HHS Public Access

Author manuscript

Ophthalmology. Author manuscript; available in PMC 2019 June 14.

Published in final edited form as:

Ophthalmology. 2018 November ; 125(11): 1776–1783. doi:10.1016/j.ophtha.2018.04.039.

Panretinal Photocoagulation vs Ranibizumab for Proliferative Diabetic Retinopathy: Factors Associated With Vision and Edema Outcomes

Susan B. Bressler, MD[1], **Wesley T. Beaulieu, PhD**[2], **Adam R. Glassman, MS**[2], **Jeffrey G. Gross, MD**[3], **Michele Melia, ScM**[2], **Eric Chen, MD**[4], **Michael R. Pavlica, MD**[5], **Lee M. Jampol, MD**[6], and **Diabetic Retinopathy Clinical Research Network**

[1]Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Jaeb Center for Health Research, Tampa, Florida; [3]Carolina Retina Center PA, Columbia, South Carolina; [4]Retina Consultants of Houston, Houston, Texas; [5]Family Eye Group, Lancaster, Pennsylvania; [6]Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Abstract

Objective: Identify baseline factors associated with change in visual acuity or development of vision-impairing central-involved diabetic macular edema (CI-DME) over 2 years when initiating treatment for proliferative diabetic retinopathy (PDR) with ranibizumab or panretinal photocoagulation.

Design: Post hoc analyses of randomized multicenter clinical trial data.

Participants: Eyes completing the 2-year visit (N = 328) or eyes without vision-impairing CI-DME at baseline (N = 302) in Diabetic Retinopathy Clinical Research Network Protocol S.

Intervention: Protocol-defined applications of intravitreous ranibizumab (0.5 mg/0.05 mL) or panretinal photocoagulation.

Main Outcome Measures: Change in visual acuity (area under the curve) and development of vision-impairing (20/32 or worse) CI-DME over 2 years.

Results: After multivariable model selection with adjustment for baseline visual acuity and central subfield thickness, no baseline factors were identified as having an association with change in visual acuity or development of vision-impairing CI-DME within the ranibizumab group. In the panretinal photocoagulation group, worse change in visual acuity over 2 years was more likely with higher Hemoglobin A_{1c} (−0.6 [95% confidence interval (CI), −1.2 to −0.1] letters for every 1% increase, continuous $P = .03$), more severe diabetic retinopathy (difference between high-risk PDR or worse vs. moderate PDR or better = −2.8 [95% CI, −5.5 to −0.2] letters, continuous $P = .003$), and higher mean arterial pressure (difference between ≥ 100 mmHg vs. < 100 mmHg = −2.0 [95% CI, −4.6 to 0.5] letters, continuous $P = .009$). Development of vision-impairing CI-DME was

Corresponding Author: Wesley T. Beaulieu, Jaeb Center for Health Research, 1530 Amberly Drive, Suite 350, Tampa, FL 33647; Phone: (813) 975-8690, Fax: (800) 816-7601, drcrstat8@jaeb.org.

Financial Disclosures: A complete list of all DRCR.net investigator financial disclosures can be found at www.drcr.net.

more likely with higher Hemoglobin A_{1c} (hazard ratio for a 1% increase = 1.31 [95% CI, 1.13 to 1.52], continuous P <.001), more severe diabetic retinopathy (hazard ratio for high-risk PDR or worse vs. moderate PDR or better = 1.46 [95% CI, 0.73 to 2.92], continuous P = .03) and the presence of cystoid abnormalities within 500 μm of the macula center on optical coherence tomography (hazard ratio = 2.90 [95% CI, 1.35 to 6.24], P = .006).

Conclusions: For eyes managed with panretinal photocoagulation, higher glycosylated hemoglobin and more severe diabetic retinopathy were associated with less vision improvement and an increased risk of developing vision-impairing CI-DME. When managing PDR with ranibizumab, on average eyes gained vision, with no baseline characteristics identified as associated with visual acuity or CI-DME outcomes.

Précis:

HbA_{1c}, arterial blood pressure, and diabetic retinopathy severity were associated with less favorable vision outcome when treating PDR with PRP, but no baseline characteristics altered the ranibizumab outcome (adjusted for baseline vision and central thickness).

INTRODUCTION

Proliferative diabetic retinopathy (PDR) has been managed with panretinal photocoagulation (PRP) for several decades.[1] However, with the advent of anti-vascular endothelial growth factor (anti-VEGF) therapy for the treatment of central-involved diabetic macular edema (CI-DME), it was recognized that anti-VEGF agents were often simultaneously reducing the level of diabetic retinopathy and the risk of worsening to more advanced diabetic retinopathy severity. Neovascularization of the disc (NVD) and retinal neovascularization elsewhere (NVE) regressed in some eyes receiving anti-VEGF agents, while rates of retinopathy worsening appeared reduced among eyes with PDR receiving anti-VEGF treatment to manage CI-DME compared to eyes receiving focal/grid laser.[2, 3]

