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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*, John H. Kempen, MD, PhD^{1,2,3}, Michael M. Altaweel, MD⁴, Janet T. Holbrook, PhD, MPH^{5,6}, Douglas A. Jabs, MD, MBA^{5,6,8,9}, Thomas A. Louis, PhD⁷, Elizabeth A. Sugar, PhD^{5,6,7}, and Jennifer E. Thorne, MD, PhD^{5,6,10}

¹Ocular Inflammation Service The University of Pennsylvania, Philadelphia, Pennsylvania ²Center for Preventive Ophthalmology and Biostatistics, The University of Pennsylvania, Philadelphia, Pennsylvania ³Department of Ophthalmology/Scheie Eye Institute, and the Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, The University of Pennsylvania, Philadelphia, Pennsylvania ⁴Fundus Photograph Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, Wisconsin ⁵Center for Clinical Trials, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland ⁶Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland ⁷Department of Biostatistics, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland ⁸Department of Ophthalmology The Mount Sinai School of Medicine, New York, New York ⁹Department of Medicine, The Mount Sinai School of Medicine, New York, New York ¹⁰Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

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Corresponding Author: John H. Kempen, M.D., Ph.D.; Center for Preventive Ophthalmology and Biostatistics; Department of Ophthalmology; University of Pennsylvania; 3535 Market Street, Suite 700; Philadelphia, PA 19104; john.kempen@uphs.upenn.edu.
Reprint Requests: Douglas A. Jabs, MD, MBA; MUST Chairman's Office; Department of Ophthalmology; Mount Sinai School of Medicine; One Gustave L. Levy Place, Box 1183; New York, NY 10029-6574; douglas.jabs@mssm.edu.

*Writing Committee: John H. Kempen, MD, PhD, Michael M. Altaweel, MD, Janet T. Holbrook, PhD, MPH, Douglas A. Jabs, MD, MBA, Thomas A. Louis, PhD, Elizabeth A. Sugar, PhD, Jennifer E. Thorne, MD, PhD.

The Credit Roster for the Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group appears in Appendix 1, available at <http://aaojournal.org>.

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Conflicts of Interest: Dr. Kempen is a consultant for Alcon Laboratories, Allergan Pharmaceutical Corporation, Lux Biosciences, Inc., and Sanofi Pasteur SA. Dr. Jabs is a consultant for Abbott Laboratories, Alcon Laboratories, Allergan Pharmaceutical Corporation, Corcept Therapeutics, Genentech, Inc., Genzyme Corporation, GlaxoSmithKline, Novartis Pharmaceutical Corp., Roche Pharmaceuticals, and Applied Genetic Technologies Corporation (AGTC). Dr. Louis is a consultant for Bristol-Myers Squibb, Medtronic, Inc., and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr. Thorne is a consultant for Heron Evidence, Ltd. Drs. Altaweel, Holbrook, and Sugar have no conflicts of interest.

Off label use of drugs: adalimumab, azathioprine, cyclosporine, cyclophosphamide, daclizumab, infliximab, methotrexate, mycophenolate mofetil, rituximab, tacrolimus.

Supplemental Material: This article contains online-only material. The following should appear online-only: Appendices 1–3, Table 1, Figure 3.

Objective—To compare the relative effectiveness of systemic corticosteroids plus immunosuppression when indicated (systemic therapy) versus fluocinolone acetonide implant (implant therapy) for non-infectious intermediate, posterior or panuveitis (uveitis).

Design—Randomized controlled parallel superiority trial.

Participants—Patients with active/recently active uveitis.

Methods—Participants were randomized (allocation ratio 1:1) to systemic or implant therapy at 23 centers (three 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 (QoL), 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—Among 255 patients randomized to implant and systemic therapy (479 eyes with uveitis), evaluating changes from baseline to 24 months, the implant and systemic therapy groups respectively had +6.0 vs. +3.2 letters' improvement in visual acuity ($p=0.16$, 95% confidence interval on difference in improvement between groups: -1.2 to $+6.7$ letters, positive values favoring implant), $+11.4$ vs. $+6.8$ units' vision-related QoL improvement ($p=0.043$), $+0.02$ vs. -0.02 change in EuroQol-EQ5D health utility ($p=0.060$), and 12% vs. 29% had active uveitis ($p=0.001$). Over 24 months, 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, $p=0.0008$). Systemic-assigned patients had more prescription-requiring infections (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.

Conclusion—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.

Introduction

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

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 United States 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.

Here we report the primary 24-month results of a randomized, controlled comparative effectiveness trial to evaluate whether fluocinolone acetonide implant or systemic therapy for non-infectious 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.

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). 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 (see Appendix 2, available at <http://aaojournal.org>).

