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

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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. *Ophthalmology 2018;125:691-700 © 2018 by the American Academy of Ophthalmology*

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Proliferative diabetic retinopathy (PDR) is the most common cause of severe visual loss in people with diabetes,[1] and it is characterized by retinal neovascularization at the disc (NVD) or elsewhere in the retina (NVE).

Vitreous hemorrhage and tractional retinal detachment are the main complications that can lead to severe visual loss or blindness in this stage of DR. Without intervention, approximately half of these

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eyes with PDR will experience profound visual loss in 5 years.[2,3]

Panretinal photocoagulation (PRP) has been the standard treatment for PDR for more than 4 decades, because it causes regression of retinal NV and reduces the risk of severe vision loss in people with PDR by destroying areas of peripheral retina to reduce the drive for NV formation but preserving central vision.[2,4] However, this destructive treatment, which may be associated with side effects (e.g., pain, transient blurring, loss of peripheral or night vision, increased risk of macular edema, and central vision loss), is not always effective.[5–7]

Vascular endothelial growth factor (VEGF) has been shown to play a role in retinal NV and retinal vascular leakage related with PDR and diabetic macular edema (DME).[5,8] Indeed, the use of anti-VEGF drugs such as pegaptanib, ranibizumab (RBZ), aflibercept, and bevacizumab have demonstrated a positive effect in the regression of NV.[6,7,9–20]

It has also been shown that treatment with repeated injections of anti-VEGF can improve visual acuity in patients with PDR.[21] Presently, the 2 main multicenter, randomized clinical trials testing this new treatment approach in PDR are the DRCR.net Protocol S[10] and the CLARITY study.[13]

The goal of the current PDR treatment with PRP laser is to induce neovascularization (NV) regression and thereby reduce the probability of visual loss with a poor quality of life for patients.

The knowledge of the mechanisms of this retinal complication is incomplete[22]; therefore, further efforts should be made to understand, characterize, and improve response to treatment. Thus, the purpose of this study was to compare the standard PRP treatment for PDR with combined intravitreal (ITV) injections of RBZ and PRP treatment. Combination treatment is thought to increase the rate of success of PRP in regression of NV with improvement in visual acuity and fewer side effects.

Methods

This was a prospective, randomized, multicenter, open-label, phase II/III study to assess the efficacy and safety of RBZ plus PRP (RBZ+PRP) versus PRP monotherapy in the treatment of patients with high-risk proliferative diabetic retinopathy (HR-PDR) for a period of 1 year (ClinicalTrials.gov no NCT01941329). This was an investigator-initiated study performed by the European Vision Institute Clinical Research Network (EVICR.net).[23,24]

The tenets of the Declaration of Helsinki were followed. Approval was obtained from the applicable ethics committee and national competent authorities. Informed consent to participate in the study was signed by all subjects.

A total of 87 participants with type 1 or 2 diabetes, age ≥18 years, were included between April 2014 and May 2016 in 13 European clinical sites and followed up over a 1-year period.

Patients with systolic blood pressure >170 mmHg or diastolic blood pressure >100 mmHg, hemoglobin A_{1C} level >11%, or recent signs of uncontrolled diabetes were excluded.

Both eyes were assessed at the screening visit for eligibility, and only 1 eye was selected from each participant as the study eye. If both eyes meet the inclusion/exclusion criteria, the eye with the larger area of NV was selected as the study eye. Ocular inclusion criteria included best-corrected visual acuity (BCVA) ≥24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters score (approximate Snellen equivalent 20/320) and HR-PDR.

The main ocular exclusion criteria for the study eye were any intraocular surgery within 6 months before trial enrolment, including prior PRP or focal/grid photocoagulation, previous yttrium aluminum garnet (YAG) laser, laser retinopexy for retinal tears; fibrovascular proliferation with retinal traction; other cause of retinal NV (retinal vein occlusion, radiation retinopathy, or others); atrophy/scarring/fibrosis/hard exudates involving the center of the macula; DME with central involvement (i.e., central macular thickness [central point thickness] >300 μm for Stratus OCT, adjusted according to the spectral domain OCT machine used);[25] previous vitrectomy; intraocular pressure >21 mmHg, and previous anti-VEGF therapy within the last 3 months. The complete eligibility criteria are described in the Appendix (available at www.aaojournal.org).

After the screening phase, visits occurred every month, in both groups, through 1 year. Eligible participants were randomized at month 0 in a 1:1 ratio to 1 of the 2 treatment groups, study group (PRP+RBZ) or control group (PRP monotherapy). In the RBZ+PRP group, the study participants received, between month 0 and month 2 (loading phase), 3 RBZ ITV injections in month 0, month 1, and month 2 combined with the standard PRP treatment, that is, with 1, 2, or 3 laser sessions (according to investigators decision) applied 2±1 weeks after each ITV injection to obtain a complete PRP treatment (according to the Study Treatment Procedure, which is based on the DRS Study [1982]. Complete PRP treatment is defined as complete PRP treatment with 1200−1600 scatter laser burns. Laser parameters must have been adjusted to obtain mild white laser burn, with spot size on the retina of approximately 500 μm, and separated 1 burn apart between them. Automated pattern laser machines [PASCAL or others] could be used, but they must have been regulated to obtain an equivalent area treated). From month 3 to month 11 (9 months follow-up/treatment phase), combination treatment composed of 1 RBZ ITV injection plus 1 PRP session (2±1 weeks after the injection) was performed on the basis of the Investigator evaluation respecting always at least 1 month interval between ITV injections. Treatment was repeated if NV was present (due to lack of regression or to recurrence) and if the investigator considered that a further treatment may benefit the participant by reducing the NV area. In the follow-up, PRP treatments were performed using a fill-in technique.[26] In the PRP monotherapy group, the control participants received between month 0 and month 2 the standard PRP treatment, with 1 mandatory laser session in month 0 and more laser sessions as needed until month 2 to complete the PRP treatment. After completing the PRP treatment, PRP sessions could be repeated from month 3 to month 11 (9-month follow-up/treatment phase), based on the investigator evaluation and according to the study treatment procedure (Fig 1).

