

In development

The ophthalmic pharmaceutical pipeline expands

Researchers focus on variety of needs including dry eye, AMD, glaucoma, cataract

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As mid-2006 approaches, the wave of innovation in ophthalmic pharmaceutical development continues. This past year has seen several FDA approvals, and novel medications continue to make their way through the ophthalmic pharmaceutical pipeline. In this article discover some of these new developments within various ophthalmic disciplines.

Dry eye

Cyclosporine 0.05% ophthalmic emulsion (Restasis, Allergan) remains the only prescription medication available for the treatment of severe, chronic dry eye, and its user base continues to increase. Additional prescription eye drops for dry eye, including diquafosol tetrasodium (Prolacria, Inspire Pharmaceuticals), ecabet sodium (ISTA Pharmaceuticals), rebamipide (Novartis), and pimecrolimus (Novartis), continue to move through the pipeline.

Diquafosol tetrasodium has been the subject of communication between the Inspire Pharmaceuticals and the FDA following its original New Drug Application in 2003. According to a press release, Inspire met with the FDA in March 2006 to review the second approvable letter they have received.¹ At the recent Association of Research in Vision and Ophthalmology (ARVO) conference, a double-masked, randomized, placebo-controlled study was presented that evaluated total tear film thickness and thinning with use of diquafosol tetrasodium. The study found that

following a 6-week course of treatment, subjects with dry eye had a thicker tear film.²

In February, ISTA Pharmaceuticals announced preliminary results from a phase II trial evaluating two concentrations of ecabet sodium (3% and 3.9%) in 162 patients with dry eye. The study revealed a trend in efficacy with the 3% solution, as measured by mean corneal staining and blink rate parameters and several subjective symptom ratings. According to ISTA's Web site, the company is in the planning stage for a confirmatory study and two future phase III studies.³

Other products in the pipeline include rebamipide, pimecrolimus, and a sodium hyaluronate-based eye drop (Moli 1901, Lantibio & TRB Chemedica). Rebamipide, which was originally developed to treat

gastric ulcers, is now in phase III trials for dry eye treatment, and pimecrolimus is progressing into phase II trials to evaluate the efficacy and safety of the eye drop at two concentrations (0.3% and 1.0%).⁴ Moli 1901, for which the phase I studies were completed in Europe, is undergoing phase II clinical trials in the United States.⁵

Novagali Pharma is developing two separate dry eye treatments using their novel cationic emulsion platform, Novasorb, which is designed to improve penetration of ocular tissues. One is a cationic emulsion formulation of cyclosporine (Nova 22007, Novagali), which has been shown to be safe in phase II trials and is now in phase III trials for efficacy.⁶ They are also preparing the European and U.S. registration of Cationorm (Nova23006/33). The results of a phase II study for Cationorm, reported at the ARVO meeting this year, indicate that the Cationorm eye drops are well tolerated and, following 1 month of treatment, there was a trend toward improvement of Schirmer's scores, tear film breakup time (TFBUT), and staining scores.⁷

The use of hormonal therapies for dry eye may represent the next generation of medication for the tear film deficiencies of dry eye. One study analyzed the records of 23 female patients, fifteen of whom wore

results of a phase II study in January. In a comparison with vehicle in subjects with moderate to severe dry eye, significant improvements in Schirmer's scores were evident after 8 and 12 weeks of twice-daily dosing.⁹

In another study, a testosterone eye drop (Allergan) was evaluated in a double-masked, randomized, vehicle-controlled study in 179 subjects with meibomian gland deficiencies. Results indicated improvements in the quality of meibomian gland secretions and less ocular discomfort after 6 months of treatment with 0.3% testosterone eye drops.¹⁰

The idea of using tear film breakup patterns (TFBUPs) to study dry eye conditions is a concept that is being developed at ORA Clinical Research and Development. Several studies were presented at the ARVO conference this year indicating that different TFBUPs may indicate differing severities and/or etiologies of dry eye. The type and distribution of patterns was shown to alter when lipid expression was increased, after reflex tearing, and as dry eye progresses from early to late stage.¹¹⁻¹³ Much additional research may be necessary in this arena before therapies are developed that target the problems identified by changes in TFBUPs. However, it is an



