Original Investigation

Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy
A Randomized Clinical Trial

Writing Committee for the Diabetic Retinopathy Clinical Research Network

IMPORTANCE Panretinal photocoagulation (PRP) is the standard treatment for reducing severe visual loss from proliferative diabetic retinopathy. However, PRP can damage the retina, resulting in peripheral vision loss or worsening diabetic macular edema (DME).

OBJECTIVE To evaluate the noninferiority of intravitreous ranibizumab compared with PRP for visual acuity outcomes in patients with proliferative diabetic retinopathy.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 55 US sites among 305 adults with proliferative diabetic retinopathy enrolled between February and December 2012 (mean age, 52 years; 44% female; 52% white). Both eyes were enrolled for 89 participants (1 eye to each study group), with a total of 394 study eyes. The final 2-year visit was completed in January 2015.

INTERVENTIONS Individual eyes were randomly assigned to receive PRP treatment, completed in 1 to 3 visits (n = 203 eyes), or ranibizumab, 0.5 mg, by intravitreous injection at baseline and as frequently as every 4 weeks based on a structured re-treatment protocol (n = 191 eyes). Eyes in both treatment groups could receive ranibizumab for DME.

MAIN OUTCOMES AND MEASURES The primary outcome was mean visual acuity change at 2 years (5-letter noninferiority margin; intention-to-treat analysis). Secondary outcomes included visual acuity area under the curve, peripheral visual field loss, vitrectomy, DME development, and retinal neovascularization.

RESULTS Mean visual acuity letter improvement at 2 years was +2.8 in the ranibizumab group vs +0.2 in the PRP group (difference, +2.2; 95% CI, −0.5 to +5.0; $P < .001$ for noninferiority). The mean treatment group difference in visual acuity area under the curve over 2 years was +4.2 (95% CI, +3.0 to +5.4; $P < .001$). Mean peripheral visual field sensitivity loss was worse (−23 dB vs −422 dB; difference, 372 dB; 95% CI, 213-531 dB; $P < .001$), vitrectomy was more frequent (15% vs 4%; difference, 9%; 95% CI, 4%-15%; $P < .001$), and DME development was more frequent (28% vs 9%; difference, 19%; 95% CI, 10%-28%; $P < .001$) in the PRP group vs the ranibizumab group, respectively. Eyes without active or regressed neovascularization at 2 years were not significantly different (35% in the ranibizumab group vs 30% in the PRP group; difference, 3%; 95% CI, −7% to 12%; $P = .58$). One eye in the ranibizumab group developed endophthalmitis. No significant differences between groups in rates of major cardiovascular events were identified.

CONCLUSIONS AND RELEVANCE Among eyes with proliferative diabetic retinopathy, treatment with ranibizumab resulted in visual acuity that was noninferior to (not worse than) PRP treatment at 2 years. Although longer-term follow-up is needed, ranibizumab may be a reasonable treatment alternative, at least through 2 years, for patients with proliferative diabetic retinopathy.

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The Authors/Writing Committee for the Diabetic Retinopathy Clinical Research Network are listed at the end of this article. A complete list of the Diabetic Retinopathy Clinical Research Network investigators who participated in this trial is available in eAppendix 1 in Supplement 1.

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Proliferative diabetic retinopathy (PDR) is a leading cause of vision loss in patients with diabetes mellitus,[1,2] resulting in 12 000 to 24 000 new cases of blindness each year in the United States.[3] Without treatment, nearly 50% of patients with high-risk PDR experience severe vision loss within 5 years.[4]

Panretinal photocoagulation (PRP) has been the standard treatment for PDR since the Diabetic Retinopathy Study demonstrated its benefit nearly 40 years ago.[4] Panretinal photocoagulation is effective in part because it reduces vascular endothelial growth factor (VEGF).[5] In a 2014 survey, 98% of retina specialists reported using PRP for initial PDR management in the absence of diabetic macular edema (DME).[6] However, PRP can cause permanent peripheral visual field loss and decreased night vision and may exacerbate DME, which makes alternative treatments desirable.[7-9] Even with timely PRP treatment, about 5% of eyes with PDR develop severe vision loss.[4,7]

DME *diabetic macular edema*

MedDRA *Medical Dictionary for Regulatory Activities*

PDR *proliferative diabetic retinopathy*

PRP *panretinal photocoagulation*

VEGF *vascular endothelial growth factor*

When used as treatment of DME, intravitreous anti-VEGF agents reduce the risk of diabetic retinopathy worsening and increase the chance of improvement,[10-12] making these agents a potentially viable PDR treatment. Therefore, we conducted a randomized trial evaluating the noninferiority of intravitreous ranibizumab compared with PRP for visual acuity outcomes in patients with PDR.

Methods

This multicenter randomized clinical trial was conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) at 55 clinical sites in the United States. The study adhered to the tenets of the Declaration of Helsinki[13] and was approved by multiple institutional review boards. Study participants provided written informed consent. An independent data and safety monitoring committee provided oversight. The study protocol and the statistical analysis plan are available in Supplement 2 and Supplement 3, respectively.

Study Population

Study participants were at least 18 years old and had type 1 or type 2 diabetes, at least 1 eye with PDR, no previous PRP, and a best-corrected visual acuity letter score of 24 or higher (approximate Snellen equivalent, 20/320 or better). Eyes with or without DME were eligible. Eligibility criteria details are described in eAppendix 2 in Supplement 1. Age was patient reported, gender was determined by study staff, and race/ethnicity (based on fixed categories) were either patient reported or determined by study staff.

Study Design

A participant could have 1 or 2 eyes included in the study. Using the DRCR.net study website to conceal the next treatment allocation and a permuted-block design, participants with 1 study eye were randomly assigned with equal probability to either PRP with ranibizumab as needed for DME treatment or ranibizumab, 0.5 mg, by intravitreous injection with PRP allowed for cases of treatment failure. Participants with 2 study eyes had 1 eye assigned randomly to PRP and the other to ranibizumab (eAppendix 2 in Supplement 1).

