Efficacy and Safety of Suprachoroidal CLS-TA for Macular Edema Secondary to Noninfectious Uveitis

Phase 3 Randomized Trial

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Purpose: Injection of pharmacotherapy into the suprachoroidal space, between the sclera and choroid, is an alternative delivery technique developed with the rationale of providing higher drug concentrations to posterior ocular structures compared with other intraocular and periocular injection procedures. This study was conducted to evaluate the safety and efficacy of suprachoroidally injected triamcinolone acetonide formulation (CLS-TA), a suspension of triamcinolone acetonide, in improving vision among patients with noninfectious uveitis complicated by macular edema (ME).

Design: Phase 3 masked, randomized trial.

Participants: One hundred sixty patients with ME secondary to noninfectious uveitis. Patients were required to have a best-corrected visual acuity (BCVA) of 5 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent, 20/800) and 70 or fewer ETDRS letters read (Snellen equivalent, 20/40) in the study eye.

Methods: Patients were randomized 3:2 to suprachoroidally injected CLS-TA or sham treatment, with administrations at day 0 and week 12.

Main Outcome Measures: The primary end point was improvement from baseline of 15 or more ETDRS letters in BCVA at week 24. The secondary end point was reduction from baseline in central subfield thickness (CST) at week 24.

Results: In the CLS-TA arm, 47% of patients gained 15 or more ETDRS letters in BCVA versus 16% in the control arm (P < 0.001), meeting the primary end point. Mean reductions in CST from baseline were 153 μm versus 18 μm (P < 0.001). No serious adverse events (AEs) related to treatment were reported. Corticosteroid-associated AEs of elevated intraocular pressure occurred in 11.5% and 15.6% of the CLS-TA and control groups, respectively. Cataract AE rates were comparable (7.3% and 6.3%, respectively).

Conclusions: Patients in the CLS-TA study arm experienced clinically significant improvement in vision relative to the sham procedure, demonstrating the efficacy of suprachoroidal injection of CLS-TA for the treatment of ME in a vision-threatening disorder. Ophthalmology 2020;127:948-955 © 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/).

Supplemental material available at www.aaojournal.org.

Suprachoroidal administration, an alternative technique for delivering ocular therapies, may facilitate more targeted delivery of therapeutic agents to chorioretinal structures than intravitreal injection1 (Fig S1, available at www.aaojournal.org). Targeted delivery was demonstrated in preclinical ocular distribution studies in which suprachoroidal injection of an investigational triamcinolone acetonide formulation (CLS-TA) yielded high levels of the corticosteroid in the retina, retinal pigment epithelium, and choroid detectable for more than 3 months (Edelhauser HF, et al. Suprachoroidal microinjection delivers triamcinolone acetonide to therapeutically-relevant posterior ocular structures and limits exposure in the anterior segment. Poster presented at: Association for Research in Vision and Ophthalmology Annual Meeting; Seattle, WA, May 1st—5th, 2016).2 Suprachoroidal injection also may limit corticosteroid exposure to the anterior chamber, iris—ciliary body, and lens, offering the potential to decrease adverse events (AEs) such as cataracts, intraocular pressure (IOP) elevation, and
exacerbation of glaucoma that commonly arise from intra-
retinal and periocular corticosteroids (Edelhauser HF, et al. Suprachoroidal microinjection delivers triamcinolone ace-
tonide to therapeutically-relevant posterior ocular structures and
limits exposure in the anterior segment. Poster presented at: Association for Research in Vision and Ophthalmology
Annual Meeting; Seattle, WA, May 1st–5th, 2016). ²

We report the first phase III study assessing a supra-
choroidally administered therapy. Specifically, supra-
choroidally administered CLS-TA was assessed in a
randomized, controlled, double-masked, phase III study
(PEACHTREE) to evaluate its ability to improve vision in
patients with macular edema (ME) associated with non-
fundamental uveitis (NIU). Uveitis, a heterogenous group of
diseases characterized by intraocular inflammation, accounts
for 10% to 15% of cases of blindness in the developed
world,³,⁴ nearly one third of which are the result of uveitis-
associated ME. ⁵ Intravitreal corticosteroids are commonly
used and effective treatments for reducing uveitic ME and
inflammation, but they are associated with elevations in IOP ranging in incidence from 20% to 60%.⁶⁻¹⁰ exacerbation
of glaucoma, and cataract development or progressioν,¹¹ resulting from corticosteroid exposure to the
anterior segment and the lens.¹²⁻¹⁴ These observations
highlight the unmet need for a targeted drug delivery
approach for treating vision loss resulting from uveitis.

