Primary open-angle glaucoma is a condition with a large number of treatment strategies, from drugs to devices to surgical interventions. The most effective drugs are available as generics or will be coming off patent soon. The stability of the therapeutic choices available (there hasn’t been a new class of glaucoma drug in more than 15 years) might lead you to think that it’s a disease that is under control with existing treatments, yet it remains a disease without a cure, a disorder with a significant ocular morbidity, and is the second-leading global cause of blindness. Of the 60 million people with this disease worldwide, 15 percent will have a severe degree of permanent visual impairment.

With the host of new therapies that are on the horizon, it’s a good time to peruse the pipeline, take a snapshot of the newest treatment modalities in various stages of development, and also examine issues that will confront efforts at therapeutic progress in the coming years.

IOP-lowering Drugs

Despite its close association with elevated intraocular pressure, glaucoma is a disease manifested at the level of the retinal ganglion cell layer, and in any new development strategies, the importance of preserving visual function should be stressed as the ultimate clinical endpoint. This hasn’t been the case so far; in a recent review of the newest surgical procedures, out of 100 clinical trials surveyed, only one used visual function as an endpoint.

Since their introduction to the market in the mid-1990s, prostaglandin analogues have moved to the top of the list for patients with mild to moderately elevated IOP. They are highly effective at reducing IOP via an enhancement of aqueous humor outflow through the uveo-scleral space. A number of other drugs, including β-adrenergic antagonists and carbonic anhydrase inhibitors, are also available. These agents reduce the production of aqueous humor to lower intraocular pressure and, while effective, require b.i.d. or t.i.d. dosing that makes compliance an issue and can significantly compromise therapeutic outcomes. The fourth current class of medications, the α2 adrenergic agonists, also act by decreasing the production of fluid by the ciliary body and enhancing outflow. Combination agents that take advantage of complementary mechanisms of action are also available. In addition, there are several new agents with novel pharmacodynamics in mid- and late-stage development that will add to the current arsenal of IOP-lowering compounds.

One approach to enhance aqueous humor outflow through the physiological pathway is to use agents designed to relax the tension in the trabecular meshwork. The TM is a tissue that is physiologically similar to muscle in that the tensile status of the myosin-actin complexes within the cells are highly dynamic, and are regulated in large part by the action of Rho GTPase kinase (ROCK). ROCK phosphorylation acts in at least three ways to increase contractile tension in the TM: directly, via phosphorylation of myosin light chain; and indirectly through inhibition of MLC phosphatase and activation of Lim kinases. A couple of ROCK inhibitors (AMA0076, Amakem Therapeutics; AR12286, Aerie Pharmaceuticals)
are in clinical development, including testing of combination therapies (AR12286 plus latanoprost). The list of new IOP lowering agents also includes LM7101, a Lim kinase 2 inhibitor (Lexicon Pharmaceuticals).

A different class of agents in development targets adenosine receptors; for example, the adenosine A1 agonist INO-8875 (Inotek) has shown promise in Phase I and Phase II for IOP reduction in patients with ocular hypertension. This compound works by enhancing outflow through the physiological pathway by stimulating the secretion of matrix metalloproteinases, enzymes that mediate connective tissue remodeling of the TM. Several other adenosine receptor-targeted therapies include ACN-1052 (Acorn Biomedical) and CF-101(Can-Fite BioPharma), but unlike the Inotek compound these drugs are aimed at the adenosine A3 receptor. Targeting this signaling pathway reduces IOP by inhibiting aqueous humor production of the ciliary epithelium. These compounds are also formulated for oral rather than topical dosing, a choice that may provide a greater duration of action and less IOP fluctuation.

Two other additions to the development pipeline are in early-phase clinical trials. One of these is a dose-ranging study of the mixed prostaglandin agonist ONO-9054 (Ono Pharma). Another dose-escalation trial is under way for SYL040012 (Sylentis). The Sylentis compound is an RNAi-based compound designed to target the same β-adrenergic pathway targeted by timolol. Instead of acting as a traditional receptor antagonist however, SYL040012 blocks the pathway by inhibiting biosynthesis of the receptor protein.

New Delivery Systems

One of the greatest hurdles in controlling IOP by means of medical treatment in glaucoma patients is that of compliance: The combination of the chronic nature of treatments, the lack of symptoms and the age of the affected population is a recipe for poor compliance. Recent estimates suggest that 60 percent of patients fail to maintain a daily medication regimen. One approach to this problem is to take the task out of the hands of the patient by employing sustained-release or other depot forms of existing drugs. A number of strategies employing this approach to drug delivery are currently in development.

Depot forms of effective drugs such as the travoprost punctal plugs (Ocular Therapeutix) are currently in clinical trials. In a recent Phase II study presented at the 2011 meeting of the American Glaucoma Society, German researcher Norbert Pfeiffer, MD, found that the travoprost-containing plugs provided a sustained IOP lowering effect of at least 6.6 mmHg that persisted for two months. Another delivery vehicle is a variant of the contact lens and is designed to reside under the lid rather than on the cornea. This device is in development at Amorphex Therapeutics, and can deliver drugs to the eye in a continuous, slow-release fashion; it is particularly easy to place or exchange if needed. Polymerized collagen gels (Euclid Systems) are a biodegradable matrix suitable for depot delivery, as demonstrated for slow release of latanoprost in vitro. (Decore DP, et al. IOVS 2011;52:ARVO E-Abstract 3421) Perhaps a bit further into the future we can expect to see nano-particle based depot delivery of drugs from companies such as Icon Bioscience.

