months (range, 7 - 65 months). The median cumulative exposure was 1.81 kg. No eyes exhibited a demonstrable improvement in retinal structure or function while off PPS. Ten subjects (83%) reported worsening of visual symptoms at the final visit. Visual acuity declined by greater than 1 line in two eyes of two subjects (8%), associated with progressive RPE atrophy in both cases. There was evolution in the pattern of FAF changes in nearly all eyes. Seven (29%) eyes had macular RPE atrophy at the baseline visit, and atrophy enlarged in all seven eyes. Two eyes (8%) of one subject developed new onset macular RPE atrophy while off PPS.

CONCLUSION PPS maculopathy continues to evolve after drug cessation. In some cases, progressive RPE atrophy poses a long-term threat to central vision. Affected patients should be counseled appropriately, and screening programs should be instituted to promote early detection. This study also yields insights into the nature of RPE degeneration that may have implications for other atrophic maculopathies.

HUMAN RESEARCH Yes: Approved by institutional review board

Nonneovascular Age Related Macular Degeneration and Fluid

- David Sarraf, MD
- Assaf Hilely, MD
- Adrian Au, MD
- Mee Yon Lee, MD, PhD
- Frederic Gunnemann, MD

OBJECTIVE To evaluate the various patterns of subretinal fluid (SRF) in eyes with age related macular degeneration (AMD) in the absence of macular neovascularization (MNV)

PURPOSE To evaluate the various patterns of subretinal fluid (SRF) in eyes with age related macular degeneration (AMD) in the absence of macular neovascularization (MNV), and to determine the future risk of macular atrophy.

METHODS This retrospective study included only eyes with non-neovascular AMD and associated SRF. Eyes with evidence of MNV were excluded. Spectral domain optical coherence tomography (SD-OCT) was obtained at baseline and at follow up and qualitative and quantitative SD-OCT analysis of macular drusen including drusenoid pigment epithelial detachment (PED) and associated SRF was performed to determine anatomical outcomes

RESULTS Seventy-four eyes (74 patients) were included in this analysis. Mean duration of follow-up was 50.1±37.9 months. SRF exhibited 3 different morphologies: crest of fluid over the apex of the drusenoid PED, drape of low-lying fluid over confluent drusen or focus of fluid at the angle of confluent drusen. Forty-four (59.5%) of the 74 eyes with fluid displayed collapse of the associated druse or drusenoid PED and 33 (44.6%) of the 74 eyes developed evidence of complete retinal pigment epithelial and outer retinal atrophy (cRORA),

CONCLUSION Non-neovascular AMD with SRF is an important clinical entity to recognize to avoid unnecessary anti-VEGF therapy. In this entity, SRF may develop in association with drusen or drusenoid PED and in the absence of MNV and may be associated with the future

development of atrophy, especially when the fluid is located over the apex of a drusenoid PED or drapes confluent drusen.

HUMAN RESEARCH Yes: Approved by institutional review board

Cognitive Testing in Patients Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Wet Age-Related Macular Degeneration

- Subhransu K. Ray, MD, PhD
- Sarah Manz

OBJECTIVE Based on the essential role of VEGF in CNS health, we evaluated whether repeated intravitreal anti-VEGF injections may be impacting cognitive health in patients with neovascular ARMD.

PURPOSE Millions of anti-VEGF IVI are performed yearly. VEGF is pathological in ARMD but plays a central role in neuroprotection. Direct communication channels exist between the vitreous cavity and CNS in several pathological states. Intravitreal anti-VEGF compounds are detected systemically in a bio-active form. Reduced CNS VEGF levels are associated with cognitive decline, and VEGF suppression can alter neuronal structure. No formal studies have been reported evaluating cognitive health post IVI.

METHODS This was a cross-sectional study comparing the BHA scores of AMD patients ages 65-85 in relation to their life-time cumulative number of anti-VEGF IVI. Cognitive function was assessed using University of California San Francisco's BHA, a peer-validated tool used for the early detection of mild neurocognitive disorders. The BHA is a 10-minute iPad based test that provides individual and composite age-corrected scores of executive function and speed, language, visuospatial, and memory tests. Study design includes 300 wet AMD (≥1 IVI) and 100 dry AMD (0 IVI) patients. Vision must have been better than 20/50 in at least one eye and the patient must have no prior history of known CNS disorders. This study reports on an interim analysis of the first 116 patients enrolled in the study.

