The DME Pipeline

The outlook for new therapies for diabetic macular edema is bright—and it will have to be to meet the rising demand for treatment.

BY PETER K. KAISER, MD

It is well known that we are in the midst of a diabetes epidemic. In the past 30 years, the number of Americans diagnosed with diabetes has increased by 373%, from 5.6 million in 1980 to 20.9 million in 2011.[1] Diabetes prevalence has increased markedly in every region of the United States (Figure 1). Only 3.8% of individuals with diabetes have diabetic macular edema (DME)[2]; however, because epidemiologic trends associated with diabetes and DME are headed in the wrong direction, we are likely to see DME prevalence increase. Not only are many more individuals being diagnosed with diabetes each year, they are also developing diabetes at earlier ages, and thus have longer duration of disease—and duration of diabetes is positively correlated with development of DME.

These trends have sparked a new commitment to finding solutions and intense interest in DME therapies in the pharmaceutical industry. With a complex disease such as diabetes, there are many potential pathways to target, and we see that reflected in the long list of therapeutic approaches now under investigation.

ANTI-VEGF AGENTS

Anti-VEGF therapy is the current first line treatment for DME. There are three very effective anti-VEGF drugs: bevacizumab (Avastin, Genentech); ranibizumab (Lucentis, Genentech); and aflibercept (Eylea, Regeneron), the last two of which are approved by the US Food and Drug Administration (FDA) for treatment of DME. Each of these drugs binds to and blocks VEGF-A, inhibiting angiogenesis and the development of vascular permeability. Aflibercept also blocks VEGF-B and placental growth factor, which may contribute to the better efficacy of aflibercept seen in the recently released DCRC.net Protocol T results. In that head-to-head-to-head comparison of the three drugs, the group receiving aflibercept required fewer laser treatments and slightly fewer injections than the other two groups, and all subjects—and in particular those with more severe disease at baseline (worse than 20/50 vision or > 400 µm macular thickness)—did significantly better on aflibercept than on the other drugs.[3]

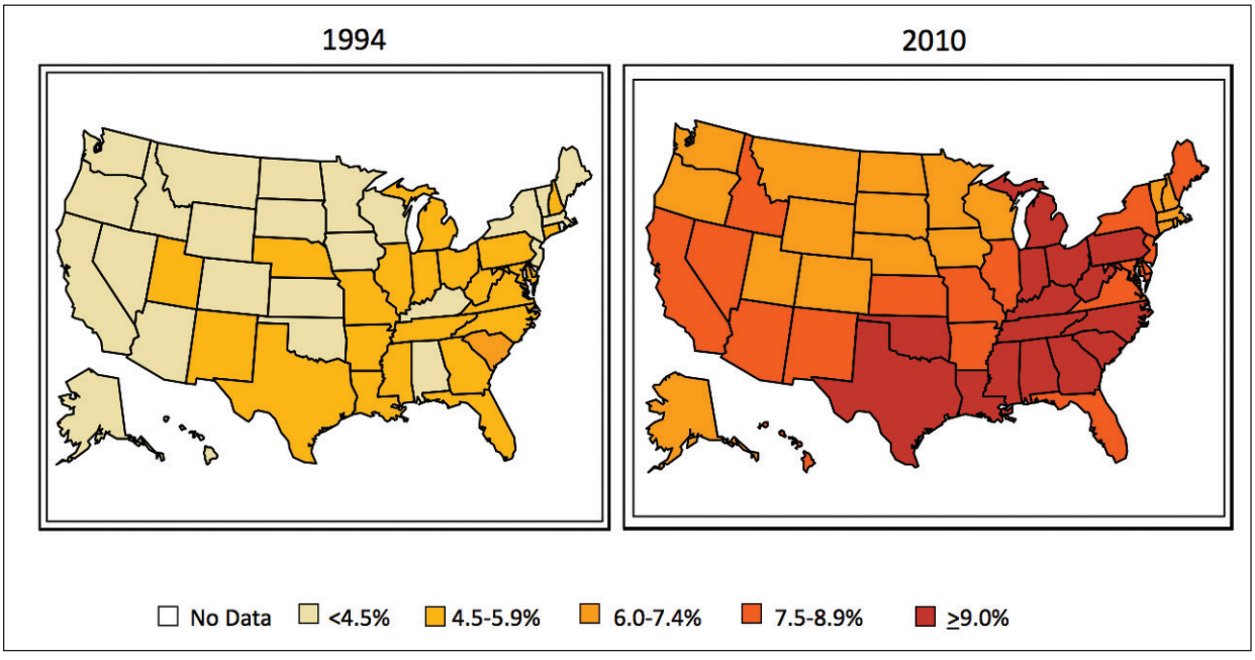

Figure 1. Age-adjusted prevalence of diagnosed diabetes among US adults, 1994 and 2010.[1]

Pegaptanib (Macugen, Valeant), an anti-VEGF agent that binds only the VEGF165 isoform, can also be considered for DME therapy. It has not been tested head-to-head versus the other anti-VEGF medications.

