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Association Between Long-Lasting Intravitreous Fluocinolone Acetonide Implant vs Systemic Anti-inflammatory Therapy and Visual Acuity at 7 Years Among Patients With Intermediate, Posterior, or Panuveitis

Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group

IMPORTANCE A randomized clinical trial comparing fluocinolone acetonide implant vs systemic corticosteroids and immunosuppression for treatment of severe noninfectious intermediate, posterior, and panuveitides did not result in a significant difference in visual acuity at 2 and 4.5 years; longer-term outcomes are not known.

OBJECTIVE To compare the association between intravitreous fluocinolone acetonide implant vs systemic therapy and long-term visual and other outcomes in patients with uveitis.

DESIGN, SETTING, AND PARTICIPANTS Nonprespecified 7-year observational follow-up of the Multicenter Uveitis Steroid Treatment (MUST) randomized clinical trial comparing the alternative treatments. Follow-up was conducted in tertiary uveitis subspecialty practices in the United States (21), the United Kingdom (1), and Australia (1). Of 255 patients 13 years or older with intermediate, posterior, or panuveitis (active within ≤60 days) enrolled in the MUST trial between December 6, 2005, and December 9, 2008, 215 consented to ongoing follow-up through at least 7 years postrandomization (last visit, February 10, 2016).

INTERVENTIONS Participants had been randomized to receive a surgically placed intravitreous fluocinolone acetonide implant or systemic corticosteroids supplemented by immunosuppression. When both eyes required treatment, both eyes were treated.

MAIN OUTCOMES AND MEASURES Primary outcome was change from baseline in best-corrected visual acuity in uveitic eyes (5 letters = 1 visual acuity chart line; potential range of change in letters read, −121 to +101; minimal clinically important difference, 7 letters), analyzed by treatment assignment accounting for nonindependence of eyes when patients had 2 uveitic eyes. Secondary outcomes included potential systemic toxicities of corticosteroid and immunosuppressive therapy and death.

RESULTS Seven-year data were obtained for 161 uveitic eyes (70% of 90 patients assigned to implant) and 167 uveitic eyes (71% of 90 patients assigned to systemic therapy) (77% female; median age at enrollment, 48 [interquartile range, 36-56] years). Change in mean visual acuity from baseline (implant, 61.7; systemic therapy, 65.0) through 7 years (implant, 55.8; systemic therapy, 66.2) favored systemic therapy by 7.2 (95% CI, 2.1-12) letters. Among protocol-specified, prospectively collected systemic adverse outcomes, the cumulative 7-year incidence in the implant and systemic therapy groups, respectively, was less than 10%, with the exceptions of hyperlipidemia (6.1% vs 11.2%), hypertension (9.8% vs 18.4%), osteopenia (41.5% vs 43.1%), fractures (11.3% vs 18.6%), hospitalization (47.6% vs 42.3%), and antibiotic-treated infection (57.4% vs 72.3%).

CONCLUSIONS AND RELEVANCE In 7-year extended follow-up of a randomized trial of patients with severe intermediate, posterior, or panuveitis, those randomized to receive systemic therapy had better visual acuity than those randomized to receive intravitreous fluocinolone acetonide implants. Study interpretation is limited by loss to follow-up.

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Supplemental content

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Noninfectious intraocular inflammation (uveitis) is an important cause of visual impairment.[1] Intermediate, posterior, and panuveitides, which involve the middle and posterior portions of the eye,[2,3] have been the forms of uveitis most likely to cause vision loss.[4-6]

Systemic corticosteroids and corticosteroid-sparing immunosuppressive drugs have been used to manage a wide range of inflammatory diseases, including uveitides. This approach has been the mainstay of treatment for severe noninfectious intermediate, posterior, and panuveitides.[3] Even though systemic adverse effects have been thought to be minimized by appropriate treatment implementation,[7] concerns regarding potential systemic adverse effects thereof have limited the utilization of such therapy.[8]

In 2005, a local therapy alternative for intermediate, posterior, and panuveitides was approved by the US Food and Drug Administration: a long-lasting, surgically placed intravitreous fluocinolone acetonide implant[9-11] with minimal systemic absorption, intended to avoid systemic adverse effects completely. The MUST Trial Research Group directly compared these contrasting long-term strategies in a 2-year randomized clinical trial,[12] succeeded by nonprespecified longitudinal follow-up of the trial cohort. Through the primary 2-year time point[13] and a subsequent observational cohort analysis through 4.5 years after randomization,[14,15] the 2 strategies demonstrated visual acuity and systemic outcomes that were not significantly different; significantly better control of inflammation, with significantly more local adverse outcomes, was observed with implant therapy. Given considerations that the latter results eventually might alter visual outcome, extended follow-up of the cohort through 7 years after randomization was conducted.

Key Points

Question Is there a significant difference in visual acuity with long-term follow-up of treatment with intravitreous fluocinolone acetonide implant or systemic anti-inflammatory therapy for severe intermediate, posterior, or panuveitis?

Findings In a nonprespecified 7-year observational follow-up of 215 participants in a randomized clinical trial, systemic therapy was associated with significantly better visual acuity compared with implant, by a mean of 7 letters; in contrast, the trial had shown no significant difference at 2 years.

Meaning After 7 years, systemic corticosteroid and immunosuppressive therapy was associated with better visual acuity compared with fluocinolone acetonide implant. However, these findings are limited by a 30% loss to follow-up, with possible selection bias.

Methods

Study Design

The Multicenter Uveitis Steroid Treatment (MUST) trial—a 2-year randomized (allocation ratio, 1:1), 23-center, parallel-treatment clinical trial—was succeeded by nonprespecified extended follow-up of the cohort (The MUST Trial Follow-up Study). The protocol for the original study is available in Supplement 2; the protocol for the follow-up study is available in Supplement 3. Previous reports detail the study designs; the trial hypothesized superiority of implant therapy.[12-15]

All participants provided written informed consent for study participation; all governing institutional review boards provided ongoing approvals. Participants who had enrolled into the trial over 3 years (between December 6, 2005, and December 9, 2008) were followed up under that protocol until 2 years after the last patient enrolled. Thereafter, when primary results were reported showing visual outcomes without statistically significant differences,[13] participants agreeing to continue in the follow-up study were encouraged to continue their assigned treatment unless contraindicated and were followed up until 7 years after their randomization (2 to 5 additional years, depending on how long they had been followed up under the trial protocol; last 7-year visit, February 10, 2016).

Enrollment of Participants, Data Collection, and Follow-up

Patients were eligible for the trial if they were 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. Patients enrolled in the trial and subsequently the follow-up study were treated at uveitis subspecialty centers in the United States (21), United Kingdom (1), and Australia (1). Study visits were conducted at least semiannually through 7 years (quarterly under the trial protocol, every 6 months thereafter). Race and ethnicity were evaluated based on self-report among US Census-defined categories, given that the incidence of some uveitic outcomes varies with race/ethnicity.[16,17]

Random Treatment Assignment

Trial participants had been randomized 1:1 to systemic or implant therapy (both eyes treated when both eyes met eligibility criteria) by variable-length (2-4 per block), permuted blocks within strata (clinical center; and intermediate vs posterior or panuveitis, given better reported outcomes for intermediate vs posterior or panuveitis).[18] After eligibility and stratum were confirmed, the study website revealed the participant's treatment assignment (produced in advance by the Coordinating Center).[19,20]

Treatment Protocol

Clinicians and participants were instructed to apply the assigned treatment strategy throughout the trial; during the follow-up study, they were encouraged to continue the same treatment regimen unless contraindicated. The implant therapy protocol required suppression of anterior chamber inflammation with topical, periocular, and/or systemic corticosteroids, then placement of an intravitreous fluocinolone acetonide implant (0.59 mg) (Bausch & Lomb) by study-certified surgeons using a recommended technique[10,21] within 28 and 56 days after randomization in the first and second (if indicated) eyes, respectively. Thereafter, the protocol required tapering and cessation of systemic corticosteroids, immunosuppressants, or both, with reimplantation on occurrence of reactivated inflammation sufficiently severe to otherwise require systemic

therapy. Best medical judgment was permitted for initial failure of implantation to control inflammation, implantation-limiting toxicity, or incident systemic disease requiring systemic therapy.

