Purpose: This study assessed relationships between best-corrected visual acuity (BCVA), central subfield thickness (CST), and ellipsoid zone (EZ) integrity in macular edema (ME) patients.

Design: Post hoc analysis of 6 clinical trials, which included verified diagnoses, protocol refractions, and reading center assessment of OCT images.

Participants: Participants (n = 1063) were diagnosed with ME from retinal vein occlusion (RVO), diabetic retinopathy (DR; diabetic macular edema, DME), or noninfectious uveitis (NIU).

Methods: For CST, 2 clinical trials for each disorder were analyzed. For EZ, 3 studies across 2 disorders were analyzed.

Main Outcome Measures: Primary outcomes were correlations between BCVA and CST, and between BCVA and 4 central subfield EZ grades.

Results: For baseline BCVA and CST, Pearson correlation coefficients were: ME from RVO, −0.56 (774 eyes; 95% confidence interval [CI], −0.61 to −0.51; P < 0.001); DME, −0.50 (91 eyes; 95% CI, −0.64 to −0.33; P < 0.001); and ME from NIU, −0.38 (198 eyes; 95% CI, −0.49 to −0.26; P < 0.001). Regarding change from baseline to 24 weeks for both BCVA and CST, Pearson correlation coefficients were: ME from RVO, −0.35 (95% CI, −0.43 to −0.27; P < 0.001); DME, −0.30 (95% CI, −0.48 to −0.09; P = 0.006); and ME from NIU, −0.42 (95% CI, −0.53 to −0.29; P < 0.001). Acute and chronic ME showed similar baseline and 24-week change linear correlations. With lower baseline CST, a trend of decreased baseline and 24-week change correlations was found. For central subfield EZ at baseline, mean BCVA progressively worsened with each of 4 EZ grades in 185 eyes with gradable EZ (DME, 41 eyes; NIU, 144 eyes; P ≤ 0.050 for all pairwise comparisons except between normal and questionably abnormal EZ grades). Eyes with normal baseline central subfield EZ showed greater 24-week change in BCVA than those with abnormal baseline EZ (15.00 letters vs. 8.16 letters; P = 0.0005, with baseline BCVA, CST, and age as covariates).

Conclusions: Despite these correlations, CST and EZ integrity, as graded herein, account for the minority of BCVA variation in patients with ME resulting from RVO, DR, and NIU. Ophthalmology Retina 2021;5:633-647 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In clinical practice, physicians often base treatment decisions on both BCVA and OCT assessment. In fact, the 2015 American Society of Retina Specialists Preferences and Trends survey of more than 2700 retina specialists in 60 countries revealed that more than 90% of retina specialists, both in the United States and internationally, use OCT-guided variable frequency anti–vascular endothelial growth factor (VEGF) treatment protocols for neovascular age-related macular degeneration. However, the correlation between BCVA and CST measured on OCT is modest at best across a spectrum of retinal disorders.2–3

Given the importance of BCVA and CST in clinical practice and in clinical trials, this study assessed the relationship between BCVA and CST in patients with ME resulting from retinal vein occlusion (RVO), diabetic retinopathy (DR, diabetic macular edema or DME), and
noninfectious uveitis (NIU) using high-quality clinical trial data (monitor-verified diagnoses per eligibility criteria, protocol refractions, study-certified imagers, and spectral-domain OCT evaluation at a centralized reading center). In a subset of clinical trials, this study also assessed the relationship between BCVA and integrity of the central subfield ellipsoid zone (EZ; previously designated as the photoreceptor inner segment–outer segment junction), another OCT anatomic feature with more recently described functional correlation in ME resulting from RVO, DME, and NIU. All clinical trials herein assessed CLS-TA (Clearside Biomedical, Alpharetta, GA), an investigational formulation of the corticosteroid triamcinolone acetonide for suprachoroidal injection, across these disorders as monotherapy or in conjunction with intravitreal anti-VEGF therapy, but treatment efficacy is not the focus of this report; rather, this report focuses on BCVA and OCT-determined anatomic correlations, regardless of treatment assignment. Although the academic retina community is well aware of these relationships, ophthalmic practitioners in general increasingly incorporate OCT into their diagnostic and therapeutic decision making; consequently, a broader understanding of the relationship between OCT anatomic features and visual function, across these common disease states, grows increasingly important for patient care.

Methods

Clinical Trials

This retrospective analysis was performed on datasets from 4 randomized controlled clinical trials and 2 open-label uncontrolled clinical trials assessing CLS-TA administered suprachoroidally either as monotherapy or in conjunction with intravitreal anti-VEGF therapy. Because this post hoc study involved analysis of already collected de-identified information, it is exempt from review by an institutional review board, but all of the clinical trial protocols were approved by an institutional review board or independent ethics committee at each study site, and these clinical trials were performed in compliance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulations. Participants provided written informed consent before these studies commenced.

Participants, nearly all of whom had ME, were diagnosed with RVO, DR, or NIU and assessed at monthly intervals for a minimum of 24 weeks. The study designs are summarized below; key eligibility features are summarized in Table 1.

Macular Edema Resulting from Retinal Vein Occlusion.

1. SAPPHIRE (A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA in conjunction with intravitreal aflibercept in subjects with retinal vein occlusion) was a phase 2 randomized, masked, active-controlled, parallel-group multicenter study in treatment-naïve patients with ME secondary to RVO, a CST of at least 300 μm, and a BCVA score between 20 and 70 letters, inclusively, in the study eye. The study was designed to compare the efficacy and safety of suprachoroidal CLS-TA (4 mg/100 μl, standard dose across trials) administered in conjunction with intravitreal aflibercept (2 mg/50 μl; the active group) versus intravitreal aflibercept monotherapy and sham suprachoroidal administration (the control group) over 48 weeks of follow-up. Four hundred sixty participants were enrolled and assigned randomly 1:1 to 1 of 2 treatment groups stratified by disease (branch RVO [BRVO] or central RVO [CRVO]). Two hundred thirty-one patients were assigned to the active arm and 229 patients were assigned to the control arm. Safety and efficacy outcomes were to be assessed monthly for 24 weeks and then every 6 weeks until the end of the study at week 48.

Patients in the active arm were to receive intravitreal aflibercept and suprachoroidal CLS-TA on day 0, week 12, and week 24; intravitreal aflibercept monotherapy at week 4; and sham intravitreal aflibercept on weeks 8, 16, and 20. Patients in the control arm were to receive intravitreal aflibercept and sham suprachoroidal administration on day 0, week 12, and week 24 and intravitreal aflibercept monotherapy at weeks 4, 8, 16, and 20. All patients were eligible for rescue at other visits as determined by predefined criteria. The study did not meet its 8-week primary end point and was terminated; however, 255 patients (55.4%) completed the study before termination.

2. TOPAZ (A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA with an intravitreal anti-VEGF in subjects with retinal vein occlusion), initiated 9 months after SAPPHIRE, was identical in design and had the same goals as SAPPHIRE, except for the anti-VEGF agent used (randomized to either bevacizumab 1.25 mg/50 μl intravitreally or ranibizumab 0.5 mg/50 μl intravitreally, instead of aflibercept). Four hundred sixty patients were to be enrolled and assigned randomly 1:1:1:1 to 1 of 4 treatment groups stratified by disease (BRVO or CRVO); however, because of the failure of SAPPHIRE to meet its primary end point, TOPAZ was terminated after randomizing 325 patients (active arms, 162 patients; control arms, 163 patients) and before any patient completed the study.

Diabetic Macular Edema.

