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Factors Associated With Visual Acuity and Central Subfield Thickness Changes When Treating Diabetic Macular Edema With Anti–Vascular Endothelial Growth Factor Therapy

An Exploratory Analysis of the Protocol T Randomized Clinical Trial

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IMPORTANCE Identifying the factors that are associated with the magnitude of treatment benefits from anti–vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME) may help refine treatment expectations.

OBJECTIVE To identify the baseline factors that are associated with vision and anatomic outcomes when managing DME with anti-VEGF and determine if there are interactions between factors and the agent administered.

DESIGN, SETTING, AND PARTICIPANTS This post hoc analysis of data from the Diabetic Retinopathy Clinical Research Network multicenter randomized clinical trial , Protocol T, was conducted between December 2016 and December 2017. Between August 22, 2012, and August 28, 2013, 660 participants were enrolled with central-involved DME and vision impairment (approximate Snellen equivalent, 20/32-20/320).

INTERVENTIONS Repeated 0.05-mL intravitreous injections of 2.0-mg aflibercept (201 eyes), 1.25-mg bevacizumab (185 eyes), or 0.3-mg ranibizumab (192 eyes) per protocol.

MAIN OUTCOMES AND MEASURES Change in visual acuity (VA) and optical coherence tomography (OCT) central subfield thickness at 2 years and change in VA over 2 years (area under the curve [AUC]).

RESULTS Among 578 participants, the median age (interquartile range) was 61 (54-67) years. Across anti-VEGF treatment groups, each baseline factor was associated with mean improvement in VA and a reduction in central DME compared with the baseline. For every decade of participant age, the mean VA improvement was reduced by 2.1 letters (95% CI, −3.0 to −1.2; $P < .001$) in the VA and 1.9 letters (95% CI, −2.4 to −1.3; $P < .001$) in the VA AUC analyses. For each 1% increase in hemoglobin A_{1c} levels, VA improvement was reduced by 1 letter in the VA (95% CI, −1.5 to −0.5; $P < .001$) and 0.5 letters (95% CI, −0.9 to −0.2; $P < .001$) in the VA AUC analyses. Eyes with no prior panretinal photocoagulation (PRP) and less than severe nonproliferative diabetic retinopathy had an approximately 3-letter improvement in the VA (95% CI, 0.9-5.4; $P = .007$) and VA AUC (95% CI, 1.3-4.2; $P < .001$) analyses compared with eyes with prior PRP. On average, African American participants had greater reductions in central subfield thickness compared with eyes of white participants (−27.3 µm, $P = .01$), as did eyes with central subretinal fluid compared with eyes without this OCT feature (−22.9 µm, $P = .01$). There were no interactions between the predictive factors and the specific anti-VEGF agent that was administered for any VA or OCT outcome.

CONCLUSIONS AND RELEVANCE Lower hemoglobin A_{1c} levels were associated with the magnitude of vision improvement following anti-VEGF therapy, providing further evidence to encourage glycemic control among persons with diabetes. Younger patients and those without prior PRP might expect greater improvement in VA than older patients or those with prior PRP.

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Supplemental content

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Protocol T was a comparative effectiveness trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) that compared 3 commonly used anti-vascular endothelial growth factor (anti-VEGF) agents, aflibercept, bevacizumab, and ranibizumab, for eyes with central-involved diabetic macular edema (DME) and vision impairment (20/32 or worse). On average, each agent was found to improve vision and reduce central retinal thickening.[1,2] However, the effects of the agents varied according to the presenting level of visual acuity (VA). When vision impairment was mild (20/32-20/40), no apparent differences between the agents were identified in vision improvement; when vision was moderately impaired (20/50-20/320), aflibercept provided larger vision gains compared with bevacizumab and ranibizumab over 2 years.[1-3]

Baseline VA and macular thickness have been shown to be associated with outcomes in prior trials of DME and neovascular age-related macular degeneration.[4-6] In general, eyes that present with mild VA impairment or mild thickening have smaller gains in VA or smaller reductions in central subfield thickness (CST) compared with eyes that have moderate VA impairment or more severe edema. These associations were apparent in Protocol T, and these associations may be largely due to ceiling effects.[1] This article presents a post hoc analysis of data from Protocol T that explores additional baseline characteristics of the trial participants to determine if there are other variables associated with vision and anatomic outcomes when administering anti-VEGF therapy. This information may help explain the variability in patient outcomes and refine physician and patient expectations when these agents are used to manage DME. It may also identify modifiable factors that can be addressed to promote more favorable outcomes.