At baseline visit, participants' body weight, height, demographics, vital signs, hematology, biochemistry, and medical history were recorded. At each visit, the study eyes underwent a standard ophthalmological examination. The BCVA was recorded for both eyes according to the ETDRS protocol[27] at screening visit and months 3, 7, and 12. The BCVA was measured according to the ETDRS protocol by experienced and certified unmasked technicians. Refraction was performed first, and BCVA was then assessed in each eye using 2 different charts (Chart 1 for the right eye and Chart 2 for the left eye). The number of letters of both eyes was scored for each participant in all visits. Spectral domain OCT was performed on both eyes using an acquisition protocol for macular thickness mapping at screening visit and months 3, 7, and 12, and adjustments between devices were done.[25]

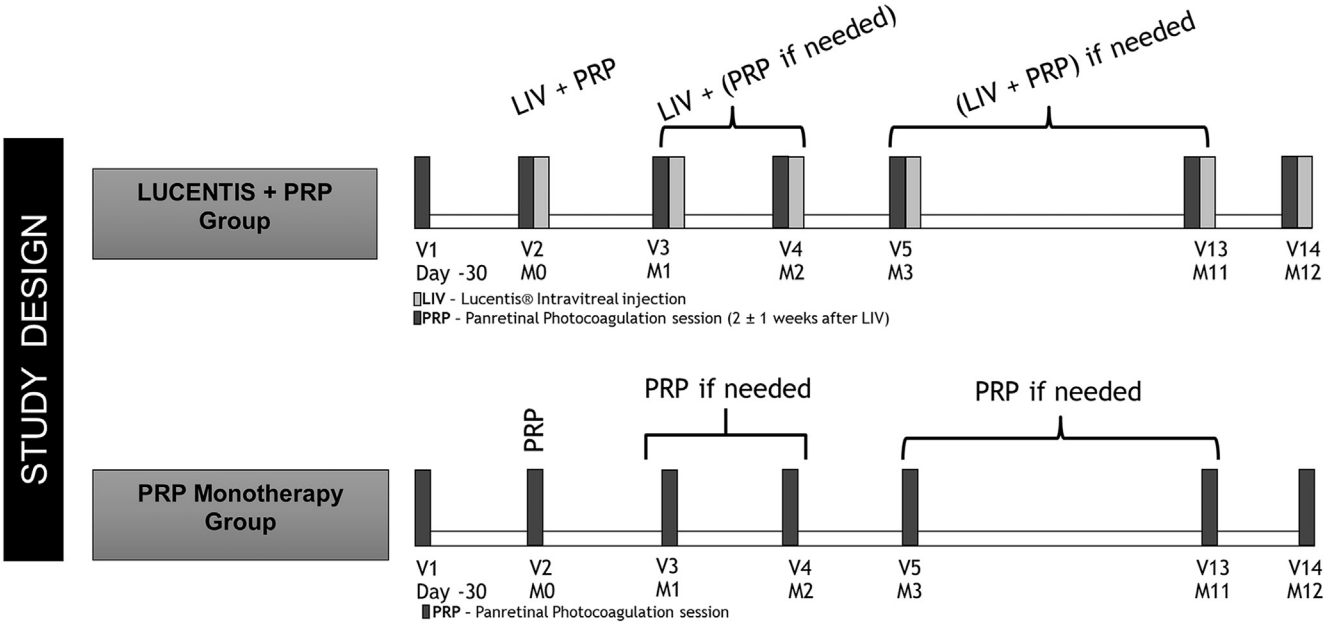

Figure 1. Study design. LIV = Lucentis intravitreal injection; PRP = panretinal photocoagulation.

Color fundus photography (7-fields color fundus photography exam at 30° to 35°) and fluorescein angiography were performed on both eyes at screening visit and at months 3, 7, and 12, and used to measure the area of NV relatively to disc area (DA) size by a central reading center (CORC-Coimbra Ophthalmology Reading Center, Portugal). The grading was done manually, and images were assessed by masked graders for the presence or absence of the defined lesions and identification of NVD or NVE areas. The assessment was always done by 1 certified grader and validated by a second experienced ophthalmologist grader. For measurement of area of interest, graders manually earmarked the NVD or NVE areas using the open source image manipulation software GIMP on all available images (fluorescein angiography or color fundus photography), taking special care to not earmark the same area on multiple fields. In addition, the optic DA was earmarked only on Field 1 images to be later used as reference. Thereafter, images were saved in GIMP native file format, XCF, which can store layered earmark images. The XCF image stacks were later fed to an automatic measurement tool developed in-house, which measures the earmarked areas in pixels and calculates the ratios between the areas identified as NV and optic disc. Because the field of view was maintained during image acquisition, session co-registration was unnecessary. During the prestudy phase, all graders were trained on the same set of images. The intergrader reproducibility was good with an intraclass correlation coefficient of 0.76 for NVD and 0.85 for NVE. The optic DA measurements presented strong agreement with an intraclass correlation coefficient of 0.96. In regard to intragrader agreement, measurements of the size of NV also showed good repeatability, with an intraclass correlation coefficient of 0.96 for NVD, 0.91 for NVE, and 0.99 for the optic DA.