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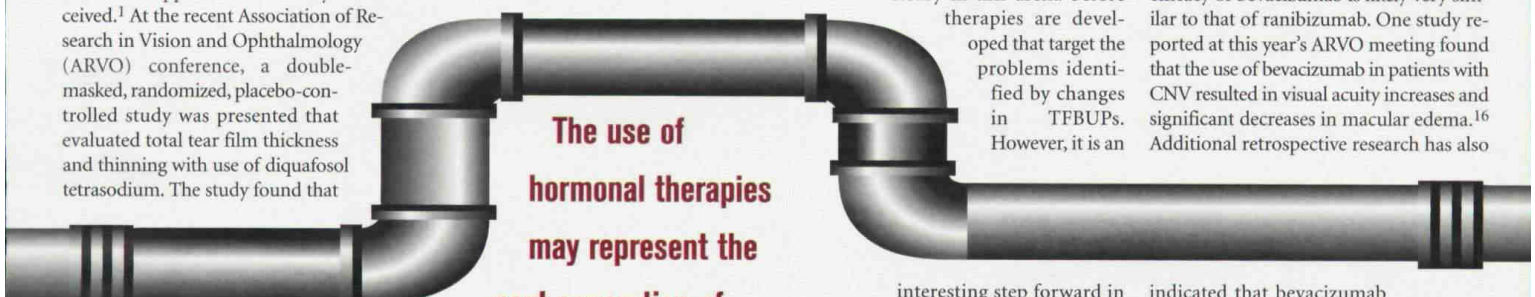
strated significant reductions in corneal staining in a 6-week study and was more acceptable with less blurring in an acute evaluation than Refresh Tears Lubricant Eye Drops (Allergan).¹⁵

AMD

Age-related macular degeneration (AMD) has certainly been in the spotlight in recent years, and the trend continues in 2006. The major players of 2005 continue to maintain a presence and the landscape of long-awaited combination therapies is coming into focus.

There remains great interest around the use of bevacizumab (Avastin, Genentech) as an intravitreally injected treatment for neovascularization secondary to AMD. The controversy is due to the fact that bevacizumab is approved for intravenous use to treat metastatic colorectal cancer, however, Rosenfeld and colleagues have written widely about use of bevacizumab for wet AMD.

Ranibizumab (Lucentis, Genentech) is a potent vascular endothelial growth factor (VEGF)-binding derivative of the bevacizumab molecule. Originally, Genentech reported that the bevacizumab molecule was too large to penetrate from the vitreous deep into the retinal layers. Subsequent studies have shown that the clinical efficacy of bevacizumab is likely very similar to that of ranibizumab. One study reported at this year's ARVO meeting found that the use of bevacizumab in patients with CNV resulted in visual acuity increases and significant decreases in macular edema.¹⁶ Additional retrospective research has also



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contact lenses, who applied testosterone cream to the eyelids twice a day for at least 3 years. Researchers found significant changes in several dry eye parameters, including Schirmer's scores, contact lens wear time, and an increase in TFBUT from 4.1 seconds at baseline to 6.1 seconds, without any increase in IOP.⁸

Another hormonal dry eye therapy in development is iDestrin (Nascent Pharmaceuticals), a topical estrogen ester compound intended for use in post-menopausal women. The company announced the re-

interesting step forward in the understanding of dry eye, and eventually, it is hoped, in the treatment of it.

Over-the-counter options for dry eye treatment continue to expand. Systane Free Lubricant Eye Drops, a recent addition to this field, is a liquid gel formulation of Alcon's original Systane Lubricant Eye Drops, which has been shown to relieve signs and symptoms of dry eye.¹⁴ Like original Systane, Systane Free contains PEG-400 and propylene glycol as active demulcents, with HP-Guar as a gelling agent. Unlike the original Systane, it is a structured gel in the bottle, while the added sorbitol controls cross-linking in the eye. It has its own unique self-preservation system. In Alcon-sponsored studies presented at the ARVO meeting this year, the new formulation demon-

indicated that bevacizumab may be effective for other forms of neovascular AMD.¹⁷ It should be noted, however, that bevacizumab, while widely used by ophthalmologists, has not undergone the same rigorous, phase III clinical testing as ranibizumab for treatment of wet AMD.