Methods

Study Design

This trial was conducted in the United States, India, and Israel
from November 2015 through January 2018. The study popu-
lation included 160 patients enrolled at 53 sites. Only 1 eye
could serve as the study eye, even if both eyes were eligible.
Patient eligibility was established during screening (day −14 to
−1). Eligible patients returned to the clinic for the baseline visit
day 0), when they were assigned randomly in a 3:2 ratio to the
treatment or control group. Patients received a single unilateral
suprachoroidal injection of CLS-TA, 4 mg (0.1 ml of 40 mg/ml),
or a unilateral sham procedure (control) at day 0 and at week 12.
The control group underwent a sham procedure to maintain masking; the procedure mimicked the suprachoroidal injection,
but no drug or vehicle was administered. To maintain masking
and to minimize bias, investigators who administered study medications were distinct from masked investigators who
assessed patients. Patients attended 8 clinic visits over 27 weeks
(Fig S2, available at www.aaojournal.org). Ocular assessments
were conducted as follows: screening and exit were performed
on both eyes, IOP was collected for both eyes, and all other
ocular assessments were performed on the study eye only.
Rescue therapy could be introduced if they had any active ocular
disease or infection in the study eye except uveitis, IOP of more
than 22 mmHg, or uncontrolled glaucoma. In patients with IOP
of 22 mmHg or less, the use of up to 2 IOP-lowering medications was
allowed. Additionally, the trial did not limit inclusion by anatomic subtype but included all eligible patients with either anterior uve-
is, intermediate uveitis, posterior uveitis, or panuveitis (Table S1,
available at www.aaojournal.org). Patients were allowed to take
systemic corticosteroids at doses of 20 mg/day or less for oral prednisone (or equivalent for other corticosteroids), stable (≥2
weeks) doses of systemic immunomodulatory therapies, or both.

Efficacy Assessments

The 24-week, prespecified, primary end point was the proportion
of patients with change from baseline of 15 or more ETDRS letters
in BCVA (≥3 lines of vision). The secondary end point was mean
change from baseline in central subfield thickness (CST) measured
by spectral-domain OCT at 24 weeks. Additional end points included mean change in BCVA in ETDRS letters by visit, mean
change in CST by visit, and changes in signs of inflammation as
evaluated by the Standardization of Uveitis Nomenclature scales¹⁵
for anterior chamber cells, anterior chamber flare, and vitreous haze.

Safety

The safety population included all randomized patients. Safety end
points included (1) frequency of treatment-related AEs and serious
AEs, grouped by organ system, relatedness to study medication
determined by the study investigator, and severity; (2) percentage
of patients whose IOP increases were more than 10 mmHg from
their baseline measurement; (3) percentage of patients whose IOP
increased to more than 30 mmHg; and (4) percentage of patients
who were introduced to 1 or more IOP-lowering medications. The
IOP evaluations pertaining to corticosteroid were at any follow-up
visit except for evaluations after injection on treatment days.
Intraocular pressure assessment is described in the Appendix
(available at www.aaojournal.org).

Rescue Therapy

Beginning at week 4 (visit 3), rescue therapy could be introduced if
certain criteria were met in the study eye or if the patient was not
improving (Table S2, available at www.aaojournal.org). Any
additional therapy administered per the study investigator’s discretion.
Statistical Analysis

The intent-to-treat (ITT) population was used for all efficacy analyses and consisted of all randomized patients. Randomized assignment of patients to treatment arms was performed by interactive response technology. This study had more than 90% power to detect a difference between treatments. A Cochran-Mantel-Haenszel test was used to test differences in the proportion of patients in the 2 groups who showed 15 or more letters of improvement in BCVA at the week 24 visit after adjusting for country effects. The last observation carried forward method was used to impute data for all data points after rescue medication had been administered or to impute missing data in the ITT efficacy analyses.

