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Suprachoroidal Triamcinolone Acetonide for Retinal Vein Occlusion: Results of the Tanzanite Study

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Purpose: To compare the safety and efficacy of treatment with suprachoroidal triamcinolone acetonide (CLS-TA) plus intravitreal aflibercept vs. treatment with aflibercept alone in patients with macular edema due to retinal vein occlusion (RVO).

Design: Randomized masked controlled clinical trial.

Subjects: Forty-six patients with RVO.

Methods: Subjects were randomized 1:1 to suprachoroidal injection of CLS-TA plus intravitreal aflibercept (combination arm) or sham suprachoroidal injection plus aflibercept (aflibercept arm), followed by aflibercept as needed at months 1, 2, and 3 in each arm.

Main Outcome Measures: The primary efficacy end point was the number of protocol-required aflibercept re-treatments through month 3. Secondary outcomes included mean improvement from baseline best-corrected visual acuity (BCVA), central subfield thickness (CST), and the percentage of participants with CST $\leq$310 μm at each time point.

Results: The number of re-treatments were reduced in the combination arm compared with that in the aflibercept arm (23 vs. 9; −61%; P = 0.013) and the percentage of participants requiring no re-treatments was increased (78% vs. 30%; $P = 0.003$). The mean improvement from baseline BCVA letter score in combination vs. that in the aflibercept arms was 16.1 vs. 11.4 ($P = 0.20$) at month 1, 20.4 vs. 11.9 ($P = 0.04$) at month 2, and 18.9 vs. 11.3 ($P = 0.09$) at month 3. The mean baseline CST in the combination arm (731.1 μm) decreased into the normal range at month 1 (284.7 μm) and remained there at months 2 and 3 (272.4 μm and 285.4 μm). The mean baseline CST (727.5 μm) in the aflibercept arm decreased to 322.8 μm at month 1 and increased at months 2 and 3 (383.4 μm and 384.6 μm). Edema resolution (CST $\leq$ 310 μm) occurred in 87.0%, 87.0%, and 78.3% of participants in the combination arm at months 1, 2, and 3, respectively, vs. 56.5%, 47.8%, and 47.8% of participants in the aflibercept arm. In the combination arm, 1 participant had cataract progression and 4 (2 with preexistent glaucoma) had increased intraocular pressure that was controlled with topical medication.

Conclusions: Combination intravitreal aflibercept and suprachoroidal CLS-TA is well tolerated and significantly reduces the need for additional intravitreal aflibercept injections over a 3-month period in patients with RVO. Preliminary evidence suggests that combination therapy may sustain edema resolution and improve visual outcomes. *Ophthalmology Retina 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

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Retinal vein occlusion (RVO) is a prevalent ischemic retinopathy, second only to diabetic retinopathy.[1,2] Central RVO (CRVO) occurs when there is thrombosis that occludes the main outflow vessel of the eye, and branch RVO (BRVO) results from occlusion of a proximal branch of the central vein. After CRVO, venous return from the entire retina is compromised, and after BRVO it is compromised from $\leq$50% of the retina. Thus, on average, CRVO tends to be more severe than BRVO. The retinal circulation is a closed system with little or no opportunity for collateral flow. Consequently, all blood that enters the retina through the central retinal artery must exit through the central retinal vein; therefore, obstruction of the central retinal vein or 1 of its main branches compromises perfusion to all the retina (CRVO) or $\leq$50% of the retina (BRVO), resulting in retinal ischemia and upregulation of hypoxia-stimulated genes.

The major cause of decreased vision in patients with RVO is macular edema. A small clinical trial demonstrated that the hypoxia-regulated gene product vascular endothelial growth factor (VEGF) is a particularly important stimulator of macular edema in RVO,[3] and this has since been confirmed in multicenter phase III trials.[4–9] Intravitreal (IVT) injection of VEGF-neutralizing proteins is now the first-line therapy for patients with macular edema due to RVO. In most patients, early outcomes are good, but there are some patients who have a suboptimal response to VEGF suppression,

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probably because other hypoxia-stimulated pro-permeability factors play a role.[10] Patients who have a good response to VEGF suppression often require intraocular injections for many years; after 4 years of treatment, 50% of BRVO patients and 46% of CRVO patients have not had resolution of edema and still require IVT injections of a VEGF-neutralizing protein to control edema.[11] Therefore, additional treatment approaches are needed.

Corticosteroids provide an alternative approach that has theoretical appeal because they cause transcriptional repression of many genes whose products participate in inflammation, vascular leakage, and angiogenesis.[12–14] IVT injection of triamcinolone acetonide (TA), no more frequently than every 4 months, provided benefit in patients with CRVO, but also induced cataract in many patients and increased intraocular pressure (IOP) in a substantial number of patients.[15] Intraocular injection of a dexamethasone implant reduces edema and improves vision in patients with RVO, but this treatment is also complicated by cataract in almost all patients and increased IOP in some patients.[16] Because of these side effects, IVT steroids are generally used as second-line treatment in patients with RVO who, despite a long course of injections of a VEGF-neutralizing protein, have residual edema or who cannot substantially extend the period between injections without recurrent edema.

