Uveitis is often a chronic disease requiring long-term treatment. This study tested the hypothesis that ADX-102, a novel aldehyde sequestering agent, could provide an efficacy profile similar to that of PA monotherapy in patients with noninfectious anterior uveitis (NAU).

Purpose: Aldehydes are pro-inflammatory mediators of allergic (TH2) and auto-immune (TH1) inflammation. ADX-102 is a novel aldehyde sequestering agent that represents a new anti-inflammatory drug class. There is evidence that prevention of toxic aldehyde formation and accumulation may diminish inflammation, fibrosis, and oxidative damage associated with uveal disease. ADX-102 has demonstrated positive Phase 2 results in allergic conjunctivitis. This Phase 2 clinical trial evaluated the safety and efficacy of ADX-102 in subjects with noninfectious anterior uveitis (NAU).

Methods: A randomized, multi-center, investigator-masked, comparator-controlled, parallel-group trial of 0.5% ADX-102 topical ophthalmic solution was conducted in 45 subjects with acute flares of NAU at 15 US sites. Subjects were randomized equally to 6 weeks of therapy with ADX-102 QID, 1% Prednisolone Acetate (PA; Pred Forte®, Allergan, Irvine, CA) QID (tapered), or a combination of ADX-102 QID and 1% PA BID (tapered). Efficacy was assessed by anterior chamber cell (ACC) counts and aqueous flare (AF).

Results: Kaplan-Meier estimates of time to ACC treatment success, ACC grade reduction, AF treatment success, and AF grade reduction were similar across treatment groups and not statistically significantly different for any ADX-102 treatment group compared with PA alone. For ACC results, improvement to Grade 0 was seen in all treatment groups over the course of the study. At Week 8, the proportion of subjects with Grade 0 ACC was similar across groups, with 47%, 46%, and 44% in the ADX-102, PA, and combination groups, respectively. ACC and AF improved over time for all treatment groups. Post hoc inference testing showed that the Least Square mean change from Baseline in ACC grade for the ADX-102 and combination treatment groups was consistently greater than the PA group. Rescue rates did not vary significantly among treatment groups (20% in ADX-102, 38% in PA, 25% in the combination group).

Conclusions: These results suggest that ADX-102 treatment alone, or in combination with PA, was effective in the treatment of NAU with an efficacy profile similar to that of PA monotherapy in this clinical trial.

Clinical Relationships: John D. Sheppard;
Todd Brady, Aldeyra Therapeutics (E); C. Stephen Foster, Aldeyra Therapeutics (F); Kenneth J. Mandell, Aldeyra Therapeutics (C); Scott L. Young, Aldeyra Therapeutics (C)

Support: Supported by Aldeyra Therapeutics

Clinical Trial: NCT02406209

Program Number: 1231
Presentation Time: 8:45 AM–9:00 AM
A Randomized, Comparator-Controlled Phase 2 Clinical Trial of ADX-102 Ophthalmic Solution in Noninfectious Anterior Uveitis
John D. Sheppard1,2, Todd Brady1, C. Stephen Foster2, Kenneth J. Mandell1, Scott L. Young1
1Ophthalmology, Eastern Virginia Medical School, Norfolk, VA; 2Cornea & Uveitis, Virginia Eye Consultants, Norfolk, VA; 3Aldeyra Therapeutics, Lexington, MA; 4Harvard Medical School, Boston, MA.

Purpose: Aldehydes are pro-inflammatory mediators of allergic (TH2) and auto-immune (TH1) inflammation. ADX-102 is a novel aldehyde sequestering agent that represents a new anti-inflammatory drug class. There is evidence that prevention of toxic aldehyde formation and accumulation may diminish inflammation, fibrosis, and oxidative damage associated with ocular disease. ADX-102 has demonstrated positive Phase 2 results in allergic conjunctivitis. This Phase 2 clinical trial evaluated the safety and efficacy of ADX-102 in subjects with noninfectious anterior uveitis (NAU).

