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Panretinal Photocoagulation vs Ranibizumab for Proliferative Diabetic Retinopathy: Comparison of Peripapillary Retinal Nerve Fiber Layer Thickness in a Randomized Clinical Trial

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Abstract

Purpose—Compare changes in retinal nerve fiber layer (RNFL) thickness between eyes assigned to intravitreous ranibizumab or panretinal photocoagulation (PRP) and assess correlations between changes in RNFL and, visual field sensitivity and central subfield thickness (CST).

Methods—Eyes with proliferative diabetic retinopathy were randomly assigned to ranibizumab or PRP. Baseline and annual follow-up spectral domain OCT RNFL imaging, OCT macular imaging, and automated static perimetry (Humphrey visual field 60-4 algorithm) were performed.

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Results—146 eyes from 120 participants were analyzed. At 2 years, for the ranibizumab (N=74) and PRP (N=66) groups respectively, mean change in average RNFL thickness was −10.9 ± 11.7μm and −4.3 ± 11.6 μm, (difference, −4.9μm; 95% CI [−7.2μm, −2.6μm], $P < 0.001$); the correlation between change in RNFL thickness and 60-4 Humphrey visual field mean deviation was −0.27 (P=0.07) and +0.33 (P=0.035); the correlation between change in RNFL thickness and CST was +0.63 (P< 0.001) and +0.34 (P= 0.005).

Conclusion—At 2 years, eyes treated with ranibizumab had greater RNFL thinning than eyes treated with PRP. Correlations between changes in RNFL thickness, visual field, and CST suggest the decrease in RNFL thickness with ranibizumab is likely due to decreased edema, rather than loss of axons.

Introduction

In a randomized clinical trial (Protocol S), the Diabetic Retinopathy Clinical Research Network (DRCR.net) compared intravitreous ranibizumab versus panretinal photocoagulation (PRP) to treat proliferative diabetic retinopathy (PDR).[1] The study demonstrated that at the 2-year visit, changes in visual acuity in the ranibizumab group were no worse than in the PRP group (5-letter non-inferiority margin).

PRP and anti-vascular endothelial growth factor (VEGF) therapy have both been reported in some studies to be associated with a reduction of RNFL thickness.[2–5] Anti-VEGF therapy decreases central retinal thickness in eyes with diabetic macular edema (DME). This decrease is thought to be due to a reduction in extracellular retinal edema. Studies have shown an impact of DME on peripapillary RNFL thickness; eyes with DME had thicker RNFL, suggesting edema of the inner retina.[6, 7] Thus, thinning of peripapillary RNFL after anti-VEGF therapy noted in some studies could be due to resolution of inner retinal edema. Another consideration is that ranibizumab might thin the retina because of loss of VEGF neuroprotection.[2]

Thinning of the nerve fiber layer in eyes with PRP could be due to direct or indirect (e.g., trans-synaptic) damage to the inner retina.[3, 4, 8] PRP results in outer retinal atrophy but its impact on the inner retina is not fully known. Investigators have shown evidence of direct damage to retinal ganglion cells and the RNFL with laser.[9] This inner retinal damage or some decrease in edema are possible explanations for thinning after PRP.

Serial observations of RNFL thickness are used routinely to monitor patients with glaucoma, since loss of RNFL may indicate disease progression.[10, 11] Some individuals with diabetes have been reported to have a higher risk of glaucoma.[12] Understanding the impact of both PRP and anti-VEGF therapy on RNFL thickness might help clinicians determine if RNFL changes can be used to monitor progression of glaucoma.

This pre-planned study compares changes in RNFL thickness among eyes treated with ranibizumab or PRP for PDR. Additional post-hoc analysis were also conducted such as correlation between changes in RNFL, and changes in visual field scores and central subfield thickness (CST).

Methods

Between February and December 2012, 305 adults (394 eyes) were enrolled at 55 clinical sites in the United States. The study adhered to the tenets of the Declaration of Helsinki and was approved by multiple institutional review boards. Study participants provided written informed consent. Study procedures and statistical methods were reported previously.[1] Eyes were randomly assigned to 0.5 mg intravitreous ranibizumab injections (Lucentis®, Genentech, South San Francisco, CA, USA) or PRP. Ranibizumab was required in eyes with DME and visual acuity 20/32 or worse at baseline in the PRP group and was permitted for treatment of DME throughout follow-up in both groups.

The RNFL ancillary study was implemented on June 21, 2012. Therefore, the first 112 enrolled participants (145 eyes) randomized before this date were not included in this analyses. Study eyes reported herein included146 [59%]) out of 249 eligible eyes with acceptable quality RNFL measurements taken using the same OCT device at baseline and follow-up visits (there are no validated equations for converting RNFL measurements across OCT machines to our knowledge). There were 77 eyes in the ranibizumab group and 69 in the PRP group. Reasons for exclusion are summarized in Table 1.

