Drugs for Diabetes-Related Eye Diseases

- Jeffrey L. Edelman, PhD, Research Investigator, Biological Sciences, Drug Discovery, Allergan Pharmaceuticals

Although the FDA has not yet approved any drugs for treating diabetic retinopathy and its complications, agents from a number of classes are in development and antioxidants are being investigated for their possible benefits. Gaining regulatory approval, however, has been a formidable obstacle because of the requirement for new drugs to show superiority to or equivalency with laser treatments and vitrectomy.

Still, research is spurred by the significant unmet medical need. Diabetic retinopathy is the leading cause of blindness in working-age individuals in the U.S. and is responsible for 12,000 to 24,000 new cases of blindness each year. Among the 230 million people worldwide with diabetes mellitus, nearly all with type-1 diabetes and 60% with type-2 diabetes will develop retinopathy. Half of those patients will be found to have retinopathy after having diabetes for 10 years, and 90% will be affected after having diabetes for 25 years. Although the lack of approved agents means a wide-open field for drug developers, many potential agents are still in the testing stages.

The primary pathophysiological impact in diabetes is on vascular integrity. Characteristic retinal damage includes capillary nonperfusion, ischemia, and dropout of vascular endothelial cells and pericytes (the slender, relatively undifferentiated, connective tissue cells found around small blood vessels). Normal capillaries have a 1:1 ratio between endothelial cells and pericytes. In individuals with diabetes, however, the ratio is 4:1, leading to a breakdown of the blood–retina barrier, ischemia, neovascularization, and retinal detachments.

“The blood vessels grow on the inner retinal surface out into the vitreous and can form attachments, which pull the retina off the back of the eye,” Dr. Edelman said.

Animal studies have shown that the vitreous has the same concentration of glucose as the blood, suggesting that other tissues in the eye may also be affected.

Diabetic retinopathy can be nonproliferative or proliferative. The nonproliferative type is associated with microaneurysms, hemorrhages, diabetic macular edema (DME), and hard exudates. The proliferative type is characterized by new blood vessel formation and fibrous tractional bands that are formed from the optic disc.

Conventional treatment targets glycemic control. Some evidence suggests a risk of worsening retinopathy with anti-hyperglycemic agents (along with the threat of hypoglycemic episodes and diabetic ketoacidosis), but glycemic control is the one approach with proven benefit. A reduction in retinal microaneurysms has also been observed with aspirin in combination with dipyridamole (Aggrenox, Boehringer Ingelheim) or ticlopidine (Ticlid, Roche).

Clinical research has confirmed the efficacy of laser treatments and surgical vitrectomy. Vitrectomy is indicated for vitreous hemorrhage and proliferative diabetic retinopathy. For some patients, vitrectomy can improve vision; it has also been effective for some individuals with DME that has been refractory to laser treatments. Steady advances in surgical techniques are widening the number of indications.

For patients with severe nonproliferative or proliferative retinopathy, pan-retinal photocoagulation has become the standard of care. Treating the associated DME with 1,500 laser burns preserves vision for many, but the method is not without hazards. Among potential risks of adverse events are constriction of the visual field, night blindness, changes in color vision, misplaced laser burns that exacerbate DME, acute glaucoma, and traction retina detachment.

Dr. Edelman said, however, “Despite all these risks, it is still the benchmark.”

The list of pharmacological agents that have been tested in diabetic retinopathy is extensive. Aldose reductase inhibitors showed no significant effects on endpoints or progression. The protein kinase C inhibitor ruboxistaurin (Eli Lilly) reduced the risk of vision loss, but the benefit was modest.

Insulin-like growth factor (IGF)–inhibiting microspheres
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demonstrated mixed results, although there is continued interest. Interest in intravitreal corticosteroids (e.g., triamcinolone acetonide [TA]), with their potent anti-inflammatory and anti-angiogenic effects, also continues. Their tendency to promote cataracts and glaucoma, however, limits the use of these agents.