Treatment with focal or grid laser was allowed during study participation for treatment of DME for participants included in both treatment groups. Participants from the PRP monotherapy group, treated with anti-VEGF for DME, were withdrawn before starting treatment in the study eye.

Vitrectomy due to occurrence of vitreous hemorrhage, tractional retinal detachment, or other complications of DR was not allowed during the study. Therefore, if vitrectomy was needed, participants were withdrawn from the study before this surgical procedure.

The primary outcome was the regression of neovascularization total (NVT), defined as the sum of NVD and NVE. Regression of NVT was defined as any decrease in the area of NV from baseline to month 12, total regression was defined as a complete regression with absence of new vessels in the retina and optic disc, and partial regression was defined as an incomplete regression with new vessels still present in the retina or optic disc.

Secondary outcomes included BCVA changes from baseline to month 12, time to complete NV regression, recurrence of NV (NVT increase after a period of improvement), recidivism of NV (NVT reappearance after NVT complete regression), change in macular retinal thickness at month 12, need for treatment for DME, need for vitrectomy due to the occurrence of vitreous hemorrhage, tractional retinal detachment or other complications of DR, and other adverse events (AEs) related to the treatments.

Statistical Analysis

Sample Size. The sample size was computed using the Stata software version 12.1 (StataCorp LP, College Station, TX) for the primary objective (NV regression at month 12), for the secondary objective (BCVA loss at month 12), for a statistical power of 95%, a 2-sided alpha level of 0.01, and a dropout rate of 30%.

For the primary objective, a minimum of 42 participants was estimated (21 per treatment group), considering a 25% reduction in the NV area in the control group and a 65% reduction in the NV area in the study group[28] (minimum difference between groups of 40% and a standard deviation [SD] of 30%). For the secondary objective, a minimum of 72 participants was estimated (36 per treatment group), considering a BCVA loss in the control group from baseline to month 12 (from 0.3 logarithm of the minimum angle of resolution [logMAR] − 85 ETDRS letters, to 0.4 logMAR − 80 ETDRS letters) and no BCVA changes in the study group from baseline to month 12 (i.e., 0.2 logMAR − 90 letters)[28] (minimum difference between groups of 10 letters and an SD of 10 letters). Considering a dropout rate of 30%, a minimum of 94 participants was estimated to be included in this study.

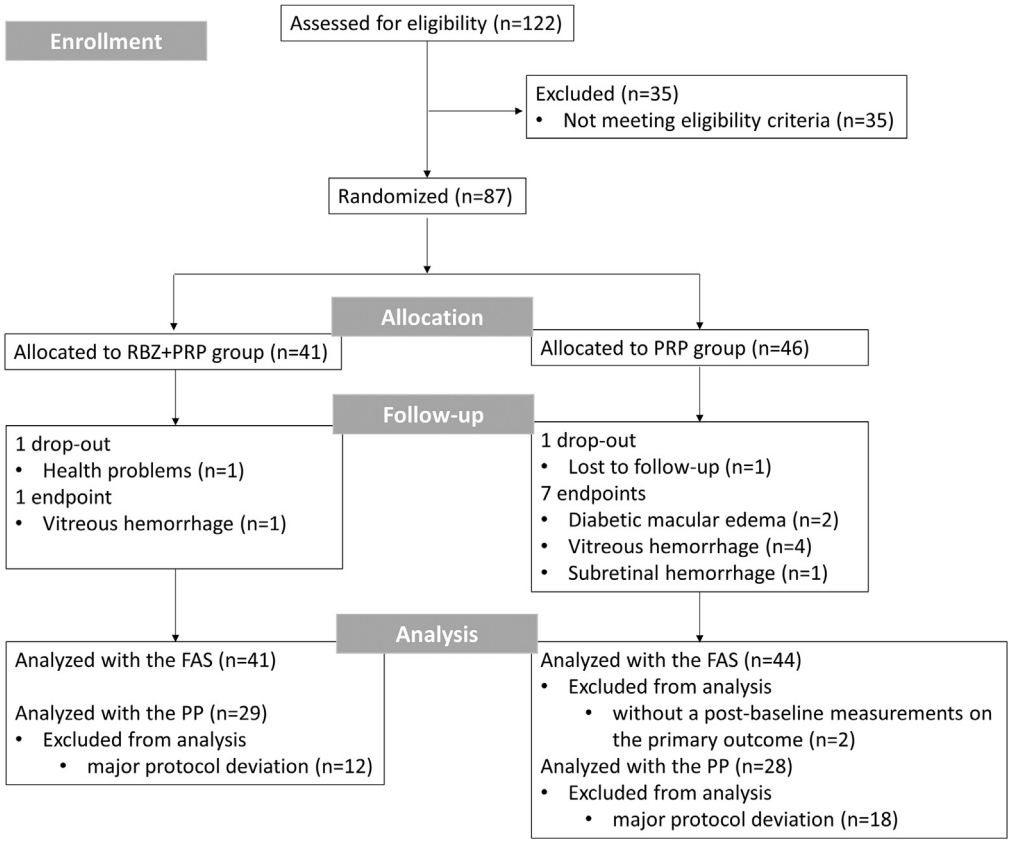

Figure 2. Consort flow chart. FAS = full analysis set; PP = per protocol; PRP = panretinal photocoagulation; RBZ = ranibizumab.

