Despite a significant increase in the scientific understanding of diabetic retinopathy, it continues to be a major cause of severe vision loss in the United States. Fortunately, investigations of novel therapies to treat neovascular age-related macular degeneration (AMD) have spilled over into the treatment of diabetic macular edema (DME). Most notably, vascular endothelial growth factor (VEGF) antagonists have gained attention in recent years as VEGF has been shown to play a crucial role in the pathogenesis of DME. The emergence of new anti-VEGF agents is largely based on the understanding of the molecular mechanisms and biological basis of the role of VEGF. Anti-VEGF therapies were highlighted at this year's Angiogenesis meeting hosted by Bascom Palmer in Miami, FL. The meeting focused on modifications in dosing strategies of direct VEGF inhibitors, as well as new therapeutic approaches that target the VEGF axis.

RANIBIZUMAB

Ranibizumab (Lucentis, Genentech, Inc.), a recombinant, humanized, monoclonal antibody fragment that inhibits all forms of VEGF, is being investigated in several trials to assess its efficacy in the treatment of DME. The Ranibizumab for Edema of the Macula in Diabetes 1 (READ 1) study concluded that VEGF is an important therapeutic target for DME. Ten patients received intraocular injections of 0.5 mg ranibizumab at baseline, month 1, 2, 4, and 6 months. There was a mean 77% reduction in foveal thickness, and a mean gain of eight letters of visual acuity at month 12. This led to READ 2, in which a group of 126 patients was randomized to monthly ranibizumab (0.5 mg), focal laser every 3 months, or combination therapy of focal plus ranibizumab every 3 months. At month 12, the ranibizumab-only group experienced a gain of 6.46 letters vs 4.48 in the combined group and 2.08 letters in the laser-only group (Figure 1). To date, ranibizumab appears to be effective in reducing optical coherence tomography (OCT) central retinal thickness (CRT) and improving vision early, although the focal laser group may catch up by the end of the 2-year trial. The READ 2 trial is currently ongoing.

Figure 1. One year visual acuity results of the READ 2 study.
and is expected to reach completion in 2010.

The RIDE and RISE studies are parallel phase 2 trials designed to evaluate intravitreal ranibizumab for the treatment of DME with respect to the magnitude and durability of effect and long term safety. In these two studies, patients were randomized into monthly low-dose ranibizumab, high-dose ranibizumab, or sham treatment for a period of 36 months. The primary efficacy endpoint is the proportion of patients with a greater than 15 letter visual acuity gain compared with baseline. Secondary endpoints include mean change of visual acuity and central foveal thickness from baseline. Results are expected in 2010.

Meanwhile, several studies have utilized higher doses of ranibizumab under the theory that VEGF concentrations are more elevated in DME than in AMD. Based on this belief, an investigator-sponsored trial (IST) is being conducted by Philip Ferrone, MD of Long Island Vitreoretinal Consultants. In this trial, 50 patients were randomized to monthly intravitreal injections of either 0.5 mg ranibizumab or 1.0 mg ranibizumab. Patients received 3 monthly injections followed by as-needed monthly injections after month 2. Patients could be retreated based on several criteria: five letter visual acuity decrease, central retinal thickness greater than 250 µm, persistent clinically significant macular edema, or at the discretion of the investigator. At 6 months, 31 eyes of 25 patients were analyzed. The higher dose ranibizumab group had a gain of 8.9 letters compared with a gain of 3.5 letters in the lower dose group, similar though the CRT reduction was fairly similar (103 µm vs 149 µm). More striking was the greater-than-15-letter gainers: five of 13 in the higher dose group vs one of 18 in the lower dose group. However, this difference was not statistically significant. At midpoint in this study, there seems to be a trend toward greater visual improvement with the higher dose of ranibizumab; however, the maximal drug effect seems to last for 4 weeks, diminishing to subtherapeutic levels by 8 weeks regardless of dose.