Enrollment of Participants, Data Collection, and Follow-up

Eligible patients were age 13 years or older and had non-infectious intermediate, posterior or panuveitis in one or both eyes (active within ≤ 60 days) for which systemic corticosteroids were indicated. Patients requiring systemic therapy for non-ocular indications were excluded (see additionally Appendix 3). Eligible patients enrolled at 23 uveitis centers in the United States, the United Kingdom, and Australia. Patients completed study visits at baseline, one month, three months, and then every three 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 two strata (clinical center, intermediate vs. posterior or panuveitis), with assignments produced by Stata 11.0 (StataCorp. 2009, Stata Statistical Software: Release 11, College Station, TX: StataCorp LP). After data entry confirmed a subject's eligibility and stratum, the study website revealed the next treatment assignment.

Treatment

Implant therapy began by using topical, periocular, and/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 following implant placement. Re-implantation was specified for re-activations, 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 non-systemic 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 four weeks had elapsed. After achieving control, 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 prior to 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 here include visual field sensitivity (the mean deviation statistic¹⁵), 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 NEI-VFQ,¹⁶ SF-36,^{17;18} and EuroQol¹⁹ 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 two consecutive visits. All outcomes specifically reported herein were pre-specified by the protocol and tracked prospectively.

Other than at the 1 and 3 month visits, when post-operative 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

Assuming bilateral disease in 67% of patients, a between eye correlation of 0.4, a standard deviation of 16 letters' change over two years, and a two-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 ETDRS letters' change in visual acuity from baseline to 24 months, a difference similar to that which drove widespread use of expensive new retinal treatments in other trials which tested them.^{20;21} One interim analysis using the O'Brien-Fleming α -spending function^{22;23} was conducted; the nominal type 1 error rate was 0.049 for the final analysis.

Statistical Analyses

Analyses were conducted "as randomized." Because all uveitic eyes (regardless of severity) are affected by systemic treatment, the primary analyses evaluated the ocular outcomes of all eyes having uveitis at enrollment in relation to treatment assignment, which included a small number of eyes with uveitis for which clinicians thought implant therapy was not indicated (Figure 1), given that outcomes of such eyes might have been affected by systemic therapy vs. lack of study therapy in the implant arm. Longitudinal models estimated parameters using generalized estimating equations (GEE).²⁴ For visual acuity, a saturated means model (including indicators for each visit and each visit-by-treatment interactions) adjusting for stratification by uveitis type (intermediate versus posterior/panuveitis) was

used; a Toeplitz covariance structure accounted for longitudinal, within eye correlation. All available visit information was incorporated into the model, with missing data indicators used to maintain the data structure. Other analyses for measured outcomes used the same mean structure with a Toeplitz, unstructured, or exchangeable covariance matrix. Event-time analyses were used to compare the incidence of adverse ocular and systemic outcomes. Analyses were conducted by the Statistical Analysis Committee (see Credit Roster, Appendix 1).

Robust standard errors were computed for all models. The bootstrap was used to calculate standard error, confidence intervals, and p values for outcomes where two eyes of the same individual were at risk (e.g., visual acuity in uveitic eyes). Bootstrap sampling was stratified by treatment group, unilateral vs. bilateral uveitis, and uveitis stratum (intermediate vs. posterior or panuveitis) with 5000 replicates. For analysis of sustained visual acuity impairment (defined as impairment at consecutive assessments) and similar outcomes, missing data were accommodated via multiple imputation.²⁵ All reported confidence intervals and p-values are nominal and not adjusted for multiple comparisons. Statistical analyses used SAS (SAS/STAT User's Guide, Version 9.1, Cary, NC:SAS Institute), Stata 11, and R (The R Project for Statistical Computing, Version 2.11.1, <http://www.r-project.org/>, accessed July 14, 2011).

Results

Between December 2005 and December 2008, 255 patients (479 eyes with uveitis) were enrolled. Baseline demographic and clinical characteristics were distributed similarly between groups (see Table 1, available at <http://aaojournal.org>), with the following exceptions. Patients in the implant group were more likely to be osteopenic or osteoporotic (45% and 9% respectively) than patients in the systemic group (34% and 6% respectively). Eyes with uveitis in the implant group had poorer visual field sensitivity than those in the systemic group (median −5.7 dB vs −3.8 dB respectively); however, the two groups did not differ substantially in baseline visual acuity (median=68, interquartile range (IQR): 46–79) vs. 71 (IQR: 53–81) letters read respectively). The degree of uveitis activity at baseline was about the same in the two groups.