Retinal nerve fiber layer thickness and retinal central subfield thickness (CST) were measured on OCT images acquired with a Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) or Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) system. For Spectralis, measurements of the following six sectors of the peripapillary RNFL were obtained: inferior-temporal, inferior-nasal, temporal, nasal, superior-temporal and superior-nasal. For Cirrus, measurements of the following 4 quadrants were obtained: inferior, superior, temporal, and nasal. Masked independent readers at the Duke Reading Center graded images. Images were readjusted by the reading center if the automated measurement was inaccurate due to decentration, artifact, or segmentation algorithm failure. If the image could not be readjusted, it was excluded.

In this report, normal RNFL thickness is defined as two standard deviations within the reported normal mean values of 106 ± 12.8 and 98.7 ± 10.9 (mean ± SD) for Spectralis (80.4-131.6 μm) and Cirrus (76.9-120.5), respectively.[13] Visual field sensitivities (e.g., mean deviation) were measured at baseline and annual visits using both the 30-2 (central) and 60-4 (peripheral) test patterns of the Humphrey visual field analyzer. Results were interpreted by the Iowa Visual Field Reading Center.

Primary Outcome

The pre-specified primary study outcome was the mean change of RNFL thickness between baseline and 2 years. The RNFL thickness was measured as an average across the four peripapillary quadrants (inferior, superior, nasal and temporal) and for each quadrant individually. For Spectralis data, the average of the split quadrants was used for the inferior and superior measurements. Analyses were performed overall and within subgroups of eyes with and without central-involved DME at baseline regardless of visual acuity, and eyes with and without central-involved DME with decreased visual acuity (of 20/32 or worse) at baseline.

Statistical Analyses

Treatment group differences in mean change of RNFL thickness both globally and by each quadrant from baseline at 1 and 2 years were obtained from an analysis of covariance (ANCOVA) model adjusting for baseline RNFL measurement and baseline randomization stratification factors (OCT CST and number of study eyes). Generalized estimating equations were used to account for the potential correlation of having both eyes in the study. Missing 2-year outcomes were imputed using last observation carried forward (LOCF) of available one-year data (15 [11%]). Subgroup analyses for each primary outcome were performed by including the subgroup (e.g., presence/absence of baseline DME) and a subgroup by treatment interaction term to the ANCOVA model. All ANCOVA model assumptions were verified. RNFL changes were truncated to ± 3 SDs from the mean to limit the influence of potential outliers (N = 7).

Pearson correlation was used to quantify the relationship between changes in the RNFL thickness measurements (global average or by quadrant) with changes in CST and changes in visual field sensitivities (mean deviation [30-2 and 60-4]) within treatment groups. Cohen's interpretation of correlation coefficient was used to evaluate the magnitude of the correlation observed.[14] *P*–values were not adjusted for multiple comparisons. All statistical analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics by treatment group for participants included or excluded from this report are summarized in Table 1; there were no notable differences identified. For the 120 participants included in this report, the median age was 50 years, 43% were women, 61% were white, and the median study-eye visual acuity was 81 letters (approximate Snellen equivalent 20/25). The treatment groups appeared to be well-balanced except for higher percentages of eyes in the PRP group with high risk PDR and Type 2 diabetes. The mean ± SD thicknesses of the average RNFL at baseline measured by Spectralis for the ranibizumab (N = 40) and PRP (N = 39) groups were 96.8 ± 18.2 μm and 96.8 ± 19.3 μm, respectively. The mean thicknesses of the average RNFL measured by Cirrus for the ranibizumab (N = 37) and prompt PRP (N = 30) groups were 92.7 ± 19.9 μm and 94.8 ± 21.2 μm, respectively. The RNFL thickness appeared balanced at baseline by treatment in all the peripapillary quadrants (Table 2). At baseline, 73% of eyes in the ranibizumab group and 77% in the prompt PRP group had normal RNFL measurements (Table 2). The reading center was not able to obtain an accurate thickness measurement at baseline on 25 of 127 (20%) images obtained by the Spectralis OCT and 33 of 108 (31%) images obtained by the Cirrus OCT.

Treatment Group Comparison of RNFL

The mean change in average RNFL thickness between baseline and 2 years in the ranibizumab (N = 74) and prompt PRP (N = 66) groups were −10.9 ± 11.7 μm and −4.3 ± 11.6 μm, respectively (difference, −4.9 μm; 95% CI [−7.2 μm, −2.6 μm]; $P < 0.001$). The RNFL was reduced more in the ranibizumab group than in the PRP group for all 4 peripapillary quadrants at 1 and 2 years ($P \leq 0.05$) (Table 3, Figure 1a). At 2 years, among eyes with normal RNFL measurements at baseline, 9 of 48 (19%) eyes in the ranibizumab

group and 3 of 42 eyes (7%) in the PRP group had a lower than normal thickness, and one eye from the PRP group had higher than normal thickness (See Supplemental Digital Content 1, which shows the 2-year peripapillary RNFL thickness by OCT machine). Sensitivity analyses using the observed non-truncated data at 1 and 2-years showed similar results (Supplemental Digital Content 2, which shows the treatment group comparison of changes in RNFL thickness at 1 and 2 years using observed data). Results were similar when the treatment group comparison was adjusted for high-risk PDR and diabetes type, the two factors with potential treatment group imbalance at baseline (difference, −3.9 μm; 95% CI [−6.9 μm, −0.9 μm]; =0.01)

