Diabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy. Within 20 years of diagnosis of diabetes, DME affects almost 30% of patients with either type 1 or type 2 of the disease. Since the time of the Early Treatment Diabetic Retinopathy Study a quarter century ago, focal/grid laser photocoagulation has been the standard-of-care treatment for DME.

Recently, interest in the possibility of pharmacologic treatment of DME has grown. Corticosteroids and vascular endothelial growth factor (VEGF) inhibiting agents have been proposed as adjunctive therapies. These alternatives have now been evaluated in several clinical trials.

A randomized controlled trial by the members of the Diabetic Retinopathy Clinical Research Network (DRCR.net) found that focal/grid photocoagulation was more effective and had fewer side effects than intravitreal injection of triamcinolone acetonide in patients with DME at both 2- and 3-year follow-up. Another DRCR.net trial found that, with 1-year follow-up, intravitreal injection of ranibizumab with prompt or deferred laser resulted in greater visual acuity gain than laser alone. In addition, intravitreal triamcinolone plus laser resulted in greater visual acuity gain in pseudophakic eyes compared with laser alone.

VEGF inhibition, therefore, appears to be a promising treatment option in DME, particularly because there is evidence to demonstrate that VEGF levels are elevated in the retina and vitreous in eyes with diabetic retinopathy. The molecule aflibercept (Eylea, formerly VEGF Trap-Eye, Regeneron Pharmaceuticals/Bayer HealthCare), a fully human VEGF receptor fusion protein, was designed specifically to be a highly potent blocker of all forms of VEGF-A, as well as the related placental growth factor (PIGF). The molecule binds to VEGF-A and PIGF with greater affinity than native receptors, and it penetrates all layers of the retina. The drug is formulated for intravitreal injection.

**DA VINCI**

DA VINCI, a double-masked randomized prospective multicenter phase 2 study, was designed to assess the safety and efficacy of aflibercept, administered in multiple doses and delivery schedules, in comparison with standard-of-care laser treatment. Eligible patients had clinically significant DME with central involvement, defined as thickness of greater than 250 µm in the central subfield on optical coherence tomography (OCT), and best corrected visual acuity (BCVA) of between 20/40 and 20/320 Snellen equivalent.

A total of 219 patients were randomly assigned equally to one of five groups: aflibercept 0.5 mg monthly, aflibercept 2.0 mg monthly (ie, every 4 weeks), aflibercept 2.0 mg every other month (ie, every 8 weeks) following three initial monthly injections, aflibercept 2.0 mg as needed (PRN) following three initial monthly injections, and standard of care (ETDRS guided laser). The primary
end secondary endpoint was change in retinal thickness on OCT at 24 weeks. Treatment was continued to 52 weeks. Exclusion criteria were standard for trials of this type, including history of vitreoretinal surgery in the study eye, laser in the study within 3 months of screening, and previous use of steroids or antiangiogenic drugs within 3 months of screening.

Laser retreatment was available to patients in the laser-only arm beginning at week 16. Laser rescue was permitted in the experimental arms beginning at week 24, with subsequent laser not more often than every 16 weeks. The criteria for laser retreatment or rescue were based on ETDRS criteria modified to include both clinical and OCT data.

For patients randomized to the PRN arm, retreatment with aflibercept after the first three loading doses was permissible if OCT central retinal thickness was 250 µm or greater, if there was an increase in central retinal thickness of more than 50 µm compared with the lowest previous measurement, if there was an increase in BCVA of one line (five letters) or more since the last visit, or if there was a loss of one line or more since the last visit with any increase in retinal thickness.

Among the 219 patients randomized, baseline characteristics were generally well balanced. There were more men than women in the study, the study population was mostly white, and type 2 diabetes predominated over type 1. Baseline BCVA, retinal thickness, and diabetic retinopathy scores were similar among the groups.

In 200 patients who completed 6-month follow-up, the primary endpoint of the study, a statistically significant improvement in BCVA was seen in all aflibercept treatment groups compared with laser. Improvement ranged from 11.4 letters in the monthly 2.0 mg group (P<.0001) to 8.5 letters in the 0.5 mg monthly group (P<.01), compared with a 2.5 letter improvement in the laser group. No statistically significant differences in BCVA change from baseline were seen among the groups receiving aflibercept.

In 176 patients followed to the completion of the study at 1 year, the gains in BCVA were maintained or numerically improved, with the monthly 2.0 mg group again achieving the greatest gain at +13.1 letters, compared with a 1.3 letter loss in the laser group (P<.0001). Again, no statistically significant differences were seen among the groups receiving aflibercept.

The improvements in BCVA were paralleled by anatomical improvements. Central retinal thickness on OCT at 6 months (a secondary endpoint in the study) were greater in the aflibercept treatment groups than in the laser group (P<.0001). The greatest decrease at 6 months, -194.5 µm from baseline, was seen in the monthly 2.0 treatment arm, although the differences among the aflibercept treatment arms were not statistically significant. The decreases in thickness seen at 6 months were maintained or numerically improved at 1 year.

Aflibercept was generally well-tolerated. No patients experienced drug-related ocular serious adverse events. The most common adverse events reported were those associated with intravitreal injections or the underlying disease. The incidence of nonocular serious events was generally well-balanced among all study arms. Six deaths occurred in the 175 patients who received the study drug (3.4%) and one in 44 patients treated with laser (2.3%) over the course of 1 year.

CONCLUSIONS

In the phase 2 DA VINCI study in patients with DME, treatment with aflibercept resulted in statistically significant improvements in BCVA from baseline in comparison with standard care at both the primary 6-month endpoint and at the trial’s 12-month conclusion. The treatment benefit was seen in all groups receiving the drug, including 2.0 mg aflibercept dosed every other month, with no statistically significant differences among the groups receiving aflibercept. Statistically significant improvements in central retinal thickness from baseline were seen in the groups receiving the drug. Aflibercept was generally well-tolerated, and adverse events were typical of those associated with intravitreal injections.

Based on these positive results, a phase 3 study of the drug in patients with DME has been initiated. One-year results of that study may be available as early as next year.

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