In the implant and systemic groups respectively 122/129 (95%) and 121/126 (96%) received their assigned therapies (Figure 1); 3 eyes of 2 patients required re-implantation within 24 months. In the systemic therapy group, 104 (86%) received corticosteroid-sparing immunosuppressive drugs as part of their treatment.

Among patients randomized, 232 (435 eyes with uveitis; 91%) completed visual acuity measurement at the 24 month follow-up visit. Overall, 4415 of 4790 study visits (92%) were completed for the primary outcome through 24 months.

Visual Function

Both the implant and systemic groups experienced improvement of best-corrected visual acuity during follow-up—respectively a mean improvement from baseline in the respective groups of 5.9 vs. 2.0 letters (5 letters=1 Snellen-equivalent line) at 6 months, 4.6 vs. 3.3 letters at 12 months, and 6.0 vs. 3.2 letters at 24 months (Table 2 and Figure 2). There was no statistically significant difference between the treatment groups in their improvement in visual acuity at 24 months ($p=0.16$). By 24 months 21% vs. 13% of eyes with uveitis assigned to implant or systemic therapy, respectively, had gained at least 15 letters (3 lines) of visual acuity ($p=0.065$). Excluding eyes with visual acuity 20/40 or better at baseline, the mean improvement by 24 months was 12.9 and 9.3 letters, in the implant and systemic groups respectively ($p=0.25$). By-patient analyses evaluating the better and the worse eye

also produced similar results. Visual acuity outcomes of each treatment group were similar regardless of phakic vs. pseudophakic or aphakic status at baseline ($p=0.68$ for lens status-treatment interaction).

Overall visual field sensitivity, reduced in both groups at baseline (median mean deviation = -5.7 dB vs. -3.8 dB respectively), did not change appreciably in either group over 24 months (see Figure 3, available at <http://aaojournal.org>).

Uveitis Activity and Macular Edema

Most eyes with active uveitis at baseline were controlled within nine months in both groups. However, in the implant group, control of uveitis was more frequent (88% vs. 71% controlled at 24 months, $p=0.001$, Table 3, Figure 4), and the rate of achieving a two-step improvement in vitreous haze⁴ was more favorable (hazard ratio (HR)=1.47, $p=0.014$).

The proportion of eyes having macular edema (Stratus OCT-3 center point macular thickness $\geq 240\mu\text{m}$)¹² was similar for the two treatment groups at baseline. By six months, fewer had macular edema in the implant than the systemic group (20% vs. 34%, as opposed to 41% vs. 39% respectively at baseline ($p<0.001$ for comparison of change from baseline between groups)). However, the proportions with macular edema by 24 months (22% vs. 30%) did not represent a substantial difference in change from baseline between groups ($p=0.071$).

Ocular and Systemic Complications

Relative to the systemic group, the implant group had a more than four-fold higher rate of (first) incidence of intraocular pressure (IOP) elevation of 10 mmHg or more, absolute IOP of 30 mmHg or more, and of needing medical and surgical treatments for elevated IOP (Table 4). Despite frequent medical and surgical intervention, glaucoma developed within 24 months in 17% vs. 4.0% (HR = 4.2, $p=0.001$) of uveitic eyes respectively. Among those at risk, the implant group also experienced higher cumulative 24 month risk of both cataract (91% vs 45%) and cataract surgery (80% vs 31%). These differences were consistent with respectively with the higher incidence of diminished visual acuity in the implant group, and the lack of a sustained impact of such diminution on the average visual acuity over time (Figure 2) in the two groups. Regarding potential complications of implant surgery, transient vitreous hemorrhage occurred more frequently in the implant group (16% vs. 5% by 24 months, HR=3.6, $p=0.002$), but the risks of ocular hypotony, retinal detachment and infectious endophthalmitis were low, without significant differences between groups.

Adverse systemic events were infrequent in both groups. In an analysis permitting multiple events per patient, the risk of a systemic infection requiring prescription therapy was lower in the implant than the systemic group (0.36 vs. 0.60 events/person-year, $p=0.034$), but the risk of hospitalization did not differ substantially (0.13 vs. 0.17 hospitalizations/person-year respectively, $p=0.35$). Inspection of adverse event reports suggested that the infections in question did not result in long-term unfavorable outcomes. In the 24-month analyses (Table 5), the rate of measured hypertension (systolic >140 mmHg or diastolic >90 mmHg at any visit) was lower in the implant group (13% vs. 27%, HR=0.44, $p=0.030$), but the rate of anti-hypertensive treatment initiation did not differ substantially (5% vs. 11%, HR=0.40, $p=0.13$). The incidence of other adverse systemic outcomes—including hyperlipidemia, diabetes mellitus, osteoporosis, fractures, and blood count/chemistry abnormalities—was not statistically distinguishable between groups. Weight was stable over time in both groups (Table 6).