These observations prompted the Diabetic Retinopathy Clinical Research Network to conduct Protocol S, a randomized multi-center clinical trial comparing intravitreous ranibizumab injections with PRP in eyes with PDR. The 2-year study outcomes provided several forms of evidence that anti-VEGF therapy is a reasonable alternative to PRP when managing PDR. These included non-inferior change in visual acuity at 2 years (5-letter non-inferiority margin), greater visual acuity improvement over 2 years, less visual field loss, reduced chance of vision-impairing (20/32 or worse) CI-DME development, and a lower vitrectomy rate. More recently, results from the CLARITY study, which compared aflibercept with PRP for eyes with PDR in the absence of CI-DME, supported many of the findings from Protocol S.[4, 5] A post hoc analysis of Protocol S data did not identify any subgroups in which PRP was superior to ranibizumab with respect to change in visual acuity (area under the curve analysis) or development of vision-impairing CI-DME over 2 years.[6] However, the relative benefit of ranibizumab over PRP for change in visual acuity was potentially greater for individuals with more advanced levels of PDR or higher mean arterial blood pressure.[6]

Ophthalmologists now have anti-VEGF treatment without PRP as an alternative therapy to PRP to manage eyes with PDR. Therefore, an enhanced understanding of patient and ocular factors that are associated with clinically relevant outcomes when using ranibizumab or PRP may be helpful in refining patient and physician expectations. This post hoc analysis seeks to identify factors within each treatment arm of Protocol S that are associated with two clinically important outcomes: change in visual acuity over 2 years and development of vision-impairing CI-DME.

METHODS

The full protocol is available on the Diabetic Retinopathy Clinical Research Network website (http://drcrnet.jaeb.org/Studies.aspxt; accessed: 15 January 2015). Study procedures were reported previously and are summarized here.[6] Three-hundred and five participants (394 study eyes) were enrolled at 55 clinical sites. Study eyes had PDR, no prior PRP, and best corrected visual acuity letter score of at least 24 (Snellen equivalent 20/320 or better) using the Electronic-Early Treatment Diabetic Retinopathy Study test.[6, 7] Participants with one study eye were randomly assigned to prompt PRP (completed in 1 to 3 sittings) or intravitreous ranibizumab injections (0.5 mg/0.05 mL) with a structured retreatment algorithm. Participants contributing two study eyes were randomly assigned to PRP in one eye and ranibizumab in the other eye. Eyes with baseline vision-impairing CI-DME received ranibizumab at baseline followed by as-needed retreatment for DME, regardless of treatment group assignment. Vision-impairing CI-DME was defined as visual acuity letter score less than or equal to 78 (Snellen equivalent 20/32 or worse) and central subfield thickness (CST) greater than 2 standard deviations above the sex/instrument-specific norm for the population (Heidelberg Spectralis ≥ 320 μm for men and ≥ 305 μm for women, Zeiss Cirrus and Optovue RTVue ≥ 305 μm for men and ≥ 290 μm for women, Zeiss Stratus ≥ 250 μm for both sexes). In addition, eyes in either arm could receive ranibizumab to treat DME at investigator discretion at any time during study participation.

Participants in both treatment groups had assessment visits approximately every 4 months (16, 32, 52, 68, 84, and 104 weeks). In the ranibizumab group, participants had additional study visits every 4 weeks in the first year to evaluate the need for ranibizumab to treat PDR. In the second year, visits in the ranibizumab group could be extended up to 16 weeks if injections for PDR were continually deferred based on the retreatment algorithm. Participants in either group who received ranibizumab for DME at investigator discretion may have had additional study visits for DME assessment and treatment. Supplemental PRP was permitted in the PRP group if the size or amount of neovascularization increased following completion of the initial PRP. Eyes in the ranibizumab group were eligible to receive PRP if pre-specified failure criteria were met. Best-corrected visual acuity using the Electronic-Early Treatment Diabetic Retinopathy Study test was obtained at all study visits. Optical coherence tomography (OCT) scans were obtained at all DME-treatment visits and at all annual visits.

Outcomes and Analysis Cohorts

Change in visual acuity over 2 years (area under the curve of time versus change in visual acuity) was calculated using the trapezoidal rule with data from the assessment visits, which were common to both treatment groups.[6] This is analogous to a weighted average of the change in visual acuity with weights proportional to the time between visits. Only eyes that completed the 2-year visit (328 of 394 [83%]) were included. Complete-case analysis is an unbiased method for handling missing data, assuming that the 2- year data are missing at random.[8] In this cohort, the mean baseline visual acuity was 76 letters (approximate Snellen equivalent 20/32) and the mean baseline central subfield thickness (CST) was 255 μm (Zeiss Stratus equivalent).

The cohort for development of vision-impairing CI-DME included the 302 eyes without vision-impairing CI-DME at baseline (77% of 394 randomized). The analysis did not require these eyes to complete the 2-year visit as it incorporated all available data and censored data from any participant in which vision-impairing CI-DME had not developed by the final visit prior to 2 years. In this cohort, the mean baseline visual acuity was 78 letters (approximate Snellen equivalent 20/32) and the mean baseline CST was 218 μm. Two-hundred fifty-six eyes were in both analysis cohorts, 72 eyes not in the DME cohort were in the change in visual acuity cohort, and 46 eyes in the DME cohort were not in the change in visual acuity cohort.