Key Points

Question Are there baseline factors other than visual acuity and central thickness that are associated with the magnitude of treatment benefit associated with anti–vascular endothelial growth factor (VEGF) therapy of diabetic macular edema?

Findings In this secondary analysis of randomized clinical trial data, younger participant age, lower hemoglobin A_{1c} levels, and the absence of prior panretinal photocoagulation were each associated with better 2-year vision outcomes in Protocol T. African American race/ethnicity and the presence of subretinal fluid were associated with a greater central subfield thickness improvement at 2 years.

Meaning Younger patients and those without prior panretinal photocoagulation may demonstrate more visual acuity improvement, irrespective of the anti-VEGF agent that is used.

Methods

The methods for Protocol T have been published elsewhere, with the complete protocol available online (http://www.drcr.net).[2,3] The study adhered to the tenets of the Declaration of Helsinki. Study participants provided written informed consent. The protocol and Health Insurance Portability and Accountability Act–compliant consent forms were approved by the institutional review board associated with each participating center. Principal eligibility criteria for eyes included central-involved DME on clinical examination with optical coherence tomography (OCT) confirmation and a best-corrected electronic Early Treatment Diabetic Retinopathy Study visual acuity letter score of 78 through 24 (approximate Snellen equivalent, 20/32-20/320) following a protocol refraction.[7] One eye of each participant was randomly assigned with equal probability to aflibercept (2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg).

Visits were every 4 weeks through the 52-week visit and every 4, 8, or 16 weeks through 104 weeks depending on the clinical course. Intravitreous anti-VEGF was required at baseline and every 4 weeks for 6 consecutive injections unless the central subfield thickness (CST) was less than sex-specific and instrument-specific cutoffs (Spectralis [Heidelberg], ≥320 µm for men and ≥305 µm for women; Cirrus [Zeiss], ≥305 µm for men and ≥290 µm for women; Stratus [Zeiss], ≥250 µm for both sexes) and the VA letter score was 84 or better (approximate Snellen equivalent, 20/20 or better) after 2 consecutive 4-week injections. After week 20, injections continued every 4 weeks if there was successive improvement or worsening in VA (≥5 letters) or CST (≥10% relative change). Otherwise, therapy was withheld starting at 24 weeks if there was no improvement or worsening of VA or CST after 2 consecutive injections (sustained stability). Injections were resumed if there was a subsequent worsening of VA or CST until sustained stability was reestablished. Focal/grid laser was given at or following 24 weeks if DME persisted, the eye had not improved in VA or CST from the last 2 consecutive injections, and there were lesions that were amenable to photocoagulation. Alternative treatments, such as intravitreous corticosteroids, were not permitted unless failure criteria were met.

All eyes completing the 2-year visit were included in this analysis. Thirty baseline variables describing persons and ocular attributes were explored for associations with 3 outcomes: change in VA from baseline at 2 years, change in VA from baseline over 2 years (area under the curve [AUC]), and change in CST from baseline at 2 years. Four variables were dropped from analysis because of the limited subgroup size (<20 eyes) within 1 or more treatment groups (eTable 1 in the Supplement). Potential predictors for each outcome were assessed using a least square regression with adjustment for baseline factors that were previously identified as associated with these outcomes at 2 years (VA, treatment group, and their interaction in the vision outcomes and VA, CST, treatment group, and their interactions with treatment group in the CST outcome).[3,6] Eyes with missing values for 1 or more of the baseline factors were not included in the regression models. A backward stepwise procedure with entry selection criterion set at $P \leq .10$ and stay criterion set at $P \leq .05$ was used for variable selection. The terms for the interaction of each of the factors with treatment were then added to the model and a backward stepwise selection procedure, using the same selection criteria, was used to create the final model. Residuals from the final models were evaluated to verify assumptions of normality and equal variance. No adjustments were made for multiplicity. All reported P values are 2-sided and all analyses were performed in SAS, version 9.4 (SAS Institute Inc). The analyses were exploratory and so $P < .05$ was considered suggestive rather than definitive of a true difference.

