Enhancing Efficacy by Continuous Delivery of AR-13154(S) in an Animal Model of Proliferative Diabetic Retinopathy

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Kevin S. Carbajal, Jindong Ding, Meredith Weksler, Lori Moore, Casey Kopczynski and Cheng-Wen Lin

Aerie Pharmaceuticals, Inc., Durham, North Carolina

Purpose

Rho-associated protein kinase (ROCK) has been implicated in the development of retinal neovascularization (NV) and vascular leakage in wet age-related macular degeneration (AMD) and proliferative diabetic retinopathy (PDR). We have previously shown that AR-13154(S), a selective multi-kinase inhibitor of ROCK/PKC/JAK/PDGFR-β, has therapeutic potential as a treatment option for wet AMD and PDR, either as monotherapy or in combination with anti-VEGF agents. This study assesses the pharmacokinetic (PK) and efficacy profiles of AR-13154(S) when delivered via the sustained delivery of a sub-conjunctival (SC) depot or via the intermittent delivery of topical eye drops.

Background

PDR and retinopathy of prematurity are associated with retinal hypoxia. This can induce NV which in turn can result in vitreous hemorrhage and retinal detachment, leading to vision loss.

ROCK:

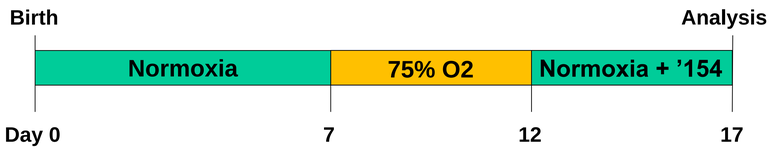
Kinase that modulates actinomyosin dynamics in many cell types, including vascular smooth muscle and endothelial cells. Inhibition reduces NV in the oxygen-induced retinopathy (OIR) animal model.

AR-13154(S):

Small molecule inhibitor of ROCK, PKC, JAK, and PDGFR-β. All are proteins with reported roles in angiogenesis and/or inflammation.

Methods

OIR Model

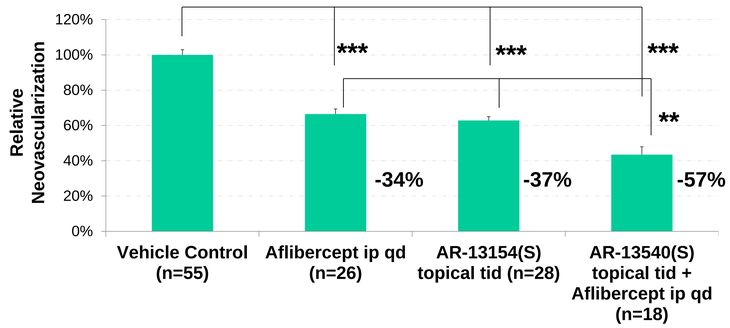


- **Neonatal C57BL/6 mice housed at 75% oxygen from postnatal day (P) P7 to P12.**
- **Mice returned to normoxia on P12 and treated with AR-13154(S) either as a 0.06% topical eye drop, t.i.d., or via a 1μL subconjunctival depot containing 1mg/mL of AR-13154(S) in thermosensitive gel.**
- **PK studies: Animals euthanized on P14 (topical, depot) or P16 (depot); AR-13154(S) concentrations in retina determined by HPLC/MS.**
- **Efficacy study: Mouse pups euthanized on P17, retinas flat-mounted and stained for NV quantification.**

Results

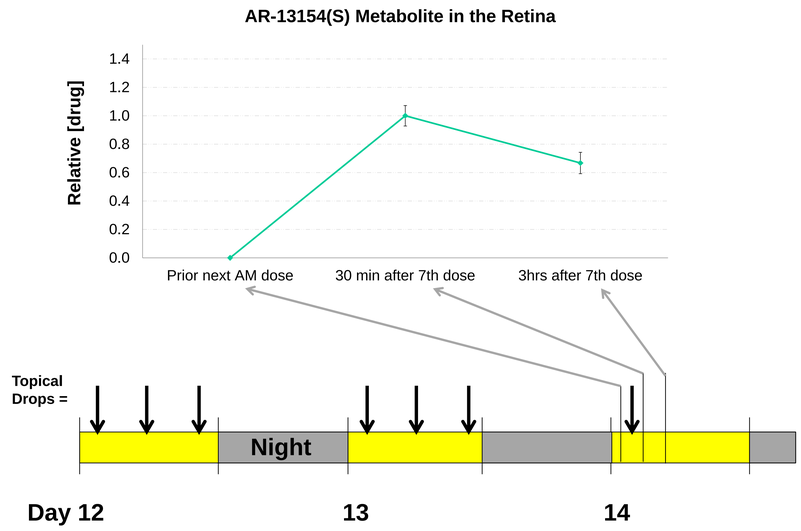
Topical Delivery of AR-13154(S)