Results

Patients

A total of 160 patients were randomized. The ITT population for efficacy analyses consisted of 96 and 64 patients in the CLS-TA and control groups, respectively. Overall, 97% (155/160) completed the study, including 95.8% (92/96) in the CLS-TA group and 98.4% (63/64) in the control group (Fig S3, available at www.aaojournal.org). Discontinuations in the CLS-TA arm (n = 4) were the result of patient withdrawal of consent (n = 2), patient noncompliance (n = 1), and loss to follow-up (n = 1). One patient in the control arm withdrew consent. Demographics and baseline features were balanced across groups, with slightly more women than men (Table 1, Table S3 available at www.aaojournal.org). Mean age in both arms was approximately 50 years. Mean BCVA in the study eye was 55 and 54 ETDRS letters (approximate Snellen equivalent, 20/80) read in the CLS-TA and control arms, respectively. Overall, the distribution of anatomic subtypes of uveitis was as follows: anterior (26%), intermediate (36%), posterior (22%), and panuveitis (32%). The distribution was comparable between the 2 arms. The mean time since uveitis diagnosis was 177.4 weeks in the CLS-TA arm versus 107.1 weeks in the control arm. The CLS-TA and control arms included 47 and 42 phakic patients, respectively.

Efficacy

Primary end point analysis showed the percentage of patients with BCVA gain from baseline of 15 or more ETDRS letters was 46.9% (45/96) in the CLS-TA group compared with 15.6% (10/64; \( P < 0.001 \)) in the control group at week 24 (Fig 1A). Improvements from baseline were observed early in follow-up; at week 4, a mean change of 9.6 ETDRS letters was observed compared with 1.3 ETDRS letters for the control arm. This improvement was maintained through week 24, with 13.8 and 3.0 ETDRS letters gained for the CLS-TA and control groups, respectively (\( P < 0.001 \); Fig 1B). At week 8, 49% of CLS-TA patients had attained vision of 70 ETDRS letters or better (approximate Snellen equivalent, 20/40) versus 15% of control

### Table 1. Baseline Characteristics and Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLS-TA N=96</th>
<th>Control N=64</th>
<th>Overall N=160</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (43.8)</td>
<td>30 (46.9)</td>
<td>72 (45.0)</td>
</tr>
<tr>
<td>Female</td>
<td>54 (56.3)</td>
<td>34 (53.1)</td>
<td>88 (55.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.4 (14.2)</td>
<td>50.0 (15.1)</td>
<td>50.2 (14.5)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>44 (45.8)</td>
<td>28 (43.8)</td>
<td>72 (45.0)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>11 (11.5)</td>
<td>11 (17.2)</td>
<td>22 (13.8)</td>
</tr>
<tr>
<td>Native Hawaiian/other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>40 (41.7)</td>
<td>25 (39.1)</td>
<td>65 (40.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.0)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>BCVA, study eye (ETDRS letters read)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>54.7 (13.9)</td>
<td>53.5 (12.9)</td>
<td>54.2 (13.5)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>57.0 (9, 89)</td>
<td>54.0 (12, 79)</td>
<td>56.0 (9, 89)</td>
</tr>
<tr>
<td>CST, study eye (µm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>480.9 (153.2)</td>
<td>525.4 (158.1)</td>
<td>498.7 (156.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>453.0 (256, 857)</td>
<td>518.5 (274, 971)</td>
<td>481.5 (256, 971)</td>
</tr>
<tr>
<td>Uveitis anatomic location, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>27 (28.1)</td>
<td>14 (21.9)</td>
<td>41 (25.6)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>34 (35.4)</td>
<td>23 (35.9)</td>
<td>57 (35.6)</td>
</tr>
<tr>
<td>Posterior</td>
<td>22 (22.9)</td>
<td>13 (20.3)</td>
<td>35 (21.9)</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>28 (29.2)</td>
<td>24 (37.5)</td>
<td>52 (32.5)</td>
</tr>
<tr>
<td>Time Since Uveitis Diagnosis (Weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>96</td>
<td>64</td>
<td>160</td>
</tr>
<tr>
<td>Mean (STD)</td>
<td>177.4 (235.91)</td>
<td>107.1 (134.70)</td>
<td>149.3 (204.04)</td>
</tr>
<tr>
<td>Median</td>
<td>66.0</td>
<td>60.5</td>
<td>65.5</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 1262</td>
<td>0, 648</td>
<td>0, 1262</td>
</tr>
<tr>
<td>Lens Status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phakic</td>
<td>47 (49.0%)</td>
<td>42 (65.6%)</td>
<td>89 (55.6%)</td>
</tr>
</tbody>
</table>

BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

*Percentages based on number of patients in respective groups.
patients \((P < 0.001; \text{Fig 1C})\). This difference between arms was maintained through week 24 and was statistically significant at all time points. Proportions of patients in CLS-TA versus control groups achieving other specified thresholds of BCVA improvement at week 24 were as follows: 5 or more letters, 76\% versus 39\%, respectively; 10 or more letters, 60\% versus 30\%, respectively; and 15 or more letters, 47\% versus 16\%, respectively.