Suprachoroidal injection provides a new route of delivery that may have advantages for administration of corticosteroids.[17] Compared with IVT injections, suprachoroidal injections of sodium fluorescein or fluorescein-labeled dextrans in rabbits resulted in vitreous fluorophotometry levels more than 10-fold higher in retina and one-tenth or less in the vitreous and anterior chamber.[18] Poorly soluble drugs or particles are present in the suprachoroidal space for several months after injection. Ocular distribution studies comparing TA levels in the retina, choroid, or anterior segment at several time points after suprachoroidal vs. IVT injections showed that after suprachoroidal injections, levels in the retina and choroid were $\geq$10-fold higher and levels in anterior segment structures were usually undetectable but when detectable were $\leq$3% of those seen after IVT injections for the same structure and time point. Thus, suprachoroidal injections of TA maximize drug levels in the retina where they are needed and minimize levels in the anterior part of the eye, which has the potential of reducing the stimuli for cataract and increased IOP. Using a syringe with a designed hub and microneedle facilitates suprachoroidal injections in an outpatient setting and minimizes the risk of an inadvertent IVT injection. A new formulation of TA (CLS-TA), which is preservative-free and terminally sterilized, can be administered through a microneedle and may be injected in an outpatient clinic. The procedure is logistically similar to an IVT injection. The Tanzanite study was designed to test the safety and efficacy of suprachoroidal injection of CLS-TA combined with IVT injection of aflibercept compared with IVT injection of aflibercept alone in patients with macular edema due to RVO.

Materials and Methods

The Tanzanite study was a phase II, multicenter, randomized, masked, active-controlled clinical trial to assess the safety and efficacy of suprachoroidal injection of 4 mg of CLS-TA combined with 2 mg of IVT aflibercept compared with 2-mg aflibercept monotherapy in patients with macular edema due to RVO. Forty-six patients with RVO were enrolled between December 2014 and November 2015 and studied at 14 sites in accordance with the International Conference for Harmonization E6 Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved at each site by an institutional review board, and the study was registered at www.ClinicalTrials.gov (NCT02303184). All participants gave written informed consent prior to entering the study. The study was funded by Clearside, who participated in coordination of the study, data collection, and data analysis. The first draft of the manuscript was written by one investigator (PAC), who along with other authors, had access to all data. Clearside performed a quality-control check to make sure all reported data and statements were correct but did not request substantive changes in message or tone.

Patient Eligibility and Exclusion Criteria

Eligible participants were male or nonpregnant female patients $\geq$18 years of age with macular edema due to RVO for $\leq$12 months and best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study[19] letter score $\geq$20 in each eye (20/400 Snellen equivalent), and $\leq$70 in the study eye (20/40 Snellen equivalent). Central subfield thickness (CST) was $\geq$310 μm measured by spectral domain-optical coherence tomography (SD-OCT). Exclusion criteria included: (1) prior suprachoroidal injection of CLS-TA or IVT injection of a VEGF-neutralizing protein in the study eye; (2) intraocular or periocular corticosteroid injection within 3 months, dexamethasone implant (Ozurdex, Allergan, Dublin, Ireland) within 6 months, Retisert (Bausch and Lomb, Bridgewater, NJ) within 1 year, or fluocinolone acetonide implant (Iluvien, Alimera Sciences, Alpharetta, GA) within 3 years in the study eye; (3) >3 macular laser photocoagulation treatments; (4) topical ophthalmic nonsteroidal anti-inflammatory drugs in the study eye within a month; (5) any ocular condition causing decreased vision other than RVO or significant media opacity that could hinder evaluation of the retina; (6) IOP >22 mm Hg, prescribed IOP-lowering medications within 30 days, or history of clinically significant IOP increase following corticosteroid treatment; (7) past vitreoretinal or glaucoma surgery in study eye; (8) myocardial infarction or stroke within 90 days of treatment; (9) uncontrolled systemic disease, immunodeficiency, or other disorders for which corticosteroid therapy are contraindicated; (10) change in an existing prescription or an investigational drug within 30 days of randomization or participation in an ocular device study within 90 days; or (11) hypersensitivity to TA, aflibercept, fluorescein, or topical anesthetics.

Study Design

During the screening visit (range, days −14 to −1), participants gave consent and BCVA, eye examination, and SD-OCT were done to assess eligibility, which was confirmed by a central reading center (EyeKor, Madison, WI). At baseline visit (day 1), participants were randomized 1:1 using blocked randomization to combination therapy of suprachoroidal injection of CLS-TA with IVT aflibercept or sham suprachoroidal injection with IVT aflibercept. The randomization code was computer generated using a central Intelligence Web Response System by an independent randomization team at a contract research organization, PPD (Wilmington,