Efficacy in OIR



Topical treatment of mouse pups with 0.06% AR-13154(S) resulted in a significant reduction of NV. Combination therapy of AR-13154(S) and afibercept (1mg/kg ip qd) had an additive effect. The NV area was normalized against vehicle controls.

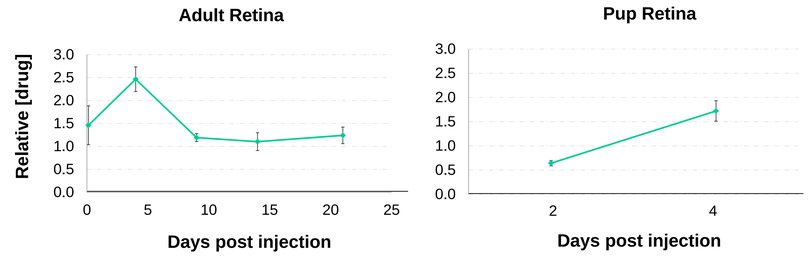
Pharmacokinetics



Pups were treated topically t.i.d starting on Day 12 for two days in the OIR model . On Day 14, retinas were harvested prior to dosing, and 30 min and 3 hours after the final (7th) dose.
No drug was measurable in retina prior to the 7th dose (16 hours after previous dose). Drug levels were highest 30 min after dosing, and dropped by 33% 150 minutes after dosing. Results are shown for the primary metabolite of AR-13154(S), which was the major form of the drug in the retina (n≥3 per group). The drug levels were normalized against the peak drug level (30 min after 7th dose).

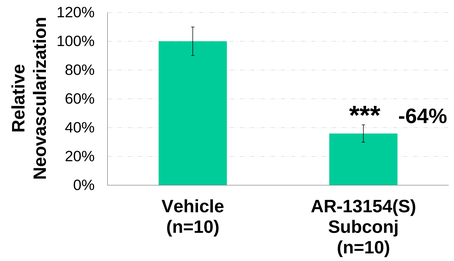
Sustained Delivery of AR-13154(S)

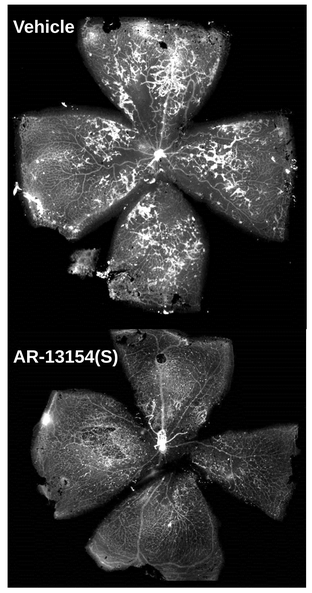
Pharmacokinetics



AR-13154(S) was delivered to mouse retinas via a 1μL SC depot. Adult retinas were harvested on Days 0 (3 hours post injection), 4, 9, 14, and 21; pup retinas were harvested 2 and 4 days post injection. Drug levels were normalized against the peak drug level obtained via topical dosing (30 min after 7th dose).
Drug levels were measurable at all time points, demonstrating sustained delivery for up to 21 days. In both adult and pup retinas, drug levels were highest on Day 4. In adult retina, drug levels remained above the peak concentration obtained by topical dosing. Results are shown for the primary metabolite of AR-13154(S) (n≥3 per group).

Efficacy in OIR





Sustained release of AR-13154(S) resulted in a ~64% reduction in NV compared to vehicle controls.

Conclusions

Sustained delivery of AR-13154(S) improved the PK and efficacy profiles of AR-13154(S) in the retina, which resulted in greater reduction in the NV area in the OIR model relative to topical t.i.d. delivery. This study illustrates the potential of sustained delivery of ROCK inhibitors for the treatment of vascular diseases of the eye.

Disclosure

All authors are employees of Aerie Pharmaceuticals, Inc.