At baseline, the CLS-TA and control groups showed similar degrees of ME, at 481 \(\mu\)m and 525 \(\mu\)m, respectively \((P > 0.05; \text{Table 1})\). Central subfield thickness was reduced from baseline in CLS-TA patients by 153 \(\mu\)m compared with a reduction of 18 \(\mu\)m in the control group at week 24, a difference of 135 \(\mu\)m \((P < 0.001; \text{Fig 2A})\). A more than 100-\(\mu\)m difference in CST reductions between study arms was observed starting at week 4.
The percentage of patients with ME resolution (CST < 300 μm) was 53% at week 4 in the CLS-TA group and 2% in the control group (Fig S4, available at www.aaojournal.org). This difference in ME resolution between the CLS-TA and control arms was maintained through week 24. A higher proportion of patients experienced a clinically meaningful 20% or more reduction in CST in the CLS-TA arm at each visit (Fig S5, available at www.aaojournal.org).

At least two thirds of the patients with active inflammation at baseline in the CLS-TA arm experienced resolution of inflammation (Standardization of Uveitis Nomenclature scores of 0 for anterior chamber cell, anterior chamber flare, and vitreous haze) at week 24. The percentages of patients requiring rescue therapy were 13.5% (13/96) in the CLS-TA arm and 72% (46/64) in the control arm over 24 weeks (Fig 3). Among rescued patients, median time to first rescue was 89 days in the CLS-TA arm versus 36 days in the control arm (P < 0.001).

A post hoc analysis was performed to compare efficacy results from the unrescued CLS-TA patients with the rescued control patients (observed data from the ITT population, without data imputation from the time point of rescue). As noted previously, predefined criteria were established for the administration of rescue therapy, and the type of rescue therapy was administered at the

Table 2. Ocular Adverse Events

<table>
<thead>
<tr>
<th>Study Eye, n (%)</th>
<th>CLS-TA 4.0 mg N=96 n (%)</th>
<th>Control N=64 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of ocular adverse events</td>
<td>122</td>
<td>54</td>
</tr>
<tr>
<td>Number of patients with ≥1 ocular AE</td>
<td>49 (51.0)</td>
<td>37 (57.8)</td>
</tr>
<tr>
<td>Treatment-related ocular AEs</td>
<td>29 (30.2)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Serious ocular AEs</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related serious AEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs leading to study drug discontinuation</td>
<td>5 (5.2)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>Number of patients with ≥1 eye disorder</td>
<td>41 (42.7)</td>
<td>34 (53.1)</td>
</tr>
<tr>
<td>Adverse events in ≥5% of patients in either treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract*</td>
<td>7 (7.3)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Cystoid macular edema</td>
<td>0</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Eye pain: time of procedure</td>
<td>12 (12.5)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Eye pain: any time post procedure</td>
<td>6 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>Elevated IOP*: time of procedure</td>
<td>8 (8.3)</td>
<td>0</td>
</tr>
<tr>
<td>Elevated IOP*: pertaining to corticosteroid†</td>
<td>11 (11.5)</td>
<td>10 (15.6)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>2 (2.1)</td>
<td>7 (10.9)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>5 (5.2)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

AE, adverse event; IOP, intraocular pressure; TEAE, treatment-emergent adverse event.

A TEAE was any AE temporally associated with the use of the study drug, whether or not considered causally related to the study drug, that occurred after the subject received the first dose of study drug.