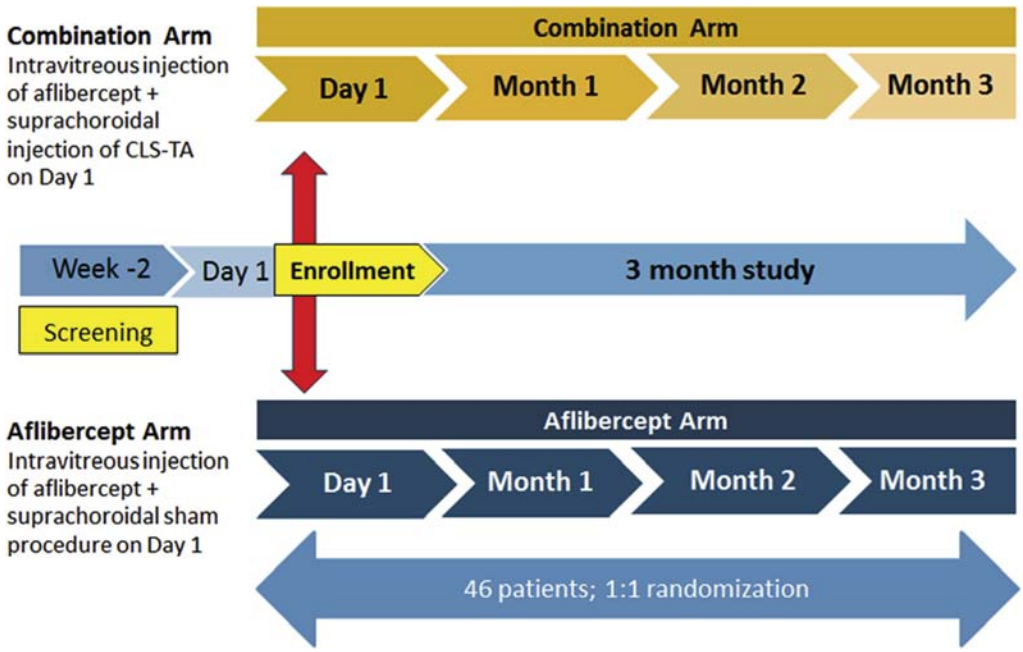

Figure 1. Tanzanite study design. At baseline, patients in the combination arm received an intravitreal (IVT) injection of aflibercept and a suprachoroidal injection of triamcinolone acetonide (CLS-TA) and patients in the aflibercept arm received an IVT injection of aflibercept and a sham suprachoroidal injection.[1] At months 1, 2, and 3, patients were given an IVT injection of aflibercept only if they met re-treatment criteria.

NC) (Fig 1). The participant, sponsor, visual acuity examiner, and reading center were masked regarding group assignment. The outer packaging of drug kits was identical to preserve masking, and masked personnel were not allowed in the treatment room when the kit was opened and the treatment administered. The treating investigator was unmasked. Participants were observed for 30 minutes after injections, and a follow-up safety phone call was made on day 2 (24–48 hours following treatment). At months 1, 2, and 3, participants received an IVT injection of aflibercept only if they met as-needed re-treatment criteria: (1) intraretinal or subretinal fluid and CST $\geq$340 μm by SD-OCT or (2) decrease in BCVA $\geq$ 10 letters from previous visit, or (3) decrease in BCVA $\geq$10 letters from best measurement and increase in CST of >50 μm from the previous visit and new fluid. If participants did not meet these criteria, they were given a sham injection. The final study evaluation was performed at month 3. The participant, sponsor, visual acuity technician, and the reading center were masked regarding treatment.

Outcome Measures

The primary efficacy end point was the number of protocol-required re-treatments with IVT aflibercept through month 3. Secondary end points included the number of participants in each arm who required aflibercept re-treatments through month 3; mean improvement from baseline BCVA and CST at months 1, 2, and 3; percentage of participants with CST $\leq$ 310 μm at months 1, 2, and 3; percentage of participants with BCVA gain $\geq$ 0, 5, 10; or 15 letters at months 1, 2, and 3; and percentage of participants with BCVA loss <15 letters at months 1, 2, and 3.

Safety end points included the incidence, relatedness to medication, and severity of treatment-emergent adverse events or serious adverse events in each arm and the percentage of participants with IOP >30 mm Hg or IOP increased >0 mm Hg from baseline at months 1, 2, and 3.

Statistical Analysis

The sample size of approximately 40 patients at approximately 10 study sites was based on clinical considerations appropriate for a randomized, phase II study. The primary end point was the total number of times subjects in each arm were required to be re-treated with IVT aflibercept through and including month 3 using predefined criteria for re-treatment as needed. A sample size of 20 in each group was calculated to have 80% power to detect an effect size of 0.80 using a 2-group *t* test with a 0.05 1-sided significance level.

A 1-sided test for primary analysis of the primary efficacy end point was used at a type I error rate of 0.05 for comparison between the combination arm and aflibercept arm. The *P* values reported for sensitivity analyses of the primary efficacy end point and statistical analyses of the secondary efficacy end points were not adjusted for multiplicity and were considered nominal. Subjects were considered as being treated if any injection (IVT aflibercept or suprachoroidal CLS-TA or sham suprachoroidal injection) was attempted (i.e., the eye was touched during an injection procedure), even if no drug was administered.

Results

Patient Demographics, Baseline Characteristics, and Disposition

A total of 46 subjects who were pharmacologically treatment naïve for their RVO were enrolled in the study, 23 in each arm. The treatment groups were well-balanced regarding age, gender, ethnicity, BCVA, which was approximately 49 in Early Treatment Diabetic Retinopathy Study letter score in each group (20/100 Snellen equivalent), and CST, which was approximately 730 μm in each group (Table 1). All subjects completed the trial and were included in safety and intent-to-treat populations.

