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Choroidal Changes after Suprachoroidal Injection of Triamcinolone in Eyes with Macular Edema Secondary to Retinal Vein Occlusion

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Abstract

Purpose—To evaluate choroidal and suprachoroidal changes following suprachoroidal injection of triamcinolone acetate injectable suspension (CLS-TA), in eyes with macular edema due to retinal vein occlusion (RVO).

Design—Prospective cohort study within a randomized, controlled phase 2 clinical trial.

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Methods—Enhanced-depth imaging optical coherence tomography (EDI-OCT) images were analyzed from 38 eyes of 38 treatment naïve patients with macular edema due to RVO, enrolled in the prospective Suprachoroidal Injection of Triamcinolone Acetonide with Intravitreal Aflibercept in Subjects with Macular Edema Due to Retinal Vein Occlusion (TANZANITE) study who received either a suprachoroidal injection of CLS-TA with an intravitreal injection of aflibercept (combination arm) or only an intravitreal injection of aflibercept (monotherapy arm) followed by monthly intravitreal aflibercept injections in both arms based on pro re nata (PRN) criteria.

Results—Macular choroidal thickness measured to the outer choroidal vessel lumen (vascular choroidal thickness, VCT), outer choroid stroma (stromal choroidal thickness, SCT), or inner scleral border (total choroidal thickness, TCT) showed no significant changes over 3 months in both study arms ($P = 0.231$ – 0.342). Eyes that received combination therapy showed a trend toward thickening of the suprachoroidal space (SCS) compared with monotherapy alone ($13.4\ \mu\text{m}$ vs $5.3\ \mu\text{m}$ at 3 months; $P=0.077$). In the 15 eyes that demonstrated a visible SCS at baseline, the SCS expanded significantly after suprachoroidal CLS-TA injection ($16.2\ \mu\text{m}$ to $27.8\ \mu\text{m}$ at 3 months; $P=0.033$).

Conclusions—Suprachoroidal injection of CLS-TA does not alter choroidal thickness in eyes with macular edema due to RVO, but may result in expansion of the SCS.

Keywords

aflibercept; drug delivery; retinal vein occlusion; suprachoroidal injection; suprachoroidal space; triamcinolone acetonide

Retinal vein occlusion (RVO) is the second leading cause of retinal vascular disease after diabetic retinopathy, with an estimated prevalence of 0.5% in people older than 50 years of age.^{1–4} Central and branch retinal vein occlusions (CRVO and BRVO) cause vascular congestion, endothelial damage, and release of inflammatory cytokines, which together contribute to the development of macular edema and vision loss in patients.⁵ Current treatments for macular edema from RVO include intraocular injections of anti-vascular endothelial growth factor (anti-VEGF) agents or steroids, although the latter have been relegated as second-line therapy due to concerns for cataract formation and intraocular pressure (IOP) elevation associated with intravitreal steroids.^{5–15}

Recent advances in OCT technology have provided a better understanding of the choroidal-scleral junction, where the suprachoroidal space may be visible in some individuals.^{16, 17} The suprachoroidal space contributes to uveoscleral outflow dynamics,¹⁸ and has been a target for glaucoma drainage devices and for temporary buckling for retinal detachments using viscoelastics.^{19–21} The suprachoroidal space provides a novel route for drug delivery with access to the retina and choroid, while potentially limiting exposure to the anterior segment and minimizing risk for cataracts and glaucoma for corticosteroid delivery.^{17, 22–28} Ocular distribution studies in rabbits showed more than 10-fold higher concentrations of triamcinolone acetonide (TA) in the posterior segment of the eye after suprachoroidal delivery, compared with higher concentrations of TA in anterior segment tissues after intravitreal injections.²⁸ Suprachoroidal administration of 0.2 mg TA was also as effective in reducing ocular inflammation in a pig model of uveitis as 2.0 mg intravitreally injected TA.

²⁶ In a phase 1/2 open-label study, a single suprachoroidal injection of 4 mg TA was well tolerated and showed possible efficacy in eight human subjects with noninfectious intermediate, posterior, or pan-uveitis, with no reports of steroid-related IOP elevation or need for IOP-lowering medication.⁶ These results in part led to the initiation of two randomized controlled phase 2 clinical trials evaluating the use of suprachoroidal TA injections in patients with non-infectious uveitis and RVO, and the planning of a third phase 2 trial in patients with diabetic macular edema.²⁹

While past animal studies have evaluated choroidal morphologic changes following suprachoroidal drug delivery, these changes have not yet been described in humans.^{23, 25, 30} The goal of this study was to evaluate choroidal thickness (CT) changes over a 3-month period in a randomized phase 2 multicenter trial comparing intravitreal aflibercept with and without a single suprachoroidal administration of CLS-TA, a 40 mg/mL preservative-free, terminally sterilized ophthalmic aqueous injectable suspension of TA, in eyes with macular edema due to RVO.