A fluocinolone acetonide intravitreal implant (Retisert, Bausch & Lomb), another steroid implant (Posurdex, Oculex/Allergan), and a preservative-free and solvent-free emulsion (Nova-63035, Novagali Pharma) have all been tested with some success. The Diabetic Retinopathy Clinical Research Network (DRCR.net) trial of patients with DME tested two Allergan TA doses against laser in more than 800 eyes. Patients were treated at four-month intervals for two years. Measures of corneal thickness and visual acuity for the 4-mg dose were superior to laser at four months and were equivalent to laser at one year. Beyond 16 months, however, laser treatment was superior. Visual acuity was superior to laser with TA at eight months but not at a year or beyond. With TA, cataracts occurred in 51% of patients and intraocular pressure increased more than 10 mm Hg in 33%.

Dr. Edelman said that TA was a very good drug in an optimized preservative-free formulation that failed to meet its primary endpoint of superiority to laser at two years; however, the many patients who were withdrawn from steroids because of adverse effects undoubtedly affected the analysis.

Among intravitreal anti-angiogenesis and anti-vascular endothelial growth factor (VEGF) agents, Pfizer’s pegaptanib sodium injection (Macugen) has demonstrated some benefit on visual acuity measures, macular thickness, the need for focal laser therapy, and regression of neovascularization.

Ranibizumab (Lucentis, Genentech) is being evaluated for DME, as is Genentech’s intravitreal bevacizumab (Avastin) in studies comparing it with laser and in combination with laser.

Opko Health, Inc., has completed phase 2 trials of a small interfering RNA molecule bevacaribamide sodium injection (Macugen) in DME. Pfizer’s gene-silencing, RNA-interference agent (siRNA), known as PF-04523655, a negative regulator of mTOR, is also being compared with laser in phase 2 testing. Macusight, Inc., is testing rapamycin, an immunosuppressant/mTOR pathway modulator.

Dr. Edelman discussed oxidative stress as a postulated cause of diabetic retinopathy, citing studies showing an association between vitreous reactive oxygen species and proliferative severity. He noted, however, that although animal studies suggest a benefit of vitamin C in iris endothelial dysfunction, no convincing clinical evidence has shown that antioxidants improve outcomes in patients with diabetic retinopathy.

He concluded with a caution to researchers: “Given the work in diabetic retinopathy by retinal specialists with multiple forms of laser and vitrectomy, it’s going to take a very good drug and a very safe drug to be successful in this area.”

Dry Eye: Why Have So Many Trials Failed?

- Kay Rittenhouse, PhD, Director and Head, Ophthalmology Translational Medicine, Pfizer Inc., and founder, Drug Development and Delivery Summit

Dry eye is a widely heterogeneous disease. The fact that it presents challenges in diagnosis and that its mechanisms are inadequately understood help make it difficult to choose clinical trial endpoints. Dry eye can be easily mistaken for seasonal allergic conjunctivitis or LASIK-associated dry eye, because perceived dryness and foreign-body presence, changes in the blink rate, ocular discharge or irritation, and burning or itching are symptoms common to both conditions. Furthermore, symptoms may occur at early stages of the disease before any clinical signs become evident, such as corneal and conjunctival redness, decreased tear production, non-uniform tear film, exposed ocular surface, and transient blurry vision.

Many generally noninvasive clinical diagnostic tests for dry eye are available, but the sensitivity, reproducibility, and predictive power of these tests are generally poor. Dr. Rittenhouse singled out tear film osmolarity tests as promising but said that their predictive value was recently reported as only 73%. Furthermore, these tests are improving and becoming easier to apply, but the instrumentation is still in the testing stages and is not commercially available.

Current therapeutic approaches include the use of tear substitutes, lubricants, or palliatives; tear-retenion strategies; nutritional aids (e.g., flaxseed), anti-inflammatory drugs and immune modulators (cyclosporine, corticosteroids, tetra-cycline antibiotics); and secretagogues. Products under investigation for dry eye include Ista’s ecabet (formerly made by Tanabe/Senju), Duramycin (Moli1901, Lantibio, formerly made by Molichem), non-antimicrobial doxycycline (ALTY-0501, Alacrity Biosciences), pimecrolimus (Novartis), rebamipide (Acucella/Otsuka), diquafosol (Prolactria, Allergan/Inspire), rimexolone (Voxel, Alcon), and cycloparsone A ophthalmic suspension (Restasis, Allergan). Other products are listed in ClinicalTrials.gov.