Serious adverse event reporting gave results similar to the prospectively ascertained ocular and systemic adverse outcomes.

Quality of Life

Changes from baseline to 24 months in generic health-related quality of life and health utility scores favored implant therapy (Table 6), but the magnitude of differences in improvement between groups was less than or equal to the threshold of previously reported minimally important differences.^{26–28} During the first six months, vision-related quality of life improved by 9.4 (out of 100) units more in the implant than the systemic group ($p<0.0001$). By 24 months both groups had improved, leaving a modest 4.6 unit advantage for the implant group ($p=0.04$), on the order of the reported minimally important difference (4–6 units).²⁷ A sensitivity analysis evaluating the percentage of individuals with a minimally important improvement^{26–28} did not differ significantly for any of the quality of life metrics (results not shown).

Discussion

Over 24 months following randomization of patients with non-infectious intermediate, posterior and panuveitis to implant or systemic therapy, on average, both groups had substantial improvement in visual acuity to a degree that was not significantly different (other than a small visual acuity improvement advantage in the implant group at six months). On average, the implant group improved by 2.8 letters more (95% Confidence Interval: -1.2 to 6.7 letters, with positive numbers favoring implant). Visual field sensitivity remained stably reduced in both groups. Many eyes required cataract surgery and other interventions, especially in the implant group; visual results may have been different if such treatments had not been available.

Our results indicate that both approaches are successful in controlling inflammation in the majority of cases, but that the implant achieves inflammatory control both faster and more often. We expected more uveitis activity early on in the systemic group, during the period when the minimal suppressive prednisone dose had to be determined empirically by tapering corticosteroids to the point of relapse. However, on average, the implant group showed better control of inflammation throughout follow-up, not just early on. Superiority of implant therapy for controlling inflammation was consistent with two small series in which implant therapy succeeded in controlling inflammation that had not responded to systemic therapy^{11;29} and a smaller trial in which systemic therapy was maintained for six months and then withdrawn.¹³ Longer follow-up will be needed to determine if superiority in controlling inflammation will result in better longer-term visual outcomes, as is widely assumed, and has been confirmed for two forms of uveitis in which it has been analyzed.^{30;31}

Quality of life outcomes suggested a clinically important advantage in vision-related quality of life for the implant group at six months, but narrowed to a small difference on the order of the minimally clinically important difference²⁷ by 24 months, paralleling improvement in visual acuity and vitreous haze. The implant group also had statistically better general self-reported quality of life outcomes, but the extent of the differences were marginal with respect to previously reported minimal clinically relevant differences.^{26;28}

Ocular complications of uveitis or treatment were more common in the implant group, which underwent many more cataract and glaucoma surgeries than the systemic group, consistent with results of the implant drug licensing trials.^{9;13;32} Nearly all phakic eyes receiving implant therapy can be expected to require cataract surgery, and about 25% of implant-treated eyes will require glaucoma surgery over 24 months. Despite IOP management, an important minority developed frank glaucomatous changes, mostly in the implant group, with visual field loss. Complications directly attributable to surgical implant

placement were infrequent, consistent with others' experience; the absolute risk of endophthalmitis and of retinal detachment was low or zero in both groups.^{9;13;32}

In contrast, systemic therapy (in which corticosteroid-sparing immunosuppressive therapy was used to minimize ongoing use of corticosteroids for the large majority of patients) was associated with relatively little additional systemic morbidity compared with implant therapy. Elevated blood pressure measurements during the trial were more frequent in the systemic group, but the proportion diagnosed with and treated for hypertension was small in both groups, and did not differ significantly. Infections requiring treatment were more common in the systemic group—a difference which may have resulted from immunosuppression or from bias in that clinicians might have been more likely to treat infections aggressively in patients on immunosuppressive therapy (or both). No other differences that were statistically significant or large in magnitude were observed, despite prospectively tracking potential complications of systemic corticosteroid therapy, including changes in body weight, incidence of diabetes, and changes in bone mineral density. These observations suggest that systemic therapy does not commonly induce morbidity when corticosteroid-sparing therapy is used aggressively to limit the duration of prednisone doses greater than 10 mg/day. Meta-analyses from other disease states also suggest that maintenance therapy with lower doses of prednisone is associated with relatively little morbidity.^{33;34} (Maintenance therapy with doses of prednisone exceeding 10 mg/day, not studied in this trial, clearly are associated with substantial morbidity⁸).