Table 1. Patient Demographics and Baseline Characteristics

Parameter	Control Aflibercept Alone (N = 23)	Active Aflibercept + CLS-TA (N = 23)	Total (N = 46)
Age, yrs, median (range)	70.0 (37–91)	67.0 (41–80)	68 (37–91)
Female, n (%)	13 (56.5)	10 (43.5)	23 (50.0)
Ethnicity, n (%)			
White	18 (78.3)	20 (87.0)	38 (82.6)
African American	4 (17.4)	3 (13.0)	7 (15.2)
American Indian or Alaska Native	1 (4.3)	0	1 (2.2)
BRVO, n (%)	5 (21.7)	14 (60.9)	19 (41.3)
HRVO, n (%)	1 (4.3)	0	1 (2.2)
CRVO, n (%)	17 (73.9)	9 (39.1)	26 (56.5)
Mean time from diagnosis to screening, mos (SD)	0.90 (2.32)	1.34 (2.29)	1.12 (2.34)
BCVA			
ETDRS letter score			
Mean (SEM)	48.7 (14.0)	48.9 (18.0)	48.8 (15.9)
Range	20–65	20–80	20–80
Snellen equivalent	20/100	20/100	20/100
CST, μm			
Mean (SD)	727.5 (260.3)	731.1 (257.8)	729.3 (256.2)
Range	406.0–1480.0	362.0–1212.0	362.0–1480.0
Phakic, n (%)	17 (73.9)	19 (82.6)	36 (78.3)
Taking IOP-lowering drop, n (%)	2 (8.9)	6 (26.1)	8 (17.4)

BCVA =best-corrected visual acuity; BRVO = branch retinal vein occlusion; CLS-TA = triamcinolone acetonide; CRVO = central retinal vein occlusion; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; HRVO = hemiretinal vein occlusion; IOP = intraocular pressure; SD = standard deviation; SEM = standard error of the mean.

Primary Efficacy Outcome

The primary outcome was the number of protocol-required aflibercept re-treatments to determine whether combining suprachoroidal CLS-TA with IVT aflibercept caused prolonged resolution of macular edema, reducing the need for as-needed IVT aflibercept during this 3-month evaluation period. Compared with the aflibercept arm, in which there were 23 re-treatments after the initial aflibercept injection at baseline, the combination arm required significantly fewer re-treatments (9 re-treatments; $P = 0.013$, Fig 2). The number of re-treatments needed at each of the follow-up visits in the aflibercept vs. combination arms was 4 vs. 2 (month 1), 10 vs. 2 (month 2), and 9 vs. 5 (month 3). Interestingly, 2 subjects in the combination group required re-treatments at all 3 follow-up visits and account for 6 out of the 9 re-treatments; the number of patients who did not require any re-treatments was 18 of 23 (78%) in the combination arm compared with 7 of 23 (30%) in the aflibercept arm ($P = 0.003$).

Secondary Efficacy Outcomes

A second important experimental question was, does combination treatment improve visual outcomes compared with aflibercept alone? Mean baseline BCVA letter score was 48.7 in the aflibercept arm and 48.9 in the combination arm. Mean improvement from baseline letter score at each time point in the combination arm vs. the aflibercept-alone arm was 16.1 vs. 11.4 (month 1, $P = 0.20$), 20.4 vs. 11.9 (month 2, $P = 0.04$) and 18.9 vs. 11.3 (month 3, $P = 0.09$) (Fig 3). The percentage of subjects who gained ≥15 letters in the combination arm vs. the control arm was 52.2 vs. 39.1 (month 1), 60.9 vs. 39.1 (month 2), and 52.2 vs. 43.5 (month 3).

A third experimental question was, does combination treatment improve anatomic outcomes compared with aflibercept alone? Mean CST was 731.1 μm at baseline in the combination arm, and at month 1 it decreased into the normal range at 284.7 μm and remained there at months 2 and 3 (272.4 μm and 285.4 μm, Fig 4). Mean CST was 727.5 μm in the aflibercept arm and decreased substantially, but it was still above the normal range at month 1 (322.8 μm) and increased at months 2 and 3 (383.4 μm and 384.6 μm). These differences were not statistically significant, but there is a ceiling effect because the normal mean CSTs for the combination arm indicate that fluid was eliminated from most retinas and further reduction in CST was not possible. The percentage with edema resolution, defined as CST ≤310 μm, at month 3 was significantly greater in the combination vs. the aflibercept arm (84.1% vs. 50.7%, $P = 0.001$).

Effects in Patients with CRVO or BRVO

In the aflibercept arm, 17 patients (74%) had CRVO, 5 (21.7%) had BRVO, and 1, who had hemiretinal vein occlusion, was included along with the BRVO patients, whereas in the combination arm 9 (39.1%) had CRVO and 14 (60.9%) had BRVO. In the aflibercept arm, 12 of 17 CRVO patients (71%) and 4 of 6 BRVO patients (67%) required ≥1 IVT aflibercept re-treatment. In the combination arm, 2 of 9 CRVO patients (22%) and 3 of 14 BRVO patients (21%) required at least 1 IVT aflibercept re-treatment. There was a slight imbalance in mean BCVA at baseline in participants with CRVO, 40.2 in the combination group vs. 46.5 in the aflibercept-alone group (Fig 5A). The lines crossed between baseline and month 1 when mean BCVA was 61.4 in the combination group vs. 56.9 in the aflibercept-alone group, and this difference was maintained at months 2 and 3. The mean change from baseline BCVA at 3 months was 22 letters in the combination group vs. 8 letters in the aflibercept arm. There was a corresponding imbalance in mean CST at baseline, 875.6 μm in the combination group vs. 777.6 μm in the aflibercept group (Fig 5B). The lines for this outcome also crossed between baseline and month 1, and the mean change from baseline CST at 3 months was 603 μm in the

