Developments in the Treatment of Diabetic Macular Edema

A review of current research involving therapeutic options in the pipeline.

WITH QUAN DONG NGUYEN, MD, MSc

Treatments for diabetic macular edema (DME) continue to be developed. *Retina Today* recently spoke with Quan Dong Nguyen, MD, MSc, to learn more about treatment options in the pipeline, how far along the clinical trials for these potential therapeutic agents are, and what research still must be done.

Retina Today: What are some possible treatments for DME that we might see in the near future?

Quan Dong Nguyen, MD, MSc: There is constant major work being performed to find new treatments for DME, which is great for our patients. Some studies are looking at the drug PF-655 (Quark Pharmaceuticals), a synthetic small interfering RNA (siRNA) that targets the gene RTP801, which is overexpressed in patients with wet age-related macular degeneration (AMD) and diabetic retinopathy. Other studies are looking at iCo-007 (iCo Therapeutics), a single-stranded antisense that degrades messenger RNA (mRNA), preventing the creation of ribosomal proteins and potentially down-regulating certain agents associated with DME. Other possibilities include examining the effect of AKB-9778 (Aerpio Therapeutics), which activates the Tie-2 pathway, a key control axis for retinal vascular stability. Tie-2 activation, via VEGF suppression, particularly in combination with anti-VEGF agents, may also block development of choroidal neovascularization (CNV) and promote regression of new CNV.

These studies are in various stages of clinical trial. The results thus far have been encouraging.

RT: What is the RTP801 gene, and how does it relate to DME?

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Dr. Nguyen: RTP801 is a gene that is triggered by various stimuli in vitro such as oxidative stress and DNA damage and is expressed in patients with various retinal disorders such as diabetic retinopathy and neovascular AMD. The RTP801 gene is unnecessary for normal organism function. PF-655 readily distributes into retinal and other ocular tissues following intravitreal injection, and targets RTP801.

In animal models, diabetic mice that received intravitreal injections of PF-655 had a 50% reduction in blood vessel leakage compared with diabetic mice injected with control siRNA. Plasma concentrations of PF-655 are very low (less than 10,000 times the vitreous concentration); pre-clinical studies show that concentrations in ocular tissues and plasmas declined in parallel over 10 days.

There are 2 phase 2 studies examining the effects of PF-655 on patients with DME: the DEGAS study and the MATISSE study.

The DEGAS study is a phase 2, multicenter, dose-ranging, laser comparator study examining 184 patients equally randomized into 4 treatment groups: 0.4 mg PF-655, 1 mg PF-655, 3 mg PF-655, and laser. Patients receive treatment at baseline, week 1, week 2, and monthly for 36 months.

At month 12, the treatment group receiving 3 mg PF-655 showed a trend toward best corrected visual acuity (BCVA) improvement. The mean gain in BCVA in the 3-mg treatment group was 5.77 letters vs 2.39 letters for laser (P = .08). There appeared to be a dose response, with the higher dosage of PF-655 showing greater bioactivity.

The MATISSE study is a phase 2b study examining the safety and efficacy of PF-655 in larger doses, either as monotherapy or in combination with ranibizumab (Lucentis, Genentech). The MATISSE study, which finished recruitment in December 2013, is looking at dose-limiting toxicity, maximum tolerated dosage, and the efficacy of monotherapy vs combination therapy.

RT: What work is being done vis-à-vis iCo-007?

Dr. Nguyen: The iDEAL study is evaluating a different treatment option for DME. Researchers in the study are investigating how iCo-007 affects patients with center-involving DME.

The drug iCo-007 is a second generation antisense inhibitor targeting C-raf kinase mRNA, which is involved in angiogenesis and vascular permeability. More stable, more potent, and less inflammatory than its first-generation counterpart, iCo-007 has a half-life of 6 to 8 weeks, and in animal models has been shown to reduce leakage in laser-induced CNV. The drug, a single-stranded antisense oligonucleotide, enters the cell and interacts with its specific target mRNA in the cytoplasm or nucleus. The antisense drug binds to mRNA, degrading the mRNA and preventing ribosomal translation of mRNA into protein. Clearance of iCo-007 is slow in the retina. The drug has the potential to down-regulate many growth factors and signal transduction pathways, including VEGF, IGF-1, and HGF.