The primary outcome follow-up visit was at 2 years, with follow-up planned through 5 years. Data through 2 years are reported herein. In both groups, visits occurred every 16 weeks. Ranibizumab group participants had additional visits every 4 weeks during the first year and every 4 to 16 weeks during the second year depending on treatment (eFigure 1 in Supplement 1).

At baseline and at each follow-up visit, certified personnel measured best-corrected visual acuity using the electronic Early Treatment for Diabetic Retinopathy Study visual acuity test.[14] Visual acuity is measured as a continuous integer letter score from 100 to 0, with higher numbers indicating better visual acuity. A letter score of 85 is an approximate Snellen equivalent of 20/20 and a letter score of 70 is approximately 20/40, the legal unrestricted driving limit in most states. A letter score of 35 is approximately 20/200, considered legal blindness when it is the visual acuity in the better-seeing eye. A 5-letter change for an individual is approximately equal to a 1-line change on a vision chart. Spectral (96% of scans) or time-domain ocular coherence tomography was performed at baseline, annually, and as needed for DME treatment assessment. Humphrey visual field testing (at select sites) on 30-2 and 60-4 patterns and digital fundus photographs were obtained at baseline and annually (eAppendix 2 in Supplement 1). Images and visual fields were graded at centralized reading centers when applicable (eAppendix 2). At baseline and annually, participants with 1 study eye completed visual function questionnaires and binocular visual acuity testing with everyday correction (**Table 1**). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Reading center graders and the medical monitor who reviewed all adverse events were masked to treatment assignments. Visual acuity and ocular coherence tomography technicians were masked to treatment group assignments at annual visits. Study participants, investigators, and study coordinators were not masked because of the nature of the treatments.

Treatment Protocol

Proliferative Diabetic Retinopathy

In the ranibizumab group, study eyes received a 0.5-mg intravitreous injection at baseline and every 4 weeks through 12 weeks. Thereafter, re-treatment was based on investigator assessment of neovascularization on extended ophthalmoscopy and any available retinal images. Injections at 16 and 20 weeks were required unless all neovascularization resolved. Starting at the 24-week visit, an injection was required every 4 weeks unless neovascularization resolved or was stable (not improved or worsened) following 2 consecutive injections. Injections resumed if neovascularization worsened. Injections for PDR could be performed at investigator discretion if not required. Panretinal photocoagulation for PDR was permitted (eFigure 1 in Supplement 1) in the ranibizumab group for treatment failure or futility.

Table 1. Baseline Characteristics

Characteristics	Ranibizumab Group (n=191 Eyes)	PRP Group (n=203 Eyes)
Participant characteristics		
Participants with 2 study eyes (included in both study groups), No. (%)	89 (47)	89 (44)
Female, No. (%)	83 (43)	92 (45)
Age, median (IQR), y	52 (44-59)	51 (44-59)
Race/ethnicity, No. (%)		
White	100 (52)	101 (50)
Hispanic	48 (25)	51 (25)
Black/African American	38 (20)	43 (21)
Asian	2 (1)	3 (1)
American Indian/Alaskan Native	1 (<1)	0
≥1 race	0	2 (<1)
Unknown/not reported	2 (1)	3 (1)
Diabetes type, No. (%)		
Type 1	43 (23)	41 (20)
Type 2	140 (73)	155 (76)
Uncertain	8 (4)	7 (3)
Duration of diabetes, median (IQR), y	18 (12-24)	17 (11-23)
Hemoglobin A_{1c}, median (IQR), %[a]	8.6 (7.5-10.4)	8.9 (7.5-10.4)
Prior myocardial infarction, No. (%)	3 (2)	4 (2)
Prior stroke, No. (%)	4 (2)	3 (1)
Arterial blood pressure, median (IQR), mm Hg[b]	99 (88-108)	99 (88-107)
Ocular characteristics		
Visual acuity		
Letter score		
Mean (SD)	75.0 (12.8)	75.2 (12.5)
Median (IQR)	77 (70-84)	78 (70-85)
Approximate Snellen equivalent, median (IQR)	20/32 (20/40-20/20)	20/32 (20/40-20/20)
No. (%)		
≥84 (≥20/20)	52 (27)	58 (29)
83-79 (20/25)	35 (18)	35 (17)
78-69 (20/32-20/40)	64 (34)	67 (33)
68-49 (20/50-20/100)	31 (16)	35 (17)
48-24 (20/125-20/320)	9 (5)	8 (4)
OCT central subfield thickness (Stratus equivalent), μm[b,c]		
Median (IQR)	223 (196-271)	230 (203-265)
Mean (SD)	262 (109)	249 (86)
No. (%)		
<225 μm	96 (51)	87 (43)
225-249	29 (15)	47 (23)
250-349	35 (19)	52 (26)
350-449	12 (6)	7 (3)
≥450	17 (9)	8 (4)
Presence of center-involved DME with visual acuity impairment, No. (%)[b,d]	42 (22)	46 (23)
Presence of center-involved DME regardless of visual acuity, No. (%)[b,e]	55 (29)	62 (31)
OCT retinal volume (Stratus equivalent), median (IQR), μL[c,f]	7.6 (6.9-8.2)	7.5 (6.9-8.2)
Neovascularization on clinical examination, No. (%)		
Of the disc	96 (50)	103 (51)
Elsewhere	166 (87)	174 (86)
Phakic lens status on clinical examination, No. (%)	170 (89)	187 (92)
Diabetic retinopathy severity (ETDRS level), No. (%)[g]		
Microaneurysms only (level 20)	0	1 (<1)
Mild NPDR (level 35)	6 (3)	4 (2)
Moderate NPDR (level 43)	2 (1)	5 (3)
Moderately severe NPDR (level 47)	10 (5)	15 (8)
Severe NPDR (level 53)	1 (<1)	1 (<1)
Prior PRP without active PDR (level 60)	0	1 (<1)
Mild PDR (level 61)	30 (16)	31 (16)
Moderate PDR (level 65)	68 (36)	67 (34)
High-risk PDR (levels 71 and 75)	69 (37)	73 (37)
Advanced PDR, macula center attached (level 81)	2 (1)	0
Advanced PDR, macula center detached (level 85)	1 (<1)	1 (<1)
Prior treatment for DME, No. (%)	43 (23)	36 (18)
Prior focal/grid laser treatment for DME, No. (%)	30 (16)	29 (14)
Prior anti-VEGF treatment for DME, No. (%)	21 (11)	13 (6)