A downside to anti-VEGF therapy is the frequency of injections required. Many patients with diabetes are of working age, and, therefore, monthly visits to a retina specialist are not possible. Several companies, including Avalanche Biotechnologies, Genzyme, and Neurotech, are testing ways to deliver anti-VEGF drugs to the eye using various gene therapy platforms that would release the active drug over a long period of time—in some cases indefinitely. This approach uses the same proven mechanism of action without the major disadvantage of anti-VEGF injections. Genentech is developing an implantable, refillable device that would release ranibizumab over extended periods of time. Alcon is testing a single-chain antibody fragment (RTH258) that has shown some promise in extending the dosing interval to 3 months in patients with age-related macular degeneration (AMD). These companies are all testing their platforms as treatments for AMD, but, if successful, they should also work in DME .

STEROIDS AND OTHER ANTIINFLAMMATORY AGENTS

Intravitreal injection of corticosteroids has long been a treatment option for DME. Compared with anti-VEGF agents, steroids are less effective and have more side effects, but inflammatory pathways are implicated in chronic DME. As with the anti-VEGF agents, there has been considerable progress in development of new drug delivery mechanisms in this area. A biodegradable polymer containing dexamethasone (Ozurdex, Allergan) and a nonerodable implant containing fluocinolone acetonide (Iluvien, Alimera Sciences) were each approved by the FDA in late 2014 for treatment of DME. These slow-release devices provide corticosteroid therapy for months (Ozurdex) to years (Iluvien). The main side effects are cataract progression and potential elevation of intraocular pressure.

An oral steroid analogue that might have antiinflammatory properties and function on endothelial cells to decrease vascular permeability in patients with diabetic macular edema is also under investigation. Danazol (Optina, Ampio Pharmaceuticals) binds to androgen and steroid-binding globulin receptors, stimulating the formation of a cortical actin ring to enhance endothelial cell barrier function. Because it is already approved for the treatment of endometriosis and other conditions, danazol was able to skip some early-stage safety testing and is now in phase 3 trials for use in DME.

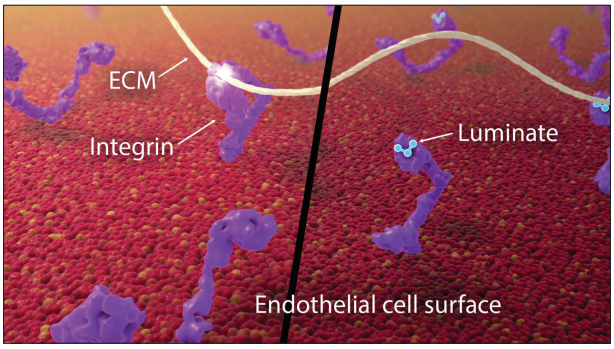

Figure 2. Integrins regulate cell functions and interactions among cells and between cells and the extracellular matrix (ECM). As they bind or attach to the ECM, integrins activate intracellular signaling pathways and proteolytic changes that promote angiogenesis. Luminate inhibits the connection between the integrins (shown here in purple) and the ECM, preventing the downstream angiogenic effects.

GlaxoSmithKline has tested oral darapladib, an Lp-PLA2 inhibitor that acts on several pathways, including phospholipase A2, to decrease inflammation in DME. A phase 2 trial was completed in 2013, but there has been little information since.

INTEGRIN PEPTIDE THERAPY

A disadvantage of anti-VEGF therapy for DME is that it does not really address the underlying vascular pathology, it just temporarily stops the leakage.

A drug now under investigation, Luminate (previously ALG-1001, Allegro Ophthalmics), has been shown not only to dry up leakage from existing neovascularization, but also to inhibit growth of abnormal blood vessels and turn off production of new blood vessels. Luminate is an integrin antagonist that blocks integrin receptors on vascular endothelial cells that mediate a number of angiogenic processes, including endothelial cell migration, proliferation, differentiation, and maturation (Figure 2).

In a phase 1 study, 15 individuals with persistent DME received three monthly injections of Luminate after a 90-day washout period from previous therapy. Subjects were then observed for 3 months off treatment. Safety was excellent. Mean peak BCVA improvement was 11 letters, or about two lines of vision, and no subjects lost vision, even during the 3 months off treatment. That is very encouraging, as it suggests that the drug's treatment effect may last longer than current therapy modalities. Eight of the 15 patients had visual acuity improvements sufficient to return them to functional vision (Figure 3).[4]

These are early results, but Luminate has been progressing rapidly through clinical trial phases for DME and