The iDEAL study is a multicenter, randomized, phase 2 trial that will assess visual acuity at 8 months and 12 months in patients with DME who receive iCo-007. Patients were randomized into 4 treatment groups. The first group received a 350-µg iCo-007 injection at baseline and another 350-µg injection at 4 months. The second group had the same treatment pattern but was given 700-µg injections. The third group received a 350-µg injection of iCo-007 at baseline, followed by laser treatment at day 7; a second 350-µg injection of iCo-007 was given at month 4 along with laser upon meeting the criteria for laser treatment. The fourth group was given a 0.5-mg ranibizumab injection at baseline, followed by a 350-µg injection of iCo-007 at week 2; another 0.5-mg ranibizumab injection was given at 4 months, followed by another 350-µg injection of iCo-007 2 weeks thereafter. The primary endpoint is at month 8. If patients meet retreatment criteria at month 8, they can receive additional treatments based on their randomization and be followed until the termination of the study at month 12.

The iDEAL trial has finished enrollment and will release its results once the data have been collected and analyzed.

> "The risks and treatment burden associated with intravitreal injection are well known to all ophthalmologists and patients; thus, these novel clinical trials are aimed toward learning how to achieve the best outcomes for patients with DME."
> –Quan Dong Nguyen, MD, MSc

RT: What is the role of angiopoietin-2 in DME?

Dr. Nguyen: Angiopoietin-2 is a ligand of the Tie-2 receptor, which is up-regulated in many forms of neovascularization. Angiopoietin-2 increases the body's response to VEGF. Studies are being conducted to determine if angiopoietin-2 inhibitor could play a role in reducing DME and improving visual acuity.

RT: Are there any systemic safety signals found in these trials for new agents for DME?

Dr. Nguyen: Thus far, none of the studies discussed above have demonstrated any systemic safety signals. There have also been no major ocular adverse events such as ocular hypertension. In the RISE and RIDE trials, which measured the safety and efficacy of ranibizumab for patients with DME, there was a trend of higher systemic adverse events among the patients who received the higher dose of ranibizumab (0.5 mg) compared with those who were treated with the lower dose (0.3 mg), which led Genentech to recommend the 0.3-mg dose to the US Food and Drug Administration (FDA) for approval for patients with DME, which the FDA did accept.

RT: Several drugs pending approval from the FDA to treat DME include the dexamethasone intravitreal implant (Ozurdex, Allergan), the fluocinolone acetonide intravitreal implant (Iluvien, Alimera) and aflibercept (Eylea, Regeneron). If these drugs are approved, how will your treatment patterns change for patients with DME?

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Dr. Nguyen: Neither the dexamethasone implant nor the fluocinolone acetonide implant has shown the equivalent type of outcomes that VEGF antagonists such as ranibizumab or aflibercept have shown for patients with DME. If these drugs were approved, they would likely be used for patients with DME who do not respond completely to anti-VEGF or who cannot receive, for whatever reasons, frequent injections of anti-VEGF agents. Also, they might be used in combination with anti-VEGF agents for DME that does not resolve completely after a series of anti-VEGF injections.

RT: What are some of the important unanswered questions raised by the trials mentioned here?

Dr. Nguyen: We are unsure if the available anti-VEGF treatment options are equal in efficacy and safety for treating patients with DME. Work is still being done to answer that question. The Diabetic Retinopathy Clinical Research Network (DRCR.net), for instance, is conducting an important trial, Protocol T, employing ranibizumab, bevacizumab, and aflibercept in a head-to-head design to compare efficacy and safety of these anti-VEGF agents. Results may be available by the end of 2014 or early 2015.

Across the United States and worldwide, additional studies are being conducted to find an optimal treatment regimen for DME. The Truhlsen Eye Institute at the University of Nebraska Medical Center is preparing to launch several of these clinical trials, investigating different targets in the pathogenesis of DME. The risks and treatment burden associated with intravitreal injection are well known to all ophthalmologists and patients; thus, these novel clinical trials are aimed toward learning how to achieve the best outcomes for patients with DME.

Another unknown is the effect of PF-655, iCo-007, or AKB-9778 monotherapy vs combination therapy with either anti-VEGF or laser. We will begin to better understand how these drugs may work in combination therapy as results from trials like iDEAL and MATISSE are published. ■

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