Among eyes with DME at baseline irrespective of vision impairment (N = 36), the adjusted difference in the average RNFL change from baseline between the ranibizumab and PRP groups was −2.3 μm (95% CIs [−6.7 μm, +2.2 μm]; $P = 0.32$), while for eyes without DME (N = 104), the difference was −5.0 μm (95% CIs [−7.8 μm, −2.3 μm]; $P < 0.001$) ([See Supplemental Digital Content 3, which shows treatment group comparisons of changes in RNFL thickness for eyes with and without baseline DME at 2 years. (Figures 1b and c). For eyes with baseline DME with vision impairment (N = 22), adjusted difference between the groups in the average RNFL change from baseline was −4.5 μm (95% CIs [−11.2 μm, +2.3 μm]; $P = 0.20$) (See Supplemental Digital Content 4, which shows treatment group comparison of changes in RNFL thickness for eyes with and without baseline DME and vision loss at 2 years). Most of the differences in RNFL thinning between the two groups were observed in the first year while thinning in the second year was about the same for both groups (Figure 1a). These results suggests that the mechanism of RNFL thinning may be different for both treatment groups. After PRP some studies have shown initial thickening followed by RNFL thinning while long term studies have shown thickening due to epiretinal changes.

Potential factors affecting RNFL changes at 2 Years

The median number of intravitreous ranibizumab injections received throughout the 2 years of the primary study was 9.[1] For this analysis cohort, eyes in the ranibizumab group that received fewer than 9 injections had a mean average RNFL change between baseline and 2 years of −7.6 ± 10.2 μm versus −13.2 ± 12.1 μm for eyes that received 9 or more injections (difference, +2.9 μm; 95% CI [−1.1 μm +6.8 μm]; $P = 0.16$) (see Supplemental Digital Content 5, which shows the comparison of changes in RNFL thickness at 2 years in the ranibizumab group by number of injections). In the PRP group, no differences in the average RNFL thickness changes were observed between the types of laser pattern (automated vs manual) or number of PRP sittings (1 vs. 2 or more) (P>0.05). Importantly among eyes in the PRP group, no definitive differences in average RNFL thickness changes were identified at 2 years between eyes that did and did not receive ranibizumab injections for DME (See Supplemental Digital Content 6, which shows the post-hoc exploratory analyses within the prompt PRP group). However, the sample sizes for each of the comparisons were small.

Correlation of changes in RNFL thickness with changes in visual field sensitivities at 2 years

At 2 years, the mean change of the mean deviation of the 60-4 visual field tests in the ranibizumab (N = 45) and prompt PRP (N = 40) group were −0.4 ± 1.9dB and −1.4 ± 2.0dB respectively (difference, +1.1dB; 95% CI [+0.6dB, +1.5dB]; $P < 0.001$). There was a weak negative correlation between change in the average RNFL thickness and changes in the mean deviation of the 60-4 test in the ranibizumab group (thinner retina, less field loss; r = −0.27; $P = 0.07$); a correlation was also observed in the PRP group (r = +0.33; $P = 0.035$) but in the opposite direction (thinner retina, more field loss, [See Supplemental Digital Content 7, Figures A and B, which show the change in average RNFL thickness by change in mean deviation of the Humphrey 60-4 visual field test at 2 years in the ranibizumab and PRP groups respectively). There was no correlation between changes in RNFL and changes in the mean deviation of the 30-2 test or combined point score (30-2 plus 60-4 point scores) in either group (See Supplemental Digital Content 8, which shows the correlation between changes in visual field sensitivities and changes in RNFL thickness at 2-years).

Correlation of changes in RNFL thickness with changes in the central subfield thickness at 2 years

In the ranibizumab group, change in the average RNFL thickness had a strong correlation with change in the CST at 2 years (r = +0.63; $P < 0.001$), while a moderate correlation was observed with the prompt PRP group (r = +0.34; $P = 0.005$) (See Supplemental Digital Content 9, Figure A and B, which show changes in average RNFL thickness by changes in CST at 2 years in the ranibizumab and RPP groups respectively). In the ranibizumab group, among eyes without DME at baseline irrespective of visual acuity, the correlation between change in average RNFL and change in CST at 2 years was +0.59 (P < 0.001, N = 56); while the correlation in the PRP group was +0.05 ($P = 0.75$, N = 48). Among eyes with DME at baseline, the correlations were +0.77 ($P < 0.001$, N = 18) and +0.58 ($P = 0.012$, N = 18) in the ranibizumab and PRP groups, respectively (See Supplemental Digital Content 10, which shows the correlation between changes in OCT CST and RNFL thickness at 2 years).