Methods: A randomized, multi-center, investigator-masked, comparator-controlled, parallel-group trial of 0.5% ADX-102 topical ophthalmic solution was conducted in 45 subjects with acute flares of NAU at 15 US sites. Subjects were randomized equally to 6 weeks of therapy with ADX-102 QID, 1% Prednisolone Acetate (PA; Pred Forte®, Allergan, Irvine, CA) QID (tapered), or a combination of ADX-102 QID and 1% PA BID (tapered). Efficacy was assessed by anterior chamber cell (ACC) counts and aqueous flare (AF).

Results: Kaplan-Meier estimates of time to ACC treatment success, ACC grade reduction, AF treatment success, and AF grade reduction were similar across treatment groups and not statistically significantly different for any ADX-102 treatment group compared with PA alone. For ACC results, improvement to Grade 0 was seen in all treatment groups over the course of the study. At Week 8, the proportion of subjects with Grade 0 ACC was similar across groups, with 47%, 46%, and 44% in the ADX-102, PA, and combination groups, respectively. ACC and AF improved over time for all treatment groups. Post hoc inference testing showed that the Least Square mean change from Baseline in ACC grade for the ADX-102 and combination treatment groups was consistently greater than the PA group. Rescue rates did not vary significantly among treatment groups (20% in ADX-102, 38% in PA, 25% in the combination group).

Conclusions: These results suggest that ADX-102 treatment alone, or in combination with PA, was effective in the treatment of NAU with an efficacy profile similar to that of PA monotherapy in this clinical trial.

Clinical Relationships: John D. Sheppard;
Todd Brady, Aldeyra Therapeutics (E); C. Stephen Foster, Aldeyra Therapeutics (F); Kenneth J. Mandell, Aldeyra Therapeutics (C); Scott L. Young, Aldeyra Therapeutics (C)

Support: Supported by Aldeyra Therapeutics

Clinical Trial: NCT02406209

Program Number: 1232
Presentation Time: 9:00 AM–9:15 AM
An Injectable Fluocinolone Acetonide Intravitreal Insert Decreases the Incidence of Recurrence in Patients with Chronic Non-infectious Uveitis Affecting the Posterior Segment of the Eye: 12 Month Results
Glenn J. Jaffe1, Dario Paggianiorno2, Gerald Riedel3
1Ophthalmology, Duke University Eye Center, Durham, NC; 2pSivida, Watertown, MA.