Citing the FDA’s approval of Restasis (a calcineurin inhibitor) as an example of a problematic process, Dr. Rittenhouse stated that the choice of inclusion and exclusion criteria can make or break a program. Including patients who have no residual ability to make tears or whose disease is so mild that they respond well to artificial tears can confound results. With this latter group, therapeutic effects of the vehicle given as the control drug can reduce the efficacy signal of the tested drug. With Restasis, the vehicle was Endura, which itself has demonstrated some efficacy. The inaccuracy of diagnostic tests, inconsistencies in disease classification, and irregular correlation between signs, symptoms and disease stage added further to the uncertainties of the drug approval status for Restasis in treating dry eye.

The FDA advisory committee panel of experts recommended against approval of Restasis in July 1999, citing failure to meet the standard of replicating benefit in signs or symptoms in two well-controlled phase 3 clinical trials. After further data submission, even though New Drug Application (NDA) approvable letters were sent in August 1999, March 2000, and October 2000, NDA 21-023 approval did not occur until late December 2002. As for diquafosol, despite two approvable letters from the FDA in 2003 and 2005, with phase 3 trials meeting endpoints inconsistently, the regulatory hurdles for this drug remain high.

Dr. Rittenhouse identified another important factor that confounds approvals for dry eye therapies:
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Early in the disease, you can assess symptoms accurately, but with more advanced disease, the nerve endings begin to die and some patients experience less discomfort. Under treatment, the nerves can come back, increasing symptoms. This makes establishing endpoints for the clinical trials and getting subsequent approval by the regulators very challenging.

Part of the solution, she suggested, is to work closely with the FDA throughout the approval process and to inform regulators about the complexities of the disease and its treatment. She said, “We have to educate them … to get these novel therapies approved.”

Dr. Rittenhouse’s final message was upbeat, despite the obstacles. With about 25 agents in the ophthalmic pipeline, she said that successful treatments were on the horizon.

REFERENCES

Onmark National Payor/Provider Forum

The nation’s leading oncology providers, as well as pharmaceutical manufacturers and health insurance executives, united in San Francisco in September to discuss solutions to improve patient care while controlling costs.

McKesson, a health care services company, played a key role along with its group purchasing organization, Onmark. The forum featured presentations by United Healthcare, the American Society of Clinical Oncology, Memorial Sloan-Kettering Cancer Center, the Cancer Clinics of Excellence, and the University of Texas Health Sciences Center. Onmark, the forum host, is a McKesson Specialty Care Solutions Company.

“Physician Extenders” Needed for Workforce Gap

- Douglas W. Blayney, MD, Medical Director, Comprehensive Cancer Center, University of Michigan Health System, Ann Arbor, Mich.

Although the death rate from the common cancers, such as lung, colorectal, prostate, and breast, and other uncommon cancers has been decreasing, this favorable momentum in oncology care is threatened by a looming workforce gap, according to Professor Blayney, incoming president of the American Society of Clinical Oncology (ASCO) for 2009 and 2010.

He noted that many factors are behind the decline in the death rate, including effective tobacco control strategies, better hormonal and chemotherapeutic treatments, and improved targeting of therapies. Mortality rates in the U.S. are particularly impressive, compared with non-U.S. rates. For example, the breast cancer mortality rate in the U.S. is at about 38%, about 7% lower than the rate in the United Kingdom (U.K.), despite the U.K.’s universal health care coverage and relatively homogeneous population.

A Less Productive Workforce and an Aging Population

The aging of the oncology care workforce is an emerging problem, Dr. Blayney said. A Rand Corporation survey commissioned by ASCO showed that younger oncologists are less productive than older ones. In the U.S., male oncologists 45 to 64 years of age in private practice conduct an average of 103.1 visits per week; male oncologists outside that age range, however, conduct only 83.9 visits weekly.

In academic settings, the number of visits is lower (63.9 for the older physicians vs. 44.5), and fewer visits also take place among female oncologists in either age group. With the capacity for conducting visits projected to rise by only about 14% in the next 15 years while the demand for visits is surging upward with the aging population by about 48% in the same time frame, the Rand report concluded that no single potential remedy would fully close that gap. The lower lifetime productivity of younger oncologists, along with better therapies expanding the ranks of cancer survivors, can only confound the problem.