Discussion

This ancillary study showed that the thinning of the RNFL in the ranibizumab group at 1 and 2 years was greater than the PRP group. There are several potential mechanisms that could be responsible for RNFL decrease in the ranibizumab group. One is a reduction of inner retinal edema (i.e., nerve fiber layer) in eyes within or above normal range. Although diabetic retinal thickening is believed to be due to edema in the outer retina, the inner retina, including the RNFL, may also become edematous.[6, 7] We thus looked at the correlations between changes in the RNFL at 2 years and changes in the OCT CST and found a strong correlation, suggesting that decreased RNFL edema might be responsible for the observed thinning of the RNFL (Figure 2).

Another potential mechanism of RNFL thinning could be loss of retinal ganglion cells (RGC) with interruption of the neuroprotective effect of VEGF. Although RGCs were not evaluated in this study, correlations of visual field changes with RNFL thinning suggests that

loss of retinal ganglion cells and axons might be a less likely cause of the observed thinning. A negative correlation (not statistically significant [P>0.05]) was observed between RNFL thinning and the 60-4 mean deviation in the ranibizumab group. Since the RNFL may be thinned in diabetic retinas with or without edema or even without retinopathy,[15, 16] the eyes with RNFL thickness below the normal range could have been damaged previously. It is also possible that damages to the RGC's were not extensive enough to translate to poor visual field function.

RNFL thinning in ranibizumab-treated eyes could have occurred due to glaucomatous loss of ganglion cells owing to acute or chronic elevated IOP secondary to the ranibizumab injections.[17] Since only a small portion of study eyes developed persistent increased intraocular pressure,[1] it is unlikely that chronic glaucoma is the culprit. However, the multiple acute elevations in intraocular pressure could be playing a role. Whether anterior chamber paracentesis at the time of injection would make a difference is unknown.

In the PRP group, 42% of eyes received ranibizumab and this treatment could be contributing to the thinning seen in these eyes. A weak positive correlation was seen between field loss (total point score) and thinning of the RNFL in the PRP group (See Supplemental Digital Content 8, which shows the correlation between changes in visual field sensitivities and changes in RNFL thickness at 2-years). This result could be due to worsening of retinal function as a result of retinal damage, causing both loss of field and thinning in the RNFL. However, the correlation was weaker than the correlation with central subfield thinning on OCT.

A small correlation between decrease in CST and RNFL thinning was seen in the PRP Group. There was no correlation between decreased CST and RNFL thinning among PRP eyes without DME. This finding also suggests that the mechanism of RNFL thinning in the PRP group may be different from the ranibizumab group.

Previous reports observed increased thickness of RNFL in eyes with center-involved DME, supporting the concept that edema is contemporaneously present in both regions.[6, 7] Prior reports on the effect of anti-VEGF treatment on RNFL vary. One study of 30 patients treated with ranibizumab for AMD found no change in RNFL at 1 month after the third injection.[18] Similar to the current study, a second study found a decrease in RNFL at 12 months in AMD patients treated with ranibizumab.[5] A third study in AMD found a decrease in ganglion cell layer thickness but not RNFL.[2]

Animal studies have shown that RNFL damage can be caused by laser.[9] A previous study found that PRP for diabetic retinopathy was associated at 6 months with a small decrease in RNFL thickness.[4] Two studies found early thickening with subsequent thinning through 2-years.[3, 8] Another study showed long after the PRP an increase in RNFL thickness.[17] In the current study, in eyes with or without vision affecting DME at baseline, there was more thinning in the ranibizumab group than the PRP group. In the PRP group, eyes given or not given ranibizumab showed a similar smaller change in RNFL (See Supplemental Digital Content 6, which shows a post-hoc exploratory analyses within the prompt PRP group).

The strengths of this study include a randomized prospective study design and preplanned measurement of RNFL in both groups. To the best of our knowledge, this is the first study to compare RNFL changes in eyes treated with ranibizumab and PRP for PDR. Limitations include the fact that some of the eyes in the panretinal photocoagulation group also received ranibizumab, however, we explored the impact of these injections on the results and did not detect a difference between PRP eyes with or without injections. In addition, many OCT scans were not analyzed due to poor quality and many of the early patients in the study did not have RNFL measurements. Also, only a portion (55%) of eyes in both groups had visual field measurements. Finally, it would be useful to have measurements of other layers of the retina (e.g., ganglion cell layer). Future studies should explore changes in the retinal ganglion cell layer and other layers in both groups and correlate these changes with visual field changes.

Conclusion

RNFL thinning after intravitreous ranibizumab in eyes with PDR was greater than that observed in eyes treated with PRP. The data do not support the hypothesis that loss of neurons or axons are responsible for RNFL thinning following intravitreous ranibizumab. Rather, we found a strong correlation between RNFL thinning and thinning of the central OCT subfield following ranibizumab. Coupled with an absence of visual acuity or visual field loss these findings together suggest that decreased edema of the inner retina is a major factor of RNFL thinning following ranibizumab. From a clinical management standpoint, OCT-derived RNFL thickness measurements are used to provide objective means to assess glaucoma progression in non-PDR eyes. Since fluid changes in the inner retina may cause RNFL thinning during ranibizumab therapy, RNFL measurements would be a poor means to diagnose and monitor the progression of glaucoma in these eyes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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.