The systemic therapy protocol followed expert panel guidelines,[7] under which initially active uveitis was treated using the lesser of 1 mg/kg/d or 60 mg/d of prednisone, followed by prednisone tapering after control of inflammation to a dose of 10 mg/d or less that was sufficient to maintain control. The initial prednisone dose was tapered for patients whose uveitis already was clinically graded as inactive at baseline (≈20%). The protocol required immunosuppression for corticosteroid sparing when uveitis consistently reactivated at prednisone doses above 10 mg/d, if intolerable corticosteroid-induced adverse effects were occurring, for specific high-risk uveitic diseases, and if corticosteroids failed to control inflammation. When immunosuppression was required, clinicians selected among standard immunosuppressive drugs the ones most suitable for each patient (see protocol in Supplement 2); administration and monitoring for toxicity followed established guidelines.[7]

In the follow-up study, these treatments were continued unless contraindicated per best medical judgment.

Outcomes and Masking

All outcomes were measured in the same way during the trial and follow-up study, except that measurement of visual acuity was performed by an unmasked certified examiner instead of a masked examiner during the follow-up study, and hyperglycemia was assessed using fasting glucose levels through January 2, 2011, and hemoglobin A_{1c} values thereafter. Visual acuity (during the trial period), glaucoma, and ocular imaging Reading Center–ascertained outcomes were masked. Patients, clinicians, and coordinators were not masked.[12]

Primary Outcome

Change in best-corrected visual acuity from baseline was the primary outcome, measured by study-certified examiners using a gold-standard protocol[22] enforced by regular site visits. Five letters equals 1 line on a logarithmic visual acuity chart. The minimal clinically important difference (MCID) for change in letters read is 7 letters, based on clinical trial results of pivotal trials of treatments that later were widely adopted for wet macular degeneration.[23-26] The range of possible values of change in letters read is −121 (+96 letters, to no light perception scored as −25 letters) to +101 (from hand motions, the lowest level of visual acuity allowed to enroll to +96 letters). The observed range of change was from −102 to +92 letters). Occurrence of legal blindness (20/200 or worse)—an alternative, prespecified way of summarizing the gold standard visual acuity data—also was studied.

Secondary Outcomes Prespecified in the Trial Protocol

Overall visual field sensitivity within 24° of fixation was measured using the mean deviation statistic,[27] an overall measure summarizing the average difference between normative results and a given eye's visual field sensitivity across points in the central 24° of the visual field, weighted by normal variability, with negative values representing loss of vision.[28] We studied the incidence of a loss of 10 dB from baseline (−6 to −12 dB is comparable to the visual impact of moderate glaucoma[29]). Overall control of intraocular inflammation (uveitis) was assessed based on clinically graded uveitis activity or inactivity. The presence or absence of macular edema was determined by optical coherence tomography images graded by the Reading Center.[30] Regarding local ocular adverse outcomes, intraocular pressure was measured as the median of 3 measurements (range, 0-80+ mm Hg; observed range, 0-60.5 mm Hg). Cataract and vitreous hemorrhage were diagnosed clinically. Use of medication or surgery for increased intraocular pressure, or of surgery for cataract, was based on the observation of such use.

Regarding systemic adverse events, potential systemic toxicities of corticosteroid therapy, immunosuppressive therapy, or both included incident diabetes mellitus (diabetes-level hyperglycemia [fasting blood glucose level ≥140 g/dL {7.77 mmol/L} or, after January 2, 2011, hemoglobin A_{1c} level ≥6.5%], explicit diagnosis, and/or had started hypoglycemic therapy); osteopenia (L2-L4 and femoral next-worst T-score between −1.00 and −2.49) and osteoporosis (T-score ≤−2.50); hyperlipidemia (had started antihyperlipemic treatment); hypertension (had started antihypertensive treatment); weight changes (from baseline in kg); systemic infection for which anti-infectious therapy was prescribed; hospitalization (and reasons for hospitalization); bone marrow suppression [white blood cell count ≤2500 cells/μL; platelet count ≤100 000/μL; hemoglobin level ≤10 g/μL]; hepatotoxicity (aspartate aminotransferase level, alanine aminotransferase level, or both ≥2-fold above upper limit of normal); nephrotoxicity (drug discontinuation for renal toxicity or observed serum creatinine level ≥1.5 mg/dL [132.6 μmol/L]); incident cancer (excluding nonmelanoma skin cancer); and death. At in-person study visits, participants were asked about interim fractures, diagnosis of cancer, treatment for hyperlipidemia or hypertension, hospitalization, and use of antibiotics prescribed for an infection. The study team confirmed reported events using medical records. A periodic audit, supplemented by a Social Security Death Master File[12] search, was conducted to ascertain mortality.

Self-reported quality-of-life (QOL) outcomes were assessed during follow-up visits semiannually. Health utility and vision- and general health–related quality of life were measured respectively using the EuroQol EQ-5D (range, less than 0.00 to 1.00, where 0.00 corresponds to immediate death and 1.00 to perfect health; MCID, 0.06-0.07 points), NEI-VFQ (National Eye Institute Visual Functioning Questionnaire) (range, 0-100; 0 corresponds to complete loss of visual function accompanied by eye pain, dependence as a result of vision loss, and anxiety about blindness; 100 reflects perfect visual function with lack of pain, anxiety, and dependence; MCID, 4-6 points), and SF-36 (36-Item Short Form Health Survey) physical health component (range, 0-100; MCID, 3-5 points) and mental health component (range, 0-100; MCID, 3-5 points) instruments (for both, 50 corresponds to population average scores and 0 and 100 correspond to 5 SDs above or below average).[31-33]

Cost-effectiveness analysis was prespecified in the study protocols but was not conducted, given considerations of dominance when outcomes are as good or better for the less expensive treatment.[34]

Nonprespecified Outcomes

Nonprespecified outcomes were limited to exploration of the causes of visual loss by masked, retrospective review of study forms through 7 years after randomization.

Statistical Analyses

Statistical analyses are detailed in the Statistical Analysis Plan available in Supplement 4. In brief, the primary analyses were based on treatment assignment; as-treated sensitivity analyses also were conducted regarding the incidence of ocular adverse outcomes. For the intention-to-treat primary outcome comparison with the available sample size at the beginning of the follow-up study—accounting for anticipated losses to follow-up, crossovers, and correlation between uveitic eyes of the same patient—the power to detect the prespecified difference of 7 standard letters in best-corrected visual acuity between randomized groups exceeded 80% at 7 years, with a 2-sided type I error probability of .05. Generalized estimating equations with saturated-means models were used to evaluate longitudinal outcomes.[35] The unit of analysis was the (uveitic) eye (including both eyes of a patient if applicable) or the patient for eye-specific (eg, visual acuity) and patient-specific (eg, QOL) outcomes, respectively. Bootstrapping addressed correlations between eyes of the same patient.

Incident adverse systemic and ocular outcomes were compared using frailty models. Comparisons between patients with and without a 7-year visit were made using χ^2 tests and Wilcoxon rank-sum tests for person-level characteristics and mixed effects for eye-level characteristics. Because assessments in this extension of the primary trial protocol were exploratory, reported 2-sided *P* values were not adjusted for multiple comparisons; ie, all tests were considered statistically significant at the .05 level.