3. TYBEE (Randomized, double masked, controlled study comparing the safety and efficacy of suprachoroidal CLS-TA with intravitreal aflibercept versus aflibercept alone in subjects with diabetic macular edema) was a phase 2 randomized, masked, active-controlled, parallel-group multicenter study in treatment-naïve patients with DME, a CST of more than 300 μm, and BCVA between 20 and 70 letters, inclusively, in the study eye. The study was designed to compare the effects of suprachoroidal CLS-TA administered with intravitreal aflibercept (the active group) versus intravitreal aflibercept monotherapy and sham suprachoroidal administration (the control group) over 24 weeks of follow-up. The study details are summarized further in Table 1 and in Barakat et al.16

4. HULK (Open-label study of the safety and efficacy of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept for the treatment of diabetic macular edema) was a phase 1/2 open-label, parallel-group, multicenter study in patients with DME, CST of more than 320 μm, and BCVA between 14 and 83 letters, inclusively, in the study eye. The study was designed to compare the effects of suprachoroidal CLS-TA administered with intravitreal aflibercept in treatment-naïve patients versus
Table 1. Studies Included in Analysis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Study</th>
<th>SAPPHIRE</th>
<th>TOPAZ</th>
<th>HULK</th>
<th>TYBEE</th>
<th>PEACHTREE</th>
<th>AZALEA</th>
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<tbody>
<tr>
<td>ClinicalTrials.gov identifier</td>
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<td>NCT02980874</td>
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<td>NCT02949024</td>
<td>NCT03126786</td>
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<td>BRVO or CRVO</td>
<td>DME</td>
<td>DME</td>
<td>NIU</td>
<td>NIU</td>
</tr>
<tr>
<td>Phase</td>
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<td>1/2</td>
<td>2</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Duration (wks)</td>
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<td>48</td>
<td>24</td>
<td>24</td>
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<tr>
<td>Study design</td>
<td></td>
<td>Randomized, double-masked, multicenter</td>
<td>Randomized, double-masked, multicenter</td>
<td>Open-label, multicenter</td>
<td>Randomized, double-masked, multicenter</td>
<td>CLS-TA at mos 0 and 3 or sham suprachoroidal injection</td>
<td>Open-label, multicenter</td>
</tr>
<tr>
<td>Treatment(s)*</td>
<td></td>
<td>CLS-TA at mos 0, 3, and 6 plus aflibercept at mos 0, 1, 3, and 6 or monthly aflibercept for 6 mos</td>
<td>CLS-TA at mos 0, 3, and 6 plus anti-VEGF at mos 0, 1, 3, and 6 or monthly anti-VEGF for 6 mos</td>
<td>Single dose of CLS-TA or CLS-TA plus aflibercept</td>
<td>CLS-TA plus aflibercept at mos 0 and 3 or monthly aflibercept for 3 mos</td>
<td>CLS-TA at mos 0 and 3</td>
<td></td>
</tr>
<tr>
<td>Key eligibility features</td>
<td></td>
<td>Diagnosis of treatment-naive ME associated with RVO; ETDRS BCVA between 20 and 70 letters; CST ≥ 300 μm</td>
<td>Diagnosis of treatment-naive ME associated with RVO; ETDRS BCVA between 20 and 70 letters; CST ≥ 300 μm</td>
<td>Diagnosis of DME; ETDRS BCVA between 14 and 83 letters; CST &gt; 320 μm</td>
<td>Diagnosis of treatment-naive DME; ETDRS BCVA between 20 and 70 letters; CST &gt; 300 μm</td>
<td>Diagnosis of ME associated with NIU; ETDRS BCVA ≥ 5 letters</td>
<td>Diagnosis of ME associated with NIU; ETDRS BCVA ≥ 5 letters</td>
</tr>
</tbody>
</table>

CLS-TA dosed at 4 mg/100 μl suprachoroidally and aflibercept dosed at 2 mg/50 μl intravitreally. AZALEA = Open-label safety study of suprachoroidal triamcinolone acetonide injectable suspension in patients with noninfectious uveitis; BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CST = central subfield retinal thickness; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HULK = Open-label study of the safety and efficacy of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept for the treatment of diabetic macular edema; ME = macular edema; NIU = noninfectious uveitis; PEACHTREE = A phase 3, randomized, masked, controlled clinical trial to study the safety and efficacy of triamcinolone acetonide injectable suspension (CLS-TA) for the treatment of subjects with macular edema associated with noninfectious uveitis; SAPPHIRE = A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA in conjunction with intravitreal aflibercept in subjects with retinal vein occlusion; TOPAZ = A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA with an intravitreal anti-VEGF in subjects with retinal vein occlusion; TYBEE = Randomized, double masked, controlled study comparing the safety and efficacy of suprachoroidal CLS-TA with intravitreal aflibercept versus aflibercept alone in subjects with diabetic macular edema.

*Patients were eligible for rescue at other visits as determined by predefined criteria.

1 Included ranibizumab 0.5 mg/50 μl intravitreally or bevacizumab 1.25 mg/50 μl intravitreally.
suprachoroidal CLS-TA monotherapy in patients having received prior therapy in the previous 12 months. The study details are summarized further in Table 1 and in Wykoff et al.17

Macular Edema resulting from Noninfectious Uveitis.

5. PEACHTREE (A phase 3, randomized, masked, controlled clinical trial to study the safety and efficacy of triamcinolone acetonide injectable suspension (CLS-TA) for the treatment of subjects with macular edema associated with noninfectious uveitis) was a randomized, masked, sham-controlled, multicenter clinical study in patients with ME associated with NIU, a CST of 300 μm or more, and BCVA of between 5 and 70 letters, inclusively, in the study eye. The study was designed to compare the effects of suprachoroidal CLS-TA versus suprachoroidal sham over 24 weeks of follow-up. The study details are summarized further in Table 1 and in Yeh et al.18

6. AZALEA (Open-label safety study of suprachoroidal triamcinolone acetonide injectable suspension in patients with noninfectious uveitis) was a phase 3, open-label, multicenter safety study in patients with NIU with or without ME and BCVA of 5 letters or more in the study eye. The study was designed to assess the safety of suprachoroidal CLS-TA over a 24-week follow-up period. Patients received 2 unilateral suprachoroidal CLS-TA injections approximately 12 weeks apart. After the second suprachoroidal injection, follow-up visits were conducted every 4 weeks for an additional 12 weeks. Thirty-eight patients, of whom 20 had ME, that is, a CST of more than 300 μm, entered the study and received at least 1 dose of suprachoroidal CLS-TA; of these patients, 37 completed the study. The study details are summarized further in Table 1 and in Henry et al.19

Central Subfield Thickness and Ellipsoid Zone Integrity as Measured by Spectral-Domain OCT

Central subfield thickness and EZ integrity were assessed via spectral-domain OCT. The central subfield is a circular area 1 mm in diameter centered around the center point. For each scan, the standard 9-field ETDRS grid was centered at the fovea by viewing all B-scans to locate foveal landmarks, which included the point at which the inner retinal layers were thinnest and the foveal depression, hyperreflective dot, or both that corresponded to reflected light at the foveal center.20 These landmarks are helpful to locate the center point, particularly in the presence of ME. No instrument-specific upper limit for CST was used for study enrollment because eligibility criteria across the clinical trials did not include an upper bound. All clinical trials included assessment of CST, whereas a subset of clinical trials (TYBEE, PEACHTREE, and AZALEA) assessed the integrity of the central subfield EZ, also known as the photoreceptor inner segment–outer segment junction. A masked reading center graded the central subfield EZ as normal, questionably abnormal, definitely abnormal (patchy), definitely abnormal (absent), and cannot grade.