Purpose: Uveitis is often a chronic disease requiring long-term medical therapy. This study tested the hypothesis that
an injectable fluocinolone acetonide intravitreal insert (FAI) delivering microdoses for 36 mo. can reduce the proportion of subjects who have a recurrence of uveitis over an extended time period after a single administration. **Methods:** We conducted a phase III, multi-national, multi-center, randomized, masked, safety and efficacy study of an FAI. The study included subjects who had been diagnosed with unilateral or bilateral chronic non-infectious uveitis affecting the posterior segment of the eye for at least 12 mo. prior to randomization. Following the injection subjects were evaluated through 36 mo. **Results:** A total of 129 subjects were enrolled in the study (all randomized population), 87 subjects and 42 subjects in the FAI and sham injection treatment groups, respectively. All randomized subjects were included in the ITT efficacy analysis and safety populations. The proportion of subjects who had a study eye uveitis recurrence within 6 mo. of treatment was significantly lower in the FAI treatment group compared with the sham injection treatment group (ITT population: 24 [27.6%] subjects and 38 [90.5%] subjects in the FAI treatment group and the sham injection treatment group, respectively (OR: 24.94; 95% CI: 8.04, 77.39; p<0.001). The recurrence rates within 12 mo. were also significantly lower in the FAI treatment group compared with the sham injection treatment group (ITT population: 33 [37.9%] subjects and 41 [97.6%], respectively (OR: 67.09; 95% CI: 8.81, 511.06; p<0.001). Filtration surgery was required in 3 [3.4%] and 1 [2.4%] subjects, and cataract surgery in 12 [13.8] and 1 [2.4%] subjects by 12 mo. in the FAI treatment group and the sham injection treatment group, respectively. The study is still open; follow-up will continue through 36 mo. **Conclusions:** The FAI very effectively reduced the number of uveitis recurrences compared to sham injection. Administration of a single FAI resulted in a 3-fold reduction in the rate of recurrence at 6 mo. compared to the sham and the effect was maintained at 12 mo. This treatment is a very promising method to provide long-term inflammation control with an office-based injection procedure and with an acceptable safety profile. **Commercial Relationships:** Glenn J. Jaffe, AbbVie (C); Dario Paggiarino, pSivida (E); Gerald Riedel, pSivida (E) **Clinical Trial:** NCT01694186 **Program Number:** 1233 **Presentation Time:** 9:15 AM–9:30 AM **Optical Coherence Tomography Evaluation of Uveitic Macular Edema and Response to Treatment with Oral Carbonic Anhydrase Inhibitor Monotherapy** Macklin H. Nguyen, Cecilia Lee, Russell N. Van Gelder, Kathryn L. Pepple. Ophthalmology, University of Washington, Seattle, WA. **Purpose:** Oral carbonic anhydrase inhibitors (CAI) such as acetazolamide are offered to patients with refractory uveitic macular edema despite fluorescein angiography (FA) studies demonstrating limited efficacy. While optical coherence tomography (OCT) cannot visualize leakage, it can detect and monitor macular edema (ME). In addition, OCT can identify structural changes in the retina that FA cannot. We hypothesized that OCT would detect a benefit of CAI therapy on ME, and that there are OCT characteristics that would predict a response to CAI therapy. **Methods:** A retrospective chart review identified patients treated with a CAI for uveitic ME between 2007 and 2014. Inclusion criteria included age ≥18, OCT with central subfield thickness (CST > 320), and follow-up OCT within 1 to 3 months. Exclusion criteria included new or increased systemic steroids, immune modulators, or Durezol within one month preceding CAI initiation or during the study. Baseline OCTs were scored for the presence of epiretinal membrane (ERM), subretinal fluid (SRF), cystic intraretinal fluid (cIRF), and vitreomacular traction (VMT). Fisher’s exact test and multivariate logistic regression were used to test for predictors of response and Vitloxon signed-rank or student’s t-test were used to evaluate the macular thickness and visual acuity changes attributable to CAI therapy. **Results:** 61 charts were screened. Sixteen subjects (19 eyes) met all criteria and were included. Subjects included nine females (56%), with a mean age of 57.9 years (19.7-81.1). The most common diagnosis was idiopathic uveitis (n=6, 31.6%) and mean duration of uveitis diagnosis was 4.4 years (0.2-27.5). Average CST decreased significantly with treatment from 471.8 ± 110.6 to 358.3 ± 50.4 (p<0.0001). Average visual acuity (LogMAR) improved significantly from 0.43 ± 0.25 to 0.27 ± 0.16 (p=0.003). Pretreatment OCTs revealed the presence of cIRF (n=19, 100%), SRF (n=8, 42.1%), ERM (n=13, 68.3%), and VMT (n=1, 5.2%). No specific characteristic was predictive of a response to therapy. **Conclusions:** There is a significant benefit on CST and vision from CAI treatment in patients with uveitic ME. The small final number of patients analyzed may have limited our ability to identify predictors of response to therapy. However, these results suggest that in patients with refractory uveitis ME, treatment with a CAI may be warranted. **Commercial Relationships:** Macklin H. Nguyen, None; Cecilia Lee, None; Russell N. Van Gelder, None; Kathryn L. Pepple, None **Support:** NIH/NEI K23EY024921 **Program Number:** 1234 **Presentation Time:** 9:30 AM–9:45 AM **Clinical, Adaptive Optics Imaging and Electrophysiologic Outcomes in Autoimmune Retinopathy Patients with Rituximab** Samaneh Davoudi, Damla Seygi, Çağla Yasa, Nazanin Ebrahimiadi, Inês Lains, Ramak Roohipoor, Evangelia Papavasileiou, Jason Comander, Lucia Sobrin. Ophthalmology, MEEI, Arlington, MA. **Purpose:** Given the proposed antibody-mediated of autoimmune retinopathy (AIR), rituximab as a therapeutic agent that targets B cells would seem reasonable. In this retrospective case series, we evaluate clinical and ancillary testing, including adaptive optics, outcomes in patients treated with rituximab. **Methods:** 16 AIR patients (37.5 % male, mean age of 56 years) treated with rituximab were enrolled. The AIR diagnosis was based on clinical symptoms, electroretinogram (ERG) depression, presence of anti-retinal antibodies and exclusion of other diagnoses. All patients were treated initially with intravenous rituximab 375 mg/ m² weekly for 4 weeks or 1000 mg every other week for two doses. Treatment was repeated every 6 months or sooner if the patients were worsening. Visual acuity (VA), ERG and spectral domain optical coherence tomography (SD-OCT) results were recorded. OCT characteristics examined included total macular volume (TMV) and central subfield macular thickness (CSMT). A subset of patients was also imaged using Adaptive Optics Scanning Laser Ophthalmoscopy (AO-SLO). Cone densities were measured in ten 150 × 150 μm² squares at each visit in the same locations at 1, 2 and 3 mm from the fovea. Outcomes before and after treatment were analyzed comparing the mixed model linear regression. **Results:** Seven patients had paraneoplastic retinopathy and nine had non-paraneoplastic AIR. The mean follow-up period was 15 months (range 7-34 months) after rituximab initiation. 63% of eyes had stable VA during rituximab therapy. 14% of eyes experienced VA improvement. ERG parameters, CSMT and TMV did not decrease to a significantly degree over the rituximab treatment period. Six
eyes had serial AO-SLO imaging. Cone densities did not change significantly over the treatment period.