Strengths of the study included its randomized trial methodology to compare active treatments, and robust methods for ascertaining important clinical outcomes. The protocol was implemented successfully with acceptable adherence to treatment assignment and good follow-up. It is unlikely that the limited number of treatment crossovers obscured real differences in the primary outcome given the study power. Masking of participants and clinicians was not implemented because of ethical and feasibility constraints; the lack of masked ascertainment of self-reported quality of life and clinically evaluated uveitis activity potentially could have affected these outcomes.³⁵

In addition to the primary visual acuity outcome, we provide results on several pre-specified secondary outcomes, to better evaluate the comparative effectiveness of the alternative treatment approaches. Because multiple comparisons increase the probability of a false positive result, caution is needed in interpreting these secondary results.³⁶ In this study, the large differences observed in uveitis activity and the risk of local complications would be statistically significant even had we applied aggressive adjustment for multiple comparisons (e.g., Bonferroni correction). However, the differences observed in most quality of life comparisons were small enough to be susceptible to false positive results, which should be taken into account (along with the consistency of the quality of life results observed and their small effect sizes) in interpreting those results.

In summary, objective visual outcomes for intermediate, posterior and panuveitis improved over 24 months in both the implant and systemic treatment groups. Neither approach was determined to be superior, with a range of plausible differences between groups from a 1.2 letter advantage for systemic therapy to a 6.7 letter advantage for implant therapy. Both approaches usually succeeded in controlling ocular inflammation, but implant therapy gained control faster and more often, consistent with ongoing delivery of substantial dose corticosteroid therapy. At 24 months, implant therapy was associated with small improvements in vision-related and general quality of life compared with systemic therapy, and a higher risk of local adverse events (typically manageable with additional surgery). Implant therapy did not substantially reduce the risk of systemic adverse events, which were generally low in both groups.

Our results indicate that both treatments are associated with improvement over 24 months for the majority of cases, without clear evidence indicating substantially superior overall effectiveness of either approach. Therefore, the choice of treatment for a specific patient should be based on the importance of the advantages and disadvantages identified with the alternative treatments in that patient's particular clinical circumstances. Additional follow-up will be valuable to determine whether better control of uveitis with implant therapy over time eventually results in objective visual benefit; further exploration of the factors associated with vision loss and glaucoma development also will be initiated to better guide such decisions.

The systemic therapy approach we studied (using corticosteroid-sparing immunosuppressive drugs to avoid use of long-term, high-dose systemic corticosteroids) is widely used for systemic and local inflammatory diseases. Our results, in a population with a low risk of systemic adverse events on the basis of their disease, provide reassurance that this strategy for management of systemic and local inflammatory diseases is not associated with a high risk of systemic complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
CONSORT Diagram. VA=visual acuity; IOP=intraocular pressure

Figure 2.
Distribution of visual acuity from baseline to 24 months in eyes with intermediate, posterior, or panuveitis assigned to implant or systemic therapy. CI=confidence interval

Figure 4. Percentage with active inflammation from baseline to 24 months in eyes with intermediate, posterior, or panuveitis assigned to implant or systemic therapy.

Table 2

Change in visual acuity over time for the implant and systemic treatment arms during the initial 2 years of follow-up (as-randomized analysis).

Sample Size *		Estimate Mean _(SE[§])		Estimated Mean Change from Enrollment _(SE[§])		Estimated Treatment Effect [†] (95% CI [§])		P-value
		Implant	Systemic	Implant	Systemic	Implant: Systemic		
Primary Outcome: <u>Visual acuity</u> (letters read)								
E=								
Enrollment	475	61.0 _(2.5)	64.4 _(2.5)	n/a	n/a	n/a	n/a	n/a
6 months	443	66.9 _(2.3)	66.4 _(2.6)	5.88 _(1.07)	1.97 _(1.14)	3.91 (0.87, 7.02)		0.014
12 months	437	65.6 _(2.4)	67.7 _(2.6)	4.61 _(1.38)	3.33 _(1.23)	1.29 (−2.32, 5.01)		0.49
24 months	435	67.0 _(2.4)	67.6 _(2.6)	6.03 _(1.41)	3.23 _(1.41)	2.79 (−1.16, 6.68)		0.16
<u>Visual acuity</u> (letters read by the better eye)								
N=								
Enrollment	254	71.3 _(2.3)	75.4 _(2.0)	n/a	n/a	n/a	n/a	n/a
6 months	236	74.5 _(2.0)	76.8 _(2.2)	3.19 _(1.13)	1.43 _(0.97)	1.76 (−1.16, 4.68)		0.24
12 months	234	74.6 _(2.0)	77.1 _(2.3)	3.30 _(1.28)	1.67 _(1.06)	1.63 (−1.64, 4.89)		0.33
24 months	232	75.2 _(2.1)	77.3 _(2.2)	3.90 _(1.29)	1.92 _(1.12)	1.98 (−1.38, 5.35)		0.25

* Sample size = the number of eyes (E) or individuals (N) with data available at each visit.