The minimum sample size necessary for analysis of the primary efficacy end point was achieved (36 per treatment group) because of a lower than estimated dropout rate (Fig 2), even though the recruitment target was not met (94 total participants).

Randomization. This study was designed in a 2-arm parallel way in which participants were randomized in a 1:1 ratio to the study or control group. The randomization list was generated by the sponsor with on Stata 12.1 (ralloc package, version 1.4) and implemented through the electronic data capture platform with the following assumptions: 47 blocks, block size 2, total number of allocations 94.

Data Analysis. Categoric variables are summarized with frequencies and percentages, and numeric variables are presented with mean and SD. To test statistically significant differences at baseline between groups, the chi-square test was used for categoric variables and the Student *t* test was used for continuous variables.

Three populations were analyzed. Efficacy analyses were conducted on the full analysis set (FAS) and with the per protocol (PP) population. The analysis on the FAS, considered as the main analysis, followed the intention-to-treat principle and included all randomized participants receiving at least 1 study treatment and having a baseline and at least 1 postbaseline measurement on the primary outcome. Participants with protocol violations likely to affect outcome were excluded. The carrying forward of the last observation was used to compensate for missing data on the primary outcome. The PP population was defined as a subset of the participants in the FAS with availability of measurements of the primary variable with no imputation done for missing data. The safety analysis population consists of participants who received at least 1 treatment (ITV injections plus PRP or PRP monotherapy).

The primary efficacy analysis (difference between groups for the number of participants with NV reduction at month 12) was tested using a 2-sided chi-square test.

For the secondary end points, BCVA changes from baseline to month 12 were tested using Student *t* test and the area under the curve; survival analysis (log-rank test) was carried out to compare time to complete NV regression between groups; recurrence of NV was tested using Fisher exact test; macular retinal thickness changes from baseline to month 12 were tested using Student *t* test; need for treatment for DME was tested using Fisher exact test; and need for vitrectomy due to the occurrence of vitreous hemorrhage, tractional retinal detachment, or other complications of DR was tested using the Fisher exact test.

An exploratory analysis was also performed considering as efficacy end point the regression of NV from baseline to the 12-month visit (primary end point) combined with the presence of significant vitreous hemorrhage or vitrectomy (secondary end points). Significant vitreous hemorrhage was defined as present when it was not possible to visualize or quantify the NV. This combined end point was defined as no success—no NV regression and/or significant vitreous hemorrhage and/or vitrectomy; or NV regression and significant vitreous hemorrhage; or NV regression and vitrectomy and success—NV regression and no significant vitreous hemorrhage and no vitrectomy. This end point was tested using the 2-sided chi-square test. Secondary end points were also analyzed considering baseline factors and possible confounders, such as age, glycated hemoglobin (HbA_{1C}), and number of study treatments using analysis of covariance adjusted for the relevant covariates, Cox regression method adjusted for the relevant explanatory variables, or logistic regression.

$P < 0.05$ was considered statistically significant. Analyses were performed with Stata version 12.1 (StataCorp LP, College Station, TX).

Results

Between April 2014 and May 2016, 87 study eyes/participants were assigned randomly to the RBZ+PRP group (n = 41 eyes) or the PRP monotherapy group (n = 46 eyes). The mean ages of participants in the RBZ+PRP and PRP monotherapy groups were 59 years (SD, 13) and 52 years (SD, 12), respectively; 32% and 41% were women, respectively. The mean baseline NVT area was 1.9 DA (SD, 2.2) and 3.1 DA (5.7), and the mean baseline BCVA on letter scores were 76.1 (SD, 10.4) and 75.1 (SD, 10.7) in the RBZ+PRP and PRP monotherapy groups, respectively. The mean baseline retinal thickness in the central subfield was 292.6 μm (SD, 37.5) and 300.4 μm (SD, 38.1) in the RBZ+PRP and PRP monotherapy groups, respectively. Baseline characteristics of the 2 groups appeared similar, with age being the only statistically significant difference between groups at baseline, with older participants in the RBZ+PRP group ($P = 0.014$) (Table 1).

Loss to Follow-up Rates

Ten participants did not complete the full visit schedule: 8 participants from the PRP monotherapy group (7 who were discontinued due to DR complications and 1 who dropped out of the study) and 2 participants from the RBZ+PRP group (1 who was discontinued due to DR complications and 1 who dropped out). The completion rates were 95.1% in the RBZ+PRP group and 82.6% in the PRP monotherapy group (Fig 2).

Primary Outcome

The number of participants with regression of NVT area during the 1-year follow-up was significantly higher in the RBZ+PRP group in comparison with the PRP monotherapy group considering both FAS and PP populations (FAS: 92.7% and 70.5%, respectively, $P = 0.009$; PP: 93.1% and 64.3%, respectively, $P = 0.008$). The primary efficacy analysis with the FAS and PP population yields similar results.

