Novel Small Molecule Aldehyde Sequestering Agents Demonstrate Broad Therapeutic Potential for Ocular Inflammation

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PURPOSE

Pro-inflammatory aldehydes, such as malondialdehyde (MDA), 4-hydroxy-nonenal, glyoxal, methylglyoxal, and retinal, have been implicated in the pathogenesis of several ocular inflammatory diseases. Aldehydes initiate activation of pro-inflammatory pathways, including the NFκB pathway. Recently, the aldehyde trap reproxalap (ADX-102) demonstrated statistically and clinically significant activity in Phase 2 clinical trials in allergic conjunctivitis, dry eye disease, and noninfectious anterior uveitis, all of which are ocular inflammatory diseases. To demonstrate the potential of aldehyde sequestration in inflammatory diseases involving the anterior and posterior segments of the eye, two structurally distinct aldehyde traps (reproxalap and ADX-103) were tested in two models of ocular inflammation.

METHODS

A mouse knockout model (abcr$^{-/-}$) of macular degeneration (MD) was used to test the activities of reproxalap and ADX-103. The retinal transport protein, ABCA4, is not expressed in these mice, allowing retinal to escape the light cycle and form a toxic metabolite with phosphatidylethanolamine: *N*-retinylidene-phosphatidylethanol-amine (A2E). Mice were treated intraperitoneally (IP) for 56 days with 10 mg/kg reproxalap (n = 24), ADX-103 (n = 24), or vehicle (n = 22), starting at week 10 to 12 of life. An untreated control group (n = 12) was sacrificed on the first day of dosing. After treatment, A2E concentrations in retinas were measured by HPLC. Statistical significance from vehicle control was determined by t-test.

In a rat model of lipopolysaccharide (LPS)-induced uveitis, 50 µg of reproxalap or ADX-103 was topically administered (TO) to the eye at hours 1, 3, 7, 10, and 17, after LPS induction, or by a single intravitreal (IVT) injection (25 µg) 1 hour after LPS induction (n = 10 per group). Ocular exams were performed 6 and 24 hours after LPS injection, after which retina-choroid specimens were processed for MDA adduct ELISA. Anterior segments were scored using a combined Draize and McDonald-Shattuck scoring system, and posterior segments were scored using 0 to 1 (vitreous, optic disc, retinal vasculature) and 0 to 4 (retinal and choroidal hemorrhage, exudation, and detachment) scales. Statistical significance from vehicle control was determined by ANOVA, followed by Tukey's *post hoc* test.

Data represent mean ± SEM. * p ≤ 0.05 compared to vehicle;
** p ≤ 0.01 compared to vehicle; *** p ≤ 0.001 compared to vehicle;
**** p≤ 0.0001 compared to vehicle

RESULTS

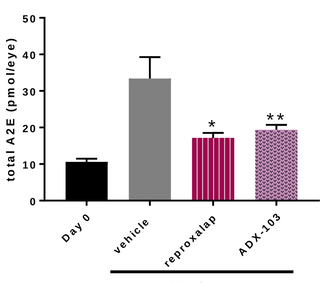

Figure 1: **Both reproxalap and ADX-103 significantly decrease the formation of A2E in the retinas of abcr$^{-/-}$ mice.** Mice were treated daily, IP, for 56 days with 10 mg/kg vehicle, reproxalap, or ADX-103

Disclosures: Macdonald (E), Halilovic (E), Brady (E)

RESULTS (continued)

In the MD model, daily reproxalap or ADX-103 treatment decreased formation of A2E by 71% or 69%, respectively, compared with vehicle controls (Figure 1). In a separate study, systemic (IP) doses of reproxalap, 5-fold greater than the effective dose in the A2E study, administered for 56 days, had no effect on dark adaptation (data not shown). Daily treatment with reproxalap or ADX-103 for 56 days had no effect on body weight, nor were any drug-related adverse effects observed.

In the LPS-induced uveitis model, ocular exam scores were significantly improved, compared to vehicle, at 6 hours and 24 hours after TO administration of reproxalap or ADX-103. After IVT administration of reproxalap or ADX-103, ocular exam scores were also significantly improved vs. vehicle. Small, although not significant, reductions in MDA adducts were observed in the reproxalap and ADX-103 groups after TO and IVT administration (data not shown). To control for variations between individual animals, a within-subject statistical analysis, examining the co-variates of treatment and time, was conducted on the retina-choroid scores from the IVT groups. Retina-choroid scores in rats were significantly improved following IVT treatment with either reproxalap or ADX-103, compared to vehicle control (Figure 7).