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Summary Statement

When eyes with PDR were treated with ranibizumab, RNFL thinning was greater than it was in eyes treated with PRP; correlations between changes in RNFL thickness, visual field, and CST suggest this is likely due to decreased edema.

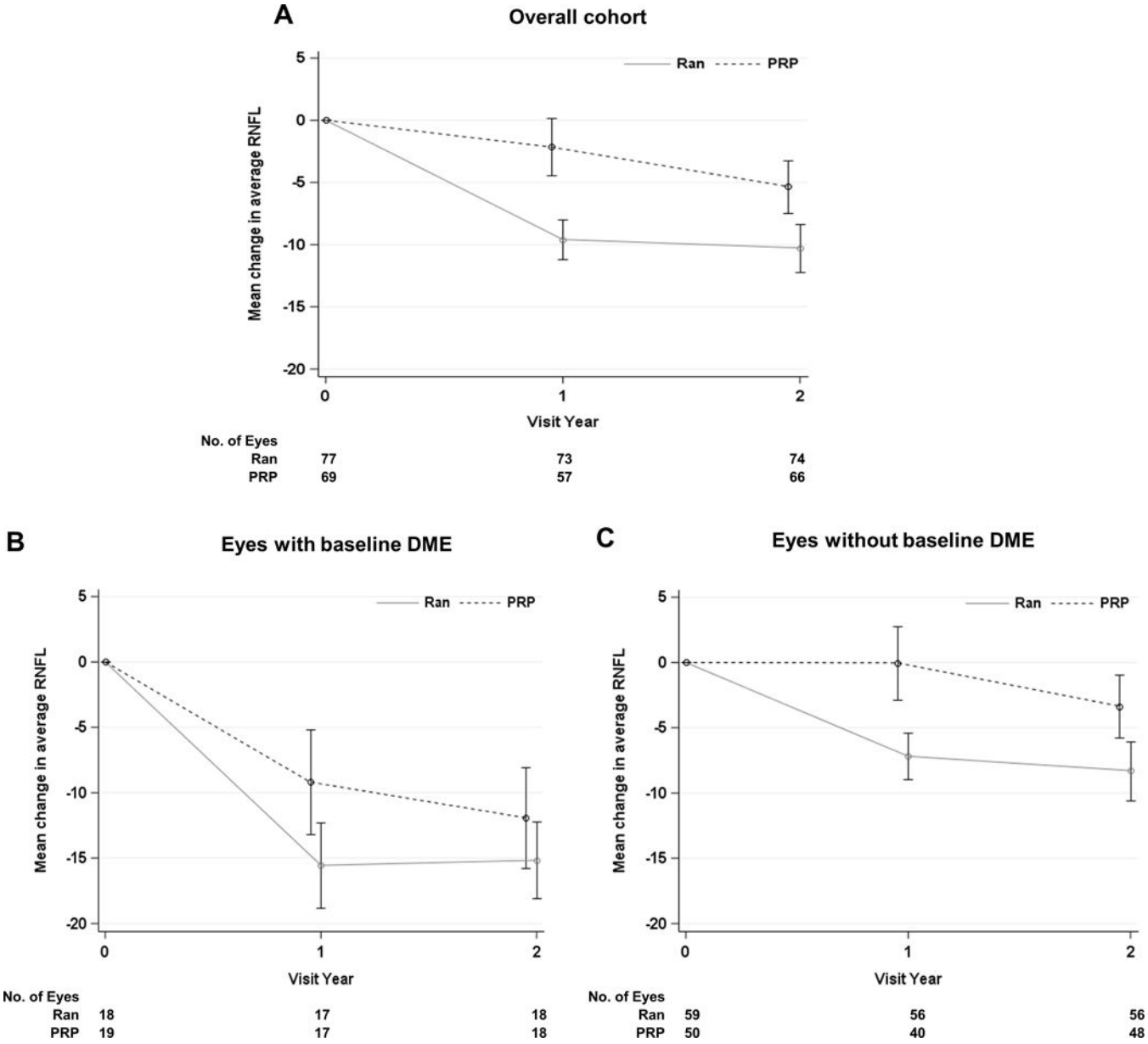
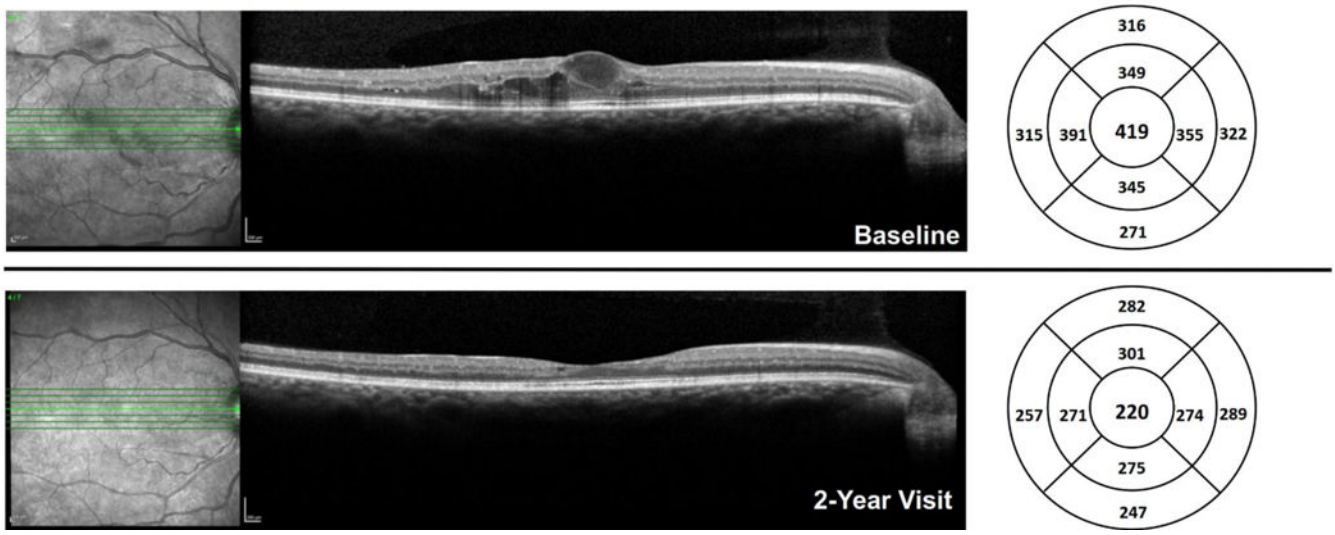