Table 1. Multivariable Analysis of Baseline Factors Associated With Visual Acuity Outcomes

Characteristic	No.	Model Estimate Difference in Letter Score (95% CI)	*P* Value[a]
Change in Visual Acuity From Baseline to 2 y[b]			
Age (each decade)	564	−2.1 (−3.0 to −1.2)	<.001
HbA_{1c} (each 1%)	564	−1.0 (−1.5 to −0.5)	<.001
PRP and DR severity			
No prior PRP and at most moderately severe non-PDR (levels 10-47)	384	3.1 (0.9 to 5.4)	.03
No prior PRP and severe non-PDR through high-risk PDR (levels 53-75, excluding 60)	86	2.7 (−0.2 to 5.7)	
Prior PRP and inactive PDR (level 60) or at least mild PDR (levels 61-75)	94	1 [Reference]	
Change in Visual Acuity Over 2 y (Area Under the Curve)[c]			
Age (each decade)	562	−1.9 (−2.4 to −1.3)	<.001
HbA_{1c} (each 1%)	562	−0.5 (−0.9 to −0.2)	<.001
Race/ethnicity			
African American	88	−2.6 (−4.4 to −0.8)	.02
White	373	−1.5 (−2.9 to −0.03)	
Other	101	1 [Reference]	
PRP and DR severity			
No prior PRP and at most moderately severe non-PDR (levels 10-47)	383	2.7 (1.3 to 4.2)	<.001
No prior PRP and severe non-PDR through high-risk PDR (levels 53-75, excluding 60)	86	3.4 (1.5 to 5.3)	
Prior PRP and inactive PDR (level 60) or at least mild PDR (levels 61-75)	93	1 [Reference]	

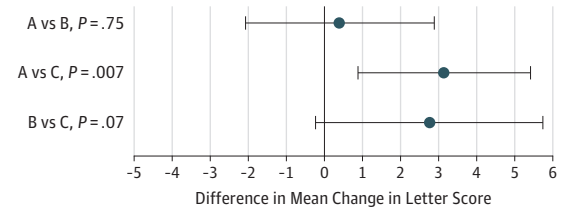
Abbreviations: DR, diabetic retinopathy; HbA_{1c}, hemoglobin A_{1c}; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VA, visual acuity.

[a] Adjusted for baseline VA, treatment, and their interaction. The backward stepwise selection method was used with a significance entry and stay level criteria of .10 and .05, respectively.

[b] The intercept for the final model = 58.06 (95% CI, 46.57-69.56). R^2 = 0.28.

[c] The intercept for the final model = 45.29 (95% CI, 37.94-52.64). R^2 = 0.44.

Figure 1. Adjusted Pairwise Differences for Change in Visual Acuity at 2 Years by Presence of Prior Panretinal Photocoagulation and Severity of Diabetic Retinopathy at Baseline



The estimates were adjusted for treatment, baseline visual acuity, and their interaction along with the age and hemoglobin A_{1c} level. A indicates no prior panretinal photocoagulation and moderately severe nonproliferative diabetic retinopathy or better (levels 10-47; n = 384); B, no prior panretinal photocoagulation and severe nonproliferative diabetic retinopathy through high-risk proliferative diabetic retinopathy (levels 53-75, excluding 60; n = 86); and C, prior panretinal photocoagulation and inactive proliferative diabetic retinopathy (level 60) or mild proliferative diabetic retinopathy or worse (levels 61-75; n = 94). Point estimates were 0.4 for A vs B, 3.1 for A vs C, and 2.7 for B vs C.