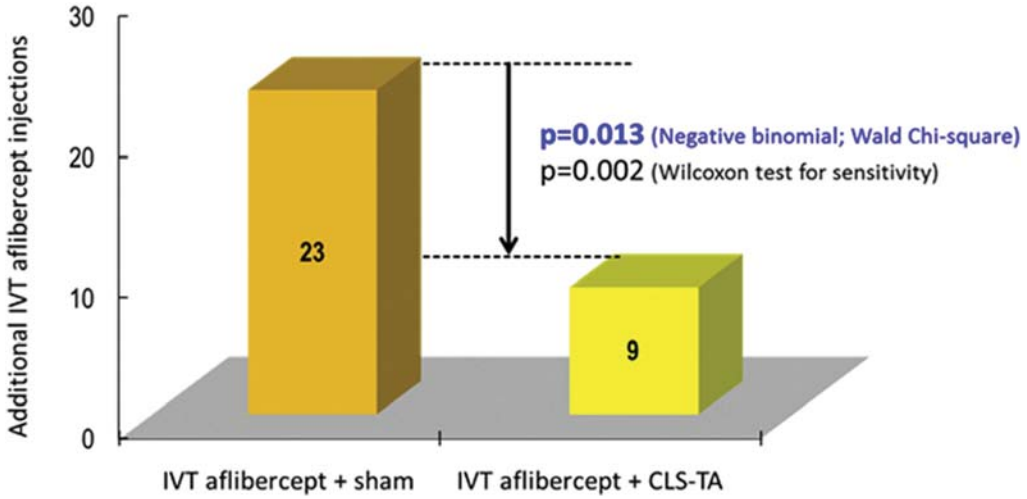

Figure 2. Combination treatment reduces the need for additional intravitreal (IVT) injections of aflibercept in patients with macular edema due to retinal vein occlusion over 3 months. Compared with IVT injection of aflibercept and sham suprachoroidal injection, suprachoroidal injection of triamcinolone acetonide (CLS-TA) combined with IVT injection of aflibercept significantly reduced the need for additional IVT injection aflibercept over 3 months.

combination group vs. 365 μm in the aflibercept group. In participants with BRVO, mean BCVA was well-balanced at baseline, whereas the mean CST was slightly worse (52 μm) in the combination group. There was little difference between the groups at subsequent time points, except at month 2, when there was a substantial worsening in mean CST and slight worsening in mean BCVA in the aflibercept-alone group (Figs 5C and 5D). The mean change from baseline BCVA at 3 months was 18 letters in both groups, and the mean change in CST was 343 μm the combination group vs. 242 μm in the aflibercept arm.

Safety

Most of the ocular adverse events were related to the injections and were similar between the 2 treatment groups (Table 2). One participant in the combination group had progression of cataract that was judged by the investigator to be unrelated to the drug. In 2 participants in the combination group who experienced an increase in IOP, this was normalized by institution of topical IOP-lowering drops. There were 2 other participants with preexisting glaucoma that had increased intraocular pressure that was