The spectral-domain OCT instrument and technician were certified before seeing any participants. The technician was encouraged to use the same certified equipment throughout the patient’s study participation. All images were obtained by the same technician, whenever possible, from each participant per research site. With the exception of HULK (phase 1/2; DME), de-identified images were uploaded to a central reading center for masked analysis and interpretation.

Best-Corrected Visual Acuity Assessment

Best-corrected visual acuity was evaluated by using ETDRS charts, standardized lighting, and standardized lanes and followed the ETDRS testing protocol. The results were reported as the total number of letters read after refraction. Visual acuity testing preceded any examination requiring contact with the eye. To provide standardization and well-controlled assessments of BCVA during the study, all BCVA assessments were performed by trained staff who were certified on the study procedure using certified visual acuity equipment and lanes. The PEACHTREE and AZALEA studies measured BCVA using ETDRS electronic visual acuity letter score in lieu of the ETDRS testing protocol. All other procedures were performed consistently among studies.

Statistical Analysis

Post hoc analysis was performed with data from the 6 controlled clinical trials examining RVO (SAPPHIRE, TOPAZ), DME (HULK, TYBEE), and NIU (PEACHTREE, AZALEA). All participants in these studies received suprachoroidal CLS-TA with or without an intravitreal anti-VEGF agent, an intravitreal anti-VEGF agent in conjunction with a sham suprachoroidal injection (anti-VEGF monotherapy), or a sham suprachoroidal injection. Because the purpose of this analysis was to assess correlations between BCVA and OCT anatomic features, and not to assess treatment efficacy, data from patients who received rescue therapy were included.

For CST, data were analyzed individually for each of the 6 studies, pooled by each of the 3 disease states, and across all disease states. Analyses of correlation were performed on data collected before dose administration at baseline and separately on the change from baseline data collected after treatment through week 24. Only participants with complete data, that is, BCVA and CST assessed on the same date, were included in the analysis.

To measure the linear relationship between baseline BCVA and CST and between the change from baseline in both BCVA and CST at week 24, Pearson correlation coefficients, 95% confidence intervals (CIs) using the Fisher z transformation, and P values from the 2-sided test for zero linear correlation were calculated. Within each study, a univariate linear regression model was used to describe the relationship between BCVA, the dependent variable, and CST, the independent variable. This relationship within the pooled data was analyzed via a multiple linear regression model that added age as an independent variable for the baseline data and added age and baseline BCVA and CST for the week-24 data. To assess the fitness of these multiple linear regression models, linear regression models were used containing CST as the independent variable. Between-disease state comparisons were performed with a linear regression model with baseline BCVA or change in BCVA at week 24 as the dependent variable and independent variables of baseline CST or change in CST at week 24 and the disease state, along with terms for interaction.

Correlations between BCVA and CST also were calculated based on chronicity of disease, with acute or chronic duration of diagnosis, respectively, defined as less than or more than the pooled median for each disorder. Likewise, correlations between BCVA and CST were stratified by baseline CST, segregated as being either more than or less than the pooled median CST by disease state.

As noted previously, a subset of studies (TYBEE, PEACHTREE, and AZALEA) included masked reading center assessment of the central subfield EZ into grades of normal, questionably
abnormal, definitely abnormal (patchy), definitely abnormal (absent), and cannot grade. Values of cannot grade were excluded from the analysis. Only participants with complete data, that is, BCVA and EZ grade assessed on the same date, were included in the analysis. Using the pooled data from these 3 studies, a 1-way analysis of variance with Tukey-Kramer adjustment for multiple comparisons was performed to compare mean BCVA across the 4 EZ grades at baseline. To assess the fitness of this model, analysis of covariance was used adding baseline CST and age as covariates. The relationship between the change from baseline in BCVA and the change in the EZ status at week 24 was assessed using an analysis of covariance model with the number of steps changed from baseline in the EZ status as a fixed effect and age, baseline BCVA, and baseline CST as covariates. Adjustment for multiple comparisons was performed using the method by Tukey-Kramer. To assess the relationship between intact baseline central subfield EZ on 24-week change in BCVA, an analysis of covariance model similarly was used with change from baseline in BCVA as the dependent variable and baseline EZ (normal vs. nonnormal) as the independent variable and baseline BCVA, baseline CST, and age as the covariates. Reported P values were not adjusted for issues of multiplicity, but were compared with critical values based on the Benjamini-Hochberg procedure21 using a false-positive rate of 0.050. Statistical analysis was conducted using SAS software version 9.4 (SAS Institute, Cary, NC). All tests were 2-sided.

Results

Demographics and baseline characteristics are summarized in Table 2. Among the RVO patients, at baseline, 455 patients in SAPPHIRE had a mean age of 65.7 years and 319 patients in TOPAZ had a mean age of 63.3 years. For DME patients, at baseline, 20 patients in HULK had a mean age of 62.5 years and 71 patients in TYBEE had a mean age of 59.5 years. For NIU patients, at baseline, 160 patients in PEACHTREE had a mean age of 50.2 years and 38 patients in AZALEA had a mean age of 52.4 years.

Association between Baseline Best-Corrected Visual Acuity and Central Subfield Thickness

Analysis of baseline BCVA and CST data included 1063 eyes from 1063 patients diagnosed with RVO (774 eyes), DR (91 eyes), and NIU (198 eyes), nearly all of whom had ME. Correlation coefficients and regression parameters, and their associated 95% CIs, are presented in Table 3. Coefficients of determination from simple and multiple linear regressions are detailed in Table 4.

The RVO patients in SAPPHIRE and TOPAZ showed similar mean baseline CST (661.5 µm and 642.8 µm, respectively) and similar mean baseline CST (661.5 µm and 642.8 µm, respectively). At baseline, both RVO trials showed a moderate negative linear correlation between BCVA and CST (SAPPHIRE: r = -0.58, P < 0.001; TOPAZ: r = -0.53, P < 0.001). As expected, the pooled data showed a moderate negative linear correlation between BCVA and CST (r = -0.56, P < 0.001). The slope of the regression line from this pooled data (Fig 1A) reflected an average increase of 3.3 ETDRS letters (95% CI, 3.0–3.6 ETDRS letters) for every 100-µm reduction in CST. At baseline, CST accounted for 31.6% of the total variation in BCVA. When including age along with CST in the multiple linear regression analysis, little difference was found, as shown in Table 4. With respect to RVO subtype, pooled baseline data

Table 2. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>SAPPHIRE</th>
<th>PEACHTREE</th>
<th>TYBEE</th>
<th>TOPAZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td>200 (44)</td>
<td>149 (47)</td>
<td>8 (40)</td>
<td>21 (30)</td>
</tr>
<tr>
<td>Duration of disease, yrs</td>
<td>25.6 (4)</td>
<td>21 (30)</td>
<td>12.5 (8)</td>
<td>20.0 (6)</td>
</tr>
<tr>
<td>Mean (range), ETDRS letters</td>
<td>50.7 (10)</td>
<td>67.2 (52)</td>
<td>66.7 (11-97)</td>
<td>54.2 (9)</td>
</tr>
<tr>
<td>Mean (range), µm</td>
<td>661.5 (234)</td>
<td>642.8 (220)</td>
<td>447.2 (328)</td>
<td>498.7 (256)</td>
</tr>
<tr>
<td>Median BCVA, ETDRS letters</td>
<td>50.7</td>
<td>67.2</td>
<td>66.7</td>
<td>54.2</td>
</tr>
<tr>
<td>Median CST, µm</td>
<td>661.5</td>
<td>642.8</td>
<td>447.2</td>
<td>498.7</td>
</tr>
</tbody>
</table>