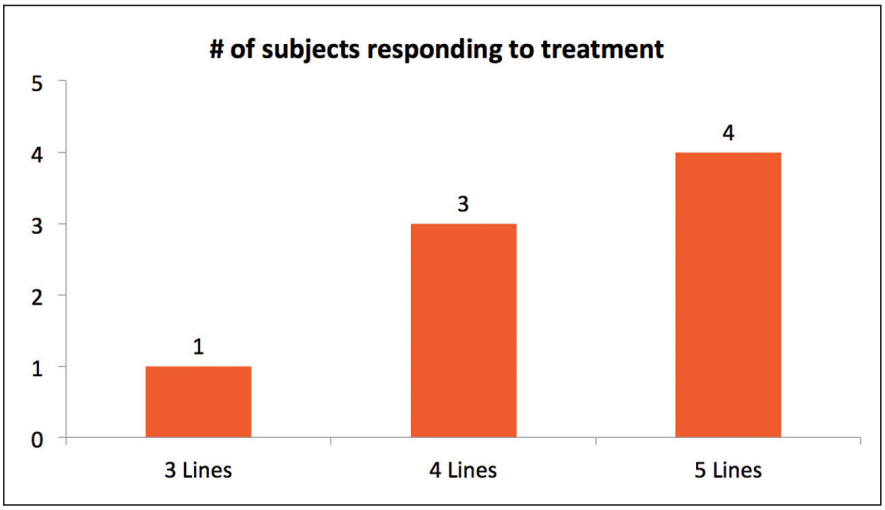

Figure 3. Eight of 15 individuals treated with Luminate gained at least 3 lines of BCVA at 90 days, and those gains were maintained through 3 months off treatment. No subjects lost BCVA or had an increase in macular thickness while off treatment.

other indications. A randomized, double-masked, phase 2 multicenter trial comparing Luminate with bevacizumab and focal laser photocoagulation in 150 subjects with DME is now under way. An additional study to evaluate this drug in patients with nonproliferative diabetic retinopathy is expected to begin in mid-2015.

INHIBITION OF INTRACELLULAR SIGNALING

Another drug with a unique mechanism of action is squalamine, an antiangiogenic small molecule. Squalamine (OHR-102, Ohr Pharmaceutical) counteracts multiple growth factors, including VEGF, pigment-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). It enters cells by an active process and, once inside, sequesters intracellular calmodulin to render the growth factor receptors inactive.

This is a topical agent capable of transscleral penetration, which results in delivery of high levels of active drug to the choroid and retina, so the potential for avoiding intravitreal injections is exciting. The company's focus thus far has been on establishing the drug as a treatment for AMD, but early results from investigator-sponsored studies of its effect in diabetic retinopathy have been promising.

ANGIOPOIETIN/TIE-2 SIGNALING PATHWAY

Another interesting pathway in DME is the Tie-2 pathway. Unlike some of the damage-inducing pathways targeted by most agents, Tie-2 is protective. When it is activated, there is improved stability of the retinal vasculature and decreased leakage. Diabetes perturbs the Tie-2 pathway due to elevated levels of the Tie-2 inhibitors angiopoietin (Ang) 1 and Ang2.

Aerpio Therapeutics is about to start phase 3 testing of a tyrosine phosphatase beta inhibitor that restores Tie-2 signaling, which should stabilize the vasculature and reduce leakage in patients with DME regardless of how much Ang1/Ang2 is present. A bonus is that Aerpio's drug is given by subcutaneous self-injection—something insulin-dependent diabetics are very comfortable doing. While we would normally prefer nonsystemic administration, this drug could have positive systemic effects by stabilizing and improving the vasculature throughout the body.

Other companies, including Regeneron, are taking the opposite approach of inhibiting Ang2, which would allow the Tie-2 receptor to be naturally activated.

CONCLUSION

The pathogenesis of DME and other diabetic complications is complex. Because of this, we are likely to see even more pathways or mechanisms of action under consideration in the near future, in addition to those described here. I am very optimistic that one or more of the agents now under investigation will prove to be even better than—or perhaps synergistic with—current anti-VEGF therapy options for DME. ■

Peter K. Kaiser, MD, is the Chaney Family Endowed Chair in Ophthalmology Research and a professor of ophthalmology at the Cole Eye Institute in the Department of Ophthalmology at Cleveland Clinic and founding director of the Digital Optical Coherence Tomography Reading Center (DOCTR). He is a consultant for Aerpio, Alcon, Allegro, Bayer, Genentech, Neurotech, Novartis, Ophthotech, Ohr Pharmaceuticals, and Regeneron. Dr. Kaiser may be reached at +1-216-444-6702; or pkkaiser@gmail.com.

1. U.S. Centers for Disease Control and Prevention. National Diabetes Surveillance System. Age-adjusted prevalence of obesity and diagnosed diabetes among U.S. adults. www.cdc.gov/diabetes/statistics. Accessed March 17, 2015.
2. Varma R, Bressler NM, Doan QV, et al. Prevalence of and risk factors for diabetic macular edema in the United States. *JAMA Ophthalmol*. 2014;132(11):1334-1340.
3. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema [published online ahead of print February 18, 2015]. *N Engl J Med*. doi:10.1056/NEJMoa1414264
4. Allegro Ophthalmics. Data on file.