The situation, Dr. Blayney said, leads to a clear conclusion: “There will be changes in our care model. We have to do our work in more efficient ways.”

Many oncologists will increase their reliance on “physician extenders,” such as nurse-practitioners and physician assistants, to arrange patients’ schedules, administer chemotherapy infusions, assess side effects of treatment, and manage symptoms and complications through both face-to-face and telephone contacts. These extenders will also write chemotherapy orders and perform procedures.

At his own institution, Dr. Blayney said that this extender group is “experienced and loyal;” about half of them have three to 10 years of oncology experience, and half have worked solely in their careers for the University of Michigan. ASCO data, however, show only a minority of physician assistants working in internal medicine and only 1% of nurse-practitioners specializing in oncology. The advantage of expanding the oncology clinical workforce through more use of physician extenders is that they will enable practitioners to see more patients and offer their services more effectively, he added.

The scope of the practice and privilege of nurse-practitioners and physician assistants is established by state law. Clearly, Dr. Blayney said, there is room to establish best practices and to engage in training and continuing education for them. Both ASCO and the University of Michigan have expressed interest in moving forward in these arenas.

“Given enough flexibility by payors,” he concluded, “I think we can offload some of the work currently done by oncologists to our collaborators who are trained professionals.”
Changes in Information Gathering

By soliciting a show of hands in the audience regarding the use of online Web sites, Dr. Blayney showed that although most of the attendees in the room regularly made on-line travel arrangements, few had made use of modern computer technology for accessing patient records. The disadvantages of relying on digitized records include losses on the “social side” (reduced personal interactions, reduced information from voice cues), the learning curves associated with adjusting to and integrating new technology, and the threat of “being turned into data entry clerks.”

While acknowledging the validity of such reservations, he commented, “The patients and our younger physician colleagues are ready for this. We need to do our work in standard ways.”

As an illustration of the power of standardized procedures, Dr. Blayney referred to the well-known published articles by Atul Gawande, MD, from Brigham and Women’s Hospital, on the enormous benefits to medicine demonstrated by the use of checklists, originally developed in aviation. In a *New Yorker* article and in a *New York Times* op-ed piece, Dr. Gawande described how a simple five-step checklist for catheter insertion, created by Peter Pronovost, MD, of Johns Hopkins University, made a vast difference clinically. The checklist cut the hospital’s catheter bloodstream infection rate in 15 months from 4% of cases to zero, saving 1,500 lives and nearly $200 million.

The list consisted of items that included washing the hands with soap; cleaning the patient’s skin with chlorhexidine antiseptic; putting sterile drapes over the entire patient; wearing a sterile mask, hat, gown, and gloves; and putting a sterile dressing over the catheter site after the line is inserted. The study of 100 Michigan hospitals using the checklist found that 30% of the time, surgical teams skipped one of the five steps. Still, the worst Michigan hospital’s infection rate was better than that of the average hospital in the U.S.

The message, Dr. Blayney said, “is do it right every time.”

Checklist strategies for guiding other processes (e.g., ordering chemotherapy) entail making processes uniform, a step that helps to reduce waste and minimize duplication of efforts. Other efforts toward monitoring internal quality improvement and creating greater efficiency in Michigan hospitals have led to reductions in the average time patients wait for infusions from 41 minutes to 20 minutes and reductions in the frequency of chemotherapy given in the last two weeks of life.

Discussing practice quality assessment tools, including ASCO’s Quality Oncology Practice Initiative (QOPI), Dr. Blayney noted that benefits emerging simply from having an institution’s or practice’s patterns observed (i.e., Hawthorne effects) come powerfully into play. The idea, he underscored, is not to pit one group against another but to allow groups to see where they stand in relation to norms.

At the beginning of the presentation, speaking about declining cancer death rates, Dr. Blayney had said, “We have a good story to tell.” At the conclusion, he said, “To continue the good news story, we need to figure out how to do our work with less expensive and potentially less well trained people.”

He added that oncologists can borrow data and quality-improvement tools from other industries to help themselves better perform their jobs.