Table 3. Correlation and Regression Analysis between Early Treatment Diabetic Retinopathy Study Best-Corrected Visual Acuity and Central Subfield Thickness

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Pearson Correlation Coefficient (95% Confidence Interval)</th>
<th>Best-Corrected Visual Acuity per 100-μm Absolute Reduction (95% Confidence Interval)</th>
<th>P Value</th>
<th>Change in Best-Corrected Visual Acuity per 100-μm Absolute Reduction (95% Confidence Interval)</th>
<th>P Value</th>
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<tr>
<td>Pooled RVO</td>
<td>774</td>
<td>-0.56 (-0.61 to -0.51)</td>
<td>3.28 (2.95 to 3.62)</td>
<td>&lt;0.001*</td>
<td>4.54 (-0.35 (-0.43 to -0.27)</td>
<td>2.87 (1.89 to 3.84)</td>
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<td>Pooled BRVO</td>
<td>426</td>
<td>-0.42 (-0.50 to -0.34)</td>
<td>1.75 (-0.59 to 4.09)</td>
<td>&lt;0.001*</td>
<td>246 (-0.43 (-0.52 to -0.32)</td>
<td>2.48 (1.81 to 3.14)</td>
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<td>Pooled CRVO</td>
<td>348</td>
<td>-0.60 (-0.66 to -0.53)</td>
<td>1.42 (-0.19 to 3.03)</td>
<td>&lt;0.001*</td>
<td>208 (-0.36 (-0.47 to -0.24)</td>
<td>1.92 (1.24 to 2.60)</td>
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<tr>
<td>Study-level RVO</td>
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<tr>
<td>SAPPHIRE</td>
<td>455</td>
<td>-0.58 (-0.64 to -0.52)</td>
<td>3.45 (3.00 to 3.89)</td>
<td>&lt;0.001*</td>
<td>421 (-0.33 (-0.41 to -0.24)</td>
<td>1.73 (1.25 to 2.21)</td>
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<td>TOPAZ</td>
<td>319</td>
<td>-0.53 (-0.61 to -0.45)</td>
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<td>&lt;0.001*</td>
<td>33 (-0.60 (-0.78 to -0.32)</td>
<td>2.84 (1.46 to 4.21)</td>
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<td>Pooled DME</td>
<td>91</td>
<td>-0.50 (-0.64 to -0.33)</td>
<td>4.38 (2.77 to 5.99)</td>
<td>&lt;0.001*</td>
<td>82 (-0.30 (-0.48 to -0.09)</td>
<td>2.43 (-0.84 to 5.71)</td>
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<tr>
<td>HULK</td>
<td>20</td>
<td>-0.38 (-0.70 to 0.08)</td>
<td>3.77 (-0.73 to 8.27)</td>
<td>0.096</td>
<td>19 (-0.01 (-0.46 to 0.45)</td>
<td>0.11 (-9.68 to 9.90)</td>
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<td>TYBEE</td>
<td>71</td>
<td>-0.50 (-0.66 to -0.30)</td>
<td>4.08 (2.39 to 5.77)</td>
<td>&lt;0.001*</td>
<td>63 (-0.29 (-0.50 to -0.05)</td>
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<td>Pooled NIU</td>
<td>198</td>
<td>-0.38 (-0.49 to -0.26)</td>
<td>3.79 (2.49 to 5.09)</td>
<td>&lt;0.001*</td>
<td>185 (-0.42 (-0.53 to -0.29)</td>
<td>4.66 (3.22 to 6.11)</td>
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<tr>
<td>Study-level NIU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEACHTREE</td>
<td>160</td>
<td>-0.31 (-0.44 to -0.16)</td>
<td>2.66 (1.37 to 3.95)</td>
<td>&lt;0.001*</td>
<td>151 (-0.40 (-0.52 to -0.25)</td>
<td>3.33 (2.08 to 4.58)</td>
</tr>
<tr>
<td>AZALEA</td>
<td>38</td>
<td>-0.20 (-0.49 to 0.13)</td>
<td>4.47 (-2.96 to 11.90)</td>
<td>0.232</td>
<td>34 (-0.39 (-0.64 to -0.06)</td>
<td>4.82 (0.74 to 8.91)</td>
</tr>
<tr>
<td>Pooled RVO, DME,</td>
<td>1063</td>
<td>-0.55 (-0.59 to -0.51)</td>
<td>3.34 (3.03 to 3.65)</td>
<td>&lt;0.001*</td>
<td>721 (-0.40 (-0.46 to -0.34)</td>
<td>3.54 (2.79 to 4.30)</td>
</tr>
</tbody>
</table>

AZALEA = Open-label safety study of suprachoroidal triamcinolone acetonide injectable suspension in patients with noninfectious uveitis; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DME = diabetic macular edema; HULK = Open-label safety study of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept for the treatment of diabetic macular edema; NIU = noninfectious uveitis; PEACHTREE = A phase 3, randomized, masked, controlled clinical trial to study the safety and efficacy of triamcinolone acetonide injectable suspension (CLS-TA) for the treatment of subjects with macular edema associated with noninfectious uveitis; RVO = retinal vein occlusion; SAPPHIRE = A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA in conjunction with intravitreal aflibercept in subjects with diabetic macular edema; TYBEE = Randomized, double masked, controlled study comparing the safety and efficacy of suprachoroidal CLS-TA with intravitreal aflibercept versus aflibercept alone in subjects with diabetic macular edema.

*Statistically significant, Benjamini-Hochberg procedure.
Table 4. Coefficients of Determination from Simple and Multiple Linear Regressions

<table>
<thead>
<tr>
<th>Study Participants</th>
<th>Change from Baseline in Best-Corrected Visual Acuity and Central Subfield Thickness</th>
<th>R² (%)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled RVO</td>
<td></td>
<td>30.0</td>
<td>Full (multiple)</td>
</tr>
<tr>
<td>Pooled DME</td>
<td></td>
<td>31.6</td>
<td>Full (multiple)</td>
</tr>
<tr>
<td>Pooled NIU</td>
<td></td>
<td>14.6</td>
<td>Full (multiple)</td>
</tr>
<tr>
<td>Pooled RVO, DME, NIU</td>
<td></td>
<td>30.1</td>
<td>Reduced (simple)</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; CST = central subfield thickness; DME = diabetic macular edema; NIU = noninfectious uveitis; RVO = retinal vein occlusion.

The coefficient of determination (R²) is the proportion of the variance that is predicted from the independent variables. For the baseline data, the full model represents a multiple linear regression with baseline BCVA as the dependent variable and baseline CST and age as the independent variables. The reduced model represents a simple linear regression with baseline BCVA as the dependent variable and baseline CST as the independent variable. For the week 24 data, the full model represents a multiple linear regression with change from baseline in BCVA as the dependent variable and baseline CST, age, and change from baseline in CST as the independent variables. The reduced model represents a simple linear regression with change from baseline in BCVA as the dependent variable and change from baseline in CST as the independent variable.

The DME patients in HULK showed better mean baseline BCVA than TYBEE patients (67.2 ETDRS letters vs. 57.6 ETDRS letters, respectively) with better mean baseline CST (447.2 µm vs. 501.3 µm, respectively). At baseline, low, but not statistically significant, negative linear correlation was found between BCVA and CST in HULK (r = -0.38, P = 0.096); however, TYBEE showed moderate negative correlation that was statistically significant (r = -0.50, P < 0.001). The slope of the regression line from this pooled data (Fig 2A) correlated to an average improvement of 4.4 ETDRS letters (95% CI, 2.8–6.0 ETDRS letters) for every 100-µm reduction in CST. Central subfield thickness accounted for only 30.1% of the total variation in BCVA at baseline; as shown in Table 4, when including age along with CST in the multiple linear regression analysis, little difference was found.