Robust standard errors were computed for all models. Binary outcomes are summarized both in terms of absolute (percent) and relative (odds ratio) differences. Worst-outcome scenarios and mixed-effects models, which are robust to data missing at random, were used to address loss to follow-up and missing data.[36] The Statistical Analysis Committee (eAppendix in Supplement 1) conducted the analyses using SAS version 9.1,[37] Stata release 9.0,[20] and R version 3.3.1.[38]

Results

Among the 255 patients enrolled in the trial (479 uveitic eyes; see **Figure 1**) the majority were female (71% in implant group; 79% in systemic therapy group) and white (56% in each group). The median ages were 46 years (interquartile range, 34-56) and 48 years (interquartile range, 35-57), respectively. Randomization assigned 129 and 126 patients (245 and 234 uveitic eyes) to receive implant and systemic therapy, respectively. At baseline, the only statistically significant differences between groups were a higher proportion with osteopenia and lower visual field sensitivity in the implant group vs the systemic therapy group.[13]

Seven-year data were obtained for 171 uveitic eyes (70%) of 90 patients assigned to implant and 167 uveitic eyes (71%) of 90 assigned to systemic therapy. Characteristics of patients completing vs not completing that visit are described in **Table 1**; potentially important differences were observed between these groups (regarding the distribution of baseline visual acuity, sex, white race, Hispanic ethnicity, anatomical location of the uveitis, presence or absence of associated systemic inflammatory disease, bone density, duration of uveitis in uveitic eyes, and lens status), even though the differences were not statistically significant.

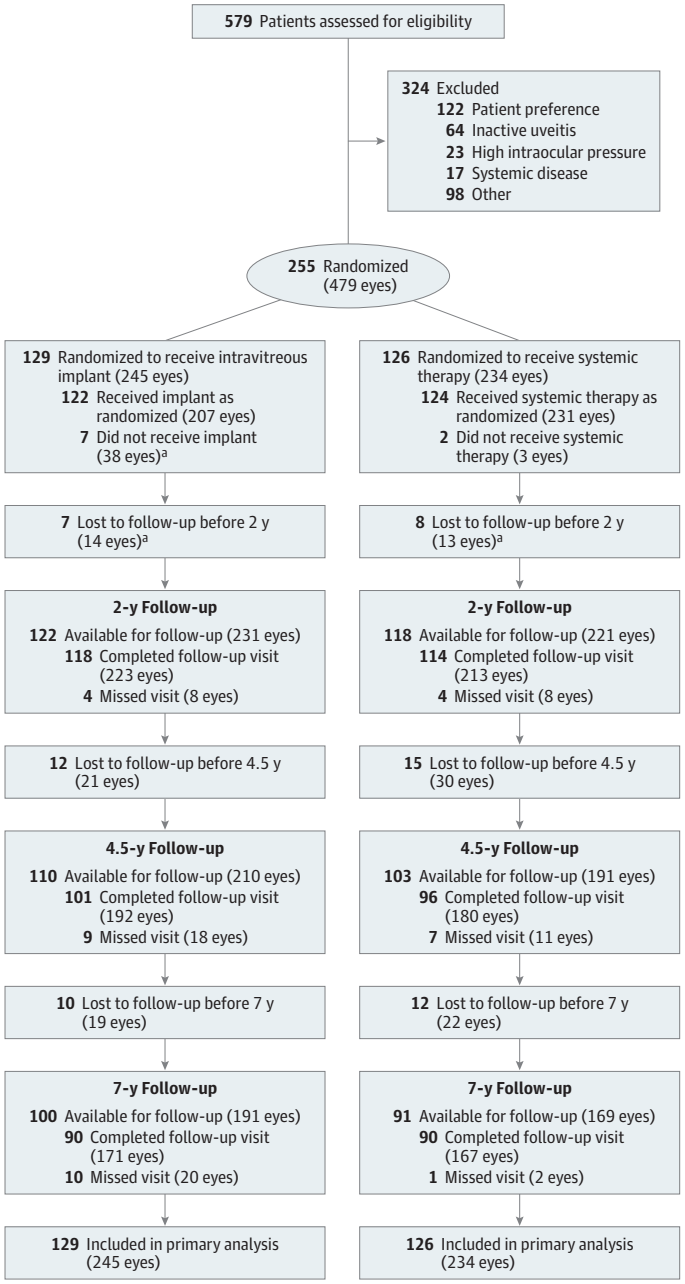
Utilization of treatment over 7 years after randomization is summarized in eFigure 1 in Supplement 1. Approximately 95% of patients in the implant and systemic therapy groups initially received their assigned therapies. Among uveitic eyes of implant-assigned patients, 84% of eyes had received 1 or more implants, 24% had received 2 or more implants, and 1.2% of eyes had 3 or more implants by 7 years (not every second uveitic eye met indications for implantation, and not all eyes experienced sufficient reactivation of uveitis to warrant reimplantation). After the first year, an average of about 20% to 25% implant-assigned patients were taking systemic corticosteroids, immunosuppressive drugs, or both at any given time. Most implanted eyes remained free of active uveitis while not receiving other treatments longer than the anticipated 3 years[9]; for most uveitic eyes, relapses of inflammation and consequent need for treatment began approximately 5 years after implantation.

In the systemic therapy group, in addition to corticosteroids, 88% of participants assigned to receive systemic therapy received immunosuppressive therapy during follow-up; at 7 years, 34% and 43%, respectively, were taking oral corticosteroids (median dose, 6.25 mg) and 1 or more immunosuppressant or biologic agents. The percentage of systemic therapy–assigned uveitic eyes treated with implant therapy increased over time, with 18% of uveitic eyes receiving an implant by 7 years (5 eyes assigned to receive systemic therapy received 2 implants).

Primary Outcome: Visual Acuity

At 6 months postrandomization, both groups experienced improved visual acuity (+5.9 vs +2.0 letters in the implant and systemic therapy groups, respectively), with an early statistically significant implant advantage in the implant group (+2.8 letters [95% CI on difference, +0.33 to +6.6 letters, favoring implant). Thereafter, with further improvement in the systemic therapy group, the groups' visual acuity outcomes did not significantly differ through 5 years, including at the trial primary outcome time point of 2 years. However, after 5 years, the average visual acuity in the implant group began declining, whereas the systemic therapy group maintained similar visual acuity on average. By 6 and 7 years, respectively, the change in visual acuity from baseline (implant, −2.6 and −6.0 letters; systemic therapy, +2.4 letters and +1.2 letters) favored systemic therapy by a mean of 5.0 letters (95% CI, 0.08 to 9.9) and 7.1 letters (95% CI, 2.1 to 12), respectively (**Table 2** and **Figure 2**).

Figure 1. Flow of Multicenter Uveitis Steroid Treatment (MUST) Follow-up Study



Losses to follow-up by 2, 4.5, and 7 years are indicated. Some participants missed the 2-, 4.5-, or 7-year visits but completed subsequent visits and hence remained in follow-up.

[a] For a number of patients with uveitis in both eyes, one eye required little or no treatment. Hence, a total of 38 eyes either belonged to these 7 patients or were mildly affected second eyes for which implant therapy was not indicated.

Sensitivity analysis regarding missing data found that among those with missing data on the change from baseline to 7 years, the difference between the change in the implant and systemic therapy groups would need to be 0.4 and 28.6 letters (both favoring implant) to make the overall differences nonsignificant or to favor the implant, respectively. This would represent a reversal of 7.5 and 35.7 letters, respectively, from what was observed. Sensitivity analyses using random-effects models to evaluate clinic effects and other possibilities all showed a statistically significant benefit for systemic therapy.