Meanwhile, as ranibizumab awaits approval in late June 2006, investigators presented 2-year efficacy data on the drug at the ARVO meeting.¹⁸ Overall, the 2-year treatment data on ranibizumab were revealed to be consistent with encouraging findings at 1 year. At 2 years, at least 90% of patients receiving ranibizumab had maintained or improved visual acuity, compared with 53% in a control group.¹⁹

Other research from this year's ARVO meeting was presented by Rosenfeld and colleagues from the Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Lucentis

(PrONTO) study.²⁰ Patients were administered three consecutive monthly injections of ranibizumab, and then re-treatment occurred if patients showed a worsening of their condition. The results of this study are limited, in that only 7 months of follow-up were reported. However, patients showed a marked decrease in the number of re-treatments required—approximately 50% of eyes required no re-treatment at the 7-month time point. These results point to the compensatory and multifaceted angiogenic mechanism that strengthens the argument for combination drug regimens for wet AMD.

Baseline characteristics from the Anecortave Acetate Risk-Reduction Trial (AART) were also presented at the ARVO meeting this year.²¹ Approximately 2,500 patients have been enrolled in this 4-year study, which is investigating anecortave acetate (Retaane, Alcon Laboratories) for the prevention of neovascularization in high-risk eyes. Anecortave seems a good choice for such a long-term trial because of its safety profile, and because it has the potential to attenuate multiple angiogenic stimuli both upstream and downstream of traditional anti-VEGF treatments. This is the only study of its kind in wet AMD and could change the way high-risk disease is managed, although preliminary results will not be reported for some time. Anecortave acetate has been approved in Australia, and is pending approval in several other countries, including the United States.

Allergy

Olopatadine HCl 0.1% ophthalmic solution (Patanol, Alcon) remains the gold standard in topical ocular treatment for allergic conjunctivitis. Recent research has shown that olopatadine significantly in-

hibits tears' ability to promote eosinophil adhesion, a key step in the production of allergic inflammation and damage.²² Although the original formula of olopatadine is currently the most widely prescribed ocular allergy treatment, the wave of the future in allergy treatments may be once-daily dosing. Olopatadine's once-daily formulation, olopatadine 0.2%, was FDA-approved in December 2004, but Alcon has not yet launched the product.

Research also continues in the area of severe, rare forms of allergy such as vernal keratoconjunctivitis. One small study indicated that probiotic eye drops improved signs and symptoms of vernal keratoconjunctivitis in four out of six patients studied. Researchers believe this is due to the probiotic's modulating influence on the Th1/Th2 balance.²³ However, there is still a need for effective long-term treatment options for severe forms of allergy.

Glaucoma

Last year, a new formulation of brimonidine tartrate 0.1% (Alphagan P, Allergan) received approval from the FDA. This follows the previous Alphagan 0.2% and Alphagan P 0.15% formulations, in attempts to limit extraneous exposure to the drug and improve the side effect profile by lowering the concentration of the active ingredient while also maintaining the necessary efficacy. According to press releases, clinical studies have exhibited comparable efficacy in lowering IOP with this formulation as compared with Alphagan 0.2%.²⁴

Focal Point

Fixed combination formulations for treating glaucoma have been on the European scene for a while.

Fixed combinations remain a theme in glaucoma treatment, and several have been developed in recent years, including Pfizer's latanoprost-timolol combination (Xalacom, Pfizer); travoprost-timolol combination (Extravan, Alcon); and twice-daily brimonidine-timolol combination (Combigan, Allergan). Bimatoprost-timolol combination (Ganfort, Allergan) has just been approved in Europe, and other combination agents are available in Europe or Canada, but the United States has not yet seen their approval.