The NIU patients in PEACHTREE showed worse mean baseline BCVA than AZALEA patients (54.2 ETDRS letters vs. 68.9 ETDRS letters, respectively) with worse mean baseline CST (498.7 µm vs. 335.9 µm, respectively), likely related to the PEACHTREE eligibility requirement for CST of 500 µm or more. PEACHTREE showed a low negative linear correlation between BCVA and CST that was statistically significant (r = -0.31, P < 0.001), whereas AZALEA showed no significant correlation between BCVA and CST (r = -0.20, P = 0.232). The pooled NIU data showed low to moderate negative linear correlation between BCVA and CST (r = -0.38, P < 0.001). The slope of the regression line from this pooled data (Fig 3A) reflected an average increase of 3.8 ETDRS letters (95% CI, 2.5–5.1 ETDRS letters) for every 100-µm reduction in CST. At baseline, CST accounted for only 14.6% of the total variation in BCVA; when including age along with CST in the multiple linear regression analysis, little difference was found, as shown in Table 4.

Between-disease state comparisons were performed for linear correlations between baseline BCVA and baseline CST. No significant differences were noted in comparison between disease states (DME vs. RVO, P = 0.283; DME vs. NIU, P = 0.168; RVO vs. NIU, P = 0.446). When pooling all 1063 patient eyes regardless of disease state, a moderate negative linear correlation was found between baseline BCVA and CST (r = -0.55, P < 0.001). The slope of the regression line from this pooled data (Fig 4A) correlated to an average improvement of 3.3 ETDRS letters (95% CI, 3.0–3.7 ETDRS letters) for every 100-µm reduction in CST. At baseline, CST accounted for 30.1% of the total variation in BCVA, on average, across disease states.

Association between Changes in Best-Corrected Visual Acuity and Changes in Central Subfield Thickness at 24 Weeks

Analyses of BCVA and CST data at week 24 included 721 eyes from 721 patients who completed 24 weeks of follow-up and had RVO (454 eyes), DME (82 eyes), and NIU (185 eyes). In the RVO trials at week 24, a low negative linear correlation between the change in BCVA and the change in CST was shown in SAPPHIRE (r = -0.33, P < 0.001), whereas TOPAZ showed...
Figure 1. Scatterplots showing correlations in retinal vein occlusion. A. Central subfield retinal thickness and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) at baseline ($r = -0.56$, $P < 0.001$). B. Change in central subfield retinal thickness and change in ETDRS BCVA at week 24 ($r = -0.35$, $P < 0.001$). Regression lines (solid) are plotted for pooled data along with lines (dashed) outlining 95% confidence intervals for mean predicted values. SAPPHIRE = A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA in conjunction with intravitreal aflibercept in subjects with retinal vein occlusion; TOPAZ = A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA with an intravitreal anti-VEGF in subjects with retinal vein occlusion.

Figure 2. Scatterplots showing correlations in diabetic macular edema. A. Central subfield retinal thickness and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) at baseline ($r = -0.50$, $P < 0.001$). B. Change in central subfield retinal thickness and change in ETDRS BCVA at week 24 ($r = -0.30$, $P = 0.006$). Regression lines (solid) are plotted for pooled data along with lines (dashed) outlining 95% confidence intervals for mean predicted values. HULK = Open-label study of the safety and efficacy of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept for the treatment of diabetic macular edema; TYBEE = Randomized, double masked, controlled study comparing the safety and efficacy of suprachoroidal CLS-TA with intravitreal aflibercept versus aflibercept alone in subjects with diabetic macular edema.

Figure 3. Scatterplots showing correlations in noninfectious uveitis. A. Central subfield retinal thickness and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) at baseline ($r = -0.38$, $P < 0.001$). B. Change in central subfield retinal thickness and change in ETDRS BCVA at week 24 ($r = -0.42$, $P < 0.001$). Regression lines (solid) are plotted for pooled data along with lines (dashed) outlining 95% confidence intervals for mean predicted values. AZALEA = Open-label safety study of suprachoroidal triamcinolone acetonide injectable suspension in patients with noninfectious uveitis; PEACHTREE = A phase 3, randomized, masked, controlled clinical trial to study the safety and efficacy of triamcinolone acetonide injectable suspension (CLS-TA) for the treatment of subjects with macular edema associated with noninfectious uveitis.
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Although numerically similar, between-disease state comparisons were performed using a linear regression model for change in BCVA and change in CST at week 24. Comparison between disease states identified a significant difference between DME and NIU only (DME vs. NIU, $P = 0.034$; DME vs. RVO, $P = 0.098$; RVO vs. NIU, $P = 0.277$).

When pooling all 721 patient eyes who completed 24 weeks of follow-up, regardless of disease state, moderate negative linear correlation was found between change in BCVA and change in CST from baseline to 24 weeks ($r = −0.40, P < 0.001$). The slope of the regression line from this pooled data (Fig 4B) correlated with an average improvement of 3.5 ETDRS letters (95% CI, 2.8–4.3 ETDRS letters) for every 100-μm decrease in CST. At week 24, in the simple linear regression analysis, change in CST accounted for only 16.2% of the total variation in the change in BCVA; in the multiple linear regression analysis, change in CST, age, baseline BCVA, and baseline CST accounted for 29.6% of the total variation in change in BCVA across disease states.

Association between Best-Corrected Visual Acuity and Central Subfield Thickness Stratified by Chronicity

Assessment of correlation between BCVA and CST also was stratified by chronicity, as summarized in Table 5, with acute duration of diagnosis defined as less than the pooled median for each disorder. When stratified into acute and chronic categories, pooled data from the RVO trials showed similar linear correlations to the nonstratified correlations at baseline. Duration-stratified correlations between the change in BCVA and the change in CST also were similar to the nonstratified data. The trends were similar for the NIU trials, with acute and chronic ME showing similar correlations to the nonstratified correlations. Because of the disparity between the DME trials in median duration of diagnosis (HULK: median, 12.5 years; TYBEE: median, 20.0 days), patients in HULK represent patients with chronic DME, whereas patients in TYBEE reflect patients in a more acute disease state.

Figure 4. Scatterplots showing correlations in all eyes pooled across disease states. A, Central subfield retinal thickness and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) at baseline ($r = −0.55, P < 0.001$). B, Change in central subfield retinal thickness and change in ETDRS BCVA at week 24 ($r = −0.40, P < 0.001$). Regression lines (solid) are plotted for pooled data along with lines (dashed) outlining 95% confidence intervals for mean predicted values. DME = diabetic macular edema; NIU = noninfectious uveitis; RVO = retinal vein occlusion.
Table 5. Correlation and Regression Analysis between Early Treatment Diabetic Retinopathy Study Best-Corrected Visual Acuity and Central Subfield Thickness for Subgroups