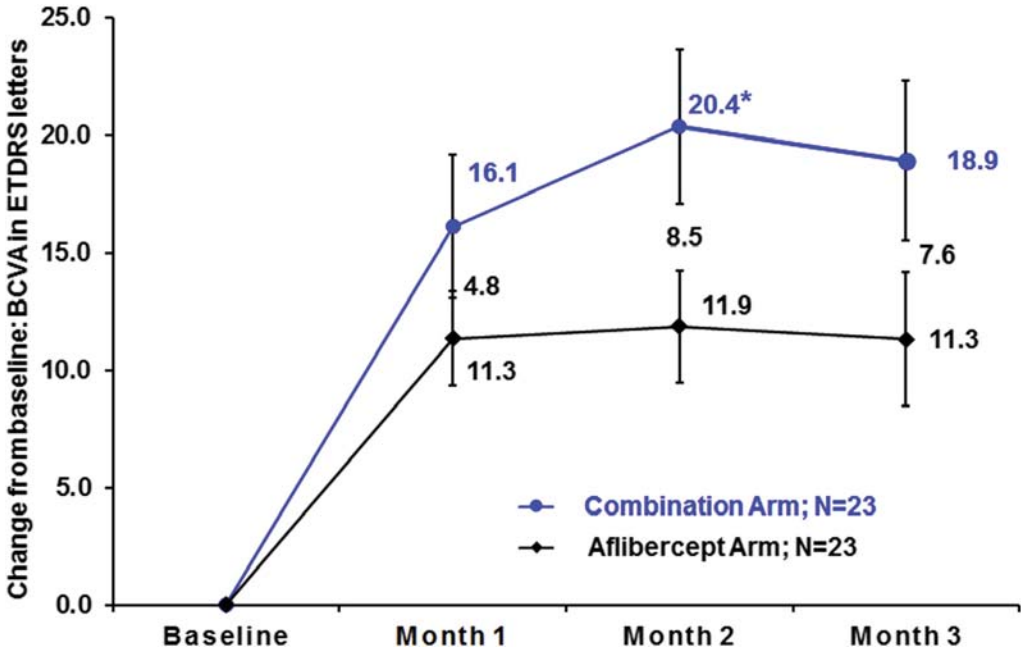

Figure 3. Mean change from baseline best-corrected visual acuity (BCVA) in the combination arm and aflibercept-alone arm. Each point represents the mean (± standard error of the mean) change from baseline BCVA letter score in the intravitreal aflibercept plus suprachoroidal triamcinolone acetonide (CLS-TA) combination arm and the aflibercept-alone arm. The differences between groups at months 1, 2, and 3 are 4.8, 8.5, and 7.6. *$P = 0.04$ for difference between combination arm and aflibercept arm by unpaired *t* test.

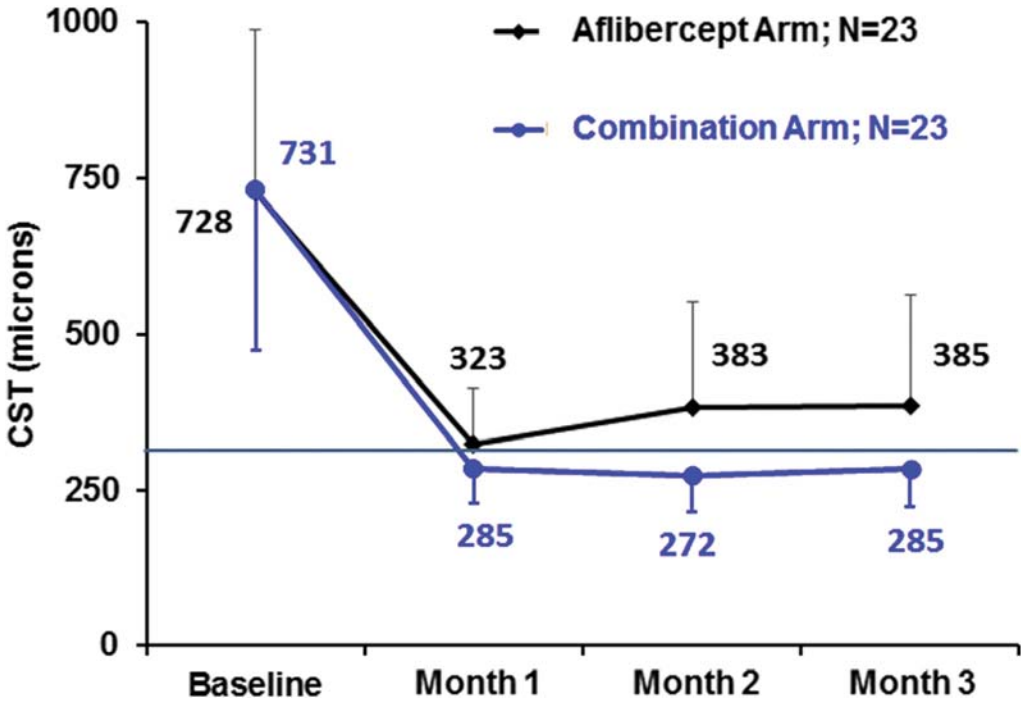

Figure 4. Central subfield thickness (CST) at baseline and months 1, 2, and 3 for combination and aflibercept groups. Points represent the mean (± standard error of the mean) CST for the combination arm and the aflibercept arm at baseline, month 1, month 2, and month 3. The mean CST for the combination group was within the normal range for CST (below line) at all time points after baseline.