Considering the FAS, the average NVT area after baseline was consistently higher in the PRP monotherapy group, and this difference was statistically significant at months 3, 7, and 12 (for the RBZ+PRP group and PRP group the difference was month 3 − 0.12±0.38 DA and 2.40±5.00 DA; $P = 0.005$; month 7 − 0.81±1.83 DA and 2.16±3.24 DA; $P = 0.021$; month 12 − 0.52±1.04 DA and 2.20±4.92 DA; $P = 0.035$; respectively).

Secondary Outcomes

Regarding NVD and NVE, the number of participants showing reduction in both NVD and NVE at month 12 was also higher in the RBZ+PRP group in comparison with the PRP monotherapy group, but this difference was significant only for the NVE reduction (NVD: 93.3% and 68.8%, respectively, $P = 0.083$; NVE: 91.4% and 73.7%, respectively, $P = 0.048$) (Table 2).

Although the average NVD area was consistently higher in the PRP monotherapy group, there were no statistically significant differences between groups for the NVD area at all visits. Likewise, the average NVE area was also consistently higher in the PRP monotherapy group and reached a statistically significant difference only at month 3 (month 3: 0.12±0.37 DA and 2.06±3.17 DA; $P = 0.001$).

The number of participants with complete regression of NV at month 12 in the study group was higher than in the control group (43.9% and 25.0%, respectively), and this difference was statistically borderline significant ($P = 0.066$). In the RBZ+PRP group, the time to complete NV regression was shorter (3.6 and 7.0 months, respectively, $P = 0.002$).

The number of participants with NVT increase after a period of improvement in both groups was not significantly different, although the number was higher in the RBZ+PRP group, 67.5% versus 57.1% in the PRP monotherapy group. Only participants from the RBZ+PRP group (66.6%) had NVT reappearance after complete regression of NVT.

There were no statistically significant differences between groups for the BCVA at all visits (Fig 3). Although the average BCVA difference from baseline to month 12 was greater in the RBZ+PRP group than in the PRP monotherapy group, this difference was not statistically significant (−0.9±12.1 letters and −5.8±15.1 letters; $P = 0.104$).

Considering the area under the curve, the letter score loss per month was −1.2 letters in the RBZ+PRP group and −3.3 letters in the PRP monotherapy group ($P = 0.295$).

Because participants in the RBZ+PRP group were significantly older, correcting for age, BCVA was statistically higher in the RBZ+PRP group at month 7 ($P = 0.027$) and month 12 ($P = 0.031$).

Macular retinal thickness in the central subfield presented significant differences at month 3 and month 7 between groups, being thinner in the RBZ+PRP group (Fig 4).

Treatment for DME was only needed in the PRP monotherapy group (4.4%). These 2 participants received primary macular laser, but because of persistent DME they dropped out of the study to receive anti-VEGF injections.

Concerning the number of participants who needed vitrectomy because of the occurrence of vitreous hemorrhage, tractional retinal detachment or other complications of DR were not significantly different (1 [2.5%] with combination therapy and 5 [11.1%] with PRP monotherapy; $P = 0.122$).

The number of participants who needed rescue treatment (needed treatment for DME or vitrectomy) was significantly higher in the PRP monotherapy group in comparison with the RBZ+PRP group; 7 (15.6%) and 1 (2.5%), respectively ($P = 0.040$).

The mean number of PRP treatments was statistically higher in the PRP monotherapy group at the loading phase and at follow-up (loading phase: 2.1±0.8 and 3.0±2.3; $P = 0.017$; follow-up: 1.4±1.0 and 2.0±1.2; $P = 0.022$) (Table 3). The mean number of PRP spots was statistically higher in the PRP monotherapy group only at the loading phase (loading phase: 1823.2±1105.6 and 2345.1±1201.8, $P = 0.041$; follow-up: 1124.5±1043.5 and 1413.1±1243.5, $P = 0.252$). The mean area of PRP laser burns was higher in the PRP monotherapy group, but this difference was not statistically significant (loading phase: 21.5±18.0 mm^2 and 27.2±24.8 mm^2, $P = 0.598$; follow-up: 10.1±11.6 mm^2 and 11.1±12.2 mm^2, $P = 0.726$).

Subgroup Analysis

Considering naïve participants and those who already had prior PRP treatments, the number of participants with NVT regression was higher in the RBZ+PRP group, but this difference was significant only for naïve participants (naïve: 94.4% and 50.0%, respectively, $P = 0.004$; not naïve: 91.3% and 80.0%, respectively, $P = 0.255$).

Multivariate Analysis

In a multivariate analysis, the baseline factors age, HbA_{1c}, and number of PRP treatments did not show a significant association with BCVA difference from baseline to month 12, and there were