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Pearson Correlation Coefficient (95% CI)</th>
<th>Baseline Best-Corrected Visual Acuity per 100-μm Absolute Reduction in Central Subfield Thickness (95% Confidence Interval)</th>
<th>P Value</th>
<th>Week 24 Change in Best-Corrected Visual Acuity per 100-μm Reduction in Central Subfield Thickness (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled RVO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute(^1)</td>
<td>384</td>
<td>-0.58 ( -0.65 to -0.51)</td>
<td>1.57 (0.05 to 3.10)</td>
<td>&lt;0.001(^1)</td>
<td>270 -0.31 ( -0.42 to -0.20)</td>
<td>1.61 (1.02 to 2.20)</td>
</tr>
<tr>
<td>Chronic(^1)</td>
<td>390</td>
<td>-0.53 ( -0.60 to -0.46)</td>
<td>2.43 (0.05 to 4.82)</td>
<td>&lt;0.001(^1)</td>
<td>184 -0.41 ( -0.52 to -0.28)</td>
<td>2.24 (1.52 to 2.97)</td>
</tr>
<tr>
<td>CST ≤ median(^1)</td>
<td>161</td>
<td>-0.04 ( -0.20 to 0.11)</td>
<td>0.48 ( -1.30 to 2.26)</td>
<td>0.598</td>
<td>217 -0.14 ( -0.27 to -0.01)</td>
<td>1.64 (0.07 to 3.21)</td>
</tr>
<tr>
<td>CST &gt; median(^1)</td>
<td>158</td>
<td>-0.46 ( -0.57 to -0.33)</td>
<td>3.28 (2.28 to 4.28)</td>
<td>&lt;0.001(^1)</td>
<td>237 -0.33 ( -0.44 to -0.21)</td>
<td>2.08 (1.32 to 2.84)</td>
</tr>
<tr>
<td>Pooled DME</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CST ≤ median(^2)</td>
<td>46</td>
<td>-0.02 ( -0.31 to 0.27)</td>
<td>0.49 ( -5.79 to 6.77)</td>
<td>0.876</td>
<td>43  0.03 ( -0.27 to 0.33)</td>
<td>-0.60 ( -6.40 to 5.20)</td>
</tr>
<tr>
<td>CST &gt; median(^2)</td>
<td>45</td>
<td>-0.44 ( -0.65 to -0.17)</td>
<td>4.91 (1.84 to 7.98)</td>
<td>0.002(^1)</td>
<td>39  -0.31 ( -0.57 to 0.01)</td>
<td>2.19 ( -0.04 to 4.43)</td>
</tr>
<tr>
<td>Pooled NIU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute(^3)</td>
<td>101</td>
<td>-0.39 ( -0.55 to -0.21)</td>
<td>5.61 (3.09 to 8.13)</td>
<td>&lt;0.001(^1)</td>
<td>95  -0.50 ( -0.64 to -0.33)</td>
<td>4.04 (2.61 to 5.48)</td>
</tr>
<tr>
<td>Chronic(^3)</td>
<td>97</td>
<td>-0.37 ( -0.53 to -0.18)</td>
<td>4.48 (1.94 to 7.01)</td>
<td>&lt;0.001(^1)</td>
<td>90  -0.29 ( -0.47 to -0.09)</td>
<td>2.79 (0.86 to 4.71)</td>
</tr>
<tr>
<td>CST ≤ median(^3)</td>
<td>99</td>
<td>-0.18 ( -0.36 to 0.02)</td>
<td>5.23 ( -0.51 to 12.97)</td>
<td>0.074</td>
<td>94  -0.46 ( -0.60 to -0.28)</td>
<td>6.40 (3.85 to 8.96)</td>
</tr>
<tr>
<td>CST &gt; median(^3)</td>
<td>99</td>
<td>-0.27 ( -0.45 to -0.08)</td>
<td>3.46 (1.02 to 5.91)</td>
<td>0.006(^1)</td>
<td>91  -0.34 ( -0.51 to -0.14)</td>
<td>3.02 (1.26 to 4.78)</td>
</tr>
</tbody>
</table>

CST = central subfield thickness; DME = diabetic macular edema; NIU = noninfectious uveitis; RVO = retinal vein occlusion.

\(^1\)For the pooled DME trials, the median CST at baseline was 461 μm.
\(^2\)For the pooled RVO trials, chronic is defined as a duration of diagnosis of 16 months or more.
\(^3\)For the pooled NIU trials, acute is defined as a duration of diagnosis less than the pooled median, that is, 15 days, and chronic is defined as a duration of diagnosis of 16 months or more.
Association between Best-Corrected Visual Acuity and Central Subfield Thickness Stratified by Baseline Central Subfield Thickness

Correlations between BCVA and CST were stratified by baseline CST, either more than or less than the pooled median CST by disease state, as summarized in Table 5. In pooled baseline data from the RVO, DME, and NIU trials, low to no linear correlation was found in the subgroup of patients with a baseline CST of less than the median, whereas patients whose baseline CST was more than the median showed correlations similar to the nonstratified data. Correlations between change in BCVA and change in CST for the pooled RVO and DME trials for patients with a baseline CST of more than the disease-specific median were consistent with the nonstratified data, whereas those with a baseline CST less than the median showed a weak correlation. For the pooled NIU trials, both subgroups showed correlations similar to the nonstratified data.

Association between Baseline Best-Corrected Visual Acuity and Baseline Central Subfield Ellipsoid Zone Integrity

Analysis of baseline BCVA and central subfield EZ status data included 185 eyes with gradable EZ from 185 patients diagnosed with DME (41 eyes) and NIU (144 eyes). Mean BCVA at baseline ranged from 64.0 letters to 37.7 letters across the 4 central subfield EZ categories, with vision generally worsening as the integrity of the central subfield EZ deteriorated (Fig 5A). All pairwise comparisons of the baseline BCVA means were statistically different ($P \leq 0.050$), with the exception of the comparison between patients with normal and questionably abnormal grades.

In the 169 eyes with available age, baseline CST, and EZ grading, CST accounted for 21.2% of the total variation in BCVA on average across the two disease states (linear regression), whereas central subfield EZ grade accounted for 26.4% of the total variation in BCVA on average (analysis of variance). Likewise at baseline, central subfield EZ grade, CST, and age together accounted for 33.2% of the total variation in BCVA on average across the two disease states (analysis of covariance).

Association between Changes in Best-Corrected Visual Acuity and Changes in Central Subfield Ellipsoid Zone Integrity at 24 Weeks

Analysis of BCVA and EZ data at week 24 included 169 eyes with gradable EZ from 169 patients who completed 24 weeks of follow-up with DME (36 eyes) and NIU (133 eyes). The number of steps changed in the status of the EZ ranged from a worsening of 3 steps, that is, worsening from normal at baseline to definitely abnormal (absent) at 24 weeks, to an improvement of 3 steps, that is, improving from definitely abnormal (absent) at baseline to normal at 24 weeks. Most patients (82.2%) experienced less than a 2-step change from baseline; few patients experienced a worsening of 2-steps or more (3.6%) or an improvement of 2-steps or more (14.2%).

Based on an analysis of covariance, mean change in BCVA at week 24 ranged from 19.3 letters to 8.7 letters with no discernable relationship to the number of steps changed in the grading of the central subfield EZ (Fig 5B). As expected, pairwise comparisons between all 7 EZ change categories did not show any statistically significant differences.

Association between 24-Week Changes in Best-Corrected Visual Acuity and Baseline Central Subfield Ellipsoid Zone Integrity

Analysis of 24-week change in BCVA and baseline EZ data included 169 eyes with gradable EZ from 169 patients who completed 24 weeks of follow-up and with DME (36 eyes) and NIU (133 eyes). Compared with eyes with abnormal baseline central subfield EZ (questionable abnormal, definitely abnormal [patchy], and definitely abnormal [absent]), eyes with normal baseline central subfield EZ experienced greater 24-week change in BCVA (15.00 letters vs. 8.16 letters; $P = 0.0005$, with baseline BCVA, baseline CST, and age as the covariates). This analysis of covariance model accounted for 27.8% of the total variation in 24-week BCVA change.