Results

The analysis cohort consisted of all study eyes from Protocol T participants who completed the 2-year visit. Of these 578 (of a total of 660) randomized participants, 201 (34.8%), 185 (32.0%), and 192 (33.2%) were in the aflibercept, bevacizumab, and ranibizumab groups, respectively. There were no substantial differences identified in the baseline characteristics of those who did or did not complete the 2-year visit.[3] The 2-year outcomes that are the focus of this analysis are summarized by treatment group in eTable 2 in the Supplement. eTable 3 in the Supplement shows the distribution of baseline characteristics in the analysis cohort, which were similar among the 3 treatment groups.

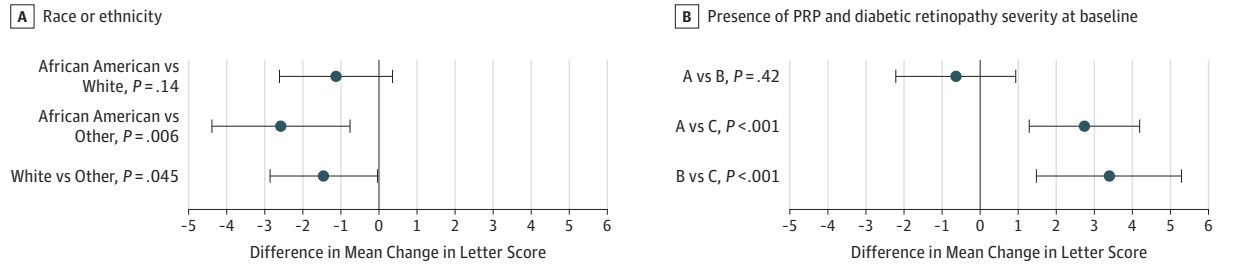
Mean Change in VA From Baseline to 2 Years

For the mean change in VA at 2 years, eTable 4 in the Supplement lists the adjusted least squares means and *P* values for each baseline factor. The mean change in VA from baseline reflected improvement in all of the subgroups of eyes that were analyzed regardless of the anti-VEGF agent used. In the final multivariable model, younger age, lower hemoglobin A_{1c} (HbA_{1c}) levels, and the absence of prior panretinal photocoagulation (PRP) were associated with larger gains in VA (**Table 1**). There were no significant interactions between these factors and drug assignments. For every increase of 10 years in participant age, the mean VA gains were 2.1 letters less (95% CI, −3.0 to −1.2). For every 1% increase in baseline HbA_{1c} levels, VA gains were 1.0 letters less (95% CI, −1.5 to −0.5). On average, eyes with no prior PRP and less than severe nonproliferative diabetic retinopathy (levels 10-47) had 3.1 letter improvement in VA (95% CI, 0.9-5.4; *P* < .007) compared with eyes with prior PRP (**Figure 1**). In addition, among eyes with a proliferative diabetic retinopathy (PDR) Early Treatment Diabetic Retinopathy Study diabetic retinopathy (DR) severity level of 61 to 75 (91 eyes [15.7%]) at baseline, prior PRP (46 eyes [8.0%]) remained associated with less VA gain (10.0 letters vs 14.1 letters). The R^2 value for change in VA from baseline to 2 years was 0.24 for the model with previously identified baseline factors (baseline VA, treatment, and their interaction) and 0.28 for the final model that includes these additional factors.