Table 1. Baseline Characteristics

Characteristics	RBZ+PRP Group (n = 41 Eyes)	PRP Monotherapy Group (n = 46 eyes)	P Value
Female, frequency (%)	13 (31.7)	19 (41.3)	0.354*
Age, mean (SD), y	58.8 (13.3)	52.0 (11.9)	**0.014**†
BMI, mean (SD), kg/m^2	29.6 (8.2)	29.2 (5.7)	0.809†
Systolic blood pressure, mean (SD), mmHg	139.6 (14.9)	136.1 (15.5)	0.293†
Diastolic blood pressure, mean (SD), mmHg	77.6 (9.3)	77.5 (11.2)	0.958†
HbA_{1c}, mean (SD), %	8.1 (1.3)	8.5 (1.6)	0.324†
IOP, mean (SD), mmHg	15.4 (2.4)	15.3 (2.9)	0.876†
NVT, mean (SD), DA	1.9 (2.2)	3.1 (5.7)	0.228†
NVD, mean (SD), DA	1.5 (2.0)	2.5 (4.6)	0.211†
NVE, mean (SD), DA	0.4 (1.1)	0.6 (2.0)	0.650†
BCVA, mean (SD), letters	76.1 (10.4)	75.1 (10.7)	0.665†
Snellen equivalent	20/32	20/32	
Central subfield thickness, mean (SD), µm	292.6 (37.5)	300.4 (38.1)	0.338†
Previous PRP, frequency (%)	23 (56.1)	31 (67.4)	0.278†

BCVA = best-corrected visual acuity; BMI = body mass index; DA = disc area; HbA_{1C} = glycated hemoglobin; IOP = intraocular pressure; NVD = neovascularization on the disc; NVE = neovascularization elsewhere; NVT = neovascularization total; PRP = panretinal photocoagulation; RBZ = ranibizumab; SD = standard deviation.
The bold values indicate a statistically significant difference between RBZ+PRP and PRP groups.
*Chi-square test.
†Student *t* test.

no statistically significant differences between treatment groups (group: $P = 0.264$, age: $P = 0.787$, HbA_{1c}: $P = 0.450$, number of PRP treatments: $P = 0.904$). Age, HbA_{1c}, and number of PRP treatments did not affect the time to complete NV regression (age: $P = 0.787$, HbA_{1c}: $P = 0.450$, number of PRP treatments: $P = 0.904$). Considering macular retinal thickness changes from baseline to month 12, statistically significance differences were only registered in relation to age in the inner ring inferior, nasal, and temporal areas (inner ring inferior: $P = 0.045$; inner ring nasal: $P = 0.047$; inner ring temporal: $P = 0.039$) and in relation to HbA_{1c} in the outer ring superior ($P = 0.007$). In a logistic multivariate analysis, NV recurrence, recidivism, and the need of vitrectomy were not affected by the treatment group, age, HbA_{1c}, and number of PRP treatments.

Safety Outcomes

Regarding AEs, a total of 125 AEs occurred in this study. A total of 104 (83.2%) were not serious and 21 (16.8%) were considered serious AEs. The number of AEs in both groups was similar. The PRP monotherapy group had 53.6% of all AEs (67), and the RBZ+PRP group had 46.4% (58).

Six vascular events (as defined by the Antiplatelet Trialists' Collaboration) occurred, 3 events in each group. Systemic and ocular AEs of interest are presented in Table 4 and in Table S1 (available at www.aaojournal.org). No suspected unexpected serious adverse reactions were observed during the study, and no deaths occurred.

Table 2. Number of Patients with Reduction of Neovascularization Total, on the Disc and Elsewhere, between Baseline and Month 12

	RBZ+PRP Group	PRP Monotherapy Group	P Value*
NVT reduction, frequency (%)	38 (92.7)	31 (70.5)	**0.009**
NVD reduction, frequency (%)	14 (93.3)	11 (68.8)	0.083
NVE reduction, frequency (%)	32 (91.4)	28 (73.7)	**0.048**

NVD = neovascularization on the disc; NVE = neovascularization elsewhere; NVT = neovascularization total; PRP = panretinal photocoagulation; RBZ = ranibizumab.
The bold values indicate a statistically significant difference between RBZ+PRP and PRP groups.
*Chi-square test.

Discussion

In this study, RBZ+PRP was more effective than PRP monotherapy in causing regression of NV area in HR-PDR eyes at 12 months follow-up, achieving our primary outcome. This conclusion reinforces the results obtained in previous studies, such as Protocol S[10] and CLARITY study.[13]

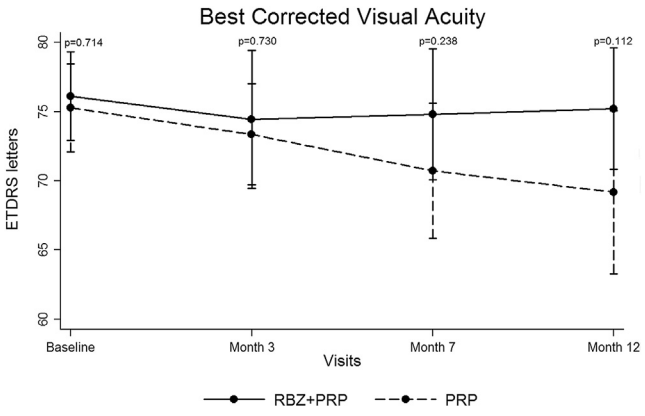

Figure 3. Mean best-corrected visual acuity (BCVA) at baseline and months 3, 7, and 12. ETDRS = Early Treatment Diabetic Retinopathy Study; PRP = panretinal photocoagulation; RBZ = ranibizumab.