IOP Monitoring Devices

Diurnal variations of IOP have been thought to play an important role in progression of disease for some time. Office visit assessments provide a single measure of IOP, so they cannot provide a comprehensive picture of daily IOP fluctuations. The arrival of continuous monitoring devices designed to provide a round-the-clock IOP measurement is a welcome step forward.

A number of different technologies in development can provide continuous IOP monitoring. One approach uses implantable micro-sensors that transmit pressure data to a handheld external device (Implandata Ophthalmic Products). Another implantable device, the iSense (AcuMEMs), is also in development. Both the Implan data and AcuMEMs systems would be implanted during cataract surgery or another surgery to allow access to the anterior chamber. An alternative technology employs a contact lens with an embedded strain gauge (Triggerfish; Sensimed AG) to record continuous 24-hour changes in ocular surface tension. While this metric is distinct from a true measure of IOP, it provides an indirect means to monitor the fluctuations associated with IOP. Using this device, a recently published study showed a nocturnal peak in tension occurs in about 70 percent of all patients with diagnosed or suspected POAG. These continuous measurement devices will likely have a significant impact on therapy of POAG going forward.

IOP-lowering Devices

Surgical approaches to reducing IOP remain an important treatment option in glaucoma therapy, but an expanding alternative to laser-based surgery that can effectively address the compliance issue is the use of implantable stents and other devices that improve the function of aqueous outflow. With few exceptions, these devices are implanted in patients during cataract surgery (similar to the IOP devices listed above) and
so are relatively low-risk. Several such implantable devices are either new to the market or in late-stage development, and each employs its own unique approach to the engineering challenge of increasing outflow. The Hydrus microstent (Ivanitis) is designed to act much like a cardiac stent; it’s placed in the canal of Schlemm and maintains a patent canal that can mediate aqueous drainage. In a recently reported trial, the patients receiving the device maintained an IOP of 21 mmHg or less without medication for six months. Another device in development is the Cypass (Transcend Biomedical), a thin polymer tube that creates a new outflow pathway when inserted under the scleral spur into the supraciliary space. A different kind of surgically implantable treatment is the stent from AqueSys. The device is a gelatin tube that is a thin rod in its dehydrated form, but when inserted becomes hydrated and soft in order to form a path for aqueous humor outflow.

The newest addition to the list of approved implants is the Glaukos iStent, which was approved by the Food and Drug Administration in June 2012.9 This device is a titanium microstent that connects the anterior chamber with Schlemm’s canal to facilitate outflow. The indication limits it to patients with normal-tension glaucoma. While current therapies, surgeries and the growing list of devices focus on lowering IOP as the path to successful glaucoma therapy, there have also been some advances in more direct approaches to treatment and prevention of the glaucomatous neuropathology that leads to visual loss.2

A key point in understanding the pathology underlying POAG is that while lowering IOP shows a strong correlation with minimizing disease progression, the connection is not absolute: Patients with normal pressures can show visual field loss, while the visual fields in others with high IOPs may remain intact. Increasingly, then, the focus of clinicians and researchers has turned to addressing the pathological consequences of the disease.

A growing body of evidence suggests that many of the drugs that are used to treat elevated IOP also have neuroprotective effects.10 For example, there is ample evidence that inflammatory cytokines from neighboring microglia are important contributors to retinal degeneration, and recent studies suggest that β2 adrenergic agonists can minimize cytokine release, perhaps through activation of brain-derived neurotrophic factor or other neurotrophic pathways.11-13 A clinical study in patients with normal-tension glaucoma has suggested that brimonidine (Alphagan) has an effect beyond lowering IOP.14 Similarly, β-adrenergic antagonists, prostaglandin F2α agonists and carbonic anhydrase inhibitors all have established neuroprotective actions that may provide a therapeutic benefit beyond their IOP-lowering action.3

Interest in neuroprotection is evident from clinical studies of the glutamate receptor antagonist memantine, animal studies of other glutamate antagonists and experimental trials with other drugs with known neuroprotective effects.15,16 Promising animal studies suggest other avenues of addressing the goal of neuroprotection. For instance, the tumor necrosis factor-α (TNF-α) inhibitor Etanercept has been shown to effectively prevent RGC loss in a rodent glaucoma model.17 The established association between retinal degeneration seen in POAG, β-amyloid deposition and the more global neurodegeneration of Alzheimer’s disease may provide a route for basic scientific advances as well as new clinical approaches.18 One compound that has shown the ability to reduce β-amyloid...
aggregation in animal models of glaucoma, MRZ-99030 (Merz Pharmaceuticals GmbH), is currently the subject of clinical trials to assess the safety of a topical formulation (NCT01714960) at clinicaltrials.gov.

Overall, the dual-action nature of many current glaucoma therapies seems to be a serendipitous consequence of redundant ocular signaling physiology, but it’s likely that future approaches will focus on the mitigation of the retinal pathology that’s the hallmark of open-angle glaucoma. Whatever the route to neuroprotection, this one-two punch of reduced IOP and diminished retinal cell loss is a goal that is in sight, and would be a major step forward in preserving visual function in patients with POAG.