Peripheral scatter laser or panretinal photocoagulation (PRP) has been the standard treatment for proliferative diabetic retinopathy (PDR) for nearly 40 years. Although this laser treatment can reduce the incidence of severe vision loss, it carries the risk of notable side effects, including loss of peripheral and night vision, due to its destructive effects on the peripheral retina.

Anti-VEGF injections have recently become a widely used treatment for diabetic macular edema (DME), and observations from many large interventional trials have suggested that the severity of diabetic retinopathy can be improved with anti-VEGF treatment. The Diabetic Retinopathy Clinical Research Network (DRCR.net) recently published 2-year outcome data from a randomized clinical trial, Protocol S, that evaluated the efficacy and safety of intravitreal ranibizumab (Lucentis, Genentech) vs. PRP for the treatment of PDR. Details of this study are reviewed herein.

**TRIAL DESIGN**

The primary outcome of Protocol S was a noninferiority comparison of visual acuity at 2 years. The potential benefits of 0.5 mg intravitreal ranibizumab treatment over PRP, including less peripheral visual acuity loss and less DME, were evaluated and quantified as important secondary outcomes. Collection of safety and efficacy data will continue for 5 years.

Protocol S was performed at 55 locations. Retinal neovascularization was present in enrolled patients’ eyes, but no prior PRP had been performed. A total of 394 eyes of 305 patients were randomly assigned to receive PRP or injections of ranibizumab. Patients who required treatment for PDR in both eyes at the start of the study received PRP in one eye and injections of 0.5-mg ranibizumab in the other eye.

Eyes with DME were included in the trial. At baseline, 22% to 23% of each cohort had center-involving DME that was causing decreased vision. These eyes were treated with 0.5-mg ranibizumab using guidance from the DRCR.net Protocol I treatment algorithm. Visual acuity and optical coherence tomography (OCT) were performed by masked individuals at study visits. At baseline and annual visits, digital fundus photographs were obtained. At selected sites, Humphrey visual field testing was performed using 30-2 and 60-4 patterns.

Eyes in the ranibizumab group were given monthly injections for 3 months, then monthly injections continued until the PDR resolved or remained stable for three consecutive visits as determined by clinical evaluation. Recurrence of neovascularization in the study eye triggered additional ranibizumab injections until stability was again achieved.

Eyes without DME at baseline received a median...
10 ranibizumab injections over 2 years. Eyes with DME at baseline received a median 14 injections over 2 years. Focal laser was performed as treatment for DME in 8% of the ranibizumab eyes. PRP was permitted for eyes that worsened despite ranibizumab injections, but this occurred in only 12 eyes (6%), eight of which worsened during vitrectomy surgery.

Eyes in the laser group received a complete PRP treatment (one to three sessions) within 8 weeks of randomization. The standard PRP treatment consisted of 1200 to 1600 burns (1800-2400 if performed with automatic pattern delivery). Throughout the course of the trial additional PRP was permitted for persisting or worsening PDR. Of patients who received complete PRP initially, 45% required supplemental PRP over the first 2 years of the study. Intravitreal injections of ranibizumab were performed in 53% of eyes in the PRP group for DME that was either present at baseline or that developed during the 2-year follow-up.

RESULTS

Visual acuity results at 2 years revealed a mean change in visual acuity of +2.8 letters for eyes treated with ranibizumab and +0.2 letters for eyes treated with PRP. This met the noninferiority outcome comparison of ranibizumab to PRP. Area-under-the-curve analysis of the visual acuity changes throughout the course of the 2 years revealed superior vision performance in eyes treated with ranibizumab compared with those treated with PRP. In both ranibizumab- and PRP-treated eyes, the greatest visual gains were seen in eyes with baseline DME.

Automated peripheral visual field testing at the 2-year visit indicated a significant cumulative worsening in PRP-treated eyes. The mean deviation decreased 0.08 dB in eyes treated with ranibizumab and 2.50 dB in those receiving PRP (P<.001). Center subfield thickness on OCT decreased by a mean 45 µm in the ranibizumab group compared with 3 µm in the PRP group (P<.001). Improvement in anatomic outcome was present in eyes with and without baseline DME.

A secondary assessment in Protocol S evaluated the development of DME in both treatment groups. In eyes that did not have DME but had decreased visual acuity at baseline, the cumulative probability of developing DME with decreased visual acuity was 28% in the PRP group and 9% in the ranibizumab group. Protocol S evaluated both groups for complications of PDR including retinal detachment, neovascular glaucoma, vitreous hemorrhage, and need for vitrectomy. The incidence of each complication was similar in both groups with the exception of vitrectomy, which was performed in 4% of the ranibizumab group and 15% of the PRP group (P <.001).

Systemic and ocular side effects were similar in the two groups. No specific signals for adverse events were identified. The rates of adverse events were similar to those of previously published large clinical trials. This study was not powered to identify specific risks. One case of endophthalmitis was identified in the ranibizumab group.

CLINICAL RELEVANCE

With Protocol S, DRCR.net demonstrated that intravitreal ranibizumab provided visual acuity outcomes at 2 years that were similar to, if not better than, those achieved with PRP in the treatment of PDR, whether or not DME was present. Secondary outcomes suggest that other aspects of visual function may be better preserved with injections of ranibizumab than with PRP treatment. The planned 5-year follow-up of Protocol S should determine whether these findings are sustained.