RESULTS Interim analysis of the first 116 patients enrolled in the study with independent-sample t-testing revealed that there was a statistically significant difference in patient BHA scores [$t(116) = 2.03$, $p=<0.05$] indicating a greater prevalence of cognitive impairment in patients with greater than 20 IVI. Patients with < 20 IVI (n=72) had significantly healthier BHA scores than those with ≥ 20 IVI (n=44). The BHA Z-scores refer to the likelihood of cognitive impairment (CI), where <-1.5Z equates to a high likelihood of CI, -1.5Z to -1.0Z equates to a moderate likelihood of CI, and >-1.0Z equates to a low likelihood of CI. The average Z-score for < 20 IVI group was -0.83, while the average Z-score for the ≥ 20 IVI was –1.27 ($p<0.05$). When grouped with respect to the cumulative number of IVI and high likelihood of CI, 0 injections (n=29) had 27.6% risk, 1-20 injections (n=44) had 31.8% risk, and >20 injections (n=43) had 41.9% risk. The mean age of the < 20 IVI group was 76.9 ± 0.4 and 78.8 ± 0.7 for the ≥ 20 IVI group. The mean number of education years for the < 20 IVI group was 15.7 ± 0.1 and 15.3 ± 0.1 for the ≥ 20 IVI group.

CONCLUSION Patients receiving frequent anti-VEGF IVI may have a greater risk of cognitive impairment. Cognitive assessment tools can be effectively used in the clinical

retina setting. This study is limited by its retrospective nature, and the interim analysis data points. Due to the frequency of IVI performed in a cognitively at-risk population, possible communication channels between the vitreous and brain in some scenarios, and the role of VEGF in CNS health, further evaluation is warranted.

HUMAN RESEARCH Yes: Approved by institutional review board

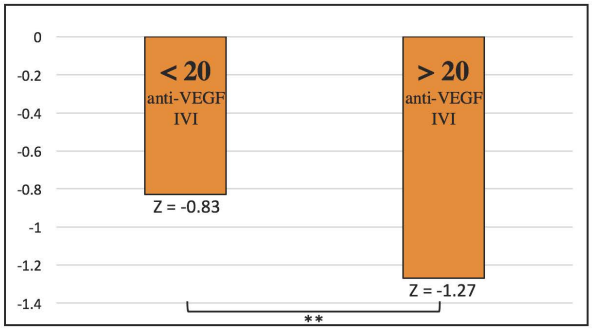


Figure 1. Patients with < 20 anti-VEGF IVI (n = 72) had significantly healthier BHA scores than those with ≥ 20 (n = 44) anti-VEGF IVI. CI = cognitive impairment, **p < 0.05

Z-score interpretations:
< -1.5Z = High likelihood of CI
-1.5 to -1.0Z = Moderate likelihood of CI
> -1.0Z = Low likelihood of CI

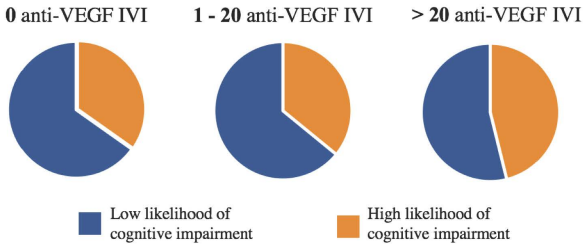


Table 1. Percentage of patients who scored with low, moderate, or high likelihoods of CI. AMD patients grouped by 0 (n = 29), 1-20 (n = 44), or > 20 (n = 43) lifetime injections. CI = cognitive impairment

	Low Likelihood of CI	Moderate Likelihood of CI	High Likelihood of CI
0 injections	51.7%	20.7%	27.6%
1- 20 injections	56.8%	11.4%	31.8%
> 20 injections	48.8%	9.3%	41.9%

Avacincaptad Pegol, A Novel C5 Inhibitor, Reached Statistical Significance in a Pivotal Clinical Trial for Geographic Atrophy Secondary to Dry AMD

- Baruch D. Kuppermann, MD, PhD

OBJECTIVE Complement C5 inhibition significantly reduces the mean rate of GA growth over 12 months.

PURPOSE The role of complement in AMD has been well established. Downstream in complement cascade, cleavage of complement C5 leads to the generation of C5a and C5b. C5a is involved in priming and activation of inflammasomes while C5b may lead to the formation of membrane attack complex (MAC). The activation of inflammasome or the accumulation of MAC may lead to RPE degeneration and cell death.