Discussion

In eyes with common causes of ME-related vision loss, this analysis assessed the relationship between BCVA and
macular anatomic features, specifically CST across 3 disease states and central subfield EZ integrity across 2 disease states. Limitations of this analysis include its post hoc design from studies not designed to assess these relationships and differing treatment regimens used across the various studies, as well as the limitations inherent in combining ME patients from different disease states in the pooled analyses. In addition, a limitation of grading the central subfield EZ into 4 discrete categories may be low sensitivity. The strengths of this analysis include the assessment of 2 OCT anatomic features thought to have functional correlation, as well as the use of high-quality clinical trial data involving monitor-verified diagnoses per eligibility criteria, protocol refractions, study-certified imagers, and spectral-domain OCT reading center assessment across common disease states at standardized intervals. Furthermore, the analysis included a large number of eyes compared with prior studies of CST or EZ in ME, and a broad range of visual acuities and CSTs across disease states was included, including 18 patients in AZALEA who showed CST of less than 300 μm at baseline. Baseline correlations, as well as the relationship between change from baseline in both BCVA and OCT anatomic features at 24 weeks, were assessed, regardless of treatment assignment. Consequently, treatment and control patients were assessed in the analysis, including CLS-TA patients, sham control patients, and patients who received CLS-TA in conjunction with an intravitreal anti-VEGF agent, as well as patients who received anti-VEGF monotherapy.

With respect to CST, consistent trends were found of low to moderate negative linear correlations between baseline BCVA and CST, significant in the 4 largest studies and not significant in the smaller HULK DME and AZALEA NIU studies. When pooled by disorder, at baseline, significant low-to-moderate negative linear correlations were found between BCVA and CST in patients with RVO, DME, and NIU, nearly all of whom had ME. Although ME resulting from RVO showed the strongest baseline correlation between BCVA and CST, followed by DME and NIU, these differences between disorders were not statistically significant. When pooling all 1063 patient eyes regardless of disease state, significant moderate negative linear correlation was found between baseline BCVA and CST, showing an average increase of 3.3 ETDRS letters for every 100-μm decrease in CST at baseline, but CST accounted for only 30.1% of the total variation in BCVA. In the multiple linear regression analysis, as shown in Table 4, including age as another independent variable resulted in minimal change; specifically, CST and age accounted for 30.6% of the total variation in BCVA. Age previously was shown to have a very modest effect in multiple regression models.

With respect to change from baseline to 24 weeks, significant but lower negative linear correlations were also found between BCVA and CST, in RVO and DME, compared with baseline correlations. In NIU patients, the 24-week change correlations were similar to the baseline correlations between BCVA and CST. When pooled by disorder, the correlations for change from baseline to 24 weeks were similar numerically between disorders, although statistically superior for NIU compared with DME. When pooling all 721 patient eyes who completed 24 weeks of follow-up, regardless of disease state, significant low-to-moderate negative linear correlation was found between change in BCVA and change in CST from baseline to 24 weeks, showing an average increase of 3.5 ETDRS letters for every 100-μm reduction in CST, but change in CST accounted for only 16.2% of the total variation in the change in BCVA; in the multiple linear regression analysis, change in CST, age, baseline BCVA, and baseline CST accounted for 29.6% of the total variation in change in BCVA.

Previous large studies compared BCVA and OCT-determined macular thickness. Although cross-study comparisons are limited because of differing eligibility criteria, baseline features, assessment techniques, and statistical analyses, the current analysis corroborated and amplified some of these findings across 3 different disease states with a different therapeutic approach. For example, a recent post hoc analysis from Diabetic Retinopathy Clinical Research (DRCR) Network protocol T, studying anti-VEGF agents in DME (with similar baseline mean CST and BCVA), showed similar baseline correlation in 652 eyes (namely lower r value at −0.36, but with overlapping 95% CIs). Likewise, with respect to correlations between baseline BCVA and change in CST, the DRCR Network protocol T analysis showed similar low negative correlations as the current study (the DRCR Network protocol T change correlations at 12 weeks, r = −0.36; at 52 weeks, r = −0.36; and at 104 weeks, r = −0.33). In DRCR Network protocol T, these correlations change in BCVA versus change in CST did not differ meaningfully over these time points or when stratified among 3 different anti-VEGF agents. When the linear regression models included previously identified baseline factors associated with BCVA changes (baseline BCVA, treatment group, BCVA and treatment group interaction, hemoglobin A1C, age, prior panretinal photocoagulation, DR severity), these factors accounted for only 29% of the total variation in change in BCVA (improving from 12% when only CST was considered).

Given these low negative linear correlations between BCVA and CST after therapy, one accompanying commentary emphasized that CST is not a meaningful surrogate end point marker for treatment of DME and suggested study of other anatomic markers such as EZ integrity, disorganization of retinal inner layers, and adaptive optics imaging of the photoreceptors. An earlier commentary aptly stated that ‘significant P values despite low correlations for the 2 parameters, indicate great certainty about a weak association’ and speculated on reasons for the disconnect, including variation of normal CST, disruption of anatomic connections such as disorganization of retinal inner layers, ischemia, neuropathic dysfunction, or functional tolerance of ME. These and other factors likely account for most of the total variation in change in BCVA, as opposed to CST.

Another post hoc analysis likewise assessed the relationship between BCVA and CST in 387 patients from 6 prospective clinical trials (4 single-center and 2 multicenter studies) of intravitreal anti-VEGF treatment for neovascular age-related macular degeneration, DME, and RVO. At baseline, pooled by disease, moderate negative correlation
was found between BCVA and CST in DME ($r = -0.42$), similar to the current study. In RVO-related ME, baseline BCVA did not correlate with baseline CST, but the authors note that these RVO studies enrolled ischemic cases, which highlights the inability of CST to reflect ischemia-related changes in BCVA. However, correlation between change in BCVA and change in CST did show moderate negative correlation for DME ($r = -0.45$) and RVO ($r = -0.35$) at 12 months, similar to the 24-week change correlations in the current study.

In the SCORE (Standard care versus corticosteroid for retinal vein occlusion) study of 271 patients with CRVO-related ME, correlation between baseline BCVA and central point thickness showed low negative correlation; correlation between change in BCVA and change in center point thickness at 4 and 12 months showed low to moderate negative correlations across the intravitreal triamcinolone and observation groups. In the GENEVA study (Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion), assessing the dexamethasone implant in CRVO- and BRVO-related ME, correlation between change in BCVA and change in CST at 6 months also showed low negative correlation in the 403 patients who received the 0.7-mg implant ($r = -0.34$), nearly identical to the current study.

In the MUST (Multicenter uveitis steroid treatment) trial comparing the fluocinolone acetonide intravitreal implant (0.59 mg) with systemic therapy involving 128 eyes with uveitic ME, BCVA, and CST showed moderate negative correlation at baseline ($r = -0.56$); change in BCVA showed moderate negative correlation with change in CST at 6 months ($r = -0.46$). These correlations were somewhat stronger than those in the current study, but the MUST study used earlier OCT technology (time-domain OCT) and different statistical analysis (Spearman rank correlation, a nonparametric equivalent to Pearson correlation). The MUST trial also concluded that a 20% change in retinal thickness represented an optimal threshold for meaningful changes in BCVA and that this may represent a suitable outcome measure in uveitic ME treatment trials.

Overall, in the current study, the fact that the CST correlations held across 3 different disease states at baseline is of interest, but the similar correlations for change in BCVA and change in CST despite different treatment methods also is intriguing. That is, BCVA may not improve meaningfully more for a given change in CST, whether it is spontaneous or mediated by intravitreal anti-VEGF agents or corticosteroids, at least for DME, RVO-related ME, and NIU-related ME.