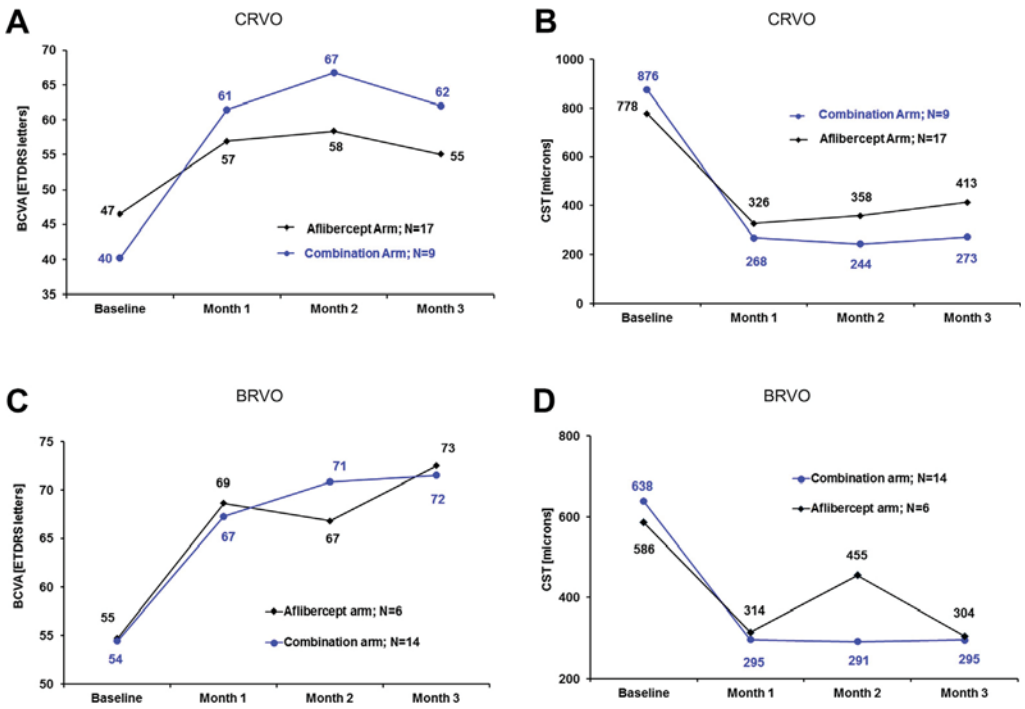

Figure 5. Mean best-corrected visual acuity (BCVA) and central subfield thickness (CST) for each treatment group in the central retinal vein occlusion and branch retinal vein occlusion subgroups. For the central retinal vein occlusion (CRVO) subgroup (**A** and **B**) and the branch retinal vein occlusion (BRVO) subgroup (**C** and **D**), the mean BCVA in Early Treatment Diabetic Retinopathy Letter Score (**A** and **C**) and the mean CST are shown for each study visit for the aflibercept-alone arm and the aflibercept plus suprachoroidal triamcinolone acetonide (CLS-TA) combination arm for patients with **A,** central retinal vein occlusion or **C,** branch retinal vein occlusion. Mean CST is shown at each study visit for the aflibercept-alone arm and the aflibercept plus CLS-TA arm for patients with **B,** CRVO or **D,** BRVO.

Table 2. Ocular Adverse Events (Study Eye)

System Organ Class Preferred Term	Intravitreal Aflibercept + Suprachoroidal Sham N = 23 n (%)	Intravitreal Aflibercept + Suprachoroidal CLS-TA N = 23 n (%)	Total N = 46 n (%)
Total number of adverse events	12	28	40
Related	0	10 (35.7)	10 (25)
Not related	12 (100)	18 (64.3)	30 (75)
Number of patients with ≥1 adverse events	8 (34.8)	12 (52.2)	20 (43.5)
Related	0	9 (39.1)	9 (19.6)
Not related	8 (34.8)	3 (13.0)	1 (23.9)
Eye disorders	8 (34.8)	12 (52.2)	20 (43.5)
Related	0	7 (30.4)	7 (15.2)
Not related	8 (34.8)	5 (21.7)	13 (28.3)
Cataract	0	1 (4.3)	1 (2.2)
Anterior chamber inflammation	0	1 (20)	1 (5)
Conjunctival hemorrhage	1 (4.3)	2 (8.7)	3 (6.5)
Conjunctival hyperemia	1 (4.3)	0	1 (2.2)
Corneal edema	0	1 (4.3)	1 (2.2)
Foreign body sensation in eyes	0	1 (4.3)	1 (2.2)
Eye pain	1 (4.3)	8 (34.8)	19 (19.6)
Lacrimation increased	0	1 (4.3)	1 (2.2)
Macular fibrosis	1 (4.3)	0	1 (2.2)
Ocular discomfort	2 (8.7)	0	2 (4.3)
Ocular hypertension	0	2 (8.7)	1 (5)
Optic disc vascular disorder	1 (4.3)	0	1 (2.2)
Optic nerve disorder	0	1 (4.3)	1 (2.2)
Punctate keratitis	0	1 (4.3)	1 (2.2)
Retinal degeneration	1 (4.3)	0	1 (2.2)
Retinal hemorrhage	0	1 (4.3)	1 (2.2)
Vision blurred	1 (4.3)	0	1 (2.2)
Visual acuity reduced	2 (8.7)	0	2 (4.3)
Vitreous humor detachment	0	1 (4.3)	1 (2.2)
Vitreous humor floaters	0	1 (4.3)	1 (2.2)
Investigations	0	2 (8.7)	2 (4.3)
Related	0	2 (8.7)	2 (4.3)
Not related	0	0	0
Intraocular pressure increased	0	2 (8.7)	2 (4.3)

CLS-TA = triamcinolone acetonide.

also controlled by the use of topical IOP-lowering drops. Thus, there were 4 IOP-related events in the combination group and none in the aflibercept group.

Discussion

In RVO, retinal ischemia leads to upregulation of several hypoxia-regulated gene products that promote retinal vascular leakage and macular edema; a particularly important one is VEGF. Neutralization of VEGF provides benefit in most patients, but it does not eliminate edema in all patients, suggesting that other pro-permeability factors participate. In the Ozurdex for Retinal Vein Occlusion study, some patients with RVO who showed a poor response to IVT injection of a VEGF-neutralizing protein showed greater edema reduction after IVT injection of a dexamethasone implant.[10] Reduction of edema after a dexamethasone implant followed by recurrence of edema after several months was correlated with a reduction and then subsequent increase in aqueous levels of other pro-permeability factors, including hepatocyte growth factor and endocrine gland-VEGF (prokineticin-1), among others. Intraocular steroids decrease levels of VEGF as well as these other pro-permeability factors and have a longer duration of action than IVT injection of a VEGF-neutralizing protein, so it is reasonable to hypothesize that combining steroids with anti-VEGF agents could have added benefit. However, intravitreous steroids cause progression of cataract in phakic patients and increased IOP in 20%–60% of susceptible individuals.[20,21] Therefore, there has been hesitancy to consider combination therapy of intraocular steroids and anti-VEGF agents as an option early in the course of RVO.