Another IST, the RESOLVE trial, was conducted at the Université Paris VII by Pascale G. Massin, MD. In this multicenter, double-masked, phase 2 study, patients were randomized to 0.3 mg ranibizumab, 0.5 g ranibizumab, or sham treatment. Following the first treatment, the doses could be doubled to 0.6 mg or 1.0 mg, respectively, if the CRT was greater than 300 µm or if the CRT was greater than 225 µm and there was less than a 50 µm reduction from baseline. Separate from doubling the dose, patients were retreated if the retinal thickness increased by 50 µm between monthly treatments or visual acuity decreased by five or more letters. The study design allowed escape to focal laser if necessary. At month 12, the lower-dose group demonstrated an increase of 9.4 letters vs 6.0 letters in the higher dose group and 1.2 letters in the sham treatment group (Figure 2). Pooled, the two groups of patients receiving ranibizumab had a CRT reduction of approximately 175 um at month 12, which resulted in a 7.6 letter increase in visual acuity.

Both these higher dose trials demonstrated clinical and statistical superiority to sham treatments in terms of visual acuity and decrease in CRT. Additional trials will be necessary to determine the most effective dosing and treatment interval strategy.

VEGF TRAP

VEGF TRAP (VEGF Trap-Eye, Regeneron, Inc.) is a soluble, human fusion protein that binds with strong affinity to all forms of VEGF-A and the related placental growth factor. It is currently in phase 3 clinical trials for the treatment of wet AMD. Studies are also under way for the treatment of DME. A study designed to test the safety, tolerability and efficacy of VEGF TRAP evaluated five DME patients with CRT greater than or equal to 250 µm. Each patient in the phase 1 study received a single injection of 4mg VEGF TRAP. This resulted in a statistically significant reduction in central retinal thickness of approximately 100 µm by 2 weeks which was maintained through 6 weeks. The improvement in visual acuity ranged between 2.6 to 6.8 letters at the 6 week time point. A phase 2 trial, DME and
VEGF Trap EYE: Investigation of Clinical Impact (DA VINCI) is currently recruiting.

ICO 007

Another research drug in clinical development is iCo-007 (iCo Therapeutics, Inc.), which utilizes a different mechanism of action to treat DME. iCo-007 is a second-generation antisense molecule targeting c-raf (raf-1) kinase that results in the down-regulation of the pathway of multiple growth factors (including VEGF, erythropoietin, and hepatocyte growth factor) that seem to play critical roles in the process of ocular angiogenesis and vascular leakage. A phase 1 dose-escalation study using a single intravitreal injection of iCo-007 in patients with diffuse DME recently completed recruitment. An example of a patient from the lowest drug dose (110 µg) is presented in Figure 3: consistent with the antisense drug mechanism of action, the reduction of retinal thickness seems to appear with a slight delay (intracellular action), but the longevity of the effect is still evident at the month 6 time point in the phase 1 trial. Results are expected in early 2010.

BEVASIRINAB

Bevasirinab (Opko, Inc.) is another drug in clinical development with a different mechanism of action. Bevasirinab utilizes siRNA technology to target the mRNA of VEGF, not the VEGF molecule itself. Each siRNA molecule can inactivate hundreds to thousands of mRNAs. A phase 2 trial compared multiple doses of bevasirinab, with injections administered at baseline and 4 weeks. CRT and visual acuity improved after the second month, most efficiently with the intermediate dose, again with a slight delay similar to iCo 007 (Figure 4).

SIROLIMUS

Sirolimus (Rapamycin, Macusight, Inc.) is a broad-acting compound that has multiple mechanisms of action, including antiangiogenic, immunosuppressive, and antiproliferative activity. A completed phase 1 clinical trial concluded that sirolimus is safe and well-tolerated when administered either subconjunctivally or intravitreally. Additionally, at 45 and 90 days after administration of the lowest doses via subconjunctival injection, patients had clinically significant mean visual acuity improvement compared with baseline. These patients also experienced mean reduction in CRT. Macusight is initiating a phase 2 clinical trial.

CONCLUSION

The outcomes of these clinical trials are sure to enlarge the armamentarium for the treatment of DME. These agents will likely be used in combination, in addition to laser photocoagulation and corticosteroids. Novel delivery technologies, including sustained delivery devices and topical medications, are also on the radar. Unlike neovascular AMD, which has in most cases responded to direct VEGF blockade, it appears likely that the treatment of DME will be more of an art form, with tailoring of treatments for individual patients.

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