Abbreviations: DME, diabetic macular edema, ETDRS, Early Treatment Diabetic Retinopathy Study; IQR, interquartile range; NPDR, nonproliferative diabetic retinopathy; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

[a] Hemoglobin A_{1c} data were missing for 7 in the ranibizumab group and 5 in the PRP group.

[b] OCT central subfield thickness measurements were missing for 2 in the ranibizumab group and 2 in the PRP group.

[c] Assessments from OCT machines other than Zeiss Stratus were converted to equivalent on Zeiss Stratus machines.

[d] For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 μm for women and ≥320 μm for men with visual acuity letter scores of ≤78 (approximate Snellen equivalent of 20/32 or worse). For Zeiss Cirrus and Optovue RTVue machines, defined as central subfield thickness ≥290 μm for women and ≥305 μm for men with visual acuity letter scores of ≤78 (20/32 or worse). For Zeiss Stratus machines, defined as central subfield thickness ≥250 μm with visual acuity letter scores of ≤78 (20/32 or worse).

[e] For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 μm for women and ≥320 μm for men. For Zeiss Cirrus and Optovue RTVue machines, defined as central subfield thickness ≥290 μm for women and ≥305 μm for men. For Zeiss Stratus machines, defined as central subfield thickness ≥250 μm.

[f] OCT retinal volume measurements were missing for 35 in the ranibizumab group and 40 in the PRP group.

[g] Diabetic retinopathy level data were missing for 2 in the ranibizumab group and 4 in the PRP group. Proliferative diabetic retinopathy could not be identified by the reading center in 46 eyes (12%) but was subsequently confirmed by other imaging modes in 29 (63%) of the 46 eyes.

In the PRP group, the PRP procedure was initiated at baseline (1200-1600 burns using conventional laser or 1800-2400 burns using an automated pattern delivery system, completed in 1-3 visits). If the neovascularization size or amount increased following completion of PRP, additional PRP could be given. In both groups, vitrectomy for vitreous hemorrhage or retinal detachment was at investigator discretion and could include intraoperative PRP.

Diabetic Macular Edema

Diabetic macular edema was defined for the protocol as a thickened central subfield on ocular coherence tomography (eAppendix 2 in Supplement 1) of at least 2 SDs beyond the gender-specific and instrument-specific norm for the population and a visual acuity letter score of 78 or lower (approximate Snellen equivalent of 20/32 or worse). Eyes not meeting both criteria were considered not to have DME for purposes of the protocol. Eyes in both treatment groups with DME could receive ranibizumab provided by the study. At randomization, ranibizumab was required for eyes with DME. Otherwise, initiation and re-treatment with ranibizumab for DME and application of focal/grid photocoagulation for DME was at investigator discretion. A follow-up visit and re-treatment regimen for DME was provided as a guideline, combined with protocol re-treatment and follow-up visits for PDR.[15]

Outcomes

The primary outcome was mean change in visual acuity letter score from baseline to 2 years. Secondary efficacy outcomes included visual acuity area under the curve, change in visual field total point score, central subfield thickness change, DME development, and proportion of eyes without PDR on fundus photographs. Prespecified adverse events related to diabetic retinopathy included vitreous hemorrhage, retinal detachment, vitrectomy, neovascular glaucoma, and iris neovascularization. Prespecified additional safety outcomes assessed included endophthalmitis, ocular inflammation, cataract surgery, serious adverse events, hospitalizations, death, Antiplatelet Trialists' Collaboration events, and events in each MedDRA system organ class.

Statistical Analysis

The sample size estimate for the primary outcome, change in visual acuity, was 380 eyes for a noninferiority margin of 5 letters with a type I error of 2.5% and 85% power (eAppendix 2 in Supplement 1). The noninferiority hypothesis was tested by determining whether one end of a 2-sided 95% confidence interval excluded the noninferiority margin. If ranibizumab was found to be noninferior to prompt PRP, the same 2-sided 95% confidence interval would be used to test ranibizumab superiority. The noninferiority margin was selected in part because it was the same margin used in a prior trial evaluating anti-VEGF agents for neovascular age-related macular degeneration.[16] The study's protocol development committee determined that a true difference exceeding 5.0 letters represented a clinically important difference.[17]

The primary analysis for comparison between treatments of mean change in visual acuity followed the intention-to-treat principle and included all randomly assigned eyes with multiple imputation by the Markov chain Monte Carlo method to impute missing 2-year visual acuities. Imputation for 2-year visual acuities was based on treatment group, baseline visual acuity, baseline central subfield thickness, and all visual acuity data from the 16 weekly visits. Within-group means were based on observed data unless otherwise specified. Treatment group differences, confidence intervals, and *P* values were estimated using analysis of covariance adjusting for baseline visual acuity and randomization stratification factors (baseline central subfield thickness and number of study eyes), with generalized estimating equations used to account for correlation between eyes of participants contributing 2 eyes. Outlying visual acuity changes were truncated to ±3 SDs from the mean. A per-protocol analysis was conducted excluding eyes not completing the 2-year visit, eyes without PDR on baseline fundus photographs, and eyes receiving alternate PDR treatment. Model assumptions were evaluated and satisfied. Sensitivity analyses using transformations, including nonparametric Van der Waerden normal scores, were conducted.