Suprachoroidal injection may provide an advantageous way to deliver steroids by maximizing drug levels in the retina, providing potential for strong efficacy, and minimizing drug levels in the anterior part of the eye, thereby reducing the risk of cataract and increased IOP. The current study supports this hypothesis because there was a low rate of adverse events typically associated with steroids in the 23 participants given a suprachoroidal injection of CS-TSA. One participant had progression of cataract judged by the investigator to be unrelated to drug. Two participants without preexisting glaucoma experienced increased IOP that was controlled with topical IOP-lowering drops. Two patients with glaucoma who were on IOP-lowering drops at baseline had an increase in IOP controlled with addition of another IOP-lowering drop. Although it is important to assess the effects of multiple

suprachoroidal injections of CLS-TA over a prolonged period of time to further assess long-term effects on lens clarity and IOP, these initial results are encouraging.

Regarding efficacy, combined treatment with suprachoroidal CLS-TA and IVT aflibercept caused prolonged elimination of edema in most participants, significantly reducing the need for additional IVT aflibercept injections over the subsequent 3 months compared with IVT injections of aflibercept alone. This injection-sparing effect was accompanied by significantly greater improvement from baseline BCVA at 2 months, with a trend toward greater improvement at 1 and 3 months. Mean CST decreased into the normal range 1 month after combination treatment and remained there for the duration of the study. This finding suggests that most participants in the combination arm had sustained edema resolution, which was also supported by the high percentage of participants with CST $\leq$310 μm through month 3 (87%, 87%, and 78%, respectively at months 1, 2, and 3). In contrast, in the IVT aflibercept-alone arm mean CST did not decrease into the normal range and only about 50% of participants had CST $\leq$310 μm at each time point throughout the 3-month study. These data suggest that combining suprachoroidal CLS-TA with an IVT VEGF-neutralizing protein such as aflibercept may improve visual and anatomic outcomes while lengthening the interval between treatments.

Although the relatively small number of participants in the trial precludes a rigorous subgroup analysis, most of the difference in BCVA improvement and edema reduction seen in the combination arm vs. the monotherapy arm seems to have occurred in participants with CRVO. However, the injection-sparing effects of combination treatment were seen equally in both CRVO and BRVO participants.

Both CRVO and BRVO are chronic diseases. The injection-sparing effects of combination therapy are not simply a matter of convenience but also could help to provide long-term visual benefits in addition to the short-term benefits as seen over 3 months in this trial. Through 4 years of follow-up in the RETAIN study, the mean number of anti-VEGF injections required for patients with BRVO was 14.0 and for patients with CRVO was 19.5.[11] At 4 years, 50% of BRVO and 56% of CRVO patients still required injections to control edema, and in those patients the mean number of injections required during the 4 year period was 15.7 for BRVO and 28.4 for CRVO. Reducing this heavy injection burden would be a substantial benefit in itself, but it could also improve long-term visual outcomes in patients with CRVO because patients who continue to require injections for 4 years have many bouts of recurrent edema, causing gradual reduction in vision over time. At the 4-year time point, 78% of CRVO patients who were no longer requiring treatment gained $\geq$15 letters and 64% had BCVA $\geq$20/40, whereas only 33% of CRVO patients who were still requiring treatment gained $\geq$15 letters and 28% had BCVA $\geq$20/40; patients in the latter group initially gained vision but gradually lost much of the gains from macular damage due to chronic/recurrent edema. Compared with VEGF suppression alone, combination treatment with suprachoroidal injections of CLS-TA and IVT injections of a VEGF-neutralizing protein may increase initial visual gains and enhance the chance of maintaining those gains. Larger studies with multiple treatments and long-term follow-up are needed to determine whether this is the case.

In conclusion, the Tanzanite study suggests that there may be benefits to combining VEGF suppression with corticosteroids in patients with macular edema due to RVO, including more rapid and complete resolution of edema, greater improvement in vision, and reduced injection frequency. It also suggests that suprachoroidal delivery of CLS-TA may be associated with less cataract progression and increased IOP than typically seen with intraocular steroids which would make it feasible to consider combination treatment early in the course of RVOs to take advantage of the potential benefits. Limitations of the study include the small number of patients and the short duration. A larger and longer study is needed to determine whether these preliminary findings may be confirmed.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **BRVO** = branch retinal vein occlusion; **CLS-TA** = triamcinolone acetonide; **CRVO** = central retinal vein occlusion; **CST** = central subfield thickness; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **HRVO** = hemiretinal vein occlusion; **IOP** = intraocular pressure; **IVT** = intravitreal; **RVO** = retinal vein occlusion; **SD** = standard deviation; **SD-OCT** = spectral domain-optical coherence tomography; **SEM** = standard error of the mean; **TA** = triamcinolone acetonide; **VEGF** = vascular endothelial growth factor.

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