Methods

Patient Selection

Enhanced depth imaging optical coherence tomography (EDI-OCT) images were obtained from all patients enrolled in the Suprachoroidal Injection of Triamcinolone Acetonide with Intravitreal Aflibercept in Subjects with Macular Edema Due to Retinal Vein Occlusion (TANZANITE) multicenter clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT02303184). The study was conducted in compliance with the Declaration of Helsinki, and informed consent was obtained from all patients prior to any study-specific procedures being performed. Institutional review boards from each site approved the study protocol prior to initiation in February 2015. Final data collection was completed for the primary outcome measure in March 2016.

The study enrolled 46 patients diagnosed with macular edema due to RVO of ≥ 12 months duration, with best-corrected visual acuity (BVCA) of 20 to 70 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters and central subfield thickness (CST) $> 310 \mu\text{m}$ as segmented and measured by the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) spectral domain optical coherence tomography (SD-OCT) instrument.³¹ Eyes were excluded if they received any prior intravitreal anti-VEGF injection for RVO, received a corticosteroid injection in the past 3 months, or had any uncontrolled ophthalmic condition other than RVO. Only one eye per patient was enrolled in the study.

Patients were randomized at baseline to receive a single 2 mg (50 μL) intravitreal injection of aflibercept followed by either a single suprachoroidal injection of 4 mg in 100 μL of CLS-TA suspension (combination arm) or a sham suprachoroidal injection (monotherapy arm). Suprachoroidal injections were administered using a proprietary syringe, which included an approximately 1-mm long, 30-gauge needle attached to a 1-mL syringe via a Luer lock, called a microinjector (Clearside Biomedical Inc., Alpharetta, GA).⁶ The CLS-TA suspension was injected 4–5 mm posterior to the limbus, approximately 200–300 μm anterior to the retina. After initial treatment, patients were examined on a monthly basis, and

additional intravitreal aflibercept was given if there was any fluid with CST > 340 μ m, any vision loss of 10 or more ETDRS letters from the prior visit, or vision loss of 10 or more letters accompanied by an increase in fluid of at least 50 μ m. For subjects in the monotherapy arm, a sham suprachoroidal procedure was performed using a needleless hub on the microinjector to simulate the suprachoroidal injection procedure, while keeping all other components of the procedure as identical to the suprachoroidal injection in the combination arm, including the use of topical anesthetics.

Image Acquisition & Analysis

EDI-OCT images were acquired using a Spectralis SD-OCT and consisted of a single 20-degree horizontal line scan (~ 5.8 mm), centered on the fovea, taken in high-speed EDI-mode using the eye-tracking Automatic Real-Time (ART) mode with 100 frames captured per image. Automated image registration using Spectralis software was employed to ensure the same B-scan location at each visit for each study eye.

Deidentified EDI-OCT images were analyzed by two masked, independent graders (ASW, VSV) using the Duke Optical Coherence Tomography Retinal Analysis Program (DOCTRAP) for semi-automatic segmentation of Bruch's membrane and the choroidal-scleral junction.³² The choroidal-scleral junction was defined as 1) the outer border of the choroidal vessel lumen, 2) the outer border of the choroidal stroma, and 3) the inner border of the sclera, to measure the vascular choroidal thickness (VCT), stromal choroidal thickness (SCT), and total choroidal thickness (TCT), respectively (Figure 1).^{17, 33} The thickness of the suprachoroidal space (SCS) was determined from the difference between TCT and SCT. Thickness measurements were acquired at 0.005 mm intervals from 1.5 mm nasal to 1.5 mm temporal to the fovea, with 601 measurements per eye averaged across the central 3 mm segment around the fovea, which provides greater reproducibility than single-location measurements.³³ Eyes that did not undergo EDI-OCT imaging, or had EDI-OCT images that were deemed ungradable due to poor image quality or to the choroidal-scleral junction being outside the scan area, were excluded from the analysis. Eyes were also graded subjectively for the presence of a visible SCS, defined as a distinct hyporeflective band between the choroidal stroma and sclera, as previously described.¹⁷

Statistical Analysis

A mixed repeated-measures analysis of variance (ANOVA) was used to compare changes between the treatment and control groups across time points in VCT, SCT, TCT, and SCS thickness. A quantitative criterion for SCS presence was determined using a receiver operating characteristic (ROC) curve and Youden's index to measure the SCS thickness threshold value that provides maximal sensitivity and specificity for SCS visibility as qualitatively determined by trained graders. Intraclass correlation coefficients (ICC) were used to determine intergrader agreement of CT measurements. All statistical analyses were performed using SPSS (v.1.0.0.407, IBM Corp., NY). A p-value of < 0.05 was considered to be statistically significant.