[§] SE = standard error, CI = confidence interval.

[†] At each of the follow-up time points, the treatment effect is the model-based comparison of within treatment group change from enrollment (the difference of differences). A positive number favors implant.

Proportion with active uveitis and with macular edema over time for the implant and systemic treatment arms during the initial 2 years of follow-up (as-randomized analysis).

Table 3

	Sample Size*	Estimated Proportion with Condition (95%CI) [§]		Ratio of Odds Compared to Baseline Odds of Having Condition (95% CI)		Estimated Treatment Effect [†] (95% CI)		P-value
		Implant	Systemic	Implant	Systemic	Implant: Systemic	Implant: Systemic	
Uveitis Activity, % active	E=							
Enrollment	471	78% (70%, 85%)	75% (67%, 83%)	n/a	n/a	n/a	n/a	n/a
6 months	440	21% (14%, 29%)	44% (35%, 54%)	0.08 (0.04, 0.12)	0.26 (0.16, 0.41)	0.30 (0.15, 0.57)	0.30 (0.15, 0.57)	< 0.001
12 months	434	15% (10%, 22%)	36% (26%, 45%)	0.05 (0.02, 0.09)	0.18 (0.11, 0.30)	0.28 (0.13, 0.56)	0.28 (0.13, 0.56)	0.001
24 months	429	12% (6%, 20%)	29% (21%, 39%)	0.04 (0.02, 0.07)	0.14 (0.08, 0.23)	0.29 (0.13, 0.60)	0.29 (0.13, 0.60)	0.001
Macular edema, %	E=							
Enrollment	436	41% (32%, 51%)	39% (32%, 51%)	n/a	n/a	n/a	n/a	n/a
6 months	398	20% (13%, 28%)	34% (13%, 28%)	0.36 (0.23, 0.51)	0.79 (0.56, 1.11)	0.45 (0.27, 0.74)	0.45 (0.27, 0.74)	0.002
12 months	385	21% (14%, 29%)	29% (14%, 29%)	0.39 (0.25, 0.55)	0.63 (0.43, 0.90)	0.61 (0.35, 1.04)	0.61 (0.35, 1.04)	0.067
24 months	403	22% (14%, 30%)	30% (14%, 30%)	0.41 (0.26, 0.60)	0.67 (0.46, 0.96)	0.61 (0.34, 1.03)	0.61 (0.34, 1.03)	0.071

* Sample size: the number of eyes with uveitis with available data at each visit.

§ CI = confidence interval. OR = odds ratio.

† At each of the follow-up time points, is the ratio of odds ratios, with 95% CI. An odds ratio less than 1 favors implant.

Table 4
Incidence of ocular complications of uveitis or its treatment for the two treatment groups, among eyes at risk at baseline.*

	<u>Implant Therapy</u>		<u>Systemic Therapy</u>		<u>Hazard Ratio</u>		<u>P-value</u>
	# Eyes at risk	Cumulative % with event by 2 years (95% CI)	# Eyes at risk	Cumulative % with event by 2 years (95% CI)	Implant/Systemic (95% CI)		
Intraocular Pressure (IOP) events							
IOP ≥ 30 mmHg	234	32.8 (27.1, 39.2)	229	6.3 (3.7, 10.3)	6.08 (3.32, 11.15)		<.0001
IOP ≥24 mmHg	234	53.1 (46.9, 59.7)	228	18.7 (14.2, 24.5)	3.59 (2.34, 5.50)		<.0001
IOP ≥ 10 mmHg increase from baseline	235	51.8 (45.5, 58.3)	230	15.5 (11.4, 20.9)	4.28 (2.78, 6.58)		<.0001
Glaucoma and IOP-lowering treatment							
Glaucoma	212	16.5 (12.1, 22.2)	202	4.0 (2.0, 7.8)	4.19 (1.82, 9.63)		0.0008
Use of any IOP-lowering therapy	201	61.1 (54.3, 67.8)	203	20.1 (15.1, 26.3)	4.16 (2.67, 6.47)		<.0001
IOP-lowering surgery	233	26.2 (21.0, 32.4)	226	3.7 (1.9, 7.2)	8.40 (3.39, 20.82)		<.0001
Cataract							
Incident Cataract	54	90.7 (81.3, 96.6)	50	44.9 (32.3, 59.8)	4.12 (2.21, 7.67)		<.0001
Cataract Surgery	140	80.4 (73.3, 86.6)	125	31.3 (23.9, 40.4)	3.33 (2.20, 5.04)		<.0001
Visual acuity worse than 20/40							
First visit with a reduced acuity	112	57.7 (48.2, 67.3)	117	35.6 (26.4, 44.8)	1.91 (1.26, 2.88)		0.0021
Reduced for two consecutive visits	112	31.2 (22.3, 40.1)	117	19.8 (12.2, 27.3)	1.68 (0.97, 2.90)		0.060
Visual acuity 20/200 or worse							
First visit with a reduced acuity	196	13.0 (8.2, 17.8)	193	9.9 (5.6, 14.1)	1.31 (0.68, 2.49)		0.41
Potential complications of implant surgery							
IOP < 6 mmHg (hypotony)	228	8.4 (5.4, 12.8)	218	6.1 (3.6, 10.2)	1.46 (0.60, 3.54)		0.41
Vitreous hemorrhage	236	15.7 (11.6, 21.0)	230	4.9 (2.7, 8.6)	3.57 (1.60, 7.96)		0.0019
Endophthalmitis	237	1.3 (0.4, 4.0)	230	0	Not estimable		
Rhegmatogenous retinal detachment	236	2.1 (0.9, 5.0)	230	0.44 (0.1, 3.1)	4.91 (0.57, 42.56)		0.15
Implant extrusion	204	0	231	0	Not estimable		