Statistical Analyses

Twenty-eight baseline characteristics were explored. To increase statistical precision, a minimum of 20 eyes within each subgroup was required for analysis (Table 1, available at www.aaojournal.org). All analyses were adjusted for baseline visual acuity (a component of each outcome) and CST (a pre-randomization factor that determined whether ranibizumab for DME was required at baseline). Change in visual acuity over 2 years was analyzed using analysis of covariance. Development of vision-impairing CI-DME was analyzed using proportional hazards regression. For the purpose of tabulation, continuous characteristics were dichotomized in tables based on approximate median values from the entire cohort. However, continuous variables were used for generating *P*-values (Table 1, available at www.aaojournal.org).

For each outcome, characteristics with $P < .10$ were entered into a multivariable model and backward stepwise selection was used to produce a final model in which only factors with $P < .05$ remained. A separate model was constructed for each treatment group. There was no formal adjustment for multiple hypothesis testing in these exploratory analyses. Therefore, $P < .05$ was considered suggestive (rather than definitive) of a true relationship. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Ranibizumab Group

The adjusted mean improvement in visual acuity over 2 years was 4.7 (95% confidence interval [CI], 3.8 to 5.6) letters in the ranibizumab group. Tables 2 and 3 show adjusted

means for individual subgroups and *P*-values for each factor. After adjustment for baseline visual acuity (worse baseline visual acuity associated with greater improvement, $P < .001$) and CST ($P = .12$), no baseline factors were associated with change in visual acuity over 2 years. The R^2 for the final model including visual acuity and CST was 0.41.

A secondary analysis was conducted that was limited to eyes without vision-impairing CI-DME at baseline that also completed the 2-year visit (N = 126 of 160 [79%]; Table 4, available at www.aaojournal.org). In this cohort, the adjusted mean improvement in visual acuity over 2 years was 3.7 (95% CI, 2.7 to 4.7) letters. After multivariable model selection, the only characteristic associated with this vision outcome was prior DME treatment. Eyes with prior DME treatment had a less favorable change in visual acuity over 2 years (difference between with vs. without prior DME treatment = −2.4 [95% CI, −4.7 to −0.1] letters; $P = .04$). Adding prior DME treatment to the model with baseline visual acuity and CST increased R^2 from 0.36 to 0.38.

Fifteen of 147 (10%) ranibizumab-assigned eyes without vision-impairing CI-DME at baseline developed vision-impairing CI-DME by 2 years. Tables 5 and 6 show the cumulative probabilities of developing vision-impairing CI-DME for individual subgroups and P-values for each factor. After adjustment for baseline visual acuity ($P = .27$) and CST (greater CST associated with increased likelihood of vision-impairing CI-DME, $P < .001$), there were no additional factors identified as associated with development of vision-impairing CI-DME.

Panretinal Photocoagulation Group

The adjusted mean change in visual acuity over 2 years was −0.3 (95% CI, −1.5 to 1.0) letters in the PRP group. Tables 2 and 3 show adjusted means for individual subgroups and *P*-values for each factor. After simultaneous adjustment for baseline visual acuity (worse baseline visual acuity associated with greater improvement, $P < .001$) and CST ($P = .20$), multivariable model selection identified Hemoglobin A_{1c} (HbA_{1c}) (−0.6 [95% CI, −1.2 to −0.1] letters for every 1% increase, continuous $P = .03$), mean arterial pressure (difference between ≥ 100 mmHg vs. < 100 mmHg = −2.0 [95% CI, −4.6 to 0.5] letters, continuous $P = .009$), and diabetic retinopathy severity (difference between high-risk PDR or worse vs. moderate PDR or better = −2.8 [95% CI, −5.5 to −0.2] letters, continuous $P = .003$) as factors associated with change in visual acuity over 2 years. When these factors were added to the model that included baseline visual acuity and CST, R^2 increased from 0.23 to 0.33. Among eyes with complete data, we identified 16 of 161 (10%) in the PRP group as having all three baseline factors that were associated with a less favorable vision outcome ($HbA_{1c} \geq$ 9%, mean arterial pressure ≥ 100 mmHg, and high-risk PDR [≥ ETDRS level 71]).

Similar to the ranibizumab group, a secondary analysis was conducted that was limited to eyes without vision-impairing CI-DME at baseline that also completed the 2-year visit (N = 130 of 168 [77%]; Table 4, available at www.aaojournal.org). In this cohort, the adjusted mean change in visual acuity over 2 years was −1.6 (95% CI, −2.9 to −0.2) letters. Multivariable model selection identified HbA_{1c} (−0.7 [95% CI, −1.4 to −0.1] letters for every 1% increase, continuous $P = .03$), diabetic retinopathy severity (difference between high-risk PDR or worse vs. moderate PDR or better = −1.8 [95% CI, −4.7 to 1.0] letters,

continuous $P = .03$) and the number of PRP spots (−0.5 [95% CI, −0.9 to −0.1] letters for every 100 additional spots placed, continuous $P = .03$) as associated with change in vision over 2 years. When these factors were added to the model that included baseline visual acuity and CST, R^2 increased from 0.13 to 0.25.