Preplanned subgroup analyses repeated the primary analysis of covariance adding subgroup and subgroup-by-treatment interactions. Safety analyses and secondary efficacy analyses used binomial regression, analysis of covariance, or the marginal Cox proportional hazards model as appropriate.[18,19] Within-group means for secondary outcomes were based on observed data unless otherwise specified. Treatment group differences, confidence intervals, and *P* values for secondary outcomes were based on the intention-to-treat cohort. *P* values and confidence intervals are 2-sided unless otherwise specified. For the primary noninferiority and superiority analyses, $P<.025$ (1-sided) or $P<.05$ (2-sided) was considered statistically significant. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Between February and December 2012, 394 study eyes among 305 participants were assigned randomly to the ranibizumab group (n = 191 eyes) or the PRP group (n = 203 eyes). In the ranibizumab and PRP groups, respectively, the median ages were 52 years (interquartile range [IQR], 44-59 years) and 51 years (IQR, 44-59 years), 43% and 45% were women, and 52% and 50% were white. Among the eyes in the ranibizumab and the PRP groups, respectively, mean baseline visual acuity letter scores were 75.0 (SD, 12.8) (approximate Snellen equivalent of 20/32) and 75.2 (SD, 12.5) (approximate Snellen equivalent of 20/32). Diabetic macular edema at baseline was present in 22% of the ranibizumab group and 23% of the PRP group. Baseline characteristics of the 2 groups appeared similar (Table 1).

Excluding 14 deaths (including 4 participants with 2 study eyes each), the 2-year visit completion rates were 88% in the ranibizumab group and 86% in the PRP group (**Figure 1**). The median number of visits was 22 (IQR, 18-24) in the ranibizumab group and 16 (IQR, 9-22) in the PRP group. eTable 1 in Supplement 1 reports baseline characteristics by 2-year visit completion status.

PDR and DME Treatment

Ranibizumab Group

Ninety-seven percent of protocol-required injections based on clinician interpretation of neovascularization were given. Eyes

without DME at baseline received a median of 7 (IQR, 5-9) injections through 1 year (n = 133) and 10 (IQR, 6-13) injections through 2 years (n = 126) (eTable 2 in Supplement 1). Eyes with DME at baseline received a median of 9 (IQR, 7-11) injections through 1 year (n = 36) and 14 (IQR, 10-17) injections through 2 years (n = 33). Focal/grid laser treatment was performed in 15 eyes (8%). Through 2 years, 12 eyes (6%) received PRP, including 8 during vitrectomy.

PRP Group

All eyes received initial PRP; 98% received protocol-defined complete PRP (eTable 3 in Supplement 1). After completion of PRP, 92 eyes (45%) received additional PRP (median time from baseline to additional PRP, 221 [IQR, 116-386] days, or approximately 7 months).

In addition to PRP, 72 eyes (35%) received ranibizumab for DME at baseline; an additional 36 (18%) received ranibizumab for DME prior to 2 years (eTable 4 in Supplement 1). Among eyes with baseline DME (n = 46), the median number of injections for DME was 5 (IQR, 3-9) prior to 1 year and 9 (IQR, 4-15) prior to 2 years. Among eyes without baseline DME (n = 155) that were later treated for DME, the median number of injections was 3 (IQR, 1-6) prior to 1 year and 4 (IQR, 2-7) prior to 2 years. Focal/grid laser treatment was performed in 21 eyes (10%).

Effect of Treatment

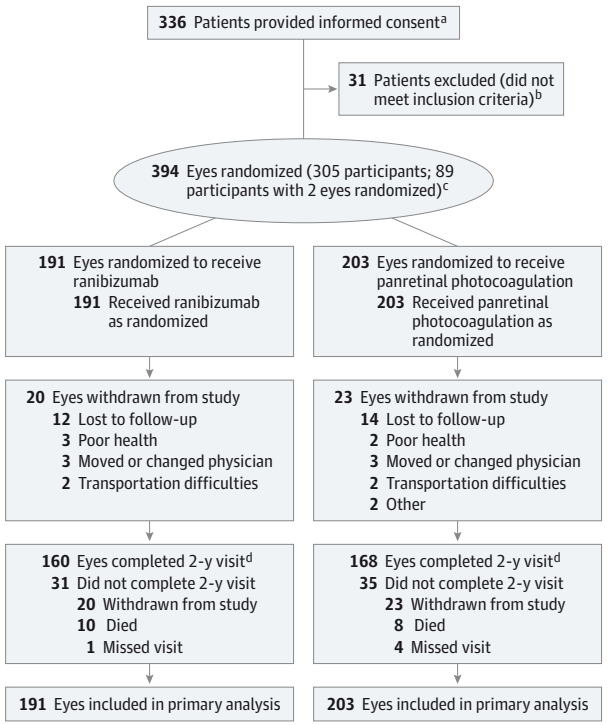
Visual Acuity

At 2 years, mean visual acuity letter score improvement from baseline was +2.8 in the ranibizumab group and +0.2 in the PRP group. The mean treatment group difference was +2.2 (95% CI, −0.5 to +5.0; $P < .001$ for noninferiority) (**Table 2**). This result met the prespecified noninferiority criterion (the lower bound of the 95% CI of −0.5 letter was greater than the noninferiority limit of −5.0 letters). Mean change in visual acuity letter score over 2 years (area under the curve) was +4.5 for the ranibizumab compared with −0.3 for the PRP group (mean difference, +4.2; 95% CI, +3.0 to +5.4; $P < .001$) (Table 2 and **Figure 2**). The difference between groups was greater at 1 year than at 2 years.