Table 5

Incidence of systemic complications for the two treatment groups, among patients at risk at baseline.*

	Implant Therapy		Systemic Therapy		Hazard Ratio	P-value
	#Patients at risk	Cumulative % with event by 2 years (95% CI) [¶]	#Patients at risk	Cumulative % with event by 2 years (95% CI) [¶]	Implant/Systemic (95% CI) [¶]	
Potential complications of corticosteroid therapy[¶]						
Hyperlipidemia (LDL ≥160 mg/mL)	97	9.8 (5.2, 18.0)	104	11.0 (6.3, 19.1)	0.91 (0.39, 2.15)	0.84
Hyperlipidemia diagnosis requiring treatment	90	1.1(0.2, 7.7)	86	6.0(2.5, 13.8)	0.19(0.02, 1.65)	0.13
Hypertension						
Measured SBP≥160 and/or DBP≥100	111	2.9(0.9, 8.6)	109	10.3(5.8, 17.8)	0.25 (0.07, 0.89)	0.030
Measured SBP≥140 and/or DBP≥90	81	12.9(7.2, 22.6)	89	26.9(18.4, 37.1)	0.44 (0.21, 0.92)	0.030
Hypertension diagnosis requiring treatment	88	4.6(1.8, 11.9)	88	10.5(5.6, 19.3)	0.40(0.13, 1.29)	0.13
Diabetes mellitus	105	1.0(0.1, 6.6)	114	3.6(1.4, 9.4)	0.26 (0.03, 2.44)	0.24
Bone						
Osteopenia	52	25.5(15.7, 39.9)	63	13.0(6.7, 24.4)	1.98(0.83, 4.70)	0.12
Osteoporosis	107	4.8(2.0, 11.2)	108	5.0(2.1, 11.6)	0.95(0, 28, 3.25)	0.93
Fractures	125	4.1(1.7, 9.5)	124	8.4(4.6, 15.0)	0.47(0.16, 1.35)	0.16
Potential complications of immunosuppressive therapy						
White blood cell count ≤ 2500 cells/ μ L	121	0.8(0.1, 5.8)	120	2.6(0.8, 7.7)	0.33(0.03, 3.15)	0.34
Platelet count ≤ 100,000/ μ L	120	2.6(0.8, 7.8)	118	1.7(0.4, 6.6)	1.43(0.24, 8.35)	0.69
Hemoglobin ≤10 g/dL	121	0.9(0.1, 6.0)	118	1.8(0.4, 7.0)	0.88(0.09, 9.00)	0.92
Elevated liver enzymes [¶]	120	5.2(2.4, 11.3)	120	0.9(0.1, 6.0)	6.45(0.88, 47.2)	0.066
Elevated creatinine [†]	122	10.1(5.9, 17.1)	120	5.2(2.4, 11.2)	2.11(0.80, 5.60)	0.13
Cancer diagnosis	126	0.8(0.1, 5.5)	124	3.2(1.0, 10.1)	0.34(0.04, 3.20)	0.34
Death	126	1.6(0.4, 6.3)	124	0	Not estimable	

Hazard ratios are adjusted for bilateral disease and uveitis stratum.

* Patients with prevalent complications or missing data at enrollment were excluded from the risk set; the table only assesses first events, not multiple events.

[¶] LDL = low density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; % = percent; CI = confidence interval.

[¶] Elevated liver enzyme is defined as twice the upper limit of normal for aspartate aminotransferase and/or alanine aminotransferase.