Results

Demographics & Baseline Characteristics

Among the 46 participants enrolled in the prospective phase 2, TANZANITE, study, 38 subjects had EDI-OCT images that qualified for inclusion in this image analysis. Of these 38 subjects, mean age was 66 (range, 37–91) and 20 participants (52.6%) were male (Table 1). Thirty-three participants (86.8%) were Caucasian/Hispanic, 4 were African American, and 1 was Native American. There were no significant differences in age, sex, and racial distribution between the combination and monotherapy arms (Table 1). There were also no statistical differences in baseline visual acuity, or mean central VCT, SCT, and TCT between the two groups. There were also no significant difference in proportion of subjects with prior ocular surgery or laser therapy ($P = 0.204$).

Choroidal Thickness Changes

Mean central VCT, SCT, and TCT showed no significant change over the 3 months after treatment in either the combination arm which received both suprachoroidal CLS-TA and intravitreal aflibercept, or the monotherapy arm that received only intravitreal aflibercept ($P=0.231-0.342$, Figure 2). There was also no significant correlation between the change in retinal thickness and any choroidal thickness measurements in either arm or at any visit ($P = 0.113 - 0.967$), consistent with previous studies.^{34, 35} There was a very slight trend toward choroidal thinning using all three posterior boundary definitions, but none of these reached statistical significance (Figure 2, Table 2). The intergrader reliability was excellent across all three CT measures ($ICC=0.94 - 0.99$), with the posterior choroidal vessel boundary (VCT) demonstrating the least reproducibility (Table 2), which was consistent with published reports.³³ There were no differences in median OCT acquisition time between subjects in the two arms at any time points ($P = 0.671$), and inclusion of image acquisition time as a co-variate showed no significant contribution from potential diurnal fluctuations ($P = 0.712$ among subjects, $P = 0.122$ between groups).

Suprachoroidal Space Thickness Changes

The SCS thickness was calculated from the difference between the TCT and SCT, which are determined by the inner border of the sclera and outer border of the choroid stroma, respectively. Eyes that received both suprachoroidal CLS-TA and intravitreal aflibercept (combination arm) showed a trend toward thickening of the SCS compared with those that had aflibercept alone in the monotherapy arm ($13.4 \mu\text{m}$ vs. $5.3 \mu\text{m}$ at 3 months; $P=0.130$; Figure 2, Supplemental Figure 1).

Using ROC analysis, the SCS was determined to be visible when SCS thickness was greater than $6.48 \mu\text{m}$ when averaged across the central 3-mm segment (Figure 3), based on a Youden's Index of 0.914 (sensitivity = 0.955, specificity = 0.959). Using this criterion, 15 out of 38 study eyes (39.5%) were defined to have a discernible SCS. A subgroup analysis of only these eyes with a visible SCS showed mild but statistically significant SCS expansion in the combination arm, where mean SCS thickness increased from $16.2 \pm 4.9 \mu\text{m}$ to $27.8 \pm 3.8 \mu\text{m}$ at 3 months, compared to the monotherapy arm which remained essentially unchanged from $10.8 \pm 4.4 \mu\text{m}$ at baseline to $10.2 \pm 3.2 \mu\text{m}$ at 3 months ($P=0.033$, Figure 4).