Results were similar in per-protocol analyses limited to participants who completed 2-year follow-up (treatment group difference, +2.1; 95% CI, −0.5 to +4.6) (eFigure 2 and eTable 5 in Supplement 1) or eyes with definite baseline PDR on fundus photographs (eTable 5). Results were similar when limiting analyses to participants with 2 study eyes (eTable 6 in Supplement 1). Results of sensitivity analyses using cube transformation (1-sided test for superiority, $P = .006$) and a nonparametric approach (1-sided test for superiority, $P = .01$) were similar to overall results (1-sided test for superiority, $P = .05$) (eTable 7 in Supplement 1). Slight differences in P values likely were a result of transformations reducing skewness and thus increasing precision; however, a priori, the untransformed analysis was designated as the primary analysis.

Percentages of eyes with a 15-letter or more improvement or worsening (considered to be clinically relevant when visual acuity is moderately impaired[17]) at 2 years and over time (eTable 8 and eFigures 3 and 4 in Supplement 1) were similar between the groups. Percentages of eyes with 10-letter worsening or more (similarly considered to be clinically relevant when visual acuity is minimally impaired) also were similar. No significant interaction of treatment with preplanned subgroups was identified except for a possible qualitative interaction of visual acuity and prior DME treatment ($P = .02$) (eTable 9 in Supplement 1). Among eyes with DME at baseline, mean change in visual acuity letter score differed between the ranibizumab and PRP groups by +3.0 (95% CI, −4.2 to +10.3) and among eyes without baseline DME, by +1.4 (95% CI, −1.5 to +4.4; $P = .84$ for interaction) (Figure 2 and eTables 9 and 10 in Supplement 1) .

Figure 1. Flow of Participants Through a Trial of Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy



[a] Participants were not formally screened prior to obtaining informed consent.

[b] Information was not collected on specific reasons for exclusion.

[c] Participants with 2 eyes in the study had 1 eye randomly assigned to receive ranibizumab and 1 eye to receive panretinal photocoagulation.

[d] Two-year completed visits include those that occurred between 644 and 812 days (between 92 and 116 weeks).

Other Vision Outcomes

At the 2-year visit, outcomes were better in the ranibizumab group than in the PRP group for binocular visual acuity (mean change from baseline, +3.4 [SD, 10.9] vs 0 [SD, 11.8], respectively; difference, +3.2; 95% CI, −0.3 to +6.1; $P = .03$) and visual field (mean change combining 30-2 and 60-4 total point scores, −23 dB [SD, 410 dB] vs −422 dB [SD, 518 dB], respectively; difference, 372 dB; 95% CI, 213-531 dB; $P < .001$) (eTables 11 and 12 in Supplement 1). There were no statistically significant differences identified in the outcome subscale scores of the National Eye Institute Visual Function Questionnaire 25 or University of Alabama-Birmingham Low Luminescence Questionnaire (eTables 13 and 14 in Supplement 1).

Table 2. Study Outcomes

Outcomes	Ranibizumab Group	PRP Group	Adjusted Difference (95% CI)	*P* Value
Visual acuity letter score[a]	n = 160 Eyes	n = 168 Eyes		
Visual acuity at 2 y				
Letter score, mean (SD)	78.7 (16.3)	76.2 (14.1)		
Snellen equivalent, mean	20/32	20/32		
Change from baseline in letter score				
Median (interquartile range)	5 (−2 to 11)	2 (−4 to 7)		
Mean (95% CI)	2.8 (0.4 to 5.2)	0.2 (−1.9 to 2.3)	+2.2 (−0.5 to 5.0)[b]	.11
Area under the curve for letter score, mean (95% CI)[c]	4.5 (3.4 to 5.5)	−0.3 (−1.5 to 1.0)	+4.2 (3.0 to 5.4)[d]	<.001
Central subfield thickness, μm[e,f]	n = 149 Eyes	n = 161 Eyes		
At 2 y, mean (95% CI)	210 (201 to 218)	243 (231 to 255)		
Change from baseline to 2 y, mean (95% CI)	−47 (−61 to −33)	−3 (−15 to 9)	−45 (−57 to −33)[g]	<.001
Changes in diabetic retinopathy[h,i]	n = 191 Eyes	n = 203 Eyes		
Retinal detachment, No. (%)				
Traction retinal detachment	10 (5)	16 (8)		
Rhegmatogenous retinal detachment	1 (<1)	1 (<1)		
Unspecified retinal detachment	3 (2)	4 (2)		
Any retinal detachment, No. (%)[j]	12 (6)	21 (10)	−4 (−9 to 1)[k]	.08
Neovascular glaucoma, No. (%)	3 (2)	6 (3)	−1 (−4 to 2)[k]	.50
Neovascularization of the iris, No. (%)	2 (1)	2 (1)	0 (−2 to 2)[k]	.96
Vitreous hemorrhage, No. (%)	52 (27)	69 (34)	−7 (−15 to 1)[k]	.09
Vitrectomy, No. (%)	8 (4)	30 (15)	−9 (−15 to −4)[k]	<.001
Diabetic retinopathy on fundus photographs at 2 y, No. (%)[l]	n = 142 Eyes	n = 148 Eyes		.41
Eyes without proliferative diabetic retinopathy (level 60 or lower)	49 (35)	44 (30)		
Eyes with regressed neovascularization (level 61A)	33 (23)	36 (24)		
Eyes with active neovascularization (level 61B or higher)	60 (42)	68 (46)		
Eyes improving ≥2 steps in diabetic retinopathy severity on fundus photographs at 2 y, No. (%)[l,m]	67 (47)	NA		

Abbreviations: NA, not applicable; PRP, panretinal photocoagulation.