Figure 1. Mean Changes in Average Retinal Nerve Fiber Layer Thickness Over Time

Changes in the average retinal nerve fiber layer at one and two years A) overall, B) eyes with and C) without baseline diabetic macular edema, irrespective of vision loss, adjusted for baseline average RNFL thickness, central subfield thickness, and number of study eyes. Error bars represent 95% confidence intervals.

A. Central Subfield Thickness (μm)



B. Retinal Nerve Fiber Layer Thickness (μm)

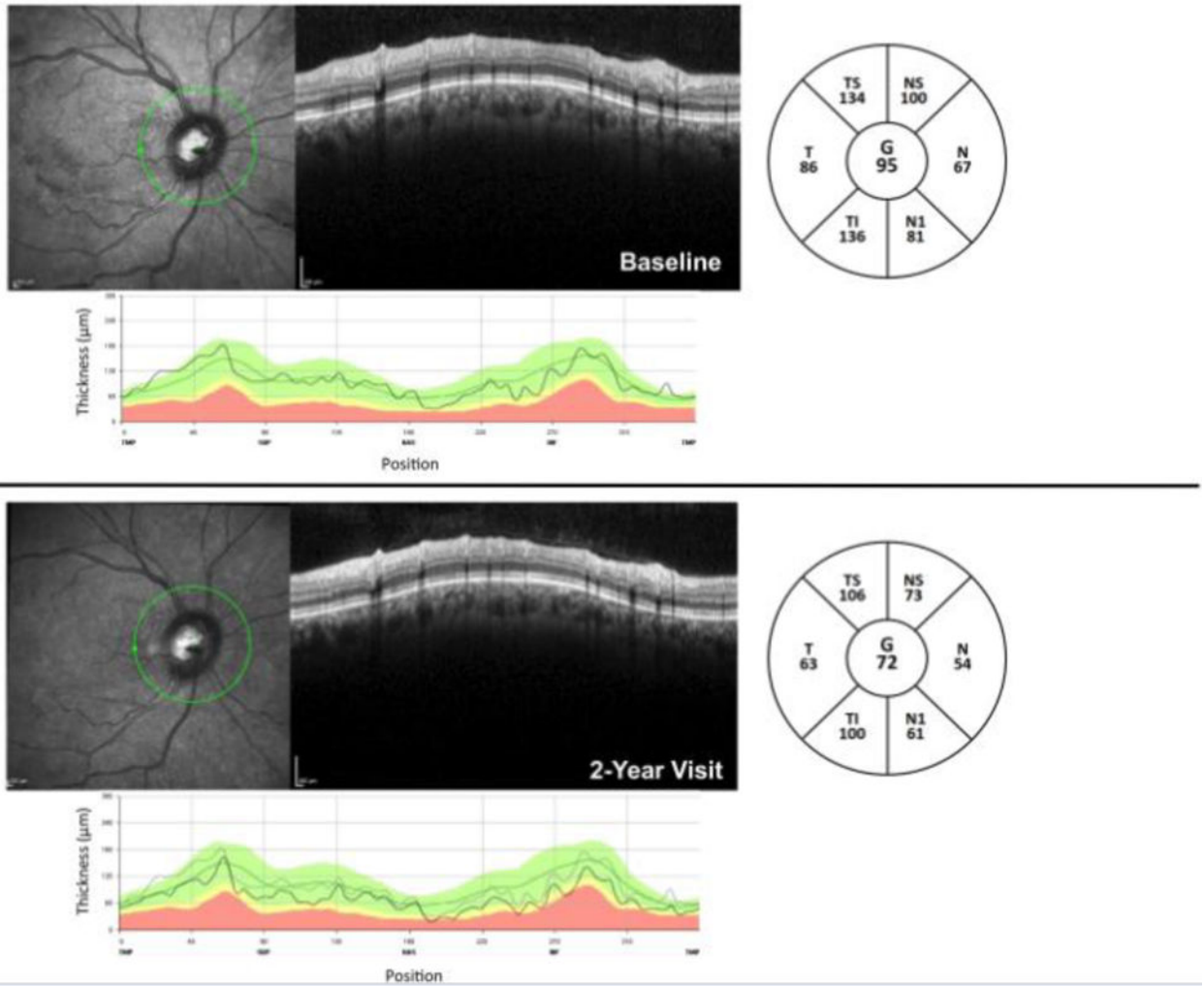


Figure 2. Baseline and 2-year CST/RNFL of an eye treated with ranibizumab

Figure A and B shows the cross-sectional B-scan images from a Heidelberg Spectralis OCT 7 line scan with the ETDRS grid map showing the central subfield thickness at baseline and two years. Figure C and D shows the cross-sectional B-scan images, temporal-superior-nasal-inferior-temporal map and a breakdown of the segmental thickness of the RNFL at baseline and two years

Table 1

Baseline characteristics of eyes included and excluded from the study

	Eyes Included		Eyes Excluded*	
	Ranibizumab N = 77	**Prompt PRP N = 69**	**Ranibizumab N = 114**	**Prompt PRP N = 134**
Participant Characteristics				
Gender: Women - N (%)	33 (43%)	30 (43%)	50 (44%)	62 (46%)
Participants with 2 study eyes - N (%)	36 (47%)	31 (45%)	53 (46%)	58 (43%)
Age (yrs) - Median (25^{th}, 75^{th} percentile)	52 (44, 59)	50 (42,57)	52 (45,59)	52 (45,60)
Race/Ethnicity – N (%)				
White	49 (64%)	40 (58%)	51 (45%)	61 (46%)
Black/African American	7 (9%)	9 (13%)	31 (27%)	34 (25%)
