NEW GLAUCOMA DRUGS COMING
ROCK inhibitors, new prostaglandins, may open additional therapeutic pathways

by Howard Larkin in San Diego

A s the early prostaglandin analogues go off patent over the next few years, rho-kinase, or ROCK inhibitors may become the first new class of glaucoma medications to hit the market in nearly two decades. Unlike existing glaucoma compounds, which lower intraocular pressure mostly by reducing aqueous production or increasing uveoscleral outflow, ROCK inhibitors target the trabecular meshwork. They have been shown in clinical studies to remodel the trabecular meshwork, restoring it as the primary aqueous outflow channel and lowering IOP about as well as restoring it as the primary aqueous outflow to remodel the trabecular meshwork, which lower intraocular pressure mostly.

In addition, new prostaglandins are under development that target a variety of cellular receptors beyond those that current drugs bind, Dr Samples said. Notably absent are neuroprotectors.

“I wish I could tell you we have a lot of neuroprotectors coming in the next year or two but we just don’t,” Dr Samples told attendees of ASCRS 2011 Glaucoma Day. But even here there is some progress, with some drugs developed for other purposes showing neuroprotective effects.

Targeting trabecular meshwork
ROCK inhibitors have been shown to increase aqueous outflow by relaxing cells in the trabecular meshwork and increasing the spaces between them. In animal models, increases in permeability of Schlemm’s canal and aqueous outflow of 80 per cent have been observed. While inflammation was an issue in early tests, recent trials suggest that ROCK inhibitors should be tolerable for most patients. There are now six companies with ROCK inhibitors in phase 1 to phase 3 trials.

Among the furthest along is AR-12286, which Aerie Pharmaceutical presented at the Association for Research in Vision and Ophthalmology 2010 meeting. In a phase 2a study of 89 patients, AR-12286 reduced IOP by up to ~6.8 mmHg, or 28 per cent. Transient mild to moderate hyperaemia was seen in some patients, but no serious side effects were reported. Aerie reported positive results of a phase 2b study in September, and plans further phase 2 studies with larger populations to establish maximum effective dosing, and may begin phase 3 trials by the end of this year. Aerie is also developing several other glaucoma drugs, including AR-13324, which the firm characterises as a new drug class with a dual mechanism. Aerie is also beginning clinical trials of a conjunctival insert that will deliver glaucoma medications over a longer term, potentially improving efficacy over daily eye drops and reducing issues of patient noncompliance.

Santen-Ube’s DE-104 ROCK inhibitors has successfully completed phase 2a trials in Japan and the US, and is undergoing phase 1 and 2a trials to establish improved efficacy at higher doses. The firm is also developing ATLA13, an A2A agonist that it licensed from Clinical Data, as a glaucoma medication.

Senjen-Novartis’ phase 2 trials of Y39983 show some side effects, but also “relaxing” effects on the trabecular meshwork. Evidence from animal models suggest it may also promote regeneration of optic nerve cells. Altheos claims that its ATS9007 and related analogues were specifically designed for easier ocular administration and an improved therapeutic index compared to other ROCK inhibitors in development. Pre-clinical studies show promise for improved safety and efficacy, the company says.

Clinical trials are planned for this year.

ROCK inhibitors are likely to appear as once- or twice-a-day drops without BAK preservatives, Dr Samples says. They appear amenable to a multitude of alternate delivery systems, including sub-Tenon’s and conjunctival inserts, punctal plugs and long-lasting gels, all of which are in development.

New prostaglandin targets
Dr Samples also expects a new round of prostaglandins that could expand their effectiveness. “All of our current prostaglandins target the EP receptor. Bimatoprost also binds EP1. Butaprost from Allergan targets EP3 and EP4, and was shown at ARVO in 2002. I really think this is the way it is going with new EP-targeting drugs.”

Promoting natural prostaglandin production is another alternative, Dr Samples noted. At the 2010 International Society for Eye Research meeting in Montreal, Allergan’s David Woodward presented a drug based on a compound present in rabbit eyes but absent in human eyes that caused the endogenous release of prostaglandins in human eyes.

“We think that drug may have a whole lot more promise,” Dr Samples said.

Neuroprotectives problematic
Ultimately, glaucoma is a neural disease, and protecting the optic nerve is the goal. But testing neuroprotective agents is expensive, time consuming and costly.

“Many [neuroprotective agents] under development borrow from the neurology and the neurosurgery literature. There are a lot of strategies, but the big problem is the cost to prove the efficacy of these drugs. Most recognise the glial cell as one of the potential culprits in glaucoma, but there are a lot of potential culprits,” Dr Samples said.

Even so, drugs developed for other uses sometimes overlap. For example, some ROCK inhibitors have been shown to have a neuroprotective effect (Yoshinori Toshima et al A new Model of Cerebral Micro thrombosis in rats and the Neuroprotective Effect of a Rho-Kinase Inhibitor. Stroke 2006; 37:2245-2250) and even to promote regrowth of nerve cells in animal studies. And the drug firm Sucampo is considering a re-launch of unoprostone, FDA approved for IOP lowering in 2000, with a neuroprotective claim and possibly indications for retinitis pigmentosa and dry age-related macular degeneration.

Other drug classes on the horizon include an adenosine-1 agonist from Innotek for which information was presented at the ISER meeting in Montreal, muscarinic selective compounds from Acadia-Allergan, and a cannabinoid CB1/2 agonist from Novartis.

“Watch for the Innotek compound, but Rho-kinase inhibitors and new prostaglandins will likely appear first.”