Forty-two of 155 (27%) PRP-assigned eyes without vision-impairing CI-DME at baseline developed vision-impairing CI-DME by 2 years. Tables 5 and 6 show the cumulative probabilities of developing vision-impairing CI-DME for individual subgroups and P-values for each factor. After simultaneous adjustment for baseline visual acuity (worse baseline visual acuity associated with increased likelihood of vision-impairing CI-DME, $P < .001$) and CST (greater CST associated with increased likelihood of vision-impairing CI-DME, $P = .003$), multivariable model selection identified HbA_{1c} (hazard ratio [HR] for a 1% increase = 1.31 [95% CI, 1.13 to 1.52], continuous $P < .001$), cystoid abnormalities within 500 μm of the macula center (HR = 2.90 [95% CI, 1.35 to 6.24], $P = .006$), and diabetic retinopathy severity (HR for high-risk PDR or greater vs. moderate PDR or better = 1.46 [95% CI, 0.73 to 2.92], continuous $P = .03$) as associated with development of vision-impairing CI-DME. Among eyes with complete data, we identified 11 of 141 (8%) in the PRP group as having all three baseline factors that were associated with greater risk of vision-impairing CI-DME development ($HbA_{1c} \geq 9\%$, cystoid abnormalities within 500 μm of the macula center, and high-risk PDR).

An additional analysis broadening the vision-impairing CI-DME outcome definition to include initiation of ranibizumab for DME during follow-up at investigator discretion was conducted, in which the 27 eyes that received ranibizumab at baseline per investigator discretion were excluded (Table 7, available at www.aaojournal.org). Among the 128 of 155 (83%) remaining eyes, the outcome was met in 47 (37%) with 27 of 47 developing vision-impairing CI-DME and 20 of 47 receiving ranibizumab at investigator discretion during follow-up. Multivariable model selection identified HbA_{1c} (HR for a 1% increase = 1.29 [95% CI, 1.11 to 1.50], continuous $P < .001$), cystoid abnormalities within 500 μm of the macula center (HR = 5.49 [95% CI, 2.57 to 11.72], $P < .001$), and hard exudates within 1800 μm of the macula center (HR = 2.10 [95% CI, 1.09 to 4.05], $P = .03$) as associated with development of vision-impairing CI-DME.

DISUSSION

Since PRP or anti-VEGF as monotherapies can be effective treatments for PDR, clinicians likely will continue to consider both in the care of patients. This report provides information on factors that potentially modulate the treatment outcomes associated with each modality, but does not provide information on selecting one treatment over the other. However, it does present information that may alter expectations regarding prognosis based on baseline factors after deciding which treatment to administer. In this post hoc analysis, when treating with PRP and adjusting for baseline visual acuity and CST, eyes that had more severe retinopathy or higher HbA_{1c} at baseline had less improvement in visual acuity, on average, and greater incidence of vision-impairing CI-DME over 2 years compared with eyes that had less severe retinopathy or lower HbA_{1c}. Furthermore, in the PRP group, participants with higher mean arterial pressure had, on average, less improvement in vision and eyes with

cystoid abnormalities within 500 μm of the macula center were more likely to develop vision impairing CI-DME. However, when treating with ranibizumab, neither these nor the other factors we evaluated were associated with change in visual acuity or CI-DME development after adjusting for baseline visual acuity and CST.

A secondary post hoc analysis limited to eyes without baseline CI-DME supported the associations of HbA_{1c} and baseline diabetic retinopathy severity with change in vision over 2 years for the PRP group. This cohort may represent a better evaluation of PRP treatment alone because these eyes were not required to receive ranibizumab at baseline to manage DME, although they could receive it based on investigator discretion at baseline or any time thereafter.

For the vision-impairing CI-DME outcome, a secondary analysis that broadened the outcome to include development of CI-DME *or* initiation of ranibizumab supported the associations with higher baseline HbA_{1c} and the presence of cystoid abnormalities within 500 μm of the macula center on OCT among eyes treated with PRP.

While no factors were associated with change in vision over 2 years in the ranibizumab group, a secondary analysis limited to eyes without baseline CI-DME identified a possible association with prior DME treatment. The treatment naïve eyes gained even more vision on average than eyes with prior DME treatment. Eyes that had no prior treatment for DME may have had subclinical or very mild macular thickening that was simultaneously treated by the ranibizumab administered for PDR.

Overall, eyes starting with better visual acuity were less likely to have large gains in vision compared to eyes starting with worse visual acuity, in part due to a ceiling effect, which is why visual acuity was included as an adjustment in all analyses.[9] Similarly, eyes starting with worse vision or greater CST were closer to meeting the definition of vision-impairing CI-DME than eyes starting with better vision or lesser CST, which is why both variables were adjusted for in these analyses. Despite these predictable relationships, only about one quarter of the variation associated with change in visual acuity over two years in the PRP group was accounted for by baseline visual acuity and CST. Even after the individual factors found to be associated with the visual acuity outcome in the PRP group were added to the model (baseline HbA_{1c}, mean arterial pressure, and retinopathy severity), approximately two thirds of the variation in visual acuity over 2 years remained unexplained. As such, even though these factors appear to be associated with the outcome, substantial uncertainty about the precise determinants of 2-year change in visual acuity remains.