Beta-blocker therapy, long the first-line treatment for treating glaucoma, has seen some innovation in the form of a modified beta-blocker (OT-730, Othera) that breaks down into inert metabolites upon entry into the bloodstream. This modification may give additional control over where in the body the drug is active, with hopes that this will improve the safety and side-effect profile of this drug. According to the company, OT-730 is currently in preclinical development, and studies to date have indicated efficacy comparable with timolol in a human tissues assay. Additionally, in an animal study, side effects (decreased heart rate, increased blood pressure) were evi-

dent with timolol, while those of OT-730 were comparable with placebo.²⁵

Santen is developing two potential glaucoma therapies. Olmesartan, an angiotensin II-receptor antagonist, has been the focus of a study that showed a dose-dependent IOP-lowering effect in a monkey model.²⁶ According to a press release, the company is now considering additional phase II trials to investigate the potential efficacy of this compound. A novel prostaglandin analogue called Tafluprost, the other Santen glaucoma drug in development, is in phase III trials;²⁷ phase II results presented this year showed short-term IOP-lowering and safety characteristics comparable with latanoprost.²⁸

Glaucoma researchers are exploring the potential of neuroprotective agents, which are already used in other disease areas. One molecule under investigation is memantine, an NMDA-receptor antagonist (Na-

menda, Forest Pharmaceuticals) currently approved to treat moderate to severe Alzheimer's disease. A large phase III clinical trial is evaluating whether an oral formulation of memantine can be used to protect the optic nerve. Other molecules under investigation for potentially useful neuroprotective effects include cyclooxygenase inhibitors and galantamine (Razadyne/Razadyne ER; Ortho-McNeil Neurologics). Research presented at this year's ARVO meeting suggests that selective COX-2 inhibitors increase, in a dose-dependent manner, the amount of surviving apoptotic retinal ganglion cells in vitro.²⁹

Another study found that galantamine, which is also approved for treatment of Alzheimer's disease, acts as an acetylcholinesterase inhibitor. In an animal model, daily oral administration was shown to preserve retinal ganglion cells better than vehicle and to protect axons in the optic nerve. These results suggest that this drug may also be applicable as a neuroprotective agent in glaucoma.³⁰

Rho-kinase inhibitors also present an avenue of interest for potential future glaucoma therapies. By inhibiting the Rho-kinase enzyme located in the trabecular meshwork and ciliary muscle, these potentially therapeutic molecules may increase the outflow of aqueous humor and lower IOP. One such molecule, Y39983, was licensed by Novartis from Senju Pharmaceutical Co. in 2005 and is in the earliest phase of development.³¹

Another agent under investigation in Japan inhibits both Rho-kinase and a second enzyme, ROCK. Researchers have shown that this Rho/ROCK inhibitor allowed the axons of injured retinal ganglion cells to regenerate in a cat model in which the optic nerve had been crushed.³² Research on another Rho-kinase inhibitor has revealed a significant reduction of IOP and aqueous outflow in normotensive eyes—but not hypertensive eyes—in a

company is preparing a New Drug Application for FDA submission.³⁶

Turning attention to anti-inflammatory agents, in the last year two non-steroidal anti-inflammatory drugs (NSAIDs)—bromfenac 0.09% ophthalmic solution (Xibrom, ISTA Pharmaceuticals) and nepafenac 0.1% ophthalmic suspension (Nevanac, Alcon)—have received an expanded indication to treat pain and inflammation following cataract surgery. One ISTA-funded study presented this year included a head-to-head comparison of bromfenac and nepafenac in normal patients that showed comparable results in the immediate and short-term anesthetic actions of the two agents, similar mild sensations of subjective burning, but significantly greater subjective stickiness in nepafenac-treated eyes when compared with bromfenac.³⁷ In another study, bromfenac's twice-daily regimen was comparable with the four-times-daily dosing of other topical NSAIDs, such as ketorolac (Acular, Allergan) and diclofenac (Voltaren, Novartis Pharmaceuticals), when used for a 3-month period of treatment for pseudophakic cystoid macular edema.³⁸

The novel histamine-binding protein rEV131 (Evolutec) continues in phase II trials toward development for use in allergy and/or inflammatory disease. This recombinant protein exhibits activity in managing both early- and late-phase in-

Glaucoma researchers are exploring the potential of neuroprotective agents.

monkey model.³³ However, this study also revealed that different Rho-kinase inhibitors may work via differing mechanisms, perhaps making the road to clinical applicability for these compounds a more winding one than previously anticipated.