Hispanic or Latino	18 (23%)	16 (23%)	30 (26%)	35 (26%)
Asian	2 (3%)	3 (4%)	0	0
American Indian/Alaskan Native	1 (1%)	0 (0%)	0	0
More than one race	0	1 (1%)	0	1 (1%)
Unknown/not reported	0	0	2 (2%)	3 (2%)
Duration of Diabetes (yrs) - Median (25^{th}, 75^{th} percentile)	19 (13, 26)	16 (11, 23)	18 (11,24)	17 (11,24)
Diabetes Type				
Type 1	21 (27%)	11 (16%)	22 (19%)	30 (22%)
Type 2	52 (68%)	55 (80%)	88 (77%)	100 (75%)
Uncertain	4 (5%)	3 (4%)	4 (4%)	4 (3%)
Ocular Characteristics				
Diabetic Retinopathy Severity† (ETDRS level)				
Severe NPDR or less	11 (15%)	9 (14%)	8 (7%)	17 (13%)
Prior PRP; without current PDR (level 60)	0	0	0	1 (1%)
Mild PDR (level 61)	13 (17%)	13 (20%)	17 (15%)	18 (14%)
Moderate PDR (level 65)	35 (47%)	21 (32%)	33 (29%)	46 (35%)
High risk PDR (level 71 and 75)	15 (20%)	23 (35%)	54 (47%)	50 (38%)
Advanced PDR (level 81 and 85)	1 (1%)	0 (0%)	2 (2%)	1 (1%)
Visual Acuity				
Letter Score - Median (25^{th}, 75^{th} percentile)	80 (75, 86)	81 (71,87)	76 (68,82)	76 (69,82)
~Snellen Equivalent - Median (25^{th}, 75^{th} percentile)	20/25 (20/32, 20/20)	20/25 (20/40, 20/20	20/32 (20/50, 20/25)	20/32 (20/40, 20/25)
OCT Central Subfield Thickness (μm, Stratus equivalent) - Median (25^{th}, 75^{th} percentile)	219 (196, 252)	227 (204, 261)	228 (197,287)	234 (202,266)
Intraocular Pressure (mmHg) - Median (25^{th}, 75^{th} percentile)	15 (12,17)	16 (12,18)	15 (13,18)	15 (13,17)

PRP = panretinal photocoagulation; ETDRS = Early Treatment Diabetic Retinopathy Study; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; OCT = optical coherence tomography.