Regarding chronicity, one might expect better correlation between BCVA and CST in acute ME compared with chronic ME, which more frequently may involve atrophy, ischemia, or neuropathic dysfunction in the contiguous retinal cellular complex. However, the current analysis did not corroborate this presupposition, further highlighting the limited correlation between BCVA and CST. Specifically, when stratified into acute and chronic categories, based on the pooled median duration for each disorder, similar correlations were found to the nonstratified correlations at baseline for RVO- and NIU-related ME. Duration-stratified correlations between the change in BCVA and the change in CST also were similar to the nonstratified data for RVO and NIU. These trends held for both disorders, despite the much greater degree of chronicity in the RVO ME patients. The chronicity analysis in DME was limited by the small sample size of the patients with chronic disease (HULK).

The impact of baseline CST on correlations is of interest. Of note, the pooled baseline data in each disease state show low to no correlation between BCVA and CST in the subgroup of patients with a baseline CST of less than the median, whereas patients with a baseline CST of more than the median showed correlations similar to the nonstratified data. Change correlations at 24 weeks showed similar trends in the pooled DME and pooled RVO studies, but not in the pooled NIU trials, in which both subgroups showed correlations similar to the nonstratified data. The trend of decreased correlation between BCVA and CST with lower baseline CST seems logical, suggesting vision loss resulting from other factors beyond ME, such as disruption of anatomic connections, ischemia, and neuropathic dysfunction.

Ellipsoid zone integrity may represent one such factor, because it reflects anatomic arrangement of photoreceptor outer segments and shows functional correlation in ME resulting from RVO, DME, and NIU. The current study demonstrated that mean baseline BCVA progressively worsened with each of 4 central subfield EZ grades in pooled eyes with DME and uveitic ME, with statistically significant pairwise comparisons except between Normal and Questionably Abnormal EZ grades. In addition, eyes with normal baseline central subfield EZ showed a meaningfully greater 24-week change in BCVA compared with eyes with abnormal baseline central subfield EZ, consistent with a prior DME study in which 122 eyes of 122 patients received intravitreal anti-VEGF therapy over 6 months. In the current study, over the course of 24 weeks, few patients showed a change in central subfield EZ grade of 2 steps or more, and consequently, it is not surprising that no relationship was found between number of EZ grades changed and mean change in BCVA. In particular, a limitation of grading the central subfield EZ into 4 discrete categories may be low sensitivity compared with specifically assessing the subfoveal central point EZ, using a continuous measure, or both.

One such continuous EZ measure includes central macular EZ—retinal pigment epithelium thickness (a surrogate for photoreceptor outer segment length), which independently correlated with BCVA at multiple visits in a 100-week clinical trial of aflibercept in 106 eyes of 106 patients with DME. In addition, that study also demonstrated significant improvement in EZ integrity, which correlated with visual function over the course of treatment. In uveitic ME, one study of adalimumab in 56 eyes of 42 patients assessed extent of EZ disruption as a continuous variable, in micrometers along 7 OCT B-scans, including 1 scan passing through the fovea and 3 scans each passing above and below the fovea. At baseline, no significant association was found between EZ disruption and BCVA, but an association was found when assessed across visits. Nevertheless, across these studies, the various measures of EZ disruption cannot account for most variation in BCVA, and consequently, many of the aforementioned studies suggest that additional OCT parameters, such as disruption of retinal inner layers, have some functionally...
predictive value. It is also important to recognize that EZ grading may be affected because of shadowing from the intraretinal cysts and from pathologic features such as retinal hemorrhage and exudates, which explains why gradable EZ values at baseline were obtained in 58% of eyes with DME and in 73% of eyes with ME resulting from NIU. As OCT imaging technology improves, future studies will assess additional measures approaching retinal cell—specific precision.

Conclusions

In summary, this analysis assessed the relationship between BCVA and CST in ME resulting from RVO, DME, and NIU using clinical trial data and involving monitor-verified diagnoses per eligibility criteria, protocol refractions, study-certified imagers, and OCT reading center assessment. At baseline, significant moderate negative linear correlations were found between BCVA and CST in patients with ME resulting from RVO, DME, and NIU, nearly all of whom had ME, but CST accounted for 30% of the total variation in BCVA. With respect to change from baseline to 24 weeks, significant but low negative linear correlations also were found between BCVA and CST across these disease states, but change in CST accounted for only 16% of the total variation in change in BCVA. When pooling data across all 3 disease states, at week 24, change in CST, age, baseline BCVA, and CST still accounted for only 30% of the total variation in change in BCVA. To account further for variation in BCVA, this analysis also assessed the relationship between BCVA and central subfield EZ grade, another OCT anatomic feature with functional implication, in the 3 studies with this information. In this subset of pooled eyes with DME and uveitic ME, CST accounted for only 21.2% of the total variation in BCVA on average, whereas central subfield EZ grade accounted for only 26.4% of the total variation in BCVA on average. Likewise at baseline, central subfield EZ grade, CST, and age together accounted for only 33.2% of the total variation in BCVA on average across these 2 disease states. Although eyes with normal baseline central subfield EZ showed a meaningfully greater 24-week change in BCVA compared with eyes with abnormal baseline central subfield EZ, the model could account for only 28% of the total variation in BCVA change. Consequently, this study corroborates and amplifies findings from prior studies, demonstrating that CST and central subfield EZ integrity, as graded herein, may provide context for clinical decision making, but may not be used reliably as surrogate end point markers for treatment in patients with ME resulting from RVO, DME, or NIU.

Footnotes and Disclosures


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HUMAN SUBJECTS: Human subjects were included in this study. Because this post hoc analysis involved assessment of already collected de-identified information, it is exempt from review by an institutional review board, but all of the clinical trial protocols were approved by human ethics committees at each study site, and these clinical trials adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent before these studies commenced.
No animal subjects were included in this study.
Author Contributions:
Conception and design: Ciulla
Analysis and interpretation: Ciulla, Kapik, Grewal, Ip
Data collection: Ciulla, Kapik
Obtained funding: Ciulla

Overall responsibility: Ciulla, Kapik, Grewal, Ip

Abbreviations and Acronyms:
AZALEA = Open-label safety study of suprachoroidal triamcinolone acetonide injectable suspension in patients with noninfectious uveitis;
BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CI = confidence interval; CRVO = central retinal vein occlusion; CST = central subfield thickness; DME = diabetic macular edema; DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; EZ = ellipsoid zone; HULK = Open-label study of the safety and efficacy of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept for the treatment of diabetic macular edema; ME = macular edema; NIU = noninfectious uveitis; OCT = optical coherence tomography; PEACHTREE = A phase 3, randomized, masked, controlled clinical trial to study the safety and efficacy of triamcinolone acetonide injectable suspension (CLS-TA) for the treatment of subjects with macular edema associated with noninfectious uveitis; RVO = retinal vein occlusion; SAPPHIRE = A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA in conjunction with intravitreal aflibercept in subjects with retinal vein occlusion; TOPAZ = A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA with an intravitreal anti-VEGF in subjects with retinal vein occlusion; TYBEE = Randomized, double masked, controlled study comparing the safety and efficacy of suprachoroidal CLS-TA with intravitreal aflibercept versus aflibercept alone in subjects with diabetic macular edema; VEGF = vascular endothelial growth factor.

Keywords:
Central subfield thickness, Ellipsoid zone, Macular edema, Photoreceptor inner segment–outer segment junction, Visual acuity.

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