Interpretation of these results is limited by the fact that the analyses were undertaken post hoc and were not specifically powered to detect associations with baseline characteristics. Therefore, the absence of a definitive association cannot be taken as evidence that an association does not exist. In addition, a large number of analyses were performed and some associations could have been identified due to chance. Furthermore, the small number of eyes in the ranibizumab group that developed CI-DME and the limited number of eyes manifesting certain characteristics, such as surface wrinkling retinopathy, both limit the statistical power for detecting associations, particularly for the vision-impairing CI-DME

outcome. It remains unknown how the findings in the PRP group might have been different if these eyes were not permitted to receive ranibizumab simultaneously to manage DME. The secondary analysis excluding eyes from the PRP group that were required to receive ranibizumab at baseline only partly addresses this issue.

More recently, the CLARITY study reported superior 1-year vision outcomes when aflibercept was compared with PRP to manage PDR.[4] The CLARITY study excluded eyes that had DME at baseline, permitted entry of eyes with active PDR despite prior PRP, and incorporated a different re-treatment regimen for the anti-VEGF arm than Protocol S. Whether the features identified in this exploratory analysis as associated with vision or DME outcomes when using anti-VEGF therapy or PRP to manage PDR would be replicated in the CLARITY study remains to be seen.

In conclusion, eyes gain vision, on average, and seldom develop vision-impairing CI-DME over 2 years when ranibizumab is used as in Protocol S to treat PDR. The findings in this post hoc analysis suggest these outcomes are irrespective of a wide array of baseline factors. In contrast, when PRP is the primary treatment modality for PDR, eyes with poor glycemic control or more severe diabetic retinopathy severity may be more apt to lose visual acuity and develop vision-impairing CI-DME than eyes with lower HbA_{1c} or less severe diabetic retinopathy, even when allowing for administration of ranibizumab to treat DME.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

A complete list of the Diabetic Retinopathy Clinical Research Network investigators who participated in this trial is available in JAMA. 2015;314(20):2137–2146.

Financial support: Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, U.S. Department of Health and Human Services EY14231, EY23207, EY18817. Genentech provided ranibizumab for the study and funds to DRCR.net to defray the study's clinical site costs.

The National Institutes of Health participated in oversight of the conduct of the study and review of the manuscript but not directly in the design or conduct of the study nor in the collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Per the DRCR.net Industry Collaboration Guidelines (available at http://www.drcr.net), the DRCR.net had complete control over the design of the protocol, ownership of the data, and all editorial content of presentations and publications related to the protocol.

REFERENCES

1. Ferris FL 3rd, Davis MD, Aiello LM. Treatment of diabetic retinopathy. N Engl J Med. 1999;341(9):667–78. [PubMed: 10460819]
2. Bressler SB, Qin H, Melia M, et al. Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. JAMA Ophthalmol. 2013;131(8):1033–40. [PubMed: 23807371]
3. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006;113(10):1695 e1–15. [PubMed: 17011951]
4. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic

retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet. 2017;389(10085):2193–203. [PubMed: 28494920]

5. Glassman AR. Results of a randomized clinical trial of aflibercept vs panretinal photocoagulation for proliferative diabetic retinopathy: Is it time to retire your laser? JAMA Ophthalmology. 2017;135(7):685–6. [PubMed: 28570733]
6. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, et al. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA. 2015;314(20):2137–46. [PubMed: 26565927]
7. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the Early Treatment of Diabetic Retinopathy Study testing protocol. Am J Ophthalmol. 2003;135(2):194–205. [PubMed: 12566024]
8. Sullivan TR, White IR, Salter AB, Ryan P, Lee KJ. Should multiple imputation be the method of choice for handling missing data in randomized trials? Statistical Methods in Medical Research. 2016;0(0):0962280216683570.
9. Beck RW, Maguire MG, Bressler NM, Glassman AR, Lindblad AS, Ferris FL. Visual acuity as an outcome measure in clinical trials of retinal diseases. Ophthalmology. 2007;114(10):1804–9. [PubMed: 17908590]

Table 2.

Change in Visual Acuity Over 2 Years (Area Under the Curve) by Baseline Participant Characteristics Adjusted for Baseline Visual Acuity and OCT Central Subfield Thickness