[a] Visual acuity is measured as a continuous integer letter score from 100 to 0, with higher numbers indicating better visual acuity. A letter score of 85 is approximately 20/20 and a letter score of 70 is approximately 20/40, the legal unrestricted driving limit in most states. A letter score of 35 is approximately 20/200, considered legal blindness when it is the visual acuity in the better-seeing eye. A 5-letter change for an individual is approximately equal to a 1-line change on a vision chart. Treatment group means were calculated from observed 2-year data (n = 31 and n = 35 were missing 2-year visual acuity data in the ranibizumab and PRP groups, respectively). Treatment group differences, 95% CIs, and *P* values were obtained using analysis of covariance, with adjustment for baseline visual acuity, number of study eyes, baseline central subfield thickness, and correlation between 2 study eyes of the same participant, with multiple imputation for missing data when indicated. Visual acuity change was truncated to ±3 SDs from the mean (−47 to +49) to minimize the effect of outliers (5 and 3 eyes for the ranibizumab and PRP groups, respectively, all on the negative end at the 2-year visit).

[b] By intention-to-treat analysis with multiple imputation.

[c] Eyes with at least 2 follow-up visits were included in the area under the curve analyses (n = 186 and n = 196 for the ranibizumab and PRP groups, respectively).

[d] Observed data.

[e] Treatment group means are calculated from observed data at the 2-year visit (n = 42 in each group were missing 2-year optical coherence tomography [OCT] data). Treatment group differences, 95% CIs, and *P* values were obtained using analysis of covariance, with adjustment for number of study eyes, baseline central subfield thickness, correlation between 2 study eyes of the same participant, and imputation of missing data with last observation carried forward. Central subfield thickness changes were truncated to ±3 SDs from the mean (−325 to +276) to minimize the effect of outliers (4 eyes in the ranibizumab group on the large decrease end and 3 eyes in the PRP group [1 with large decrease, 2 with large increase] at the 2-year visit). All baseline and 2-year optical OCT scans were evaluated by the OCT reading center. In addition, a random sample of OCT images from other visits and images for which the investigator believed central grading was needed also were graded at the OCT reading center.

[f] Optical coherence tomography values obtained by spectral-domain OCT were converted to time-domain equivalent values for analysis and reporting as follows: −43.12 + 1.01 × Zeiss Cirrus; −72.76 + 1.03 × Spectralis.[20]

[g] By intention-to-treat analysis with last observations carried forward.

[h] Unless otherwise specified, diabetic retinopathy outcomes were collected at any time during study follow-up through the 2-year visit. If the 2-year visit was completed, then the visit date was used to define the 2-year time point; otherwise, 728 days was used.

[i] *P* values are based on binomial regression adjusting for the correlation between 2 study eyes of the same participant or multinomial regression.

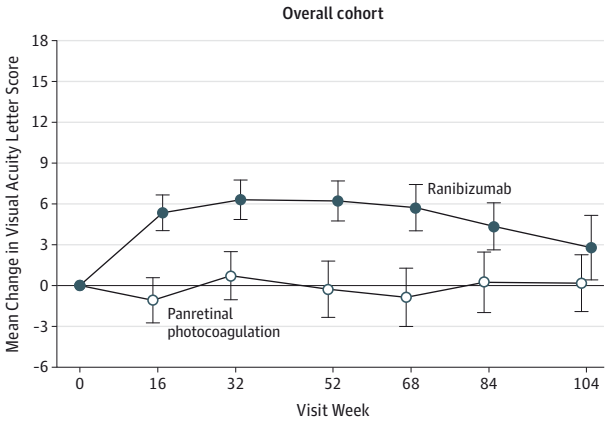
[j] After database lock, 4 cases of reported retinal detachment (3 in the ranibizumab group and 1 in the PRP group) were identified as macular traction and not a traction retinal detachment. Primary data reported reflect available information prior to database lock. However, excluding the 4 misclassified cases, retinal detachment rates were 9 (5%) vs 20 (10%) in the ranibizumab and PRP groups, respectively.

[k] By intention-to-treat analysis. Data are percentage change (95% CI).

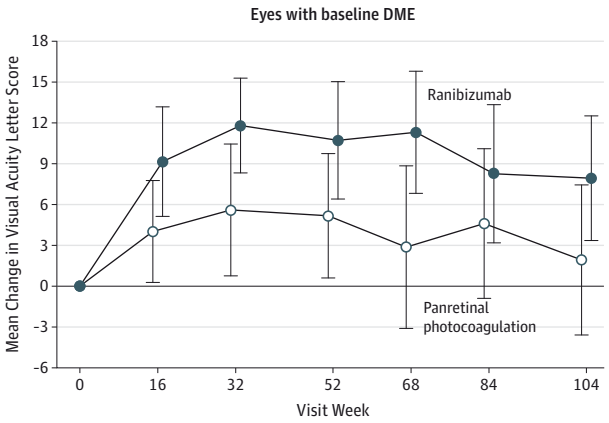
[l] Only includes eyes with baseline diabetic retinopathy level 61B or worse (active neovascularization) as graded by the reading center. Last-observation-carried-forward analysis was used for 23 eyes in the ranibizumab group and 25 eyes in the PRP group missing photographs at 2 years if 1-year fundus photographs were available.

[m] Eyes graded by the reading center as receiving PRP (level 60) at follow-up are counted as not improving.