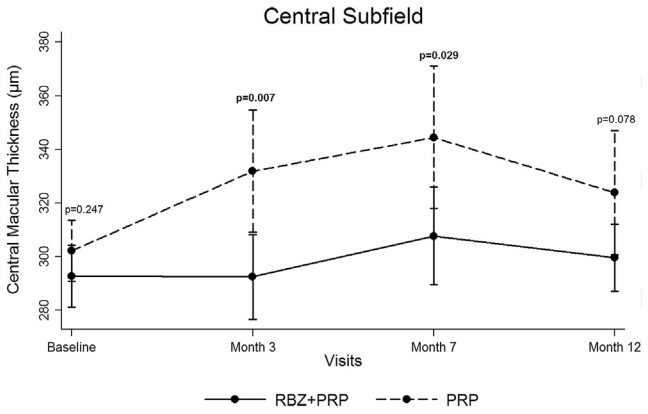

Figure 4. Mean macular thickness in the central subfield at baseline and months 3, 7, and 12. PRP = panretinal photocoagulation; RBZ = ranibizumab.

While considering regression of NVD and NVE separately, the proportion of participants with NVD and NVE reduction at month 12 was higher in the study group in comparison with the control group, but this difference was significant only for NVE reduction. There are several hypotheses that can contribute toward explaining the observation of significant differences in NVE regression compared with NVD regression in this study: (1) The DA of neovascularization is much smaller than the retinal area elsewhere, making it more difficult to detect area changes in NVD; (2) the number of participants with NVD at baseline is much smaller (n = 31) compared with the number of participants with NVE (n = 73); and (3) NVD is more resistant to regression than NVE, remaining more constant throughout the participant follow-up. Arevalo et al[29] also reported similar findings with bevacizumab with 55.6% of eyes with NVD and 73.1% of eyes with NVE showing regression at 12 months. These observations were maintained at 24 months follow-up, with 40.7% of the eyes with NVD showing complete regression of NV, whereas 59.1% of the eyes with NVE had complete regression of NV.

The baseline characteristics of the study population were well balanced between treatment groups, but even with participants randomly assigned for each group, age was significantly different (participants from the RBZ+PRP group are, on average, 6.8 years older).

On the whole, there was no statistically significant difference between treatment groups for the BCVA in any visit. The average BCVA difference from baseline to month 12 was greater in the study group than in the control group, but this difference was not statistically significant. However, after correcting for age, there was an improvement in BCVA in the RBZ+PRP group, which was statistically significant at month 7 and month 12.

Complete NV regression was observed significantly earlier in the combined treatment group compared with the control group (3.6 and 7.0 months, respectively), and this new treatment approach seems to be a good option when a more rapid regression of NV is desired, particularly when florid and more aggressive proliferative retinopathy is present.

Approximately 67% of the eyes in the study group that achieved a total regression of NV had a recurrence of new vessels. In contrast, reactivation of NV did not occur in the PRP monotherapy group, highlighting a more consistent and permanent effect of PRP on the regression of NV. The addition of RBZ to laser treatment shows a less lasting effect. However, the monotherapy group received more laser burns, and therefore complete PRP treatment may explain the lower recurrence rate.

The HR-PDR eyes can develop complications as vitreous hemorrhage or retinal detachments that need to be treated with vitrectomy. The PRP laser used to treat those eyes is frequently associated with onset or worsening of DME. In this study, the number of participants who needed rescue treatment (need for DME treatment or vitrectomy) was significantly higher in the control group in comparison with the study group. This finding was also observed in the Protocol S and CLARITY study.

The 2 participants who developed DME during the study were in the control group. They received anti-VEGF treatment and were withdrawn from the study.

As already mentioned, the Protocol S and the CLARITY study also compared anti-VEGF therapy (RBZ and aflibercept, respectively) versus PRP in PDR. However, our study population had more advanced disease because we included only eyes with HR-PDR, whereas only 37% of eyes in the Protocol S and 23% in CLARITY study were in this stage.

Our therapeutic approach was also different because we used a combination of intravitreous injections of RBZ plus PRP in the study arm. We consider this combination to have a synergistic effect with an eventual reduction of NV compared with anti-VEGF monotherapy.

Table 3. Panretinal Photocoagulation and Ranibizumab Injection Treatments

	Loading Phase		Follow-up Phase	
Group	*Patients, n (%)*	*Treatments, Mean (SD)*	*Patients, n (%)*	*Treatments, Mean (SD)*
PRP+RBZ				
PRP	41 (100)	2.1 (0.8)	34 (82.9)	1.4 (1.0)
RBZ	41 (100)	3.0 (0.2)	34 (82.9)	1.6 (1.2)
PRP				
PRP	44 (100)	3.0 (2.3)	39 (88.6)	2.0 (1.2)
RBZ	0 (0)	0 (0)	0 (0)	0 (0)

PRP = panretinal photocoagulation; RBZ = ranibizumab; SD = standard deviation.

Table 4. Systemic and Ocular Adverse Events of Interest

Events	Ranibizumab + PRP Group	PRP Monotherapy Group
Systemic AEs	**28**	**35**
Vascular events defined by APTC	**3**	**3**
Nonfatal myocardial infarction	0	2
Nonfatal stroke	1	0
Vascular events	2	1
Significant events	**11**	**18**
Death from any cause	0	0
Hospitalization	5	8
Serious adverse event	5	10
Hypertension	1	0
Ocular AEs	**30**	**32**
Endophthalmitis	0	0
Inflammation	0	0
Retinal tear	0	0
Cataract surgery	2	0
Elevation in intraocular pressure	3	4
Retinal detachment	0	2
Vitreous hemorrhage	11	9
Vitrectomy	2	1
Other	12	16

AD = adverse event; APTC = Antiplatelet Trialists' Collaboration; PRP = panretinal photocoagulation.
Bold values are the sum of the values Systemic AEs and Ocular AEs, respectively.

