Soft ROCK Inhibition as Novel Treatment Mechanism for Glaucoma

N. Kindt¹, S. Van de Velde², K. Castermans¹, S. Boland¹, O. Defert¹

¹Amakem Therapeutics, Agoralaan ABis, Belgium
²KU Leuven - University of Leuven, Department of Neurosciences, Laboratory of Ophthalmology, Belgium

1. INTRODUCTION
Glaucoma is a leading cause of irreversible blindness. The most common form of glaucoma is Primary Open Angle Glaucoma (POAG), which affects more than 2 million persons over 40 years of age in the USA alone¹. Elevated intraocular pressure (IOP) is the only proven treatable risk factor in multiple forms of glaucoma including POAG². A number of IOP-lowering agents are therefore used in clinical practice. However, the majority of these agents do not improve the outflow of aqueous humor through the trabecular meshwork³, which represents an important component of elevated IOP (Figure 1).

ROCK inhibitors represent a potential class of IOP-lowering agents that would target trabecular outflow. However, clinical development of ROCK inhibitors is hampered by their low therapeutic window. In particular, conjunctival hyperemia is a very common adverse event resulting from on-target activity and has been reported with all clinically evaluated ROCK inhibitors⁴. As a result, development of several ROCK inhibitors have been abandoned.

Amakem’s Localized Drug Action platform aims to produce biologically active compounds that are designed to undergo metabolic inactivation towards a predictable, nontoxic metabolite with negligible functional activity. AMA0076 is a soft ROCK inhibitor⁵ that has been designed to be active in the aqueous humor and be inactivated rapidly in other eye tissues and in systemic circulation. It has been tested in rabbit models to test its IOP lowering efficacy and to score hyperemia-induction⁶.

Keyword(s): IOP, AMA0076, rabbit model, soft ROCK inhibitor
2. PURPOSE
- To determine the IOP lowering efficacy of AMA0076 in an acute ocular hypertensive rabbit model and compare it to a non-soft ROCK inhibitor and the gold standard in clinic
- To score hyperemia and use it as a measure of the soft profile of AMA0076 in comparison to a non-soft ROCK inhibitor

3. MATERIALS AND METHODS
The IOP lowering effect of AMA0076 was investigated in a new ocular hypertensive rabbit model, based on the intracameral injection of visco-elastic material. Using this model AMA0076 was tested at different concentrations and compared to Y-39983, a non-soft ROCK inhibitor with similar on-target potency and Latanoprost (Xalatan® 0.005%), the gold standard in clinic.

Hyperemia was scored after a single topical instillation of AMA0076 and compared to Y-39983. Scoring was based on the scale that was developed by Alcon Research®, whereby a number is given to the area of conjunctival vasodilatation.

4. RESULTS
In the ocular hypertensive model, topical administration (TID) of AMA0076 prevented IOP rise induced by the injection of visco-elastics at the doses tested (overall P<0.0001) (Figure 2). Administration of Y-39983 0.3% significantly reduced IOP rise in the hypertensive model compared to the control eye (overall P<0.0001). An attenuated IOP decrease was also observed in the control eye, presumably due to the systemic absorption of Y-39983 (Figure 3). AMA0076 appeared to be significantly more potent in blocking the IOP elevation in the hypertensive model compared to Latanoprost (overall P=0.0004) (Figure 4).

Figure 2: Repeated administration of AMA0076 prevented IOP rise at all concentrations tested (overall P<0.0001 for all concentrations).
Figure 3: Administration of Y-39983 0.3% (TID) attenuated IOP rise induced by the injection of visco-elastics compared to the vehicle-treated contralateral eye (overall P<0.0001). An IOP lowering effect is clearly visible in the control eye.

Figure 4: Repeated administration of Latanoprost 0.005% and AMA0076 0.3% inhibited IOP rise induced by the injection of visco-elastics. AMA0076 more efficiently prevented the IOP rise compared to Latanoprost (overall \( P=0.0004 \)).
Since ROCK inhibitors are known to induce mild to severe transient conjunctival hyperemia, the hyperemic effect of AMA0076 0.3% and Y-39983 0.3% was investigated in ocular normotensive NZW rabbits. Single administration of Y-39983 induced significant hyperemia in the NZW rabbits. In contrast, AMA0076 treatment only caused very mild hyperemia (Figure 5).

![Figure 5: Hyperemic effect of AMA0076, Y-39983, and vehicle in NZW rabbits before, 1, 4, and 8 hours after dosing.](image)

5. CONCLUSIONS
ROCK inhibitors represent valuable IOP-lowering agents for the treatment of glaucoma. In particular, ROCK inhibitors would target trabecular aqueous humor outflow, an important component of elevated IOP that is not improved by the commonly prescribed medications. However, clinical development of ROCK inhibitors has so far been hampered by their side-effect profile and in particular by the high incidence of conjunctival hyperemia, which is a direct consequence of on-target activity. By applying its Localized Drug Action approach to ROCK inhibitors, Amakem has discovered AMA0076, a soft ROCK inhibitor that is designed to undergo metabolic inactivation towards a functionally inactive metabolite. These preclinical animal studies show that the original profile of AMA0076 enables this compound to effectively separate the desired IOP-lowering effects from the undesired conjunctival hyperemia.

6. REFERENCES


[7] Ogundele AB, Earnest D, McLaughlin MA. In vivo comparative study of ocular vasodilation, a relative indicator of hyperemia, in guinea pigs following treatment with bimatoprost ophthalmic solutions 0.01% and 0.03%. Clin Ophthalmol. 4:649–652 (2010).