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Commentary Open Access

Where Should We Be Looking for the Future of IOP Lowering Drugs? Commentary on "New Therapeutic Targets for Intraocular Pressure Lowering"

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Commentary

Since the release of "New Therapeutic Targets for Intraocular Pressure Lowering" [1] some of the potential therapeutics has shown promising results, and interestingly their mechanisms of action focus mainly in the trabecular meshwork (TM), which is probably the main target that has not been fully used when trying to lower intraocular pressure (IOP). First of all, some Rho-associated kinase (ROCK) inhibitors have reached phase 3 trials. AR-13324 (Rhopressa™, Aerie Pharmaceuticals, California) can lower IOP, not only by increasing outflow through the conventional (trabecular meshwork) pathway, but also by reducing episcleral venous pressure [2] and inhibition of norepinephrine transporter (NET; which reduces the amount of aqueous produced) [3]. In a 3-arm phase 3 trial, Rocket 2 (held in the United States of America, USA), Rhopressa™ (0.02% qd or 0.02% bid) was compared to timolol (0.5% bid) in subjects with baseline intraocular pressure >20 and <25 mmHg. All three groups had similar baseline demographic characteristics and the primary endpoint of non-inferiority was achieved in all timepoints (evaluation until 3 months). The most common side effect reported was conjunctival hyperemia, deemed mild, in 83% of patients (with qd dosing) [4]. New results of this molecule are expected in mid-2016, when Rocket 4 trial results are presented and submission to the USA Food and Drug Administration (FDA) is planned. Alongside Rhopressa™, research is also being done with a fixed combination of Rhopressa™ and latanoprost, named Roclatan™ (Aerie Pharmaceuticals), since these two drugs lower IOP through different mechanisms. A phase 2 trial (USA, 297 patients) reported superiority of Roclatan in lowering IOP comparing to latanoprost alone (from 25.1 mmHg at baseline to 16.5 mmHg at day 29; about 2 mmHg greater reduction), at every time point in the study [5]. Phase 3 studies of Roclatan™, held in the USA, have started in 2015 and results are still to be reported. No systemic side effects were reported both for Rhopressa™ and Roclatan™, and conjunctival hyperemia seems to be the greatest limitation found so far. Another ROCK inhibitor showing promising results is K-115 or Ripasudil (Glanatec™, approved for glaucoma treatment in Japan), with a recent report of a 52-week prospective, multicenter trial with 388 patients receiving Ripasudil 0.4% bid. An IOP decrease of 3.7 mmHg from baseline was achieved. This compound achieved a greater reduction if combined with latanoprost or timolol, when comparing to the latter in monotherapy. The most common side effect, similarly to Rhopressa™, was conjunctival hyperemia (74.6% of patients vs 1.9% with placebo), however most cases were mild, transient and had spontaneous resolution [6]. Altough the results seem promising, a combination with latanoprost or timolol might not be possible, since this compound needs bid dosing and it reduces the ocular bioavailability of timolol [7].

Apart from ROCK inhibitors, nitric oxide (NO) is also one of the molecules with interesting results in recent published literature. NO agonists, like ROCK inhibitors, increase aqueous outflow through the TM. Latanoprostene bunod 0.024% (Vesneo™, Bausch+Lomb and Nicox), an NO-donating prostaglandin F2α receptor agonist, combines latanoprost acid with butanediol mononitrate, which is an NO-donating molecule. It has shown in phase 3 clinical trials to be more effective than timolol in lowering IOP, with qd dosing regimen (effect lasts 24 hours) [8], and is also able to increase ocular perfusion pressure [9]. It is not commercially available as yet, but is pending approval by the USA FDA (set for July 2016).

Lastly, adenosine agonists have also shown interesting results. Three of the four receptors found to exist in human's TM have the potential to lower IOP (A1, A2a, A3; the latter can also increase IOP), and several drugs are already being used in human trials targeting several of these receptors. Trabodenoson (Inotek Pharmaceuticals), an A1 mimetic, proved its ability to lower IOP in a recent phase 2 clinical trial with 144 patients, by decreasing IOP 7 mmHg by day 28, as compared to placebo, with a qd dosing regimen [10]. No systemic side effects were detected and patients had less hyperemia than what is known to happen with currently used prostaglandin analogues. This drug is currently in a phase 3 clinical trials. There are also other drugs, targeting A2a receptor (OPA-6566, Acucela and Otsuka Pharmaceuticals; ATL313, Santen Pharmaceuticals) that have shown ability to lower IOP, but couldn't reach the results of trabodenoson.

These three ways of lowering IOP (ROCK inhibitors, NO donors and adenosine agonists) have all shown promising results and have several drugs in advanced stage human trials. They all lower IOP through modulation of the TM, which might be the key to enhance our pharmacological arsenal for glaucoma patients.

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