Randomized Comparison of Systemic Anti-inflammatory Therapy Versus Fluocinolone Acetonide Implant for Intermediate, Posterior, and Panuveitis: *The Multicenter Uveitis Steroid Treatment Trial*

*The Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group**
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Objective: To compare the relative effectiveness of systemic corticosteroids plus immunosuppression when indicated (systemic therapy) versus fluocinolone acetonide implant (implant therapy) for noninfectious intermediate, posterior, or panuveitis (uveitis).

Design: Randomized controlled parallel superiority trial.

Participants: Patients with active or recently active uveitis.

Methods: Participants were randomized (allocation ratio 1:1) to systemic or implant therapy at 23 centers (3 countries). Implant-assigned participants with bilateral uveitis were assigned to have each eye that warranted study treatment implanted. Treatment-outcome associations were analyzed by assigned treatment for all eyes with uveitis.

Main Outcome Measures: Masked examiners measured the primary outcome: change in best-corrected visual acuity from baseline. Secondary outcomes included patient-reported quality of life, ophthalmologist-graded uveitis activity, and local and systemic complications of uveitis or therapy. Reading Center graders and glaucoma specialists assessing ocular complications were masked. Participants, ophthalmologists, and coordinators were unmasked.

Results: On evaluation of changes from baseline to 24 months among 255 patients randomized to implant and systemic therapy (479 eyes with uveitis), the implant and systemic therapy groups had an improvement in visual acuity of +6.0 and +3.2 letters ($P = 0.16$, 95% confidence interval on difference in improvement between groups, −1.2 to +6.7 letters, positive values favoring implant), an improvement in vision-related quality of life of +11.4 and +6.8 units ($P = 0.043$), a change in EuroQol-EQ5D health utility of +0.02 and −0.02 ($P = 0.060$), and residual active uveitis in 12% and 29% ($P=0.001$), respectively. Over the 24 month period, implant-assigned eyes had a higher risk of cataract surgery (80%, hazard ratio [HR] = 3.3, $P < 0.0001$), treatment for elevated intraocular pressure (61%, HR=4.2, $P < 0.0001$), and glaucoma (17%, HR=4.2, $P = 0.0008$). Patients assigned to systemic therapy had more prescription-requiring infections than patients assigned to implant therapy (0.60 vs 0.36/person-year, $P=0.034$), without notable long-term consequences; systemic adverse outcomes otherwise were unusual in both groups, with minimal differences between groups.

Conclusions: In each treatment group, mean visual acuity improved over 24 months, with neither approach superior to a degree detectable with the study's power. Therefore, the specific advantages and disadvantages identified should dictate selection between the alternative treatments in consideration of individual patients' particular circumstances. Systemic therapy with aggressive use of corticosteroid-sparing immunosuppression was well tolerated, suggesting that this approach is reasonably safe for local and systemic inflammatory disorders.

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**Group members listed online in Appendix 1 (available at http://aaojournal.org).*

Uveitis (intraocular inflammation) is an important cause of visual impairment.[1,2] Intermediate, posterior, and panuveitis[3,4] are the forms of uveitis most likely to cause vision loss.[5,6] Because of its earlier onset, uveitis results in a longer duration of blindness and more economic cost per case than more common age-related ocular diseases.[7]

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Systemic corticosteroids (supplemented, when indicated, by corticosteroid-sparing immunosuppressive drugs) have been the mainstay of treatment for chronic, vision-threatening cases of uveitis, based on their established advantages over alternative approaches, as was affirmed by an expert panel review of the subject conducted in 2000.[8] In 2005, the US Food and Drug Administration approved a surgically placed intravitreal fluocinolone acetonide implant for treatment of intermediate, posterior, and panuveitis. The implant delivers corticosteroid intravitreally for approximately 3 years with minimal systemic absorption.[9–11] The relative effectiveness and risk(s) of these alternative treatments require further characterization.

We report the primary 24-month results of a randomized, controlled comparative effectiveness trial to evaluate whether fluocinolone acetonide implant or systemic therapy for noninfectious intermediate, posterior, or panuveitis is superior. The study's aims were to compare visual outcomes, control of inflammation, incidences of local ocular and systemic complications of disease or therapy, and vision-related and general quality of life.

Materials and Methods

Study Design

The Multicenter Uveitis Steroid Treatment (MUST) Trial is a randomized (allocation ratio 1:1), partially masked, 23-center parallel treatment comparative effectiveness superiority trial (ClinicalTrials.gov identifier: NCT00132691) (The Research Group that conducted the trial is listed in Appendix 1, available at http://aaojournal.org). A previous report details the design and outcome definitions used.[12] All patients provided written informed consent; all governing institutional review boards provided approval. The protocol was modified during early enrollment, broadening eligibility to improve recruitment and make results more generalizable (Appendix 2, available at http://aaojournal.org).