The proportion of patients with legal blindness (20/200 or worse), a prespecified way of summarizing the primary outcome data, at 7 years vs baseline was 8% more in the implant group and 1% less in the systemic therapy group (difference, 9.1% [95% CI, 1.3% to 17.2%] favoring systemic therapy). A post hoc assessment of clinic-reported causes of incident visual impairment to 20/50 or worse found that chorioretinal lesion causes (excluding potentially reversible epiretinal membranes and macular edema) increased more in the implant group at 6 years (43%, vs 15% in the systematic therapy group; difference, 29% [95% CI, 11% to 46%]; $P < .001$) and 7 years

Table 1. Comparison of Baseline Characteristics for Participants Completing or Not Completing the Year-7 Visit

	No. (%)			
	Overall	Did Not Complete Year-7 Visit	Completed Year-7 Visit	*P* Value[a]
Patient Characteristics				
No. of Participants	255	75 (29)	180 (71)	
Age, median (IQR), y	47 (34-56)	44 (31-59)	48 (36-56)	.34
Female	191 (75)	53 (71)	138 (77)	.31
Race/ethnicity				
White	142 (56)	36 (48)	106 (59)	.27
Hispanic	33 (13)	13 (17)	20 (11)	
Black	66 (26)	20 (27)	46 (26)	
Other	14 (5)	6 (8)	8 (4)	
Bilateral uveitis	224 (88)	66 (88)	158 (88)	.96
Posterior or panuveitis uveitis site	158 (62)	53 (71)	105 (58)	.07
Associated systemic inflammatory disease	69 (27)	24 (32)	45 (25)	.25
Bone density[b]				
Normal	132 (53)	41 (56)	91 (51)	.18
Osteopenia	99 (40)	30 (41)	69 (39)	
Osteoporosis	19 (8)	2 (3)	17 (10)	
Eye Characteristics				
No. with uveitis	479	141 (29)	338 (71)	
Eye-specific duration of uveitis, median (IQR), y	3.70 (1.20 to 7.86)	2.99 (0.70 to 6.80)	4.15 (1.51 to 8.13)	.16
Visual acuity, median (IQR), standard letters[c]	70.1 (49.1 to 80.1)	72.1 (46.1 to 81.1)	69.1 (52.1 to 80.1)	.63
Mean deviation, median (IQR), dB[d]	−5.16 (−9.59 to −2.97)	−5.75 (−10.68 to −3.28)	−4.95 (−9.17 to −2.87)	.14
Active uveitis	373 (79)	109 (79)	264 (79)	.95
Lens opacities				
Absent or trivial cataract	106 (22)	33 (23)	73 (22)	.64
Cataract	166 (35)	52 (37)	114 (34)	
Aphakic or pseudophakic	207 (43)	56 (40)	151 (45)	
Intraocular pressure, median (IQR), mm Hg	14 (11 to 17)	15 (12 to 17)	14 (11 to 17)	.36
Macular edema	155 (36)	45 (34)	110 (36)	.71

Abbreviation: IQR, interquartile range.

[a] *P* values for the participants are based on χ^2 and Kruskall-Wallis tests for categorical and continuous variables, respectively. *P* values for eye-level variables are based on mixed-effects models to adjust for between-eye correlations.

[b] Osteopenia defined based on dual-energy x-ray absorptiometry as a T-score between −1 −2.49 inclusive at the spine or femoral neck (whichever is worse). Osteoporosis was defined as a T-score of −2.5 or worse at the spine, femoral neck, or both.

[c] Standard letters with best refractive correction (20/40 is the Snellen equivalent of 70 letters read; a 5-letter difference is 1 line of visual acuity. The range of possible values is +96 letters to no light perception, scored as −25 letters).

[d] The mean deviation statistic[27] is an overall measure summarizing the average difference between normal results and a given eye's visual field sensitivity across points on the visual field (range of possible values, +2.0 to −30.0 dB).

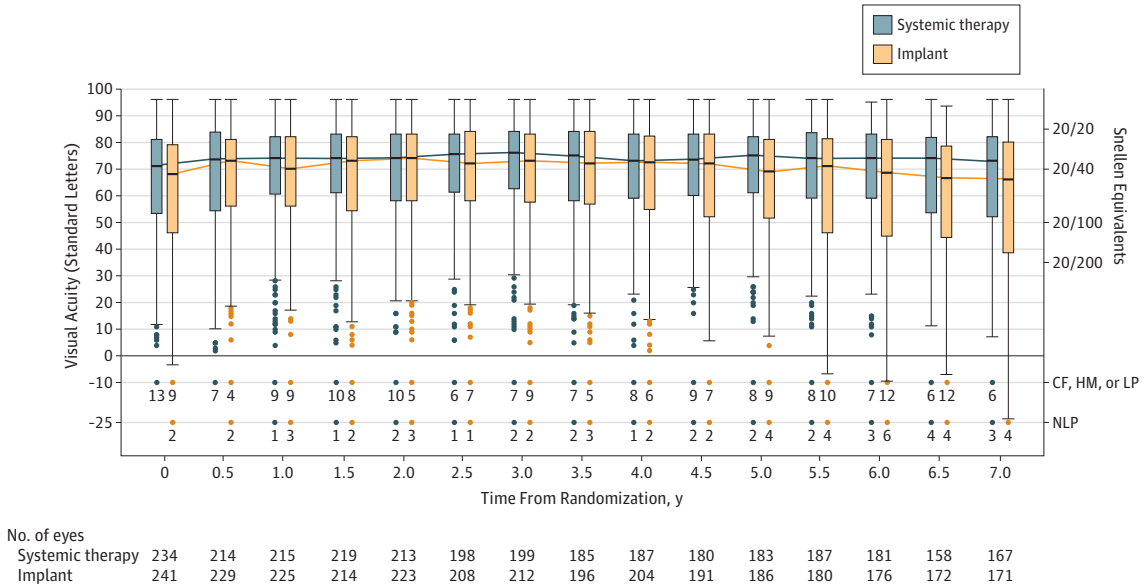
Table 2. Best-Corrected Visual Acuity Outcomes Among Uveitic Eyes Over 7 Years After Randomization to Intravitreous Fluocinolone Acetonide Implant Therapy or Systemic Therapy (Linear Model)

	Visual Acuity (Standard Letters)[a]							
	Implant		Systemic Therapy		Change From Baseline Within Each Treatment Group, Mean (95% CI)		Difference in Change From Baseline, Implant vs Systemic Therapy, Mean (95% CI)[b]	
Time Point	No.	Estimate, Mean (95% CI)	No.	Estimate, Mean (95% CI)	Implant	Systemic Therapy		*P* Value
Baseline	241	61.7 (56.7 to 66.6)	234	65.0 (60.0 to 69.9)	NA	NA	NA	
2 y	223	67.7 (62.7 to 72.4)	213	68.1 (62.6 to 73.3)	5.93 (3.14 to 8.64)	3.09 (0.24 to 5.95)	2.84 (−1.04 to 6.84)	.15
4 y	204	65.1 (59.9 to 70.0)	187	67.8 (62.3 to 72.9)	3.38 (0.33 to 6.43)	2.76 (−0.47 to 5.91)	0.61 (−3.83 to 5.08)	.78
5 y	186	62.0 (56.3 to 67.1)	183	68.6 (63.2 to 73.5)	0.22 (−3.53 to 3.86)	3.58 (0.71 to 6.42)	−3.37 (−8.07 to 1.10)	.15
6 y	176	59.2 (53.4 to 64.4)	181	67.4 (61.9 to 72.4)	−2.56 (−6.61 to 1.33)	2.40 (−0.60 to 5.38)	−4.96 (−9.88 to −0.08)	.045
7 y	171	55.8 (49.7 to 61.3)	167	66.2 (60.3 to 71.5)	−5.96 (−10.33 to −1.91)	1.15 (−2.07 to 4.32)	−7.12 (−12.4 to −2.14)	.006

[a] Snellen 20/40 is the equivalent of 70 letters read; a 5-letter difference is 1 line of visual acuity. The minimal clinically important difference for change in letters read is 7 letters (see "Methods"). The range of possible values of change in letters read is from −121 (+96 letters to no light perception scored as −25 letters) to +101 (from hand motions, the lowest level of visual acuity allowed to enroll to +96 letters). The observed range of change from baseline was −102 to +92 letters.