[†] Elevated creatinine is defined as > 1.5 mg/dL and/or > 30% increase from baseline.

Table 6

Change in Quality of Life (QoL) and weight over time for the implant and systemic treatment arms during the initial 2 years of follow-up (as-randomized analysis).

	Sample Size*	Estimated Mean I(SE §)	Estimated Mean Change from Enrollment _(SE)	Estimated Treatment Effect † (95% CI§)	P-value	
		Implant	Systemic	Implant	Systemic	Implant: Systemic
<u>Vision-related QoL</u>						
VFIQ-25 (Overall Composite Score)	N=					
Enrollment	255	60.6 _(2.4)	64.9 _(2.5)	n/a	n/a	n/a
6 months	233	71.4 _(2.4)	66.3 _(2.5)	10.77 _(1.31)	1.41 _(1.38)	9.37 (5.64, 13.09)
12 months	235	72.7 _(2.5)	69.7 _(2.5)	12.13 _(1.60)	4.86 _(13.8)	7.27 (3.11, 11.42)
24 months	232	72.1 _(2.5)	71.7 _(2.6)	11.44 _(1.67)	6.80 _(1.58)	4.64(0.14, 9.15)
<u>Generic health-related QoL</u>						
SF-36 (Mental Component Summary Score)	N=					
Enrollment	255	47.5 _(1.3)	48.3 _(1.2)	n/a	n/a	n/a
6 months	236	51.1 _(1.12)	45.5 _(1.4)	3.58 _(1.12)	-2.75 _(1.14)	6.33 (3.19, 9.47)
12 months	234	51.0 _(1.1)	46.5 _(1.3)	3.52 _(10.5)	-1.81 _(1.11)	5.33 (2.33, 8.33)
24 months	232	50.0 _(1.2)	47.2 _(1.4)	2.55 _(1.11)	-1.07 _(1.15)	3.62(0.49, 6.76)
SF-36 (Physical Component Summary Score)	N=					
Enrollment	255	46.5 _(1.2)	48.4 _(1.1)	n/a	n/a	n/a
6 months	236	46.4 _(1.2)	46.6 _(1.1)	-0.07 (0.73)	-1.81 (0.67)	1.73 (-0.21, 3.67)
12 months	234	47.5 _(1.2)	46.6 _(1.1)	1.02 (0.78)	-1.87 (0.87)	2.89(0.60, 5.18)
24 months	232	47.6 _(1.2)	46.6 _(1.1)	1.15 (0.83)	-1.79 (0.90)	2.95 (0.54, 5.36)
<u>Health utility</u>						
EuroQoL (Visual Analog Scale)	N=					
Enrollment	253	72.7 _(1.9)	74.3 _(2.0)	n/a	n/a	n/a
6 months	233	75.0 _(2.1)	72.5 _(2.0)	2.34 _(1.61)	-1.85 _(1.90)	4.19 (-0.69, 9.07)
12 months	234	77.3 _(1.9)	71.3 _(2.2)	4.66 _(1.36)	-3.00 _(1.78)	7.65 (3.26, 12.05)
24 months	232	78.0 _(1.8)	73.4 _(1.9)	5.29 _(1.28)	-0.88 _(1.88)	6.17 (1.87, 10.47)
EuroQoL (EQ-5D HealthUtility Index)	N =					

	Sample Size*	Estimated Mean I (SE §)		Estimated Mean Change from Enrollment _(SE)		Estimated Treatment Effect † (95% CI§)	P-value
		Implant	Systemic	Implant	Systemic	Implant: Systemic	
Enrollment	254	0.81 _(0.02)	0.83 _(0.02)	n/a	n/a	n/a	n/a
6 months	236	0.83 _(0.02)	0.82 _(0.02)	0.01 _(0.01)	-0.01 _(0.02)	0.03(-0.02, 0.07)	0.25
12 months	235	0.83 _(0.02)	0.80 _(0.02)	0.02 _(0.02)	-0.03 _(0.02)	0.05(0.00, 0.10)	0.041
24 months	232	0.84 _(0.02)	0.81 _(0.02)	0.02 _(0.02)	-0.02 _(0.02)	0.04 (-0.01, 0.09)	0.060
Weight (kg)							
Enrollment	N=	87.8 _(2.6)	86.0 _(2.7)	n/a	n/a	n/a	n/a
6 months	255	88.2 _(2.7)	87.0 _(2.7)	0.40 _(0.54)	0.96 _(0.75)	-0.56 (-2.38, 1.26)	0.54
12 months	231	87.4 _(2.7)	86.4 _(2.7)	-0.38 _(0.70)	0.38 (0.81)	-0.76 (-2.87, 1.34)	0.48