ANTIGLAUCOMA MEDICATION CLASSES GREATLY EXPANDED,
giving clinicians five major classes from which to
choose: prostaglandin analogues, β-blockers, selective
$\alpha_2$-adrenergic agonists, carbonic anhydrase inhibitors, and
miotics. The last is rarely used for long-term management.

Looking into the phase 3 pipeline today suggests that clini-
cians may be on the verge of another exciting era of new
medications that act directly on the tissue of pathology,
the trabecular meshwork (Table). These agents in develop-
ment include Rho kinase (ROCK) inhibitors (Rhopressa
and Roclatan; Aerie Pharmaceuticals), adenosine agonists
like trabodenoson (Inotek Pharmaceuticals), and nitric
oxide (NO) donors such as latanoprostene bunod (Vesneo;
Bausch + Lomb and Nicox) and NCX 667 (Nicox). If these
agents make it to market, eye care providers could have
important new options for the millions of patients affected
by glaucoma.

ROCK INHIBITORS
Rhopressa (AR-13324) shows great potential for lower-
ing IOP by three cooperative mechanisms. The first two
act via ROCK inhibition both to increase aqueous humor
outflow through the trabecular meshwork and reduce epi-
scleral venous pressure, as demonstrated in normotensive
primate eyes. The third mechanism of norepinephrine
transporter inhibition, which decreases the total amount
of fluid produced, was shown in a rabbit study. Rhopressa
offers unique yet complementary therapy to the market-
leading prostaglandin analogues, which primarily increase
uveoscleral outflow.

Compared with latanoprost, Rhopressa was less effective
at reducing IOP by 1 mm Hg and was associated with a higher
incidence of ocular hyperemia at both concentrations (0.01% or 0.02%). That said, 0.02% Rhopressa decreased
IOP from the controls by 5.7 mm Hg after 28 days of treatment in the
phase 2b clinical trial. In Rocket 2, a phase 3 registration trial, Rhopressa
successfully achieved the primary efficacy endpoint in the second phase 3 trial of Rocket 2. With
once-daily administration, the most common side effect
was hyperemia, which was mild in 83% of patients taking
the drops. For twice-daily administration, side effects were
slightly more common, but the IOP-lowering effects were
also more pronounced. An additional, fourth phase 3 regis-
tration trial, Rocket 4, commenced as planned in September
of this year, and Aerie expects to file a new drug application
with the FDA in 2016.

Aerie is also developing Roclatan, a fixed combination
of Rhopressa and latanoprost that works through the
combined mechanisms of the respective drugs to decrease
IOP. With Rhopressa’s three mechanisms of action plus
the known mechanism of latanoprost, Roclatan would use
many of the known means of lowering IOP in a single drop.

Roclatan recently achieved its primary efficacy end-
point in a phase 2b clinical study that demonstrated the
agent’s superiority over latanoprost alone. The study had
297 patients, and Roclatan decreased mean diurnal IOP
from 25.1 to 16.5 mm Hg (34%). This is about 2 mm Hg
more than the reduction in IOP seen after treatment
with latanoprost alone. At every time point in the study,
Roclatan significantly exceeded latanoprost’s efficacy.

Because latanoprost is one of the most efficacious glau-
coma drugs worldwide, the availability of Roclatan could
be a huge step forward in glaucoma treatment.

The agent demonstrated no systemic side effects, similar to Rhopressa,
and caused only mild hyperemia in about 40% of patients.
Aerie initiated its first phase 3 registration trial of Roclatan
this September and anticipates conducting two additional
trials in 2016.
ADENOSINE AGONISTS

Adenosine agonists are another promising class of medication. Of the four adenosine receptors found in the human trabecular meshwork, three of them (A1, A2A, A3) lower IOP when activated, but one of these (A3) also has the potential to cause an increase in IOP.11 Manipulation of these receptors is a promising, novel mechanism for glaucoma treatment. Inotek’s A1 mimetic, trabodenoson, demonstrated positive end-of-phase 2 results in its most recent clinical trial. In the study of 144 patients, the drug decreased IOP by 7 mm Hg after 28 days compared to the placebo with no detectable systemic side effects and less hyperemia than the currently used prostaglandin analogues.12 In addition, this drug’s IOP-lowering effects persisted for 24 hours following the final dose, which makes it an excellent candidate as a once-a-day drop. Inotek initiated the first phase 3 trial of trabodenoson this year, with completion anticipated in late 2016.13

Although Inotek’s trabodenoson is by far the most up-and-coming adenosine agonist, there are several others in the pipeline.14 Acucela and Otsuka Pharmaceuticals are currently deciding the next steps on their A2A agonist, OPA-6566, with which they conducted a phase 1/2 clinical trial in 2012. The drug increases aqueous humor outflow via the conventional pathway of the trabecular meshwork and Schlemm canal rather than the uveoscleral pathway used by prostaglandin analogues.15 Santen Pharmaceuticals also has a selective A2A agonist, ATL313, that has significantly decreased IOP in vivo, but the company has not released any recent updates on further development of this drug.14,16

NITRIC OXIDE DONORS

Another potential treatment involves the modulation of ocular NO levels. NO has been shown to play a role in IOP regulation and to have neuroprotective qualities.17-20 Nicox and Bausch + Lomb have demonstrated the potential of NO in glaucoma treatment with latanoprostene bunod, an NO-donating prostaglandin F2α-analog. In two phase 3 clinical trials, the drug was more effective at lowering IOP than timolol and only had to be administered of NO without the side effects and dosing limitations of the parent drug.21-24

CONCLUSION

This is an exciting time in glaucoma. Treatments are changing, new ideas are emerging, and clinicians’ and scientists’ knowledge of the disease itself is growing. It is to be hoped that some of the drugs described herein soon become a part of physicians’ arsenal against glaucoma.

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