Characteristic	Ranibizumab			PRP		
	N	Adjusted Mean, letters (95% CI)	*P*-Value	N	Adjusted Mean, letters (95% CI)	*P*-Value
Sex						
Female	71	4.0 (2.6, 5.4)	.17	77	0.9 (−1.0, 2.7)	.11
Male	89	5.3 (4.1, 6.5)		91	−1.3 (−3.0, 0.5)	
Age (y)						
< 50	71	5.7 (4.3, 7.1)	.12	78	−1.1 (−3.0, 0.7)	.34
≥ 50	89	3.9 (2.7, 5.1)		90	0.5 (−1.3, 2.2)	
Race/ethnicity *						
White	88	4.2 (3.0, 5.5)	.25	84	0.2 (−1.6, 2.0)	.45
Non-White	71	5.3 (3.9, 6.7)		82	−0.7 (−2.6, 1.1)	
Diabetes type †						
Type 1	38	5.0 (3.0, 6.9)	.73	30	0.3 (−2.7, 3.4)	.51
Type 2	117	4.6 (3.5, 5.7)		131	−0.8 (−2.2, 0.7)	
Duration of diabetes (y)						
< 20	85	4.6 (3.4, 5.9)	.26	100	−1.1 (−2.7, 0.5)	.29
≥ 20	75	4.8 (3.4, 6.2)		68	0.9 (−1.1, 2.9)	
HbA_{1c} (%) ‡						
< 9	90	5.6 (4.3, 6.8)	.11	86	1.3 (−0.4, 3.0)	.02
≥ 9	65	3.6 (2.2, 5.1)		77	−1.8 (−3.6, 0.1)	
Mean arterial pressure (mmHg)						
< 100	88	4.5 (3.3, 5.7)	.27	93	0.6 (−1.1, 2.3)	.01
≥ 100	72	5.0 (3.6, 6.4)		75	−1.4 (−3.3, 0.5)	
Hypertension						
No	53	4.4 (2.8, 6.0)	.65	52	−0.7 (−3.0, 1.6)	.66
Yes	107	4.9 (3.7, 6.0)		116	−0.1 (−1.6, 1.4)	

CI = confidence interval; PRP = panretinal photocoagulation; HbA_{1C} = Hemoglobin A_{1C}

[*] Race/ethnicity unknown or not reported for 1 ranibizumab and 2 PRP eyes

[†] Diabetes type unknown for 5 ranibizumab and 7 PRP eyes

[‡] HbA_{1C} unavailable for 5 ranibizumab and 5 PRP eyes

Ophthalmology. Author manuscript; available in PMC 2019 June 14.

Table 3.

Change in Visual Acuity Over 2 Years (Area Under the Curve) by Baseline Ocular and Treatment Characteristics Adjusted for Baseline Visual Acuity and OCT Central Subfield Thickness

Characteristic	Ranibizumab			PRP		
	N	Adjusted Mean, letters (95% CI)	*P*-Value	N	Adjusted Mean, letters (95% CI)	*P*-Value
Prior treatment for DME						
No	122	5.2 (4.1, 6.2)	.08	137	−0.4 (−1.8, 1.0)	.75
Yes	38	3.3 (1.4, 5.1)		31	0.2 (−2.8, 3.1)	
Prior focal/grid laser treatment for DME						
No	131	4.9 (3.9, 5.9)	.43	143	−0.7 (−2.1, 0.6)	.11
Yes	29	3.9 (1.7, 6.1)		25	2.2 (−1.1, 5.6)	
Vitreous hemorrhage at baseline						
No	113	4.7 (3.6, 5.9)	.94	111	0.7 (−0.8, 2.2)	.03
Yes	47	4.7 (2.9, 6.5)		57	−2.2 (−4.3, 0.0)	
Visual acuity (letter score)						
≥ 79 (20/25 or better)	79	1.8 (0.2, 3.3)	<.001	82	−2.7 (−4.7, −0.8)	<.001
< 79 (20/32 or worse)	81	7.6 (6.1, 9.1)		86	2.1 (0.2, 4.0)	
Neovascularization on clinical examination *						
NVD or NVE only	103	4.3 (3.2, 5.4)	.97	107	0.6 (−1.0, 2.1)	.02
NVD+NVE	51	4.3 (2.8, 5.9)		57	−2.5 (−4.7, −0.4)	
OCT central subfield thickness (Stratus equivalent, μm) †						
< 250	109	4.5 (3.4, 5.7)	.12	115	−0.3 (−1.9, 1.2)	.20
≥ 250	50	5.2 (3.5, 6.9)		52	−0.5 (−2.9, 1.8)	
OCT retinal volume (Stratus equivalent, μL) ‡						
< 8	93	5.0 (3.7, 6.2)	.11	95	−1.1 (−2.9, 0.6)	.90
≥ 8	41	3.3 (1.1, 5.4)		40	−0.6 (−3.5, 2.3)	
Epiretinal membrane within 500 μm of the macula center §						
No	133	4.9 (3.9, 5.9)	.95	138	0.2 (−1.0, 1.4)	.51
Yes	20	4.8 (2.0, 7.6)		24	−0.9 (−3.9, 2.1)	
Cystoid abnormalities within 500 μm of the macula center ‖						