* Cataract includes the preferred terms (a) cataract, (b) cataract subscapular, and (c) cataract nuclear.
† Elevated IOP includes the preferred terms (a) IOP increased, (b) ocular hypertension, and (c) glaucoma.
‡ Includes all events of elevated IOP that did not occur on the day of the procedure.
§ All IOP adverse events in the control group occurred after rescue with local corticosteroid administration.
to baseline CST was 519.7 letters, and in 46 of 64 (71.9%) rescued control patients who completed the study showed a mean improvement of 15.7 letters, compared with a 10.9-letter improvement in 44 of 61 (72.1%) rescued control patients who completed the study (95% CI for difference, −0.5 to +9.6 letters; \( P = 0.080 \)). Analysis of CST showed a similar trend. In 83 of 96 (86.4%) unrescued CLS-TA patients, mean baseline CST was 480.6 \( \mu \)m, and in 46 of 64 (71.9%) rescued control patients, mean baseline CST was 519.7 \( \mu \)m (95% CI for difference, −95.1 to +20.8 \( \mu \)m; \( P = 0.207 \)). At week 24, 77 of 90 (85.6%) unrescued CLS-TA patients who completed the study with gradable images showed a 174.0-\( \mu \)m improvement, compared with the 148.5-\( \mu \)m improvement in 44 of 61 (72.1%) rescued control patients who completed the study with gradable images (95% CI for difference, −88.2 to −2.0 \( \mu \)m; \( P = 0.040 \)).

**Safety**

The percentage of patients with 1 or more ocular AEs was 51% in the CLS-TA arm and 58% in the control arm (Table 2 and S4, available at www.aaojournal.org). The incidence of AEs considered by the investigator to be treatment related was 29 (30.2%) in the CLS-TA arm and 8 (12.5%) in the control arm. The 3 most frequent ocular AEs were cystoid ME (0% vs. 17.2% of patients in CLS-TA and control arms, respectively), eye pain at time of procedure (12.5% vs. 4.7%, respectively), and elevated IOP associated with corticosteroid (11.5% vs. 15.6%, respectively). All patients who experienced AEs of elevated IOP in the control arm had undergone rescue therapy with local corticosteroids, with elevated IOP AEs in 10 of the 37 control arm patients (27.0%) who were administered intravitreal or periocular corticosteroid injection as additional therapy. Cataract incidence was comparable between the CLS-TA and control groups: 7.3% and 6.3%, respectively.

Three serious AEs occurred, all of which were identified in the CLS-TA arm: sialadenitis, posttraumatic lumbar compression fracture, and a retinal detachment. The retinal detachment occurred approximately 8 weeks after the suprachoroidal injection procedure and was in a different quadrant than the procedure. It was assessed by the study investigator as possibly related to underlying disease state. None of the serious AEs were deemed treatment related by the study investigator or led to study discontinuation.

**Discussion**

PEACHTREE was the first phase III trial to evaluate suprachoroidal injection of a therapeutic agent for the treatment of an ocular disease. In preclinical studies, suprachoroidally administered CLS-TA rapidly achieved high levels in the choroid and retina, detectable for more than 3 months (Edelhauser HF, et al. Suprachoroidal microinjection delivers trimacinolone acetonide to therapeutically relevant posterior ocular structures and limits exposure in the anterior segment. Poster presented at: Association for Research in Vision and Ophthalmology Annual Meeting; Seattle, WA, May 1–5, 2016).2 which could explain, in part, the functional and anatomic improvements observed in NIU patients with ME in this clinical trial setting. PEACHTREE also was the first phase III pivotal uveitis trial to study changes in visual acuity as a primary end point and showed that suprachoroidally injected CLS-TA significantly improved vision in patients with ME secondary to uveitis, with visual acuity gains of 3 lines or more (≥15 ETDRS letters) in nearly half of patients receiving treatment. This clinically meaningful improvement represents a doubling of the visual angle (i.e., patients were able to read ETDRS letters half the size after study therapy compared with study entry). Moreover, patients receiving suprachoroidal CLS-TA derived a mean visual acuity benefit of approximately 14 letters versus the 3 letters gained in the control arm at 24 weeks. A difference of 2 lines of improved vision was observed between groups starting at week 4, the first evaluation time point. By week 8, the next evaluation time point, the proportion of patients with 20/40 or better visual acuity (i.e., legal driving vision in most states of the United States) approached 50% after suprachoroidal CLS-TA administration. Improvement in vision was accompanied by significant reduction of ME and normalization of retinal architecture, with resolution of ME in more than 50% of patients treated with CLS-TA. Improvement in functional and anatomic end points occurred regardless of the primary anatomic site of inflammation, including anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis.