Change in VA From Baseline Over 2 Years: AUC

For the change in VA over 2 years (AUC), eTable 5 in the Supplement lists the adjusted least squares means and *P* values for each baseline factor. In the final multivariable model, younger age (*P* < .001), lower HbA_{1c} levels (*P* < .001), other race (*P* = .04), and no prior PRP (*P* < .001) were associated with greater improvement (Table 1, **Figure 2**A). Among the other race/ethnicity group, 88 of the 103 eyes (85.4%) were from participants of Hispanic eth-

Figure 2. Adjusted Pairwise Differences for Change in Visual Acuity Over 2 Years (Area Under the Curve)



A, Estimates were adjusted for treatment, baseline visual acuity, and their interaction along with age, panretinal photocoagulation (PRP)/proliferative diabetic retinopathy severity, and hemoglobin A_{1c} level. Point estimates were −1.1 for African American vs white, −2.6 for African American vs other, and −1.4 for white vs other. B, Estimates were adjusted for treatment, baseline visual acuity, and their interaction along with age, race/ethnicity, and hemoglobin A_{1c} level. A indicates no prior PRP and moderately severe nonproliferative diabetic retinopathy or better (levels 10-47; n = 383); B, no prior PRP and severe nonproliferative diabetic retinopathy through high-risk proliferative diabetic retinopathy (levels 53-75, excluding 60; n = 86); and C, prior PRP and inactive proliferative diabetic retinopathy (level 60) or mild proliferative diabetic retinopathy or worse (levels 61-75; n = 93). Point estimates were −0.6 for A vs B, 2.7 for A vs C, and 3.4 for B vs C.

Table 2. Multivariable Analysis of Baseline Factors Associated With Change in CST at 2 Years

Characteristic	No.	Model Estimate (95% CI) Difference CST	*P* Value[a]
Race/ethnicity			
African American	88	−12.0 (−37.0 to 13.0)	
White	367	15.3 (−4.0 to 34.6)	.02
Other	98	1 [Reference]	
Subretinal fluid within 500 µm of the macula center			
Yes	167	−22.9 (−40.2 to −5.6)	.01
No	386	1 [Reference]	

Abbreviations: CST, central subfield thickness; VA, visual acuity.

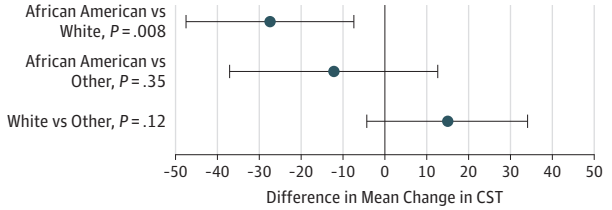
[a] Adjusted for baseline VA, baseline CST, treatment, and their interaction. The backward stepwise selection method was used with a significance entry and stay level criteria of .10 and .05, respectively. The intercept for the final model = 139.16 (95% CI, 70.95-207.38). R^2 = 0.65.

nicity. There were no significant interactions between these factors and drug assignment. For every 10-year increase in participant age, the mean change in VA over 2 years was −1.9 letters less (95% CI, −2.4 to −1.3) whereas for every 1% increase in baseline HbA_{1C} levels, the VA change over 2 years was −0.5 letters less (95% CI, −0.9 to −0.2). Eyes of African American participants had −2.6 letters less (95% CI, −4.4 to −0.8) improvement and eyes of white participants had −1.5 letters less (95% CI, −2.9 to −0.0) improvement than eyes of participants of other race/ethnicity (Figure 2A). Eyes with prior PRP had approximately 3 letters less improvement compared with those who did not have prior PRP (Figure 2B). Among eyes with PDR at baseline, prior PRP remained associated with less VA gain when compared with eyes with no prior PRP (9.5 letters vs 13.2 letters). The R^2 for the change in VA AUC over 2 years was 0.37 for the model with previously identified baseline factors (baseline VA, treatment, and their interaction) and 0.44 for the final model that accounted for these factors.