Ocular Exam Scores Following Topical Ocular Dosing

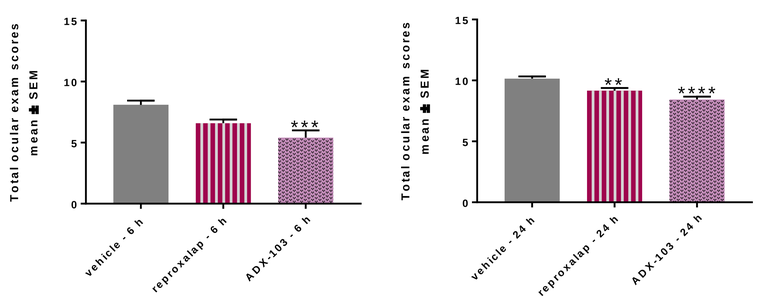

Figure 2: **Both reproxalap and ADX-103 decrease total ocular inflammation.**

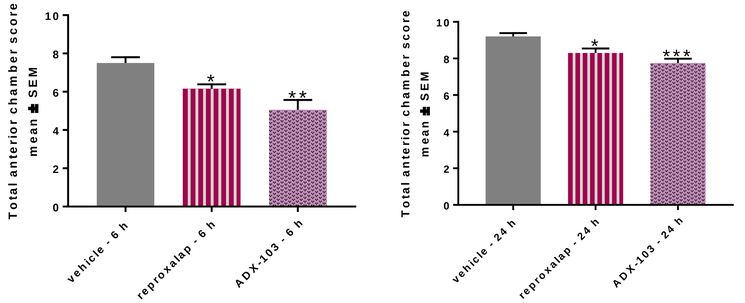

Figure 3: **Both reproxalap and ADX-103 decrease anterior chamber inflammation.**

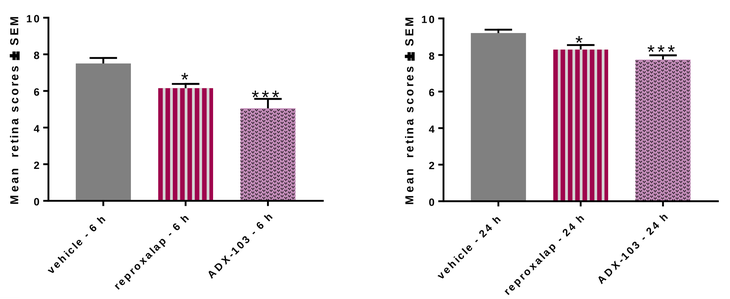

Figure 4: **Both reproxalap and ADX-103 decrease retina-choroid inflammation.**

Ocular Exam Scores Following Intravitreal Dosing

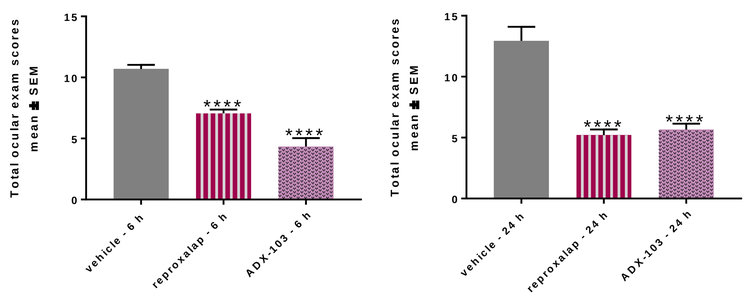

Figure 5: **Both reproxalap and ADX-103 decrease total ocular inflammation.**

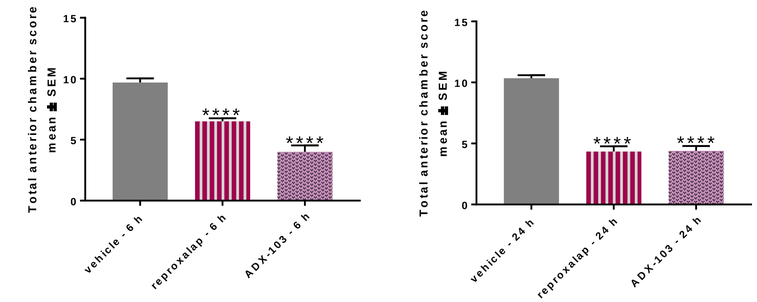

Figure 6: **Both reproxalap and ADX-103 decrease anterior chamber inflammation.**

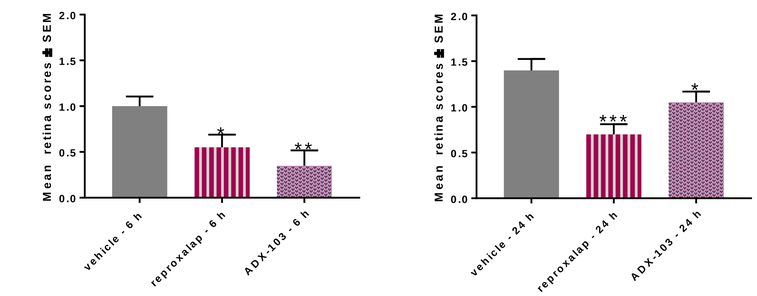

Figure 7: **Both reproxalap and ADX-103 decrease retina-choroid inflammation.**

CONCLUSIONS

Two structurally distinct aldehyde traps have shown activity in two models of ocular inflammation following ocular (TO, IVT) and systemic (IP) administration. No evidence of ocular or systemic toxicity was noted with any route of administration. Overall, the data suggest that aldehyde sequestration has broad potential for the treatment of a range of ocular diseases in which inflammation plays a role, including diseases involving the posterior pole and the anterior chamber.