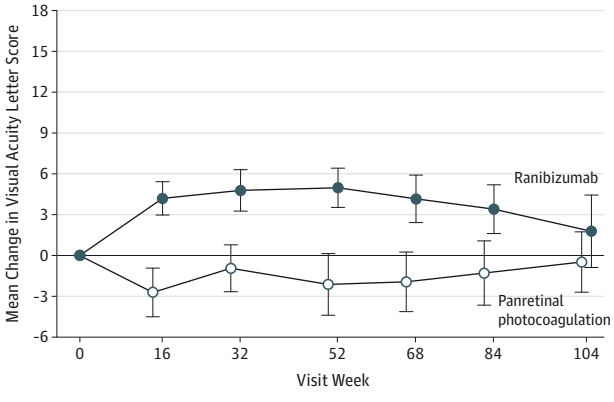
Figure 2. Changes in Visual Acuity Over Time for the Overall Cohort, for Eyes With Baseline DME, and for Eyes Without Baseline DME



No. of eyes							
Ranibizumab	191	183	172	170	163	152	160
Panretinal photocoagulation	203	189	178	178	163	159	168
No. of eyes truncated to 3 SDs from the mean							
Ranibizumab		1	1	0	0	1	5
Panretinal photocoagulation		2	4	8	6	6	3



No. of eyes							
Ranibizumab	42[a]	41	37	36	35	29	33
Panretinal photocoagulation	46[a]	42	42	42	36	37	37



No. of eyes							
Ranibizumab	147[a]	140	134	133	127	122	126
Panretinal photocoagulation	155[a]	146	135	135	127	121	130

DME indicates diabetic macular edema. Error bars represent 95% CIs. Outlying values were truncated to 3 SDs from the mean; numbers of eyes at each visit week to which this applies are shown for the overall cohort; the numbers of eyes with and without DME are similar.

[a] At baseline, 2 eyes in each treatment group were missing ocular coherence tomography data and could not be classified as either with or without DME.

Retinal Thickening

At the 2-year visit, among eyes with baseline DME (n = 68), central subfield thickness decreased on average by 153 µm (SD, 129 µm) in the ranibizumab group and by 48 µm (SD, 124 µm) in the PRP group receiving ranibizumab for DME (adjusted difference, −65 µm; 95% CI, −126 to −4.5 µm; P = .04)

Table 3. Systemic and Ocular Adverse Events of Interest Through 2 Years of Follow-up[a]

Events	Participants With 2 Study Eyes (1 in Each Group)	Ranibizumab Group	PRP Group	*P* Value
Systemic adverse events, No. (%)[b]	n=89	n=102 Participants with 1 study eye	n=114 Participants with 1 study eye	
Vascular events defined by APTC[21] criteria occurring at least once through 2 y				
Nonfatal myocardial infarction	2 (2)	3 (3)	2 (2)	.89
Nonfatal stroke	1 (1)	2 (2)	4 (4)	.63
Death due to potential vascular cause or unknown cause	4 (4)	4 (4)	1 (<1)	.22
Any event	7 (8)	9 (9)	7 (6)	.80
Prespecified events occurring at least once through 2 y				
Death from any cause	4 (4)	6 (6)	4 (4)	.70
Hospitalization	37 (42)	48 (47)	40 (35)	.20
Serious adverse event	38 (43)	49 (48)	42 (37)	.26
Hypertension	14 (16)	26 (25)	21 (18)	.23
Ocular adverse events occurring at least once through 2 y, No. (%)[c]		n=191 Eyes	n=203 Eyes	
Endophthalmitis		1 (0.5)	0	
Inflammation[d]		2 (1)	9 (4)	.02
Retinal tear		0	0	
Cataract surgery		4 (2)	12 (6)	.06
Elevation in intraocular pressure[e]		17 (9)	27 (13)	.16

Abbreviations: APTC, Antiplatelet Trialists' Collaboration; PRP, panretinal photocoagulation.

[a] Unless otherwise specified, adverse event data were collected at any time during study follow-up. If the 2-year visit was completed, then the visit date was used to define the 2-year time point; otherwise, 728 days was used.

[b] Systemic adverse events were classified as occurring in the group of participants with both eyes in the study (1 in each treatment group), participants with 1 eye in the study in the PRP group, or participants with 1 eye in the study in the ranibizumab group. The Fisher exact test was performed to compare the 3 groups.

[c] *P* values are based on binomial regression adjusting for the correlation between 2 study eyes of the same participant.

[d] Inflammation included the presence of inflammatory cells or flare in the anterior chamber, choroiditis, episcleritis, iritis, and the presence of vitreal cells.

[e] Elevated intraocular pressure was defined as an increase in intraocular pressure of 10 mm Hg or more from baseline at any visit, an intraocular pressure of 30 mm Hg or more at any visit, the initiation of medication to lower intraocular pressure that was not in use at baseline, or glaucoma surgery.

(eTable 15 in Supplement 1). Among eyes without baseline DME (n = 242), the mean change in central subfield thickness was −18 µm (SD, 37 µm) in the ranibizumab group vs +10 µm (SD, 54 µm) in the PRP group (difference, −31 µm; 95% CI, −41 to −21 µm; $P < .001$) (eTable 15). The cumulative probability of developing central DME with vision impairment by 2 years was 9% in the ranibizumab group vs 28% in the PRP group (adjusted difference, 19% more frequently in the PRP group; 95% CI, 10%-28%; $P < .001$) (eFigure 5 in Supplement 1). Changes in retinal volume are shown in eTable 16 in Supplement 1.

Diabetic Retinopathy

A vitreous hemorrhage developed in 52 eyes (27%) within the ranibizumab group and 69 eyes (34%) within the PRP group (difference, 7% more in the PRP group; 95% CI, 15% more in the PRP group to 1% more in the ranibizumab group; $P = .09$) (Table 2) and a retinal detachment occurred in 6% vs 10%, respectively (difference, 4% more in the PRP group; 95% CI, 9% more in the PRP group to 1% more in the ranibizumab group; $P = .08$). A vitrectomy was performed in 8 eyes (4%) in the ranibizumab group vs 30 eyes (15%) in the PRP group (difference, 9% more in the PRP group; 95% CI, 4%-15% more in the PRP group; $P < .001$), including 2% vs 14% among the 302 eyes without baseline DME and 12% vs 17% among the 88 eyes with baseline DME, respectively. The timing of events related to complications of PDR is shown in eTable 17 in Supplement 1. Rates of neovascular glaucoma were 2% in the ranibizumab group and 3% in the PRP group. New iris neovascularization was 1% in both groups.