Characteristic	Ranibizumab			PRP		
	N	Adjusted Mean, letters (95% CI)	*P*-Value	N	Adjusted Mean, letters (95% CI)	*P*-Value
No	74	5.3 (3.8, 6.8)	.47	78	0.7 (−1.0, 2.4)	.25
Yes	77	4.5 (3.1, 5.9)		83	−0.7 (−2.4, 0.9)	
Diabetic retinopathy severity (ETDRS level) ¶						
≤ 65 (moderate PDR and below)	99	5.3 (4.1, 6.5)	.29	106	0.9 (−0.7, 2.5)	.002
≥ 71 (high-risk PDR and above)	59	3.8 (2.2, 5.3)		59	−2.5 (−4.6, −0.4)	
Hemorrhages or microaneurysms within 1800 µm of the macula center #						
None, questionable, or <std1	53	4.5 (3.0, 6.1)	.88	48	1.5 (−0.8, 3.7)	.08
<std2a, <std2b, or ≥std2b	102	4.4 (3.3, 5.5)		114	−0.9 (−2.4, 0.5)	
Hard exudates within 1800 µm of the macula center **						
None	49	5.0 (3.4, 6.7)	.59	60	−0.8 (−2.8, 1.2)	.59
Questionable or definite	108	4.5 (3.4, 5.6)		102	−0.1 (−1.6, 1.5)	
PRP laser type ††						
Single-spot laser				139	0.0 (−1.4, 1.4)	.32
Pattern-scan laser				29	−1.7 (−4.7, 1.4)	
Number of PRP spots ††						
< 1400 single-spot laser / 2200 pattern-scan laser				78	0.9 (−1.0, 2.7)	.002
≥ 1400 single-spot laser / 2200 pattern-scan laser				90	−1.3 (−3.0, 0.4)	
Number of PRP sittings ††						
1				89	−0.9 (−2.7, 0.8)	.31
2 to 3				79	0.4 (−1.4, 2.3)	

CI=confidence interval; DME=diabetic macular edema; ETDRS=Early Treatment Diabetic Retinopathy Study; NVD=neovascularization of the disc; NVE=neovascularization elsewhere; OCT=optical coherence tomography; PC IOL= Posterior Chamber Intraocular Lens; PDR=proliferative diabetic retinopathy; PRP=panretinal photocoagulation; VEGF=vascular endothelial growth factor.

* Neovascularization type unavailable for 6 ranibizumab and 4 PRP eyes

† Central subfield thickness unavailable for 1 ranibizumab and 1 PRP eye

‡ Retinal volume unavailable for 26 ranibizumab and 33 PRP eyes

§ Epiretinal membrane presence unavailable for 7 ranibizumab and 6 PRP eyes

‖ Cystoid abnormalities presence unavailable for 9 ranibizumab and 7 PRP eyes

Ophthalmology. Author manuscript; available in PMC 2019 June 14.

¶ Diabetic retinopathy severity level unavailable for 2 ranibizumab and 3 PRP eyes

Presence of hemorrhages or microaneurysms unavailable for 5 ranibizumab and 6 PRP eyes

** Presence of hard exudates unavailable for 3 ranibizumab and 6 PRP eyes

†† PRP group only. Subject to investigator discretion. The protocol recommended 1200 to 1600 burns with single-spot laser or the equivalent area treated with pattern-scan laser.

Table 5.

Development of Vision-Impairing Central-involved Diabetic Macular Edema (CI-DME)[*] Through 2 Years by Baseline Participant Characteristics Adjusted for Baseline Visual Acuity and OCT Central Subfield Thickness

Characteristic	Ranibizumab			PRP		
	N	Cumulative Probability, % (95% CI)	*P*-Value	N	Cumulative Probability, % (95% CI)	*P*-Value
Sex						
Female	66	17 (10, 31)	.08	67	33 (23, 45)	.34
Male	81	7 (3, 15)		88	26 (18, 36)	
Age (y)						
< 50	71	9 (4, 18)	.82	80	33 (24, 44)	.38
≥ 50	76	13 (7, 24)		75	25 (18, 35)	
Race/ethnicity[†]						
White	79	16 (9, 27)	.08	70	24 (17, 35)	.20
Non-White	67	5 (2, 15)		82	33 (24, 44)	
Diabetes type[‡]						
Type 1	37	13 (5, 30)	.63	33	24 (13, 44)	.55
Type 2	105	10 (5, 18)		119	30 (23, 38)	
Duration of diabetes (y)						
< 20	76	11 (6, 20)	> .99	90	29 (21, 38)	.90
≥ 20	71	11 (6, 23)		65	29 (20, 42)	
HbA_{1c} (%)[§]						
< 9	80	12 (6, 22)	.68	71	24 (17, 35)	.006
≥ 9	61	9 (4, 19)		79	34 (25, 45)	
Mean arterial pressure (mmHg)						
< 100	84	13 (7, 23)	.08	83	25 (17, 36)	.04
≥ 100	63	8 (4, 18)		72	33 (24, 44)	
Hypertension						
No	48	15 (8, 28)	.26	46	30 (19, 45)	.86
Yes	99	9 (5, 17)		109	28 (21, 37)	

CI=confidence interval; HbA_{1C} = Hemoglobin A_{1C}; PRP=panretinal photocoagulation.

[*] Visual acuity letter score ≤ 78 (Snellen equivalent 20/32 or worse) and OCT central subfield thickness greater than 2 standard deviations above the sex- and instrument-specific norm for the population (Heidelberg Spectralis ≥ 320 μm for men and ≥ 305 μm for women, Zeiss Cirrus and Optovue RTVue ≥ 305 μm for men and ≥ 290 μm for women, Zeiss Stratus ≥ 250 μm for both sexes)

[†] Race/ethnicity was unknown/not reported for 1 ranibizumab and 3 PRP eyes

[‡] Diabetes type unknown for 5 ranibizumab and 3 PRP eyes

[§] HbA_{1c} unavailable for 6 ranibizumab and 5 PRP eyes

Ophthalmology. Author manuscript; available in PMC 2019 June 14.