Discussion

Suprachoroidal drug delivery is a relatively unexplored approach for the treatment of retinal diseases with the potential to maximize drug exposure to posterior segment tissues while also reducing drug exposure to the anterior portions of the eye, including the lens. In the phase 2 TANZANITE trial, subjects who received both suprachoroidal CLS-TA and intravitreal aflibercept in the combination arm achieved both greater visual and anatomic improvements over a 3-month period following treatment at baseline, as compared to subjects in the monotherapy control arm, who only received intravitreal aflibercept at baseline.³⁶ In addition, suprachoroidal injections of CLS-TA were well tolerated with the potential to reduce the risk of glaucoma or cataract formation associated with intravitreal steroids.³⁶ In this study, we evaluated choroidal and suprachoroidal changes in the central macula following a single suprachoroidal CLS-TA injection combined with intravitreal aflibercept, and found no significant thickness change in any choroidal layers. We observed a trend toward expansion of the SCS in the combination arm as compared to the monotherapy arm, which was statistically significant in eyes with a visible SCS ($P=0.033$). We suspect that the effect was best seen in eyes with a visible SCS because eyes with a thicker SCS at baseline are more likely to allow a small thickness change to be detected, and also eyes with a wider SCS may be more susceptible to SCS expansion following suprachoroidal injection. Because there was no control arm where vehicle-only was injected into the SCS, we cannot conclude whether the mild SCS expansion is a result of the physical volume effect of the suprachoroidal fluid injection or a pharmacologic effect of the CLS-TA drug suspension. Interestingly, this SCS expansion appeared to occur within the first month after suprachoroidal administration, and remained essentially unchanged for up to the 3 months of the trial. Since the first follow-up EDI-OCT images were not obtained until 1 month after treatment, during which time the injected fluid had likely dispersed into other tissues and the choroidal circulation,^{23–25} we cannot determine if a greater degree of SCS expansion might have been present in the immediate post-injection period. However, the persistence of the SCS expansion at 3 months is consistent with the 90-day window when TA concentrations are detectable in preclinical animal models, and the use of EDI-OCT imaging as a potential measure of sustained drug presence in the SCS warrants further exploration.³⁷ Nevertheless, since data were not collected past the 3 month time period, it is unclear if this apparent expansion of the SCS will diminish over time. It is also important to note that while the reproducibility of CT measurements have been well studied, the reliability of SCS measurements have not been validated and such small changes may be susceptible to measurement variability. The inclusion of additional time points immediately after SCS injections, or additional scan patterns such as high-density macular cubes for volumetric measurements may allow more robust analyses of SCS changes in future studies.

The clinical utility of measuring CT in RVO patients remains unclear to date. Recent reports suggest that baseline CT may predict visual outcomes in RVO eyes.³⁸ The choroid in eyes with macular edema due to RVO was found to be thicker than in fellow eyes, although choroidal thinning has also been noted following both intravitreal steroid and intravitreal anti-VEGF therapy including aflibercept.^{35, 38, 39} In this study, we noted no significant change in CT using three different posterior boundary definitions in either arm, suggesting

that this single suprachoroidal CLS-TA injection may not affect the overall structure of the submacular choroid in eyes with RVO. Additional larger studies to evaluate CT changes after suprachoroidal injections for both RVO and other indications would help us better understand the utility of choroidal measurements. The randomized, masked, controlled phase 2, Suprachoroidal Injection of Triamcinolone Acetonide in Subjects with Macular Edema Following Non-Infectious Uveitis study (DOGWOOD; NCT02255032) has been completed, but the absence of a control arm that did not receive suprachoroidal CLS-TA and smaller sample size precludes a robust analysis of the choroidal effect from suprachoroidal injections from that clinical trial.

Observations from TANZANITE showed that 4 subjects in the combination treatment arm developed steroid-related IOP elevations, two of whom had pre-existing glaucoma. In the imaging analysis study, we evaluated the SCS thickness changes in these 4 subjects and found no significant difference with the other subjects who did not experience any increases in IOP ($P = 0.285$). Given the rapid tissue dispersion of agents injected into the SCS, any mild, subclinical thickness changes in the choroid or SCS are unlikely to impair aqueous humor production or outflow, in contrast to more clinically-apparent choroidal effusions that may occur in pathologic conditions.

Our findings provide novel insights into the ocular distribution and anatomic effects of suprachoroidal CLS-TA injection in human eyes with macular edema due to RVO. The suprachoroidal space influences both posterior and anterior segment disease processes, and continues to be a target for new interventions including glaucoma drainage devices, IOP monitoring, and injections of pharmacologic agents. Advantages of suprachoroidal drug administration include the reduction of anterior segment exposure, lower risk of cataracts and glaucoma, and potentially more targeted or sustained drug delivery for treatment of retinal conditions. Possible concerns include a learning curve for the more complex technique, inadvertent intravitreal administration, or failed delivery if the microneedle is not completely orthogonal to the ocular contour. Nevertheless, the suprachoroidal space remains a promising new route for ocular drug delivery that warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Semi-automated choroidal segmentation of EDI-OCT images before and after suprachoroidal triamcinolone acetonide and intravitreal aflibercept injection in an eye with ME due to RVO.

Images are shown before injection (top row), and at 1 month (second row), 2 months (third row), and 3 months (bottom row) after treatment, with (left column) and without (right column) segmentation boundaries, including the inner limiting membrane (white line), RPE/Bruch's membrane complex (purple line), vascular choroidal thickness boundary (blue line),

stromal choroidal thickness boundary (yellow line), and total choroidal thickness boundary (green line). The fovea is labeled with a yellow asterisk.