[*] Participants were excluded if they enrolled prior to implementation of the retinal nerve fiber layer (RNFL) ancillary study (N = 145 eyes); quality of the baseline images were determined to be unacceptable by a central reading center (Duke University Reading Center, N = 59 eyes). Unacceptable baseline measurements were caused by image acquisition errors such as boundary line issues and centration issues (N = 59). Forty-one eyes had at least one of the following: 1) vitreomacular adhesion deformation, 2) epiretinal membrane or 3) hemorrhage (N = 6 eyes); participant was lost to follow-up prior to the 1-year visit (N = 27 eyes); image quality of the RNFL was graded as either poor or grades were missing at both annual follow-up visits (N = 13 eyes); the RNFL was measured on an imaging device different from that used at baseline (N = 4 eyes)

[†] Five missing: 2 from the Ranibizumab group and 3 from the PRP group among those included in this analyses; 1 missing from the PRP group among participants excluded

Table 2

Baseline Peripapillary RNFL Thickness on Optical Coherence Tomography

	Ranibizumab		Prompt PRP	
Average RNFL Thickness at Baseline*				
Lower than Normal	16 (21%)		11(16%)	
Normal	56 (73%)		53 (77%)	
Above Normal	5 (6%)		5 (7%)	
Average RNFL Thickness at Baseline within Each Quadrant				
	Heidelberg Spectralis	**Zeiss Cirrus**	**Heidelberg Spectralis**	**Zeiss Cirrus**
	N = 40	**N = 37**	**N = 39**	**N = 30**
Inferior				
Mean ± SD	123.6 ± 29.2	113.5 ± 29.1	125.7 ± 26.9	115.4 ± 20.6
Median – 25th, 75th percentile	130 (105,139)	110 (92,134)	124 (105,146)	109 (96,129)
Superior				
Mean ± SD	114.2 ± 22.1	112.1 ± 22.1	114.3 ± 24.4	111.4 ± 21.8
Median – 25th, 75th percentile	117 (99,130)	110 (96,122)	113 (97,132)	108 (96,127)
Nasal				
Mean ± SD	70.5 ± 18.3	72.3 ± 17.8	71.9 ± 18.7	71.8 ± 13.7
Median – 25th, 75th percentile	67 (59,81)	68 (62,81)	70 (57,86)	70 (64,79)
Temporal				
Mean ± SD	78.4 ± 15.7	71.4 ± 22.5	74.7 ± 16.4	72.4 ± 18.7
Median – 25th, 75th percentile	76 (70,87)	66 (57,79)	71 (63,88)	69 (56,91)
Average				
Mean ± SD	96.8 ± 18.2	92.7 ± 19.9	96.8 ± 19.3	94.8 ± 21.2
Median – 25th, 75th percentile	96 (85,106)	90 (78,104)	95 (82,112)	89 (81,102)

PRP = panretinal photocoagulation; RNFL = retinal nerve fiber layer

*Lower than normal defined as < 76.9 μm for cirrus and < 80.4 μm for Heidelberg OCT; normal defined as 76.9-120.5 μm for cirrus and 80.4-131.6 μm for Heidelberg OCT; above normal defined as > 120.5 μm for cirrus and >131.6 μm for Heidelberg OCT RNFL normal range defined as within ± 2SDs from the instrument specific norm of the population

Table 3

Mean Change in RNFL Thickness Measurements from Baseline to 1 and 2 Years

RNFL Quadrant (μm)	Ranibizumab Mean ± SD*	Prompt PRP Mean ± SD	Adjusted Mean Difference† (95%CI)	P-value
1 year	**N = 73**	**N = 57**		
Inferior	−12.4 ± 17.7	−2.7 ± 14.1	−9.7 (−14.8, −4.6)	<0.001
Superior	−9.3 ± 12.1	−3.5 ± 14.3	−5.7 (−9.1, −2.3)	<0.001
Nasal	−7.9 ± 9.6	−1.3 ± 10.0	−7.3 (−9.9, −4.7)	<0.001
Temporal	−7.7 ± 11.4	+1.8 ± 11.1	−9.4 (−12.6, −6.2)	<0.001
Average	−9.6 ± 10.8	−1.9 ± 12.3	−7.4 (−10.0, −4.9)	<0.001
2 years	**N = 74**	**N = 66**		
Inferior	−14.8 ± 18.8	−6.5 ± 16.8	−7.6 (−11.6, −3.7)	<0.001
Superior	−11.9 ± 14.7	−6.4 ± 16.0	−4.5 (−8.4, −0.6)	0.023
Nasal	−8.8 ± 10.4	−3.1 ± 10.0	−5.5 (−8.0, −2.9)	<0.001
Temporal	−7.4 ± 13.0	+0.8 ± 13.3	−7.6 (−11.4, −3.8)	<0.001
Average	−10.9 ± 11.7	−4.3 ± 11.6	−4.9 (−7.2, −2.6)	<0.001

PRP= panretinal photocoagulation; RNFL = retinal nerve fiber layer

*Truncated to ± 3 standard deviation from the mean; inferior, 3 eyes; superior, 3 eyes; nasal, 1 eye; temporal, 2 eyes; average, 2 eyes.

†Adjusted mean difference, confidence intervals obtained from ANCOVA model adjusting for baseline RNFL thickness measurements, central subfield thickness and laterality