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Quality of Life and Risks Associated with Systemic Anti-inflammatory Therapy Versus Fluocinolone Acetonide Intraocular Implant for Intermediate, Posterior or Panuveitis: 54 month results of *The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study*

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Conflicts of Interest: In the last three years, Dr. Kempen has served as a consultant for AbbVie, Alcon, Allergan, Can-Fite, Clearside, Lux Biosciences, and Xoma; Dr. Jabs is a consultant for Santen, Inc. and serves on Data and Safety Monitoring Committees for Novartis Pharmaceutical Corp., and Applied Genetic Technologies Corporation (AGTC); and Dr. Thorne has served as a consultant for Heron Evidence, Ltd. Drs. Altaweel, Drye, Holbrook, and Sugar report no relationships that might be perceived as conflicts of interest.

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

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Abstract

Purpose—To evaluate the risks and quality of life (QoL) outcomes of fluocinolone acetonide implant versus systemic therapy with corticosteroid and immunosuppression when indicated for intermediate, posterior, and panuveitis.

Design—Additional follow-up of a randomized trial cohort

Participants—255 patients with intermediate, posterior or panuveitis, randomized to implant or systemic therapy.

Methods—Randomized subjects with intermediate, posterior, or panuveitis (479 eyes) were followed over 54 months, with 79.2% completing the 54 month visit.

Main Outcome Measures—Local and systemic potential complications of the therapies and self-reported health utility, vision-related and generic health-related QoL were studied prospectively.

Results—Among initially phakic eyes, cataract and cataract surgery, occurred significantly more often in the implant group (hazard ratio (HR)=3.0, $p=0.0001$ and HR=3.8, $p<0.0001$ respectively). In the implant group, most cataract surgery occurred within the first two years. IOP elevation measures occurred more frequently in the implant group (range of HR's=3.7-5.6, all $p<0.0001$), and glaucoma (assessed annually) also occurred more frequently (26.3% vs. 10.2% by 48 months, HR=3.0, $p=0.0002$). In contrast, potential complications of systemic therapy including measures of hypertension, hyperlipidemia, diabetes, bone disease, and hematological and serum chemistry indicators of immunosuppression toxicity did not differ between groups through 54 months. Indices of QoL initially favored implant therapy by a modest margin. However, all summary measures of health utility and vision-related or generic health-related QoL were minimally and non-significantly different by 54 months with the exception of the SF-36 physical component summary score which favored implant by a small margin at 54 months (3.17 on a scale of 100, $p=0.01$, not adjusted for multiple comparisons). Mean QoL results were favorable in both groups.

Conclusions—These results suggest that fluocinolone acetonide implant therapy is associated with a clinically important increased risk of glaucoma and cataract with respect to systemic therapy, suggesting that careful monitoring and early intervention to prevent glaucoma is warranted with implant therapy. Systemic therapy subjects avoided a significant excess of toxicities of systemic corticosteroid and immunosuppressive therapies in the trial. Self-reported QoL measures initially favored implant therapy, but over time the measures converged, with generally favorable QoL in both groups.

Uveitis frequently is complicated by cataract and intraocular pressure-related problems,¹ which can occur either as a result of scarring from the disease itself or its treatment with corticosteroids, especially when corticosteroids are topically administered or placed in or around the eye.²⁻⁵ Systemic therapy with corticosteroids is associated with lower risk of ocular complications than local therapy,^{1;3;4} but has its own set of potential complications

such as corticosteroid-induced diabetes mellitus, hypertension, hyperlipidemia, reduced bone mineral density, weight gain and others. Such complications occur especially when systemic corticosteroids are used at high doses for long periods of time.⁶ However, doses of 5-7.5 mg of prednisone daily reportedly are associated with minimal risk, with incidences of these complications similar to patients not taking systemic corticosteroids.⁷ When substantially higher doses of corticosteroids are required to control sight-threatening disease, corticosteroid-sparing therapy is recommended.⁶ Such therapy in turn is associated with potential agent-specific risks, typically requiring monitoring for immunosuppressant-induced side effects.⁶ Both success in treating inflammation and complications of therapy potentially could impact patient quality of life.⁸

Comparative data regarding the risks of complications of uveitis itself and of treatments in relation to the treatment strategy employed have been scarce. In the Multicenter Uveitis Steroid Treatment (MUST) Trial, we directly compared use of an intravitreal corticosteroid implant (fluocinolone acetonide, 0.59 mg, Bausch & Lomb, Rochester, New York) versus systemic therapy following consensus recommendations⁶ as treatment for active or recently active (within 60 days) intermediate, posterior, or panuveitis in a prospective randomized clinical trial.^{1;9} Here we report the incidence of local and systemic adverse outcomes in the randomized cohort through 54 months after randomization, and assess self-reported indices of quality of life, comparing the alternative treatment groups.

Methods

Study Design

As detailed in the companion manuscript¹⁰ and previous reports,^{1;9} we followed participants in the Multicenter Uveitis Steroid Treatment (MUST) Trial—a randomized 23-center controlled trial comparing fluocinolone acetonide implant vs systemic therapy for intermediate, posterior and panuveitis (clinicaltrials.gov identifier NCT00132691)—at least every six months through 54 months after randomization. The study was conducted following the principles of the Declaration of Helsinki, including informed consent and maintenance of study approval of institutional review boards at all participating centers.