**Conclusions:** VA was stable or improved in a majority of AIR patients while being treated with rituximab. OCT and ERG parameters, as well as AO-SLO cone densities, were stable during treatment. Studies with additional patients and longer follow up periods are needed to further explore the utility of rituximab in the management of AIR.

**Commercial Relationships:** Samaneh Davoudi, None; Damla Sevgi, None; Cagla Yasa, None; Nazanine Ebrahimie db, None; Inès Lains, None; Ramak Roohipoor, None; Evangelia Papavasilieou, None; Jason Comander, None; Lucia Sobrin, None

**Program Number:** 1235
**Presentation Time:** 9:45 AM–10:00 AM

**Development of mouse anti-mouse CD6 monoclonal antibodies (mAbs) for treating experimental autoimmune uveitis in mice**

Lingjun Zhang,1 Wen Qiu,1 Brent A. Bell,1 Li Yan,1 Timothy S. Kern,1 Rachel R. Caspi,1 Feng Lin,1

1Immunology, Cleveland Clinic, Cleveland, OH; 2Cleveland Clinic, Cleveland, OH; 3Department of Medicine and Ophthalmology, Case Western Reserve University, Cleveland, OH; 4Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD.

**Purpose:** CD6 is emerging as a promising target for treating T-cell-mediated autoimmune diseases, but whether it could be targeted for treating autoimmune uveitis remains unknown. Disease models developed in mice are widely used to evaluate the potentials of new therapies; however, all existing anti-mouse CD6 mAbs were developed in rats or other animals. These mAbs are highly immunogenic in mice, making long-term and/or multiple treatment studies difficult. We aimed to develop mouse anti-mouse CD6 mAbs and to test their efficacy in treating experimental autoimmune uveitis (EAU).

**Methods:** CD6 knockout (KO) mice were immunized with a recombinant mouse CD6 protein to develop mAb-producing hybridomas. Mouse anti-mouse CD6 mAbs produced by these hybridomas were screened by ELISA, flow cytometry and in vitro T-cell inhibition assays. Finally, one of the identified mouse anti-mouse CD6 mAbs was prepared and tested for its efficacy in halting the development of uveitis induced by already primed uveitogenic T cells in a model of adoptively transferred EAU. Indirect ophthalmoscopy, scanning laser ophthalmoscopy and spectral-domain optical coherence tomography were used to evaluate uveitis severity.