[b] Positive numbers favor implant treatment; negative numbers favor systemic treatment.

Figure 2. Distribution of Best-Corrected Visual Acuity Among Uveitic Eyes Assigned to Receive Intravitreous Fluocinolone Acetonide Implant or Systemic Therapy



Best-corrected visual acuity results in standard letters are given for the first 7 years of follow-up; Snellen equivalents are provided for key cutpoints on the right hand side of the plot (20/20 = 85 letters; 20/40 = 70 letters; 20/100 = 50 letters; 20/200 = 35 letters). Count fingers (CF), hand motion (HM), or light perception (LP) and no light perception (NLP) are assigned values of −10 and −25 letters, respectively, because these levels of visual acuity are much lower than reading 1 letter on the chart; these values are included in the summary estimates. The middle line of each box indicates the median; ends of each box indicate the interquartile range (IQR). The whiskers cover the shorter of 1.5 times the IQR or the interval to the maximal or minimal value. Circles below whiskers indicate outlier values; numbers below circles indicate the number of eyes with a visual acuity of count fingers, hand motion, or light perception and no light perception. Change from baseline transiently favored implant at 6 months (P = .03) and favored systemic therapy from year 6 onward (P < .045).

(52% vs 31%; difference, 21% [95% CI, 2% to 39%]; P = .02). The distributions of other causes of reduced visual acuity (including current uveitis activity, current macular edema, and glaucoma) did not significantly differ between groups.

Prespecified Secondary Outcomes

Visual Field Sensitivity

The change in the proportion with a −10-dB loss in overall visual field sensitivity from baseline was not significantly different between groups throughout follow-up (15% vs 8%, respectively; difference, 7.0% [95% CI, −3.5% to 17.2%]) (**Table 3**).

Uveitis Activity and Macular Edema

Throughout follow-up, most uveitic eyes in both groups had controlled eye inflammation. Significantly fewer eyes assigned to receive implant therapy had active inflammation through 4.5 years, but by 5 years, the proportion of inflamed eyes in the implant group increased to a level not statistically significantly different from that in the systemic therapy group (**Figure 3**A), as reactivations of uveitis began to occur more frequently. The increased proportion with uveitis activity in the implant group occurred approximately simultaneously with divergence of the visual acuity outcomes.

Fewer eyes had macular edema in the implant group than in the systemic therapy group at 6 months (Figure 3B).[13] The reverse pattern was observed at 6 years (reduction from baseline, −15% vs −28% [95% CI on difference, +0.9% to +25% favoring systemic therapy])—coincident with the increase in uveitis activity. At other time points, macular edema outcomes did not significantly differ between groups.

Ocular and Systemic Adverse Outcomes

Throughout follow-up, the implant group had clinically and statistically significantly higher incidences of elevated intraocular pressure; need for medical and surgical treatments for elevated intraocular pressure; and glaucoma (**Table 4**). By 7 years, 45% of eyes assigned to receive implant therapy vs 12% assigned to receive systemic therapy had undergone surgery to lower intraocular pressure, and 90% of phakic eyes assigned to receive an implant in the implant group had undergone cataract surgery (mostly in the first 2 years) vs 50% in the systemic therapy group. In as-treated analyses, both intraocular pressure–related and cataract-related differences between groups were larger, because these outcomes occurred more often in eyes in the systemic therapy group that had received implant therapy (eTable 1 in Supplement 1 reports the as-treated analysis). Transient vitreous hemorrhage occurred more frequently in implanted eyes (nearly always surgery-related) but resolved promptly without sequelae.

Among protocol-specified, prospectively collected systemic adverse outcomes (Table 4; eTable 1 in Supplement 1), the cumulative 7-year incidence in both groups was less than 10%, with the exceptions of hyperlipidemia (6.1% vs 11.2%), hypertension (9.8% vs 18.4%), osteopenia (41.5% vs 43.1%), fractures (11.3% vs 18.6%), hospitalization (47.6% vs 42.3%), and antibiotic-treated infection (57.4% vs 72.3%) in the implant

Table 3. Best-Corrected Visual Acuity, Uveitis Activity, Macular Edema, and Visual Field Mean Deviation Outcomes Among Uveitic Eyes Over 7 Years After Randomization to Intravitreous Fluocinolone Acetonide Implant Therapy or Systemic Therapy (Logistic Model)

Time Point	No. of Eyes With Outcome/Total No.		Percentage of Eyes Within Each Treatment Group, % (95% CI)[a]		Change From Baseline Within Each Treatment Group, % (95% CI)		Difference in Change From Baseline, % (95% CI)	*P* Value	OR Within Each Treatment Group (95% CI)		Ratio of ORs (95% CI)[b]	*P* Value
	Implant	Systemic Therapy	Implant	Systemic Therapy	Implant	Systemic Therapy			Implant	Systemic Therapy		
Visual Acuity 20/200 or Worse												
Baseline	39/241	35/234	16.3 (11.3 to 21.6)	15.0 (10.2 to 20.1)					1 [Reference]	1 [Reference]		
2 y	22/223	22/213	10.9 (6.5 to 16.0)	10.4 (6.3 to 15.0)	−5.3 (-9.9 to -0.9)	−4.6 (-8.5 to -0.8)	−0.8 (−6.8 to 5.1)	.80	0.63 (0.40 to 0.93)	0.66 (0.44 to 0.93)	0.96 (0.54 to 1.64)	.88
4 y	25/204	21/187	14.4 (9.4 to 19.9)	11.9 (7.5 to 16.6)	−1.9 (-7.0 to 3.3)	−3.1 (-7.3 to 1.1)	1.2 (−5.4 to 7.7)	.71	0.87 (0.56 to 1.29)	0.76 (0.52 to 1.10)	1.13 (0.64 to 1.95)	.65
5 y	26/186	22/183	16.5 (11.2 to 22.3)	11.5 (7.3 to 16.2)	0.2 (-5.4 to 5.8)	−3.4 (-7.4 to 0.4)	3.7 (−3.0 to 10.5)	.28	1.02 (0.66 to 1.56)	0.74 (0.51 to 1.04)	1.38 (0.81 to 2.39)	.24
6 y	29/176	22/181	17.4 (11.6 to 23.6)	12.0 (7.7 to 16.9)	1.2 (-4.3 to 7.0)	−2.9 (-7.1 to 1.2)	4.1 (−2.8 to 11.1)	.24	1.09 (0.72 to 1.65)	0.78 (0.53 to 1.12)	1.40 (0.81 to 2.42)	.22
7 y	37/171	23/167	24.2 (17.9 to 30.8)	13.7 (8.8 to 19.2)	7.9 (1.1 to 14.7)	−1.2 (-5.7 to 3.1)	9.1 (1.3 to 17.2)	.025	1.64 (1.07 to 2.56)	0.91 (0.61 to 1.29)	1.81 (1.05 to 3.30)	.04
Uveitis Activity[c]												
Baseline	192/239	181/232	80.3 (74.2 to 86.1)	78.0 (71.6 to 83.7)					1 [Reference]	1 [Reference]		
2 y	29/220	70/209	13.7 (8.5 to 19.8)	33.7 (25.8 to 42.0)	−66.6 (-73.9 to -58.7)	−44.2 (-53.9 to -34.0)	−22.4 (−35.1 to −9.9)	<.001	0.04 (0.02 to 0.07)	0.14 (0.08 to 0.24)	0.27 (0.11 to 0.55)	<.001
4 y	17/203	54/187	9.4 (4.9 to 14.4)	29.0 (21.3 to 37.0)	−71.0 (-78.2 to -63.7)	−48.9 (-58.6 to -39.1)	−22.0 (−34.3 to −10.2)	<.001	0.03 (0.01 to 0.05)	0.12 (0.06 to 0.19)	0.22 (0.08 to 0.47)	<.001
5 y	29/185	44/179	17.3 (11.3 to 24.0)	25.1 (17.2 to 33.4)	−63.0 (-71.3 to -54.3)	−52.9 (-63.1 to -42.1)	−10.1 (−23.9 to 3.1)	.14	0.05 (0.02 to 0.09)	0.10 (0.05 to 0.17)	0.53 (0.23 to 1.19)	.13
6 y	50/178	50/176	28.2 (20.8 to 35.9)	27.9 (19.7 to 36.6)	−52.1 (-61.6 to -42.6)	−50.0 (-60.8 to -38.5)	−2.1 (−17.1 to 12.1)	.78	0.10 (0.05 to 0.16)	0.11 (0.05 to 0.20)	0.86 (0.38 to 1.89)	.71
7 y	33/171	23/165	18.7 (12.0 to 25.7)	13.8 (7.8 to 20.4)	−61.7 (-70.5 to -53.0)	−64.2 (-72.8 to -55.2)	2.5 (−10.0 to 14.6)	.69	0.06 (0.02 to 0.10)	0.05 (0.02 to 0.09)	1.22 (0.51 to 2.91)	.65
Macular Edema												
Baseline	80/220	75/216	36.3 29.2 to 43.4)	34.7 (28.0 to 41.9)					1 [Reference]	1 [Reference]		
2 y	37/206	52/197	18.9 (13.3 to 24.7)	26.6 (20.0 to 33.6)	−17.4 (-25.0 to -9.8)	−8.1 (-15.6 to -1.0)	−9.2 (−19.5 to 1.3)	.08	0.41 (0.26 to 0.60)	0.68 (0.46 to 0.95)	0.60 (0.34 to 1.04)	.06
4 y	28/180	33/176	16.4 (10.5 to 22.4)	18.6 (13.1 to 24.5)	−19.9 (-28.0 to -11.6)	−16.2 (-23.6 to -9.0)	−3.7 (−14.5 to 7.4)	.50	0.34 (0.20 to 0.54)	0.43 (0.27 to 0.62)	0.80 (0.41 to 1.49)	.48
5 y	20/171	24/164	11.6 (6.9 to 16.9)	13.7 (8.1 to 20.0)	−24.7 (-32.8 to -16.1)	−21.0 (-29.1 to -12.9)	−3.6 (−15.2 to 7.9)	.53	0.23 (0.12 to 0.39)	0.30 (0.16 to 0.49)	0.77 (0.34 to 1.68)	.51
6 y	33/156	12/164	21.4 (14.9 to 28.3)	7.2 (3.3 to 11.8)	−14.9 (-24.4 to -5.1)	−27.5 (-34.9 to -20.6)	12.7 (0.9 to 24.8)	.04	0.47 (0.27 to 0.77)	0.14 (0.06 to 0.25)	3.29 (1.50 to 8.06)	.005
7 y	21/145	9/142	15.2 (9.8 to 20.8)	7.3 (2.9 to 12.4)	−21.1 (-29.7 to -12.3)	−27.4 (-35.9 to -19.0)	6.4 (-5.5 to 18.5)	.30	0.31 (0.17 to 0.51)	0.14 (0.05 to 0.28)	2.14 (0.90 to 6.39)	.13