Change in CST From Baseline at 2 Years

For the mean change in CST at 2 years, eTable 6 in the Supplement lists the adjusted least squares means and *P* values for each baseline factor. The mean change in CST from the baseline reflected an improvement in all of the subgroups of eyes analyzed regardless of the anti-VEGF agent used. In the final multivariable model, African American participants (model estimate, −12.0; 95% CI, −37.0 to 13.0; *P* = .02) and eyes with centrally located subretinal fluid (model estimate, 15.3; 95% CI, −4.03 to 34.6; *P* = .01) had greater reductions in CST (**Table 2**). On average, eyes of African American participants had 27.3 µm (95% CI, −47.5 to −7.1) of additional thickness reduction compared with white participants (**Figure 3**). Eyes with subretinal fluid within 500 µm of the macula center on OCT images thinned by an additional 22.9 µm (95% CI, −40.2 to −5.6) compared with eyes that did not have central subretinal fluid (Table 2). There were no significant interactions between these factors and drug assignments. The R^2 value for the 2-year change in CST was 0.63 for the model with previously identified baseline factors (baseline VA, baseline CST, treatment, and their interaction) and 0.65 for the final model.

Figure 3. Adjusted Pairwise Differences for Change in Central Subfield Thickness (CST) at 2 Years for Race/Ethnicity



Estimates were adjusted for treatment, baseline visual acuity, baseline optical coherence tomography, and their interaction along with subretinal fluid within 500 µm of the macula center. Point estimates were −27.3 for African American vs white, −12.0 for African American vs other, and 15.3 for white vs other.

Discussion

Anti-VEGF therapy has altered the vision outcomes that may be achieved by patients with vision-impairing central-involved DME. Treatment requires frequent and regular examinations, particularly in the first year of anti-VEGF therapy. Currently, 3 anti-VEGF agents are commercially available, each capable of providing vision improvement and anatomic resolution for more than half of treated eyes. However, among eyes with a presenting VA of 20/50 or worse, the magnitude of improvement in VA is smaller when treated with bevacizumab throughout 2 years of follow-up.[2,3] Affected individuals manifest several presenting demographic and ocular characteristics, and the question arises whether all patients benefit equally with each anti-VEGF agent. This exploratory analysis of Protocol T supports a finding reported from Protocol I[5,8] that there was no identifiable participant profile for which anti-VEGF therapy was associated with a mean decrease in VA or mean increase in central retinal thickness compared with the baseline. As such, all eyes with central-involved DME in persons with a range of DR features, as well as ocular and systemic comorbidities, remain viable candidates for therapy.

Although several baseline characteristics that covered a range of patient demographics and ocular findings were evaluated, the magnitude of treatment benefit was found to vary with respect to only a few presenting features. Participant age was associated with each of the 2 vision outcomes analyzed. Younger participants had larger gains in VA over and at 2 years. This association supports previous findings from Protocol I ranibizumab-assigned eyes in direction and magnitude. In Protocol I, there was a mean increase of 2.2 letters (95% CI, 1.1-to 3.3) in VA gains at 1 year for every 10 years of younger participant age; in Protocol T, irrespective of the anti-VEGF agent used, there was a mean increase of 2.1 letters (95% CI, 1.3-3.0) in VA gain at 2 years for every 10-year age decrement. In a pooled analysis of 502 eyes with DME assigned to monthly ranibizumab in the RIDE and RISE trials, for every 5-year increase in participant age, the odds of realizing at least a 15 letter gain at 2 years fell (odds ratio, 0.88; 95% CI, 0.79-0.98).[6] Younger patients appear to be less vulnerable to the adverse effects of DME on longer-term vision function; similar observations have also appeared in the neovascular age-related macular degeneration literature.[9]

The other variable also associated with superior VA outcomes at and over 2 years was lower HbA_{1c} levels irrespective of the anti-VEGF agent used. This factor was considered but not found to be associated with changes in VA in Protocol I (which used a similar dosing regimen to that of Protocol T) or in the RIDE/RISE trials (in which participants received monthly dosing for 3 years).[6,10] Each of these other studies enrolled participants with a similar range of glycemic control as identified in Protocol T. However, in an integrated analysis of data from patients treated with aflibercept in the VISTA and VIVID DME trials, the mean improvement in VA at 2 years was dependent on HbA_{1c} levels (lowest HbA_{1c} quartile, 12.6 letters vs highest HbA_{1c} quartile, 9.7 letters; $P = .04$).[11] Thus, the results from Protocol T and VISTA/VIVID suggest that the vision outcomes associated with anti-VEGF treatment for DME may not be independent of glycemic control. This provides additional evidence to recommend that patients who are undergoing treatment for DME actively address deficiencies in their glycemic management.