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Figure 2.

Change in mean central choroidal thickness in eyes treated with suprachoroidal triamcinolone acetonide and intravitreal aflibercept (combination arm) versus intravitreal aflibercept only (monotherapy arm). Abbreviations: **VCT**, vascular choroidal thickness; **SCT**, stromal choroidal thickness; **TCT**, total choroidal thickness; **SCS**, suprachoroidal space; **IVT**, intravitreal, **TA**, triamcinolone acetonide)

Figure 3.
Receiver operating characteristic (ROC) curve using Youden's Index (YI) to measure the threshold for determining the presence or absence of a visible suprachoroidal space.

Figure 4.

Change in mean central choroidal thickness in eyes with a visible suprachoroidal space treated with suprachoroidal triamcinolone acetonide, and intravitreal aflibercept (combination arm) versus aflibercept only (monotherapy arm). Abbreviations: **VCT**, vascular choroidal thickness; **SCT**, stromal choroidal thickness; **TCT**, total choroidal thickness; **SCS**, suprachoroidal space; **IVT**, intravitreal; **CLS-TA**, preservative-free, terminally sterilized triamcinolone acetonide.

Table 1

Study Demographics

	All Subjects (n=38)	Suprachoroidal CLS-TA + Intravitreal Aflibercept - Combination Arm (n=21)	Intravitreal Aflibercept Only - Monotherapy Arm (n=17)	P-value
Age (years $\pm$ SD)	65.7 $\pm$ 12.1	67.1 $\pm$ 9.0	64.1 $\pm$ 15.3	0.451
Gender (male / female)	20 / 18	13 / 8	7 / 10	0.343
Race (CH / AA / AI)	33 / 4 / 1	19 / 2 / 0	14 / 2 / 1	0.509
Baseline VA (ETDRS letters)	50.3 $\pm$ 14.9	50.2 $\pm$ 17.1	50.5 $\pm$ 12.5	0.952
Baseline CT (mean $\pm$ SE μm)				
VCT	219.9 $\pm$ 14.2	234.9 $\pm$ 24.3	208.5 $\pm$ 15.0	0.369
SCT	248.9 $\pm$ 14.9	263.3 $\pm$ 25.4	233.5 $\pm$ 14.8	0.327
TCT	256.3 $\pm$ 15.0	272.9 $\pm$ 25.6	238.7 $\pm$ 14.5	0.262
SCS Present (%)	15 (39.5%)	9 (42.9%)	6 (35.3%)	0.744

¹ Abbreviations: CH, Caucasian/Hispanic; AA, African American; AI, American Indian; VA, visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VCT, vascular choroidal thickness; SCT, stromal choroidal thickness; TCT, total choroidal thickness; n, number; SD, standard deviation; SE, standard error; SCS, suprachoroidal space.

Table 2

Choroidal Thickness Comparisons

	VCT			SCT			TCT			SCS	
n=38	Mean Thickness (µm)	SE	ICC (95% CI)	Mean Thickness (µm)	SE	ICC (95% CI)	Mean Thickness (µm)	SE	ICC (95%CI)	Mean Thickness (µm)	SE
Suprachoroidal CLS-TA + Intravitreal Afibercept (combination arm)											
Baseline	230.10	23.41	0.94 (0.85–0.97)	258.80	24.37	0.99 (0.99–1.00)	268.00	24.66	0.99 (0.99–1.00)	9.27	2.91
Month 1	216.60	17.79		250.00	18.73		263.00	18.93		13.03	3.23
Month 2	215.10	17.46		249.80	18.69		263.50	18.67		13.69	3.28
Month 3	218.80	18.79		253.60	20.70		267.00	20.65		13.43	3.20
Intravitreal Afibercept only (monotherapy arm)											
Baseline	208.50	15.00	0.94 (0.85–0.97)	233.50	14.79	0.99 (0.99–1.00)	238.70	14.51	0.99 (0.99–1.00)	5.15	1.63
Month 1	200.00	19.09		229.80	18.11		235.30	17.51		5.49	1.25
Month 2	196.40	18.32		222.30	17.49		229.40	16.54		6.71	1.97
Month 3	186.90	15.79		218.10	17.01		223.40	16.56		5.32	1.62

Abbreviations: VCT, vascular choroidal thickness; SCT, stromal choroidal thickness; TCT, total choroidal thickness; SCS, suprachoroidal space thickness; IVT, intravitreal; CLS-TA, preservative-free, terminally sterilized triamcinolone acetate; n, number; SE, standard error; ICC, intra class correlation coefficient