Table 6.

Development of Vision-Impairing Central-involved Diabetic Macular Edema (CI-DME)* Through 2 Years by Baseline Ocular and Treatment Characteristics Adjusted for Baseline Visual Acuity and OCT Central Subfield Thickness

Characteristic	Ranibizumab			PRP		
	N	Cumulative Probability, % (95% CI)	*P*-Value	N	Cumulative Probability, % (95% CI)	*P*-Value
Prior treatment for DME						
No	115	12 (7, 20)	.46	130	32 (25, 40)	.08
Yes	32	7 (2, 24)		25	15 (6, 34)	
Prior focal/grid laser treatment for DME						
No	122	12 (8, 20)	.29	135	32 (25, 40)	.07
Yes	25	5 (1, 26)		20	13 (5, 33)	
Vitreous hemorrhage at baseline						
No	102	12 (7, 21)	.70	103	27 (20, 37)	.58
Yes	45	9 (4, 23)		52	31 (21, 44)	
Visual acuity (letter score)						
≥ 79 (20/25 or better)	87	10 (5, 18)	.27	93	17 (11, 26)	<.001
< 79 (20/32 or worse)	60	14 (7, 26)		62	49 (37, 62)	
Neovascularization on clinical examination†						
NVD or NVE only	95	10 (5, 18)	.48	97	25 (17, 34)	.06
NVD+NVE	49	14 (7, 28)		55	38 (27, 51)	
OCT central subfield thickness (Stratus equivalent, μm)						
< 250	125	8 (4, 14)	<.001	133	25 (19, 33)	.003
≥ 250	22	34 (17, 61)		22	53 (35, 73)	
OCT retinal volume (Stratus equivalent, μL)‡						
< 8	102	12 (6, 21)	.84	101	32 (24, 42)	.75
≥ 8	22	3 (1, 17)		29	26 (15, 44)	
Cystoid abnormalities within 500 μm of the macula center§						
No	83	11 (6, 21)	.94	85	18 (11, 30)	.01
Yes	54	11 (5, 22)		63	38 (27, 51)	
Diabetic retinopathy severity (ETDRS level) ‖						

Characteristic	Ranibizumab			PRP		
	N	Cumulative Probability, % (95% CI)	*P*-Value	N	Cumulative Probability, % (95% CI)	*P*-Value
≤ 65 (moderate PDR and below)	97	9 (5, 18)	> .99	97	26 (19, 36)	.03
≥ 71 (high-risk PDR and above)	49	14 (7, 28)		55	34 (24, 47)	
Hemorrhages or microaneurysms within 1800 µm of the macula center[¶]						
None, questionable, or <std1	56	7 (3, 20)	.23	47	21 (12, 35)	.11
<std2a, <std2b, or ≥std2b	86	15 (8, 25)		102	33 (26, 43)	
Hard exudates within 1800 µm of the macula center[#]						
None	53	8 (3, 23)	.51	59	20 (12, 32)	.04
Questionable or definite	91	13 (7, 21)		91	35 (26, 45)	
PRP laser type[**]						
Single-spot laser				125	26 (20, 34)	.07
Pattern-scan laser				30	42 (27, 60)	
Number of PRP spots[**]						
< 1400 single-spot laser / 2200 pattern-scan laser				70	20 (12, 31)	.22
≥ 1400 single-spot laser / 2200 pattern-scan laser				85	36 (27, 46)	
Number of PRP sittings[**]						
1				80	25 (17, 35)	.23
2 to 3				75	33 (24, 44)	

CI=confidence interval; DME=diabetic macular edema; ETDRS=Early Treatment Diabetic Retinopathy Study; NVD=neovascularization of the disc; NVE=neovascularization elsewhere; OCT=optical coherence tomography; PC IOL= Posterior Chamber Intraocular Lens; PDR=proliferative diabetic retinopathy; PRP=panretinal photocoagulation; VEGF=vascular endothelial growth factor.

[*] Visual acuity letter score ≤ 78 (Snellen equivalent 20/32 or worse) and OCT central subfield thickness greater than 2 standard deviations above the sex- and instrument-specific norm for the population (Heidelberg Spectralis ≥ 320 µm for men and ≥ 305 µm for women, Zeiss Cirrus and Optovue RTVue ≥ 305 µm for men and ≥ 290 µm for women, Zeiss Stratus ≥ 250 µm for both sexes)

[†] Neovascularization type unavailable for 3 ranibizumab and 3 PRP eyes

[‡] Retinal volume unavailable for 23 ranibizumab and 25 PRP eyes

[§] Cystoid abnormalities presence unavailable for 10 ranibizumab and 7 PRP eyes

[//] Diabetic retinopathy severity level unavailable for 1 ranibizumab and 3 PRP eyes

[¶] Presence of hemorrhages or microaneurysms in grid unavailable for 5 ranibizumab and 6 PRP eyes

[#] Presence of hard exudates unavailable for 3 ranibizumab and 5 PRP eyes

** PRP group only. Subject to investigator discretion. The protocol recommended 1200 to 1600 burns with single-spot laser or the equivalent area treated with pattern-scan laser.