METHODS Pivotal, randomized, double masked, sham controlled clinical trial evaluating the safety and efficacy of avacincaptad pegol (Zimura®), a novel complement C5 inhibitor, for the treatment of geographic atrophy. Patients who received treatments of either Sham, Zimura 2mg, or Zimura 4mg were analyzed for statistical analysis. The inclusion criteria include: the presence of non-foveal GA; a total GA area ≥2.5 and ≤17.5 mm2; GA in part within 1500 microns from the foveal center; and BCVA between 20/25–20/320, inclusive. The primary efficacy endpoint was the mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12.

RESULTS 286 patients were enrolled in this study. The reduction in the mean rate of GA growth over 12 months was 27.38% (p-value = 0.0072) for the Zimura 2 mg group as compared to the corresponding sham group and 27.81% (p-value = 0.0051) for the Zimura 4 mg group as compared to the corresponding sham group. These data for both dose groups were statistically significant. Although efficacy data from patients receiving Zimura 1 mg was not part of the prespecified statistical analysis, preliminary descriptive analysis indicated that, on average, the percent GA growth from baseline to month 12 for Zimura 1 mg group was less than for the corresponding sham group. The overall data suggest a dose response relationship across treatment arms. Zimura was generally well tolerated over 12 months of administration. There was no Zimura-related inflammation, no Zimura-related adverse events, no ocular serious adverse events, and no cases of endophthalmitis reported in the study eye in this ongoing trial.

CONCLUSION Complement C5 is a viable target for inhibition to potentially prevent or slow RPE cell death in patients with GA. A second pivotal clinical trial is initiating to further confirm the efficacy and safety of Zimura in GA. The downstream location of C5 in the complement cascade may offer additional advantage of decreasing the potential safety impact of upstream complement inhibition in the eye.

HUMAN RESEARCH Yes: Approved by institutional review board

Impact of Baseline OCT Characteristics on Response to Risuteganib for the Treatment of Intermediate Age-Related Macular Degeneration

- Justis P. Ehlers, MD
- Glenn J. Jaffe, MD
- Joseph Abraham
- Peter K. Kaiser, MD
- David S. Boyer, MD
- Jeffrey S. Heier, MD
- Julia Kornfield, PhD
- Baruch D. Kuppermann, MD, PhD
- Hugo Quiroz-Mercado, MD
- Janine Aubel, BS, MBA
- Lisa Karageozian, MBA
- Vicken Karageozian
- Melvin Sarayba, MD

OBJECTIVE To assess the impact of baseline OCT features on response to risuteganib in the treatment of intermediate non-exudative age-related macular degeneration

PURPOSE The purpose of the study was to perform a post-hoc analysis to explore the effect of baseline anatomic characteristics identified on optical coherence tomography (OCT) on best-corrected visual acuity (BCVA) response with risuteganib from the completed Phase 2 study in subjects with dry age-related macular degeneration.

METHODS The Phase 2 clinical study was double-masked, placebo-controlled evaluating eyes with BCVA between 20/40-20/200 randomized to intravitreal 1.0mg risuteganib or sham injection at baseline. At week 16, subjects in the risuteganib group received a second 1.0 mg dose and the sham group crossed over to receive a dose of 1.0mg risuteganib. The primary endpoint was percentage of subjects with ≥ 8 letters BCVA gain from baseline to week 28 in the risuteganib group vs baseline to week 12 for the sham group. Two independent masked reading centers evaluated baseline anatomic characteristics on OCT to explore for features associated with positive response to risuteganib.

RESULTS Forty-five subjects were enrolled in the study. At baseline, mean age was 78.8 and 75.9 years and mean BCVA was 67.1 and 64.4 letters in the sham and risuteganib groups, respectively. The primary endpoint was met during the study with 48% of subjects in the risuteganib group at week 28 and 7% of patients in the sham group at week 12 gaining > 8 letters from baseline (p=0.013). Of the risuteganib subjects, 20% gained > 15 letters at week 28, and no patients in the sham group at week 12 achieved this visual acuity gain. Quantitative assessment, using multi-layer segmentation, demonstrated that greater outer retinal volume/thickness, increased ellipsoid zone integrity, and surrogates for photoreceptor outer segment length were associated with enhanced BCVA response to risuteganib. Risuteganib demonstrated a good safety profile in this study.

CONCLUSION Risuteganib showed significant benefit over sham in subjects with dry AMD with respect to proportion of subjects gaining > 8 letters of BCVA from baseline. This post hoc analysis provides preliminary insights into baseline OCT features that may help to determine likelihood of BCVA response to risuteganib. These findings will be confirmed in an upcoming larger trial.

HUMAN RESEARCH Yes: Exempt from approval