Anti-infectives/anti-inflammatories

Azithromycin (AzaSite, InSite Vision) is a candidate topical product to treat bacterial conjunctivitis that is being investigated for b.i.d. dosing on days 1 and 2 and q.d. on days 3 to 5. Its formula includes a patented drug-delivery system, DuraSite, intended to prolong the release of the active agent, leading to a reduced dosing schedule. This would be likely to improve compliance in the pediatric population. Promising data have been presented from two phase III studies on efficacy³⁴ and safety,³⁵ and the

inflammation, preventing activation of histamine receptors.³⁹

A combination tobramycin and prednisolone acetate eye drop (ISTA Pharmaceuticals) has had positive results in a phase III trial, demonstrating both a favorable safety profile and bioequivalence between the combination product and prednisolone acetate 1.0% in the treatment of steroid-responsive inflammatory ocular conditions, according to the company.⁴⁰

Cataract

Othera is developing OT-551, a compound that has been shown to metabolize to an antioxidant scavenger in the eye. It may protect against cataract and the dry form of AMD. The eye drop, formulated to penetrate the corneal barrier, is intended as a preventative medication, protecting the lens and back-of-the-eye tissues from free rad-

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Prevention

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ical damage. It is hoped that it will prevent or arrest the progression of cataracts in patients who have undergone vitrectomy surgery. OT-551 has been shown to prevent hydrogen peroxide-induced cataracts in vitro, and in a rat model, systemic administration was shown to protect retinal photoreceptor cells against light-induced damage.⁴¹

Drug delivery

Research into delivering drug to hard-to-reach, targeted locations is increasingly yielding useful and innovative results. For example, Posurdex (Allergan) is a sustained-release implant made of bioerodable materials that delivers dexamethasone sodium phosphate to the back of the eye for the treatment of macular edema; the system is currently being studied in phase III trials.⁴²

A fluocinolone-delivery intravitreal implant (Retisert, Bausch & Lomb) was approved by the FDA last year for the treatment of chronic non-infectious posterior uveitis. The device delivers drug for approximately 30 months.⁴³

Another novel means of reaching the back of the eye is the posterior juxtasclear depot used to deliver anecortave acetate. The method uses a blunt, curved cannula to deliver the drug to the macula without penetrating the globe. This mechanism allows the drug to diffuse across the sclera and choroid into the macular portion of the retina over a period of 6 months. In contrast, other AMD therapies require direct injection into the eye, as often as 9 to 12 times a year.

A novel sustained-release system using a non-biodegradable, implantable helix with a polymer coating (InnoRx, SurModics) is being developed for delivering therapeutics into the posterior chamber of the eye. The system could eventually be a means of drug delivery for diabetic macular edema or AMD. The corkscrew shape of the insert allows the insertion point to be less than 0.5 mm in diameter, while maximizing surface area of the device. A phase I trial in patients with diabetic macular edema began in June 2005.⁴⁴

As mentioned previously, another new development is a cationic emulsion system (Novasorb, Novagali), in which the cationic charge of the oil within the emulsion facilitates spreading across the ocular surface and absorption of the cyclosporine. Novagali plans to use its Novasorb cationic technology for development of posterior segment and intravitreal drug-delivery applications, including treatments for dry eye, allergy, glaucoma, inflammation, and AMD.

Microspheres appear to be an avenue of some interest as well, with animal research

indicating that pegaptanib sodium (Macugen, OSI/Eyetech Pharmaceuticals) microspheres may present a viable means of sustained-release delivery for intraocular drug delivery for AMD.⁴⁵ In addition, alginate microspheres are being examined as a means of delivering protein, and an in vitro study indicates that this may be an appropriate delivery vehicle for drugs needing a long resident time in the eye.⁴⁶

The coming year will see this varied pipeline of ophthalmic drugs and devices develop further, changing the field quickly in some areas, and more gradually in others. The ever-changing landscape of the ophthalmic drug and device innovations is a testament to the quality and quantity of basic research being conducted. This solid foundation allows researchers and pharmaceutical companies to build upon advances in understanding of disease states of the eye to create novel and effective therapies. **OT**

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Focal Point

Drug delivery methods targeting the back of the eye are gaining ground for various eye diseases.

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