Percentages of eyes without active or regressed neovascularization at the disc or elsewhere on fundus photographs (excluding PRP lesions) at 2 years were 35% among 142 eyes in the ranibizumab group and 30% among 148 eyes in the PRP group (difference, 3%, 95% CI, −7% to 12%; $P = .58$) (Table 2). At 2 years, 48% of eyes in the ranibizumab group improved by 2 or more steps in diabetic retinopathy severity on fundus photographs, an outcome not assessable after PRP.

Adverse Events

Injection-related endophthalmitis occurred in 1 eye (0.5%) in the ranibizumab group and 0 eyes in the PRP group (0.04% of 2581 total injections, 0.33% among the 299 eyes receiving ranibizumab). Ocular inflammation excluding endophthalmitis was reported in 2 eyes (1%) in the ranibizumab group and 9 eyes (4%) in the PRP group ($P = .02$). Cataract extraction occurred in 4 (2%) and 12 (6%), respectively ($P = .06$). Additional ocular events are reported in **Table 3**.

There were no significant differences identified between groups in the number of participants with a serious adverse event, hospitalization, death, Antiplatelet Trialists' Collaboration arteriothromboembolic events (Table 3),[21] or events in each individual MedDRA system organ class (eTable 18 in Supplement 1). However, differences with a *P* value not meet-

ing the significance threshold of $P < .05$ with fewer events in the PRP group were seen in 6 of 22 system organ classes: cardiac disorders ($P = .01$), endocrine disorders ($P = .02$), infections/infestations ($P = .02$), respiratory disorders ($P = .04$), skin and subcutaneous tissue disorders ($P = .03$), and surgical and medical procedures ($P = .01$). eTable 19 in Supplement 1 lists all systemic adverse events.

Discussion

In this randomized clinical trial, intravitreous ranibizumab met the primary noninferiority outcome of visual acuity change at 2 years being no worse than in the PRP group for treatment of PDR. There was no statistically significant visual acuity difference between the ranibizumab and PRP groups at 2 years, with the recognition that 53% of the PRP group received ranibizumab injections for DME. Ranibizumab resulted in better visual acuity when evaluated over 2 years (area under the curve), although the clinical importance of this difference is unknown. More peripheral visual field loss occurred (95% CI for difference, 213-531 dB) and more vitrectomies were performed in the PRP group compared with the ranibizumab group (95% CI for difference, 4%-15%). Among eyes without center-involved DME at baseline, development of DME with vision impairment was substantially more frequent in the PRP group (95% CI for difference, 10%-28%). Only 12 eyes (6%) in the ranibizumab group received PRP; more than half of the eyes in the PRP group received ranibizumab for DME; thus, the protocol essentially tested ranibizumab for PDR vs PRP plus ranibizumab when needed for DME treatment.

No systemic safety concerns with ranibizumab were identified in the prespecified major safety outcomes. Differences in the MedDRA system organ classes of cardiac, endocrine, infections/infestations, respiratory, skin, and surgical disorders could be real, due to chance, or due to ascertainment bias because the ranibizumab group had more frequent visits than the PRP group. Interpreting the safety findings is difficult because a large proportion of the PRP group received ranibizumab for DME. Rates of endophthalmitis or other injection-related serious adverse events were very low, consistent with other studies.[9,22,23]

Several limitations related to the study design and conduct are important when interpreting these results. Participant retention through 2 years (87% of those who had not died) was lower than desired. Although participants who completed the 2-year visit had slightly better baseline visual acuities than those who did not, no visual acuity differences between treatment groups with respect to the 2-year visit completion status were apparent, limiting the possibility of differential treatment bias. Considering that the final visual acuity in the PRP group, but not in the ranibizumab group, was better for those who did vs those who did not complete the 2-year visit, if bias was present, it likely favored the PRP group. The nature of the treatments precluded masking participants and clinicians. Although DME treatment was at investigator discretion, the fixed PRP or anti-VEGF regimen for PDR limited clinician discretion, and protocol treatment adherence was high, limiting the bias of clinician unmasking except for consideration of vitrectomy, which was at clinician discretion. Visual acuity testers were masked at the primary outcome visit and the computerized testing methods minimized acquisition bias.[14]

Cost analyses, including cost-effectiveness analyses, are beyond the scope of this article. It is unknown if results would have been similar with another anti-VEGF agent. When this protocol was designed, another trial evaluating ranibizumab for DME had secondary analyses supporting the potential for ranibizumab to prevent worsening of PDR.[23] No such data were available for aflibercept or bevacizumab at that time. Thus, from a scientific perspective, DRCR.net investigators judged ranibizumab to be the best anti-VEGF agent for this trial as enrollment began.

In applying these results to clinical practice, PRP treatment sometimes can be completed in 1 visit and not require additional procedures, although in this study, 45% needed additional PRP. Panretinal photocoagulation may cost less than ranibizumab injections and carries no risk of endophthalmitis or systemic anti-VEGF exposure. Weighing the relative benefits of treatment of PDR with PRP vs ranibizumab may be influenced by whether DME is present. When DME is present for which ranibizumab treatment is planned, PRP may be unnecessary because ranibizumab will treat both the PDR and the DME, assuming access to ranibizumab and patient adherence to follow-up. Regardless of presence of DME, the results of this study suggest that ranibizumab is more effective than PRP for mean visual acuity outcomes over 2 years, with less visual field loss and fewer eyes developing DME or undergoing vitrectomy. Nevertheless, treatment cost, adherence to and frequency of follow-up, and patient preference should be considered.

Conclusions

Among eyes with PDR, treatment with ranibizumab resulted in visual acuity that was noninferior to (not worse than) PRP at 2 years. Although longer-term follow-up is needed, ranibizumab may be a reasonable treatment alternative at least through 2 years for patients with PDR.

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