**Results:** 28 positive mouse anti-mouse CD6 mAbs were identified by ELISA: 7 of the 28 were positive in flow cytometry assays; 3 of those 7 inhibited antigen-specific T-cell responses in vitro; 1 of the final 3 functional mAbs that showed a cross-reaction with human CD6 was tested in treatment studies in vivo. This mAb significantly reduced the severity of uveitis, as assessed by the ocular imaging techniques described above.

**Conclusions:** Mouse anti-mouse CD6 mAbs have been developed, and one of these mAbs is highly effective in treating EAU induced by already activated uveitogenic T cells, suggesting that (a) targeting CD6 would be a new approach for treating autoimmune uveitis and (b) this mouse anti-mouse/human CD6 mAb might be further developed as a new therapeutic for clinical use.

**Commercial Relationships:** Lingjun Zhang, None; Wen Qiu, None; Brent A. Bell, None; Li Yan, None; Timothy S. Kern, None; Rachel R. Caspi, None; Feng Lin, None

**Program Number:** 1236
**Presentation Time:** 10:00 AM–10:15 AM

**Neuroprotective effects of IL-22 during CNS inflammation**

Rachel R. Caspi, Rachael C. Rigden, Jennifer L. Kielczewski, Carlos R. Zara te-Blades, Anthony J. St. Leger, Phyllis B. Silver, Yingyos Jittayasothorn, Chi-Chao Chan, Mary J. Mattapallil, Laboratory of Immunology, National Eye Inst/NIH, Bethesda, MD.

**Purpose:** IL-22 has opposing effects in different tissues, from pro-inflammatory (skin, joints) to protective (liver, intestine) but little is known about its effects on neural tissue. We examined this using the induced models of experimental autoimmune uveitis (EAU) and experimental autoimmune encephalomyelitis (EAE).

**Methods:** EAU or EAE were induced in WT or IL-22−/− mice by active immunization with a peptide from IRBP or from MOG, respectively, in Freund’s complete adjuvant. Intravitreal injections of the substances specified below were administered to anesthetized mice in a volume of 1 µl. Neuroprotection was assessed after intravitreal glutamate injection by counting surviving retinal ganglion cells (RGC) following retrograde fluorogold labeling.

**Results:** During EAU, IL-22 was produced by CD4+ eye-infiltrating cells, many of which co-produced IL-17. IL-22−/− mice immunized for EAU or for EAE developed exacerbated disease, as did wild type mice immunized for EAU and treated systemically or intraocularly with anti-IL-22 during the expression phase of disease. Mechanistic studies revealed that retinal glial Müller cells in uveitic eyes had upregulated IL-22 mRNA expression. IL-22 upregulated IL-22 mRNA expression in cultured primary Müller cells and enhanced their ability to suppress T cell activation in vitro. Finally, IL-22 injected into the eye concurrently with IL-1β, inhibited IL-1–induced expression of multiple proinflammatory and proapoptotic genes in retinal tissue. ‘Ingenuity’ pathway analysis suggested activation of neuroprotective pathways. In keeping with this, co-injection of IL-22 had protective effects on RGC in vivo in a model of glutamate-induced neurotoxicity.

**Conclusions:** These results suggest that IL-22 activates multiple molecular and cellular pathways within the CNS tissue to limit inflammatory damage and provide neuroprotection.

**Commercial Relationships:** Rachel R. Caspi, None; Rachael C. Rigden, None; Jennifer L. Kielczewski, None; Carlos R. Zarate-Blades, None; Anthony J. St. Leger, None; Phyllis B. Silver, None; Yingyos Jittayasothorn, None; Chi-Chao Chan, None; Mary J. Mattapallil, None

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