Ranibizumab Plus Panretinal Photocoagulation versus Panretinal Photocoagulation Alone for High-Risk Proliferative Diabetic Retinopathy (PROTEUS Study)

Purpose

Comparison of the efficacy of ranibizumab (RBZ) 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP alone in the regression of the neovascularization (NV) area in subjects with high-risk proliferative diabetic retinopathy (HR-PDR) over a 12-month period.

Design

Prospective, randomized, multicenter, open-label, phase II/III study.

Participants

Eighty-seven participants (aged ≥18 years) with type 1/2 diabetes and HR-PDR (mean age, 55.2 years; 37% were female).

Methods

Participants were randomized (1:1) to receive RBZ+PRP (n = 41) or PRP monotherapy (n = 46). The RBZ+PRP group received 3 monthly RBZ injections along with standard PRP. The PRP monotherapy group received standard PRP between day 1 and month 2; thereafter, re-treatments in both groups were at the investigators' discretion.

Main Outcome Measures

The primary outcome was regression of NV total, on the disc (NVD) plus elsewhere (NVE), defined as any decrease in the area of NV from the baseline to month 12. Secondary outcomes included best-corrected visual acuity (BCVA) changes from baseline to month 12, time to complete NV regression, recurrence of NV, macular retinal thickness changes from baseline to month 12, need for treatment for diabetic macular edema, need for vitrectomy because of occurrence of vitreous hemorrhage, tractional retinal detachment or other complications of DR, and adverse events (AEs) related to treatments.

Results

Seventy-seven participants (88.5%) completed the study. Overall baseline demographics were similar for both groups, except for age. At month 12, 92.7% of participants in the RBZ+PRP group presented NV total reduction versus 70.5% of the PRP monotherapy participants ($P = 0.009$). The number of participants with NVD and NVE reductions was higher with RBZ+PRP (93.3% and 91.4%, respectively) versus PRP (68.8% and 73.7%, respectively), significant only for NVE ($P = 0.048$). Complete NV total regression was observed in 43.9% in the RBZ+PRP group versus 25.0% in the PRP monotherapy group ($P = 0.066$). At month 12, the mean BCVA was 75.2 letters (20/32) in the RBZ+PRP group versus 69.2 letters (20/40) in the PRP monotherapy group ($P = 0.104$). In the RBZ+PRP group, the mean number of PRP treatments over month 12 was 3.5±1.3, whereas in the PRP monotherapy group, it was 4.6±1.5 ($P = 0.001$). No deaths or unexpected AEs were reported.

Conclusions

Treatment with RBZ+PRP was more effective than PRP monotherapy for NV regression in HR-PDR participants over 12 months.

Abbreviations and Acronyms:

AE (adverse event), BCVA (best-corrected visual acuity), DA (disc area), DME (diabetic macular edema), ETDRS (Early Treatment Diabetic

Retinopathy Study), FAS (full analysis set), HbA1C (glycated hemoglobin), HR-PDR (high-risk proliferative diabetic retinopathy), ITV (intravitreal), logMAR (logarithm of the minimum angle of resolution), NV (neovascularization), NVD (neovascularization at the disc), NVE (neovascularization elsewhere), NVT (neovascularization total), PDR (proliferative diabetic retinopathy), PP (per protocol), PRP (panretinal photocoagulation), RBZ (ranibizumab), SD (standard deviation), VEGF (vascular endothelial growth factor)

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HUMAN SUBJECTS: This study includes human subject/tissues. Study protocol was approved by IRB/Ethics Committees (Comitato Etico

Centrale IRCCS, Comitato Etico Interaziendale Milano Area A, Comitato Etico per la Sperimentazione dell'Azienda Ospedaliera di Padova, Comitato Etico Ospedale San Raffaele, West Midlands – Edgbaston Research Ethics Committee, CEIC – Comissão de Ética para a Investigação, CPP Ile-de-France IV). Informed consent was obtained from all human subjects. All tenets of the Declaration of Helsinki were followed.

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