(continued)

Table 3. Best-Corrected Visual Acuity, Uveitis Activity, Macular Edema, and Visual Field Mean Deviation Outcomes Among Uveitic Eyes Over 7 Years After Randomization to Intravitreous Fluocinolone Acetonide Implant Therapy or Systemic Therapy (Logistic Model) (continued)

Time Point	No. of Eyes With Outcome/Total No.		Percentage of Eyes Within Each Treatment Group, % (95% CI)[a]		Change From Baseline Within Each Treatment Group, % (95% CI)		Difference in Change From Baseline, % (95% CI)	P Value	OR Within Each Treatment Group (95% CI)		Ratio of ORs (95% CI)[b]	P Value
	Implant	Systemic Therapy	Implant	Systemic Therapy	Implant	Systemic Therapy			Implant	Systemic Therapy		
Visual Field Mean Deviation Less Than −10 dB												
Baseline	57/233	48/226	25.5 (18.8 to 32.9)	21.4 (15.0 to 28.1)					1 [Reference]	1 [Reference]		
2 y	55/208	43/205	27.6 (20.6 to 34.9)	22.4 (15.8 to 29.6)	2.1 (−4.0 to 7.9)	1.0 (−5.4 to 7.8)	1.1 (−8.5 to 9.8)	.82	1.12 (0.80 to 1.55)	1.07 (0.71 to 1.60)	1.04 (0.60 to 1.75)	.87
4 y	64/196	37/176	33.6 (26.5 to 40.9)	23.3 (16.2 to 30.6)	8.1 (2.0 to 14.3)	1.9 (−4.5 to 8.5)	6.2 (−3.1 to 15.1)	.17	1.50 (1.10 to 2.09)	1.13 (0.76 to 1.66)	1.33 (0.80 to 2.21)	.26
5 y	56/169	36/169	36.5 (28.6 to 44.2)	22.8 (15.8 to 29.9)	10.9 (4.2 to 17.5)	1.4 (−6.0 to 8.8)	9.6 (−0.4 to 19.7)	.06	1.72 (1.24 to 2.42)	1.09 (0.69 to 1.70)	1.57 (0.91 to 2.86)	.11
6 y	56/150	47/167	42.2 (33.7 to 50.5)	29.9 (22.3 to 37.5)	16.7 (9.4 to 23.6)	8.5 (1.3 to 15.6)	8.1 (−2.3 to 18.3)	.12	2.20 (1.56 to 3.17)	1.60 (1.08 to 2.35)	1.37 (0.80 to 2.34)	.24
7 y	52/148	42/151	40.2 (32.2 to 47.9)	29.1 (21.5 to 36.6)	14.7 (7.6 to 21.4)	7.7 (0.2 to 14.8)	7.0 (−3.5 to 17.2)	.18	2.01 (1.43 to 2.84)	1.54 (1.02 to 2.29)	1.31 (0.77 to 2.25)	.32

Abbreviation: OR, odds ratio.

[a] Percentages based on the model estimates.

[b] Numbers less than 1 favor implant treatment; numbers greater than 1 favor systemic treatment.

[c] Uveitis activity indicates clinician-determined status of intraocular inflammation as active (as opposed to inactive/suppressed).

vs systemic therapy groups, respectively. Hospitalizations for infection were infrequent in both the implant and the systemic therapy groups (9 hospitalizations vs 6, respectively). Change in weight did not significantly differ between the groups (eFigure 2 in Supplement 1). Bone marrow suppression and indicators of liver or renal injury were infrequent in both groups, sometimes with higher incidence in the implant group. Overall cancer (excluding nonmelanotic skin cancer) and mortality incidences were low in both groups.

Quality of Life

Mean health utility- and health-related QOL remained similar to baseline through 7 years in both groups (eTable 2 in Supplement 1), whereas vision-related QOL improved from baseline through 7 years to a degree at the low end of a minimally clinically important difference (+4.7 and +5.7 units in the implant and systemic therapy groups, respectively). Regarding change in QOL measures from baseline for the treatment groups, most differences between groups were close to zero by 7 years, whereas most scales had suggested a small advantage for implant therapy on the order of the MCID at 2 years (eTable 2 in Supplement 1). The only scale exhibiting a MCID between groups at 7 years (mental health component of the SF-36, +4.28-unit advantage for implant) was not consistent in this advantage over time, having also shown a minimally clinically important difference in favor of implant through 2 years, but not at years 3 through 6.