In the present study, as in the CLARITY study, we excluded patients with macular edema, whereas approximately 23% of eyes in the Protocol S had this condition at baseline. This option in our study design, as well as the exclusion of patients who required anti-VEGF treatment for DME during the study, limited the population evaluated in this trial and slightly increased the number of dropouts, but allowed a perfect control group treated with PRP monotherapy, whereas in Protocol S, more than half of the eyes (53%) in the control group received RBZ for the treatment of DME.

This study shows the superiority of the combined treatment, reinforcing the results obtained in Protocol S and CLARITY studies, which have shown that anti-VEGF monotherapy is at least noninferior in terms of change in visual acuity compared with conventional PRP.

Similar to the CLARITY study, our study also included eyes with or without prior PRP treatment because we believe that this population is more representative of PDR patients in clinical practice. On the contrary, only naive patients were included in Protocol S, and in our study the combination of RBZ with PRP was more effective in this subgroup of participants (the number of participants with NVT regression was significantly higher in RBZ+PRP group, when considering only naïve participants).

Treatments were generally well tolerated, no deaths occurred, and no suspected unexpected serious AEs were observed. Two tractional retinal detachments occurred in the PRP group, and none occurred in the combined PRP+RBZ group. This complication has been associated with anti-VEGF injections in PDR eyes,[30] but we did not have any cases of this probably because we excluded eyes with fibrovascular proliferation with retinal traction.

In the Protocol S study, the subgroup of eyes without DME at baseline that received RBZ in monotherapy received a median of 7 injections through 1 year and 10 injections through 2 years. In this study, as in the CLARITY study, participants received fewer injections than in Protocol S with a median number of injections of 4. This difference can be explained by the number of injections performed in the loading phase (6 in Protocol S vs. 3 in the CLARITY and in the present study).

The beneficial effect of combined treatment of anti-VEGF plus PRP versus anti-VEGF alone in NV regression in PDR eyes in the long term is still unclear and must be clarified in future clinical trials.

The main limitation of this study is the short follow-up time of 1 year. Longer follow-up studies are clearly needed to establish the benefit of combined therapy (PRP + anti-VEGF injections) for PDR. Another limitation is the fact that the investigators were aware of treatment assignment because only 1 group received ITV injections.

The number of participants included in this study was slightly under the planned sample size because of the strict eligibility criteria and temporal limitations, which made it difficult to enroll the patients. However, because the dropout rate was inferior to that estimated in the sample size calculation, the number of participants completing the study ensured the planned statistical power. The restriction on the eligibility criteria may reduce the representativeness of our study population and the generalizability of our findings. In future studies, a more clear definition of re-treatment criteria should be considered to avoid observer bias.

In conclusion, panretinal photocoagulation associated with RBZ was more effective than PRP monotherapy in the regression of NV area in HR-PDR eyes during 1-year follow-up. No safety concerns have been identified in this population.

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Footnotes and Financial Disclosures

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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; **HbA_{1C}** = 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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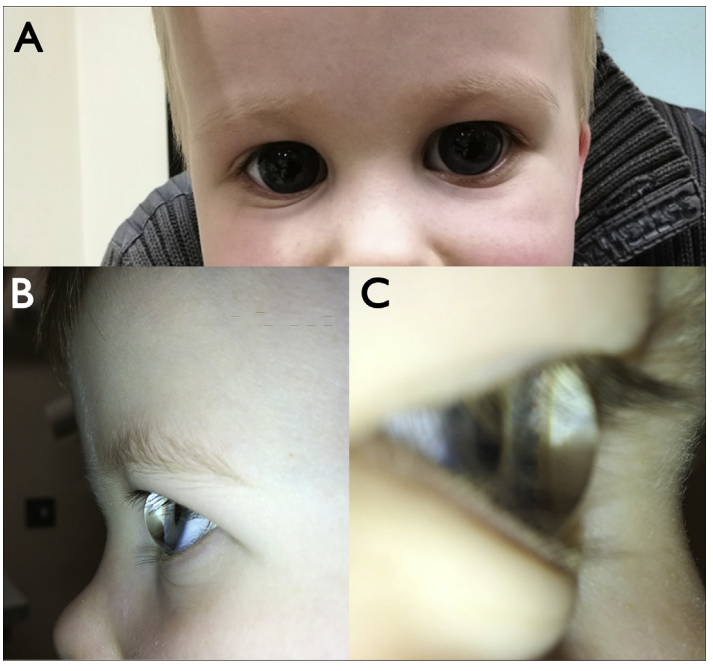
Pictures & Perspectives



Direct View of the Angle Structures in Bilateral Congenital Megalocornea

A 3-year-old boy presented to the pediatric ophthalmology department with a diagnosis of bilateral congenital megalocornea. On observation, he had extremely large corneal diameters with minimal sclera show (Fig 1**A**), and the appearance of large palpebral apertures. There was a corneal optical aberration when viewed from the side (left eye; Fig 1**B**) and when magnified, it is possible to view the angle structures (right eye; Fig 1**C**) without the aid of a gonioscopy lens. Apart from the corneas, all anterior segment structures appeared to be normal, with no evidence of glaucoma. He has good vision (logMar 0.00) in each eye.

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