Enrollment of Participants, Data Collection, and Follow-up

Eligible patients were aged 13 years or older and had noninfectious intermediate, posterior, or panuveitis in 1 or both eyes (active within ≤60 days) for which systemic corticosteroids were indicated. Patients requiring systemic therapy for nonocular indications were excluded (for complete eligibility criteria, See Appendix 3, available at http://aaojournal.org). Eligible patients enrolled at 23 uveitis centers in the United States, the United Kingdom, and Australia. Patients completed study visits at baseline, 1 month, 3 months, and then every 3 months for at least 24 months (contiguous visit windows).

Random Treatment Assignment

Patients were randomized to implant or systemic therapy; patients with bilateral uveitis were assigned to receive implants in each eye meeting eligibility criteria. Randomization (1:1 ratio) was by variable length, permuted blocks within 2 strata (clinical center, intermediate vs posterior or panuveitis), with assignments produced by Stata 11.0 (StataCorp 2009, Stata Statistical Software: Release 11; StataCorp LP, College Station, TX). After data entry confirmed a subject's eligibility and stratum, the study Web site revealed the next treatment assignment.

Treatment

Implant therapy began by using topical, periocular, or systemic corticosteroids to suppress any anterior chamber inflammation. Surgical fluocinolone acetonide implant (0.59 mg, Bausch & Lomb, Rochester, NY) placement followed in the first eye within 28 days of randomization and in the second eye (if indicated) within 28 additional days. Study-certified surgeons placed implants using a recommended technique.[10,13] The protocol dictated tapering and discontinuation of any systemic corticosteroids and immunosuppressive drugs initially in use after implant placement. Reimplantation was specified for reactivations, but best medical judgment was permitted for initial failure to control inflammation, treatment-limiting toxicity, or incidence of systemic disease requiring systemic therapy. Second eyes for which implantation was not indicated could be managed using nonsystemic treatments.[12]

Systemic therapy followed expert panel guidelines.[8] Most cases had active inflammation at baseline and received 1 mg/kg/day up to 60 mg/day of prednisone until either the uveitis was controlled or 4 weeks had elapsed. After control was achieved, prednisone was tapered per study guidelines. Cases already suppressed at baseline began by tapering from their initial prednisone dose. Immunosuppression was indicated for (1) failure to initially control inflammation using corticosteroids; (2) corticosteroid-sparing in cases consistently reactivating before reaching a prednisone dose of 10 mg/day; and (3) specific high-risk uveitis syndromes.[8] When indicated, clinicians selected the approved immunosuppressant most suitable for each patient; administration and monitoring for toxicity followed guidelines.[8] Uveitis experts regularly monitored treatment regimens for protocol compliance at site visits.

Outcomes and Masking

Study-certified visual acuity examiners measured best-corrected visual acuity as the number of letters read from standard logarithmic visual acuity charts;[14] change in this measure from baseline to 24 months was the primary outcome. Other important outcomes reported include visual field sensitivity (the mean deviation statistic[15]), clinically graded uveitis activity/control, ocular and systemic complications of uveitis or its treatment, and patient-reported vision- and general health-related quality of life and health utility (using the National Eye Institute Visual Function Questionnaire,[16] 36-Item Short Form,[17,18] and EuroQol[19] instruments, respectively). In phakic eyes, cataract was graded by biomicroscopy; among eyes free of cataract at baseline, incident cataract was identified if biomicroscopy confirmed a cataract at 2 consecutive visits. All outcomes specifically reported were prespecified by the protocol and tracked prospectively.

Other than at the 1- and 3-month visits, when postoperative signs were expected to be visible, visual acuity examiners were masked. A glaucoma specialist reviewed visual field, clinical data, and fundus photographs to diagnose glaucoma. A second glaucoma specialist independently confirmed all cases and a 32% random subset of non-cases; disagreements were adjudicated by consensus. Reading Center image evaluations for ocular sequelae of uveitis and of therapy, and glaucoma assessments all were masked. Patients, clinicians, and coordinators were not masked.[12]

Sample Size Determination

By assuming bilateral disease in 67% of patients, a between eye correlation of 0.4, a standard deviation of 16 letters' change over 2 years, and a 2-sided type 1 error rate of 0.05, a sample size of 250 provided 91% power (assuming 10% crossover) to detect a treatment difference of 7.5 standard Early Treatment of Diabetic Retinopathy Study letters' change in visual acuity from baseline to 24