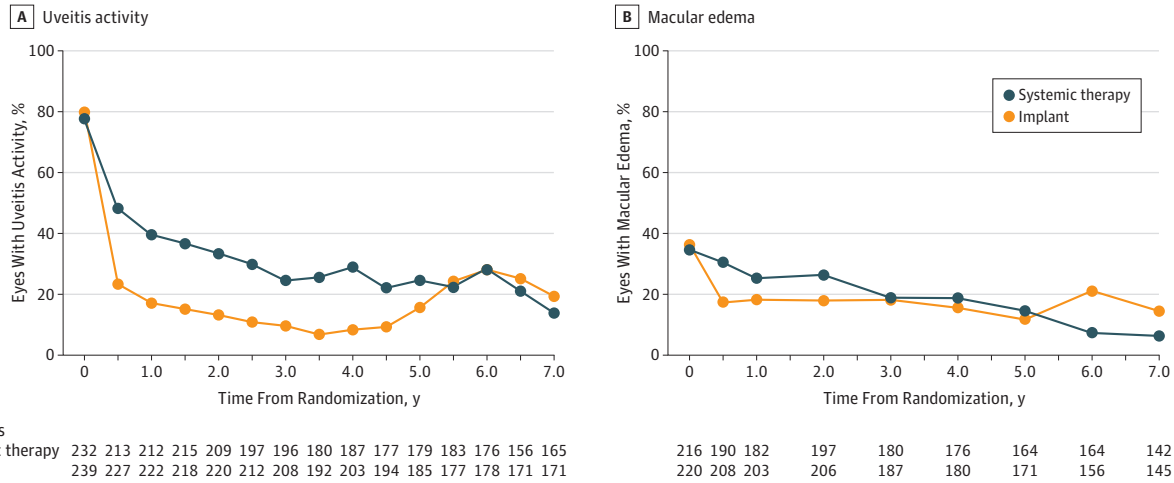
Discussion

In this 7-year extended follow-up of a randomized trial of patients with intermediate, posterior, or panuveitis, those randomized to receive systemic therapy had better visual acuity than those randomized to receive intravitreous fluocinolone acetonide implants. The mean difference between groups at 7 years was on the order of the average treatment benefit observed in clinical trials foundational to approval of treatments for choroidal neovascularization in the era before the introduction of vascular endothelial growth factor inhibitors[23-26]—moderate benefits that led to the adoption of the therapies by many ophthalmologists.

The difference in visual outcome was due to a decline in the implant group that occurred at the time uveitis reactivations began occurring in many implanted eyes, which a post hoc analysis found to arise disproportionately from irreversible chorioretinal lesions in the implant group, possibly related to severe inflammatory recurrences. Scheduled replacement of implants prior to uveitis relapse may have had better results but has not been used in clinical practice. While such replacement may be useful in appropriate cases,[39] it would be challenging to implement across the board because of variation on the order of 1 year in the duration of effect of the implant and the frequent ocular adverse outcomes after first implantation, which would constrain reimplantation in some cases.

Although eyes assigned to receive systemic therapy had better visual acuity outcomes, both groups had favorable visual outcomes overall, with maintenance of baseline vision in

Figure 3. Proportion of Uveitic Eyes With Uveitis Activity and Macular Edema Over Time



No. of eyes

Systemic therapy	232	213	212	215	209	197	196	180	187	177	179	183	176	156	165
Implant	239	227	222	218	220	212	208	192	203	194	185	177	178	171	171

216	190	182	197	180	176	164	164	142
220	208	203	206	187	180	171	156	145

Regarding uveitis activity, there were statistically significant differences from 6 months through 54 months, favoring implant therapy; differences were not statistically significant thereafter. For macular edema, there were statistically significant differences only at 6 months (favoring implant therapy) and 72 months (favoring systemic therapy). See also Table 2.

the systemic group and loss of a mean of 6 letters over 7 years in the implant group. Many eyes, especially in the implant group, required cataract surgery and other ophthalmic medical and surgical interventions, indicating that ongoing management was necessary to achieve and maintain these favorable results.

Although both approaches usually were successful in controlling inflammation, implant therapy achieved inflammatory control both faster and more often during the first 5 years after implantation. Implant therapy sometimes was used to rescue patients whose uveitis did not respond to systemic therapy, as reported elsewhere[10,40]; implant therapy also controlled uveitis about 50% longer than had been anticipated, suggesting advantages of this approach when systemic therapy fails or is not feasible. After 5 years, uveitis reactivations occurred often enough to make the proportion controlled not significantly different thereafter. Superiority in controlling inflammation during the first 5 years did not result in better longer-term visual outcomes; most patients in the systemic therapy group whose uveitis was incompletely controlled had improved inflammation,[14] whereas the period of severe inflammation at the time of relapse in the implant group may have caused more damage than lower-grade relapses with slow tapering of treatment in the systemic group.

Ocular adverse outcomes of uveitis or its treatment were more common in the implant group, whereas the incidence of most systemic adverse outcomes was less different between the 2 groups. Despite prospective follow-up in the context of a clinical trial and subsequent prospective cohort study, a large proportion of patients developed glaucoma—mostly with implant therapy—confirming that frequent, diligent monitoring for elevated intraocular pressure and early aggressive management (usually surgical) is especially essential after placement of fluocinolone acetonide implants. Serious complications directly attributable to surgical implant placement were infrequent.

Oral corticosteroid therapy combined with immunosuppressive drugs to achieve low prednisone maintenance doses—or no prednisone at all—was well tolerated by most patients, even though continued low-dose corticosteroid treatment was used for many years for a large proportion. The prospectively studied broad range of potential complications of systemic corticosteroids and of immunosuppressive drugs had incidences that did not differ much between groups. The exception of a higher number in the systemic therapy group receiving antibiotics for infections did not result in poor long-term outcomes and may have been affected by unmasked clinicians' and patients' knowledge of treatment with corticosteroids and immunosuppression. With the available study power, increased risk of rare events with one of the treatments would not have been detected, but low increases in risk on that order for the prespecified systemic outcomes would not likely limit use of a therapy unless the risk of cancer or death diverged further over time. Further study regarding those issues would be valuable. These exploratory observations suggest that use of systemic anti-inflammatory therapy in this manner, as is done for a wide variety of diseases, is unlikely to induce large amounts of systemic adverse effect morbidity at least over a period of up to 7 years.

Limitations

This study has several limitations. The follow-up after completion of the 2-year clinical trial was not prespecified, so the associations observed after 2 years should be viewed as exploratory. Furthermore, losses to follow-up of 30% by 7 years—with some potentially important differences between patients lost and those followed up—could have introduced a selection bias if there was a sufficient interaction between follow-up status and treatment assignment in relation to outcome (which sensitivity analysis indicated is unlikely).

Incomplete masking (given a surgical treatment with ophthalmoscopically visible intraocular implant) raises the

Table 4. Incidence of Ocular and Systemic Adverse Outcomes Over 7 Years of Follow-up for Participants Randomized to Intravitreous Fluocinolone Acetonide Implant Therapy or Systemic Therapy