Although suprachoroidal administration of CLS-TA was not compared with other treatments in PEACHTREE, the data suggest that suprachoroidal CLS-TA may provide a valuable addition to the therapeutic armamentarium. Although cross-trial comparisons have limitations, a retrospective cohort analysis of more than 1000 patients with uveitic ME who were treated with systemic immunosuppressive therapy demonstrated that approximately one half of patients gained 10 letters or more in vision at 6 months.17 In PEACHTREE, approximately one half of patients treated with CLS-TA gained 15 letters or more at 6 months. For additional context, the recent Periocular and Intravitreal Corticosteroids for Uveitic Macular Edema Trial (ClinicalTrials.gov identifier, NCT02374060), a National Institutes of Health-funded prospective clinical trial, compared 3 commonly administered local corticosteroids for uveitic ME. The 6-month results showed that intravitreal triamcinolone acetonide and intravitreal dexamethasone outperformed periocular corticosteroid treatment, both achieving approximately 9 letters of improvement compared with approximately 4 letters gained in the periocular arm.18 In PEACHTREE, the mean gain in visual acuity was approximately 14 letters at 6 months.

With respect to safety, reported rates of IOP elevation with the use of local triamcinolone acetonide in the eye range from 20% to 60%,19 compared with the 11.5% rate observed in PEACHTREE for 2 CLS-TA injections during the 24-week trial. In the Periocular and Intravitreal Corticosteroids for Uveitic Macular Edema Trial, approximately 24% to 33% of patients in each arm required IOP-lowering medication. Although cross-trial comparisons have limitations, 7.3% of patients in the treatment arm of
PEACHTREE required medication to lower IOP. These data suggest an IOP-sparing benefit, arguably because of the unique compartmentalization and ocular distribution inherent to the suprachoroidal administration of CLS-TA. Preclinical studies investigating suprachoroidal administration support this assertion, demonstrating low corticosteroid exposure within the anterior chamber and trabecular meshwork (Edelhauser HF, et al. Suprachoroidal microinjection delivers triamcinolone acetonide to therapeutically relevant posterior ocular structures and limits exposure in the anterior segment. Poster presented at: Association for Research in Vision and Ophthalmology Annual Meeting; Seattle, WA, May 1—5, 2016). This benefit is supported further by the control arm of PEACHTREE, which showed that 27.0% of patients receiving intravitreal or peribulbar corticosteroid injection rescue demonstrated IOP AEs.

Limitations of this trial include a lack of comparison with other local corticosteroid therapies and only 6 months of efficacy and safety follow-up. Nonetheless, the PEACHTREE study showed robust outcomes that were observed as early as week 4 and were sustained through week 24, with longer-term outcomes to be assessed in the MAGNOLIA follow-up study (ClinicalTrials.gov identifier, NCT02952001).

In summary, the results of PEACHTREE support the clinical use of suprachoroidally injected CLS-TA as a new treatment option for patients with ME associated with NIU, demonstrating clinically meaningful improvements in vision for nearly half of the patients treated. As the first phase III trial to evaluate suprachoroidal injection for the treatment of an ocular disease, PEACHTREE also paves the way for research on suprachoroidal administration to deliver other therapeutics in a targeted approach to choroidal and retinal tissues. Suprachoroidal administration could enhance delivery of therapies for a variety of ophthalmic conditions in which a precise anatomic drug application may yield safety, efficacy, and durability benefits over current therapies (Edelhauser HF, et al. Suprachoroidal microinjection delivers triamcinolone acetonide to therapeutically relevant posterior ocular structures and limits exposure in the anterior segment. Poster presented at: Association for Research in Vision and Ophthalmology Annual Meeting; Seattle, WA, May 1—5, 2016). In the future, suprachoroidal administration may even be assessed for some gene therapies, because preclinical work supports the potential for minimally invasive targeted ocular gene therapy, without the risks of vitrectomy surgery and subretinal administration (Taraborelli D, et al. A one-week study to evaluate safety, tolerability, and retinal cell transfection of non-viral DNA nanoparticles administered by suprachoroidal injection. Poster presented at: Association for Research in Vision and Ophthalmology Annual Meeting; Honolulu, HI, April 29-May 3, 2018).

References

Footnotes and Financial Disclosures

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*A complete listing of the members of the PEACHTREE Study Group is available in the Appendix (available at www.aaojournal.org)

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HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees/IRB at each site approved the study (see supplementary appendix [available at www.aaojournal.org] for full list of sites and investigators). All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

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Conception and design: Yeh, Khurana, Kissner, Noronha
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Abbreviations and Acronyms:
AE = adverse event; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; ITT = intent-to-treat; ME = macular edema; NIU = noninfectious uveitis; POINT = PeriOcular and INTravitreal Corticosteroids for Uveitic Macular Edema Trial.

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