Efficacy of a RARγ selective agonist eye drop formulation on improvement of tear production and corneal fluorescein staining in the BTX-B mouse model of dry eye disease

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Background and Objective

Despite the reported mucocutaneous side effects of systemic retinoids, including dry eye, multiple clinical studies have demonstrated the potential beneficial effects of topical retinoids on dry eye disease. Retinoic acid receptors (RAR) α, β and γ are widely distributed in ocular tissues. In vitro data suggest that the beneficial effects of retinoids on ocular health are mediated via RARγ (Kimura et al. *J. Mol. Biol.* 2015). The purpose of this study was to evaluate the in vivo effects of palovarotene, a RARγ selective agonist, in a dry eye disease animal model.

Methods

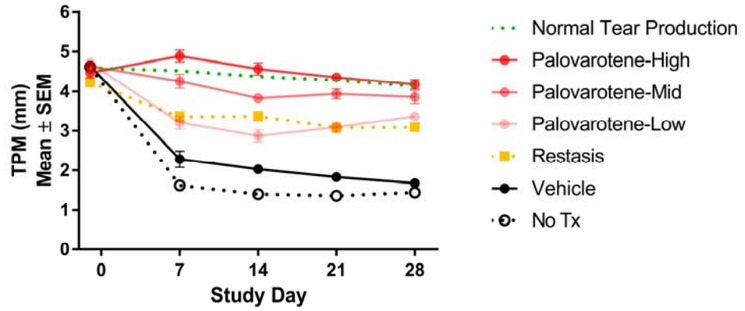
Dry eye animal model
CBA/J female mice: ~ 20 g / 9 weeks of age.
Injection of Botulinum Toxin B (BTX-B, 50 µL, 20 mU) into the anterior lacrimal gland of the right eye with contralateral control.
Characterized by normal blink rate, decreased tear production and increased CFS score starting 3 days post BTX-B injection with defects maintained for up to 4 weeks. Decreased goblet cells and increased TNFα and IL-β (mRNA & protein) has been reported.

Study design
Eye drop formulations at 3 doses of palovarotene (low, mid, high) and vehicle, were administered by daily topical instillation (QD, 10µL) immediately after BTX-B injection, for 28 consecutive days and compared to current standard of care, Restasis® (BID, 0.05%).
One group of mice received no treatment (No Tx).
Sample size = 10 mice per group

Endpoints
Gross ocular observations, daily.
Ophthalmic examinations (combined Draize and McDonald-Shadduck Scoring System), tear production measurement (TPM) by phenol red-impregnated cotton threads and corneal fluorescein staining (CFS) using a scoring system of 0 to 4, weekly.
Histopathology: eyelids (upper and lower) with palpebral conjunctiva, lacrimal gland, and eye globe with attached bulbar conjunctiva and optic nerve collected, fixed and stained with PAS or H&E.

Results

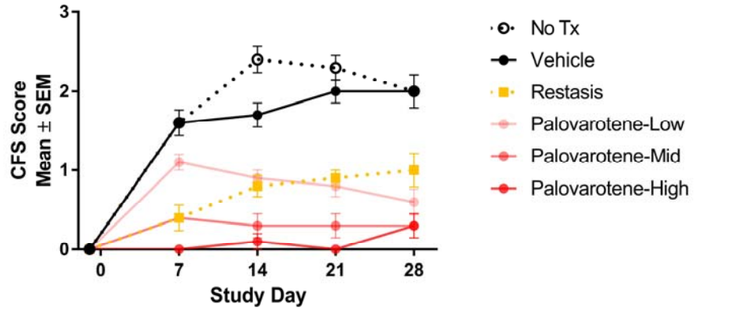
Palovarotene dose-dependently and significantly increases tear production



% Increase in tear production relative to No Tx

Study Day	7	14	21	28
Palovarotene				
Low	106	104	126	132
Mid	180 *	172 *	188 *	166 *
High	219	224	218	188
Restasis®	118*	139*	125*	113*

Palovarotene dose-dependently and significantly decreases corneal fluorescein staining



% Decrease in CFS score relative to No Tx

Study Day	7	14	21	28
Palovarotene				
Low	31†	63	65	70
Mid	75	88 *	87 *	85 *
High	100 *	96	100	85
Restasis®	75*	67*	61*	50*

* *P*<.0001 compared with No Tx group
† *P*<.05 compared with No Tx group
Repeated measures two-way ANOVA
Dunnett's multiple comparisons test

Findings

Clinical Observations	**All palovarotene doses were well tolerated**
Gross Ocular Examination	Redness/swelling (slight to moderate) of the eyelids were observed from Day 5/7 in all high-dose palovarotene-treated animals and from Day 7/8 in 50% of mid-dose palovarotene-treated animals. No redness/swelling of the eyelids was observed in the low dose palovarotene and control groups (No Tx, Restasis® and Vehicle).
Ophthalmic Examination	No findings
Histopathology	No treatment related findings in Meibomian glands and conjunctiva. No findings in tissues such as iris, ciliary body, optic nerve, retina, posterior/anterior chamber, sclera. Minimal inflammatory cell infiltration and apoptosis observed in lacrimal gland of <28% of the –mid and –high dose groups. Minimal to mild epidermal hyperplasia, hair follicular hyperplasia, hyperkeratosis, brown pigmented macrophages, inflammatory cell infiltration, ulceration, and crust were found in the eyelids from palovarotene- and/or Restasis®-treated mice. **Palpebral/bulbar conjunctiva goblet cell density was improved in palovarotene-treated animals compared to No Tx.**

Conclusion

These results indicate a beneficial therapeutic effect of palovarotene in the BTX-B animal model of dry eye disease and support further development of a palovarotene ocular formulation for the treatment of human dry eye disease.

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