	Implant Therapy		Systemic Therapy		ImplantTherapy vs Systemic Therapy[a]	
	No. With an Event/ No. at Risk[b]	Cumulative % With Event Within 7 y (95% CI)[c]	No. With an Event/ No. at Risk[b]	Cumulative % With Event Within 7 y (95% CI)[c]	HR (95% CI)[d]	*P* Value
Ocular Outcomes (Among Uveitic Eyes)						
Glaucoma and IOP events						
IOP ≥30 mm Hg	95/234	41.9 (34.4-48.7)	23/229	10.5 (5.7-15.1)	4.92 (3.00-8.05)	<.001
IOP ≥24 mm Hg	143/234	62.3 (54.4-68.9)	55/228	24.9 (17.7-31.5)	3.40 (2.34-4.94)	<.001
IOP ≥10-mm Hg increase from baseline	147/235	63.9 (55.7-70.6)	48/230	21.6 (15.2-27.6)	4.12 (2.83-5.97)	<.001
Glaucoma[e]	78/220	37.1 (28.6-44.5)	31/212	15.7 (9.1-21.7)	2.85 (1.75-4.63)	<.001
Use of IOP-lowering therapy (medicine, surgery)	147/196	77.0 (67.7-83.6)	70/202	34.4 (25.0-42.7)	3.53 (2.44-5.09)	<.001
IOP-lowering surgery[e]	96/219	45.3 (37.1-52.4)	25/215	12.0 (6.3-17.4)		
Before 2 y	59/219	27.3 (19.4-34.5)	7/215	3.3 (0.5-6.1)	9.63 (3.98-23.30)	<.001
2 y or later (among those at risk at 2 y)	37/150	28.4 (19.5-36.3)	18/199	11.4 (4.7-17.6)	2.93 (1.56-5.48)	<.001
Cataract events						
Incident cataract	54/54	98.9 (96.0-99.7)	45/50	83.8 (66.5-92.2)	3.00 (1.75-5.14)	<.001
Cataract surgery	124/140	89.5 (82.7-93.6)	59/125	50.9 (37.9-61.2)	3.70 (2.56-5.35)	<.001
Potential complications of implant surgery						
IOP ≤6 mm Hg (hypotony)	60/226	25.1 (18.0-31.6)	35/218	17.1 (10.5-23.3)	1.71 (1.04-2.82)	.03
Vitreous hemorrhage[e]	43/236	17.7 (12.0-20.7)	20/230	9.3 (4.5-13.9)		
Before 2 y	37/236	15.6 (10.2-20.7)	11/230	4.9 (1.3-8.3)	3.54 (1.59-7.87)	.002
2 y or later (among those at risk at 2 y)	6/190	4.1 (0.8-7.3)	9/211	4.7 (1.0-8.2)	0.69 (0.22-2.06)	.50
Systemic Outcomes (Among Patients)						
Hyperlipidemia, placed on treatment	7/90	6.1 (0.7-11.3)	9/86	11.2 (3.9-17.9)	0.70 (0.26-1.89)	.48
Hypertension, placed on treatment	11/88	9.8 (3.0-16.2)	17/88	18.4 (9.4-26.5)	0.58 (0.27-1.26)	.17
Diabetes mellitus	5/105	4.2 (0.07-8.3)	7/114	6.8 (1.7-11.6)	0.75 (0.23-2.38)	.63
Osteopenia	19/56	41.5 (22.9-55.7)	22/69	43.1 (26.7-55.8)	1.10 (0.60-2.03)	.75
Osteoporosis	7/110	6.7 (1.7-11.5)	9/109	8.2 (2.5-13.6)	0.77 (0.28-2.06)	.60
Fractures	16/125	11.3 (5.2-17.0)	22/124	18.6 (11.0-25.6)	0.68 (0.35-1.29)	.23
Hospitalization	58/125	47.6 (37.3-56.2)	57/124	42.3 (32.3-50.9)	0.97 (0.67-1.41)	.88
Infection requiring treatment	70/125	57.4 (47.3-65.5)	87/124	72.3 (62.5-79.6)	0.68 (0.49-0.93)	.02
White blood cell count ≤2500 cells/μL[d]	1/122	0.8 (0.0-2.5)	5/119	3.5 (0.06-6.8)	0.19 (0.02-1.66)	.13
Platelet count ≤100 000/μL[e]	7/120	5.4 (1.0-9.5)	3/118	1.8 (0.0-4.3)	2.00 (0.50-8.01)	.33
Hemoglobin ≤10g/dL[e]	2/122	1.7 (0.0-4.1)	7/117	2.9 (0.0-6.2)	0.38 (0.07-1.96)	.25
Hepatotoxicity[e,f]	6/118	5.2 (1.0-9.2)	5/116	4.0 (0.07-7.7)	1.22 (0.37-4.01)	.74
Nephrotoxocity[e,g]	9/118	7.9 (2.7-12.7)	6/117	5.4 (1.0-9.6)	1.52 (0.54-4.28)	.43
Cancer[h]	3/126	2.7 (0.0-5.8)	5/124	2.5 (0.0-5.2)	0.59 (0.13-2.46)	.46
Death	4/128	2.4 (0.0-5.1)	6/126	3.4 (0.06-6.6)	0.65 (0.18-2.30)	.50

Abbreviations: HR, hazard ratio; IOP, intraocular pressure.

[a] Ratios greater than 1.0 indicate more events in the implant group.

[b] Excludes those with prevalent complications or missing data at baseline.

[c] Calculated using Kaplan-Meier model; percentages will not equal those that would be obtained using raw counts.

[d] Significant change in HR before vs after 2 years for IOP surgery (*P* = .02 for interaction) and vitreous hemorrhage (*P* = .009 for interaction).

[e] Measured annually.

[f] Aspartate aminotransferase or alanine aminotransferase level greater than twice the upper limit of normal.

[g] Creatinine level greater than 1.5 mg/dL (132.6 μmol/L) or discontinuation of an immunosuppressive drug stopped because of renal toxicity.

[h] Excludes all nonmelanoma skin cancers.

possibility of a measurement bias. However, the timing of evolution of differences in visual acuity did not correspond to the point at which unmasking of the visual acuity examiner occurred; neither was there a change in the method of ascertainment of uveitis activity after 5 years. Also, fully masked outcomes (eg, glaucoma) followed the same pattern as corresponding unmasked outcomes (treatment for elevated intraocular pressure).

Crossover treatment in about 20% in each group affected ascertainment of comparative efficacy; if systemic therapy has inherently better outcomes in the long run, then crossovers to implant per clinician and patient judgment might have led to underestimation of the benefit. However, most crossovers occurred when patients assigned to systemic therapy could not achieve adequate control with systemic therapy, when repeat implant therapy was judged contraindicated owing to adverse outcomes, or when incident systemic disease required systemic therapy. In a clinical trial comparing initial treatment strategies, such crossovers may reflect appropriate management for the minority of patients who required a change in strategy based on clinical course, as would happen in clinical practice.

Last, the original study design incorporated a formal α-spending plan for the 2-year primary outcome. Given the effect sizes and consistency of pattern, type I errors are unlikely as a cause of the major observations. However, multiple comparisons should be considered in interpreting nonextreme *P* values, since the analyses did not adjust for multiple comparisons in the follow-up study.

Conclusions

In 7-year extended follow-up of a randomized trial of patients with intermediate, posterior, or panuveitis, those randomized to receive systemic therapy had better visual acuity than those randomized to receive intravitreous fluocinolone acetonide implants. Study interpretation is limited by loss to follow-up.

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A complete list of the members of the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group is available in the eAppendix in Supplement 1.

Author Contributions: The Writing Committee Chairman (Dr Kempen) and Statistical Analysis Committee Chair (Dr Sugar) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The Statistical Analysis Committee (see eAppendix in Supplement 1) conducted the statistical analysis of data reported herein.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kempen, Sugar.
Critical revision of the manuscript for important intellectual content: Kempen, Altaweel, Holbrook, Sugar, Thorne, Jabs.
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Supervision: Kempen, Altaweel, Holbrook, Jabs.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Kempen reported serving as a consultant for AbbVie, Alcon, Allergan, Can-Fite, Clearside, Lux Biosciences, Roche, Sanofi Pasteur, Santen, Vitae, and Xoma; receiving other investigator-initiated grants from EyeGate Pharma, the Lions Club International Foundation, the US Food and Drug Administration, Research to Prevent Blindness, and the National Eye Institute; and paid service for the National Institute of Allergy and Infectious Diseases (Study Section) and the Office of AIDS Research (advisory committee member) since beginning work on the project in 2002. Dr Thorne reported serving as a board member for AbbVie; serving as a consultant for Allergan, Gilead, Xoma, and Santen; and receiving grants from Allergan and NightstaRx. Drs Altaweel, Holbrook, Sugar, and Jabs reported no potential conflicts of interest. Conflict of interest disclosures for the remainder of the MUST Research Group are on file at the MUST Coordinating Center.

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