Prior PRP with or without active PDR had a negative association with the amount of vision improvement in both VA outcomes that were evaluated. In Protocol I, the same association was seen in the univariate analysis. The final multivariable model for Protocol I did not combine PRP status and level of DR severity in the same manner as was done in this Protocol T analysis, but it did find that PDR or PRP remained negatively associated with changes in VA. In the RIDE and RISE trials, participants receiving PRP before or during the trial were less likely to have a VA of 20/40 or better at 2 years.[6] It is unknown why having had PRP may hinder the magnitude of improvement or the ability to attain the best levels of acuity. This finding should not be interpreted to indicate that there is a direct negative association of PRP with VA outcomes because eyes with the greatest severity of DR often receive PRP, and these eyes may have more macular ischemia or other damage that affects the potential to recover VA.

The presence of central subretinal fluid was associated with a larger anatomic response, which is consistent with data from RIDE/RISE that showed that eyes with subretinal fluid were nearly 2.5 times more likely to achieve a central foveal thickness of 250 µm or less at 2 years.[6] It is unclear why eyes that have subretinal fluid contributing to their CST would be particularly responsive to anti-VEGF therapy as compared with eyes without subretinal fluid. Race/ethnicity also appeared to affect anatomic responses in Protocol T, with African American participants found to have the largest thickness reduction, particularly compared with white participants. However, this observation was inconsistent with our VA outcomes in which the VA AUC analysis showed that African American participants have smaller VA benefits compared with other (predominantly Hispanic) participants and a trend compared with white participants as well. As the associations between race and VA AUC and the CST outcomes reported in this article have not been previously reported to our knowledge, they should be interpreted cautiously. This also highlights the imperfect association between VA and CST and change in VA and CST.[12]

In this exploration of factors that may explain the variability in outcomes experienced by patients receiving anti-VEGF therapy for DME, it should be emphasized that outcomes remain positive even in the presence of variables that are associated with a less optimal response. For example, from the final multivariable model for the change in VA at 2 years, a 67-year-old with an HbA_{1c} level of 9.0% and prior PRP would have an expected gain of 6.8 letters (95% CI, 4.7-9.0) from baseline to 2 years, whereas a 54-year-old with an Hb_{A1c} level of 6.8% and no prior PRP and moderate-severe non-PDR or better who started with the same baseline VA of 65 letters (Snellen equivalent, 20/63) and was treated with the same agent (ranibizumab) would have an expected gain of 14.8 letters (95% CI, 13.4-16.3).

Limitations

These analyses are limited by the post hoc design and large number of comparisons, which increase the risk of detecting associations that may have occurred by chance. However, the factors identified in this article that replicate previous findings gain more credence. In addition, this study was not specifically powered to

detect subgroup associations, so the lack of significance does not necessarily indicate a lack of an association. The strengths of this study include the large number of participants, prospective design, incorporation of standardized treatment regimens, standardized outcome measurements, and excellent longer-term completion rates.

Conclusions

Two-year vision and anatomic outcomes obtained when managing central-involved DME with anti-VEGF therapy remained favorable in all of the subgroups that were evaluated. We found only a few factors, in addition to those previously identified (ie, baseline VA and CST), that influence the magnitude of the 2-year vision and anatomic outcomes obtained when anti-VEGF therapy is used to treat DME. The association of these factors was similar across the 3 anti-VEGF drugs included in Protocol T. The variation in outcomes is partially explained by baseline characteristics of the individuals, 2 of which are modifiable: glycemic control and the application of PRP. Encouraging glycemic control in the context of DR management may optimize vision outcomes when using anti-VEGF for DME.

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