Implant therapy consisted of initial control of inflammation with topical, injected or systemic corticosteroid therapy followed by surgical implantation of a fluocinolone acetonide implant; reactivations were treated in the same manner.¹ Systemic therapy consisted of oral corticosteroids supplemented by immunosuppressive therapy following guidelines promulgated by an expert panel.⁶ Ancillary therapy was permitted to supplement these therapies or treat uveitis-associated complications, but not as primary therapy.^{1;9;10} The favorable degree of adherence to the assigned therapy, including after completion of the trial phase of the study when adherence no longer was required, is described in the companion manuscript.

Outcomes

Patients, clinicians and coordinators were not masked. The incidences of ocular complications of uveitis or its treatment were noted prospectively as pre-specified in the

protocol. Outcomes of interest included intraocular pressure (the mean of 2-3 measurements by Goldmann tonometry), use of IOP-lowering medication and surgery, incidence of cataract (among initially phakic eyes free of cataract at baseline, per clinical evaluation), and occurrence of cataract surgery (among initially phakic eyes). Glaucoma was diagnosed annually by an outcomes committee consisting of two glaucoma specialists: the first reviewed visual field, clinical data, and fundus photographs to diagnose glaucoma and the second independently confirmed all cases and a random subset of non-cases, adjudicating disagreements by consensus.¹¹ Potential complications of vitreous surgery—including vitreous hemorrhage, endophthalmitis, and rhegmatogenous retinal detachment—were noted prospectively by certified ophthalmologists.

Potential complications of systemic therapy also were studied prospectively. Fasting blood draws were evaluated by local labs for hyperlipidemia annually. Fasting blood glucose also was assessed annually until completion of the MUST Trial, after which hemoglobin A1c was used to ascertain occurrence of hyperglycemia starting in January, 2011. Blood pressure (the average of two mercury sphygmomanometer or digital measurements) and weight (using a beam or electronic balance scale) were measured at in-person study visits. Bone densitometry was conducted annually. Participants were asked at in-person visits about interim fractures, diagnosis of cancer, treatment for hyperlipidemia or hypertension, hospitalization, and use of antibiotics prescribed for an infection and reported events were confirmed by the study team. Vital status was assessed by a periodic audit supplemented by a Social Security Death Master File¹² search. Incidence of hyperlipidemia was based on incidence of elevated low density lipoprotein (LDL $\geq$ 160 mg/mL) or use of lipid-lowering medication. Incidence of hypertension was assessed based on observations of elevated systolic and/or diastolic blood pressure, or use of antihypertensive medication. Diabetes mellitus was diagnosed based on clinical history obtained at each study visit. Osteopenia and osteoporosis was defined based on WHO recommendations, defined based on the worse measurement between the L2-L4 spine and the femoral neck bone densities. Osteopenia was defined as a t-score of -1 to -2.49 inclusive, and osteoporosis was defined as a t-score of $\leq$ -2.5 or worse.^{13;14}

During the MUST Trial period, potential complications of immunosuppressive therapy also were prospectively assessed. Specimens were collected for white blood cells, platelets, hemoglobin, liver enzymes and creatinine during annual visits. During MUST-FS, interim complications of neutropenia (white blood cell count $\leq$ 2500 cells/ μ L), thrombocytopenia (platelet count $\leq$ 100,000/ μ L), anemia (hemoglobin $\leq$ 10 g/dL), elevated liver enzymes (elevated liver enzymes over time confirmed by medical records), and nephrotoxicity (serum creatinine $\geq$ 1.5 mg/dL discontinuation of an immunosuppressant for renal toxicity) were ascertained at each in-person visit by review of medical records and patient interview.

Quality of life (QoL) outcomes were self-reported by patients during follow-up visits semi-annually. Health utility,¹⁵ general health-^{16;17} and vision-related quality of life¹⁸ were measured respectively using the EuroQol, SF-36 and NEI-VFQ instruments. Changes from baseline values were calculated, and interpreted with respect to prior reports of minimally important difference thresholds.¹⁹⁻²¹

Statistical Analyses

The analysis was based on the MUST Trial/Follow-up Study database that was frozen in May 2014. The primary analyses were conducted as randomized, with sensitivity analyses based upon treatment received (implant ever placed versus not). Follow-up occurred every 3 months during the MUST Trial and every 6 months during the MUST Follow-up Study, with the exception of glaucoma and lab tests which were evaluated annually. Incidence of each event is reported among those free of the event at baseline. Cox proportional hazards models were used to compare the time-to-first event for ocular and systemic complications between the two treatment groups, adjusting for uveitis stratum (intermediate uveitis vs. posterior or panuveitis) and bilaterality of disease. The proportionality assumption of Cox regression was tested by including a time-varying covariate and a treatment-by-time interaction term. If the interaction term was significant, indicating that the proportionality assumption was violated, the analysis was stratified by time period (0-24 months, 25-54 months). Negative binomial regression models, adjusting for uveitis stratum and bilaterality of disease, were used to compare the rates of events per visit between the two treatment groups as well as between the MUST Trial and the subsequent MUST Trial Follow-up Study. The actual event dates were available for cataract surgery and IOP-lowering surgery. For all other ocular complications, events were identified at each visit either from measurements taken at that specific visit (e.g. VA worse than 20/40) or from information solicited from the patient covering the period since the last visit (e.g. use of IOP-lowering medication). In these cases, analyses of the event rates were based upon data from the 6-month visits only, in order to be comparable throughout the course of follow-up. Longitudinal models estimated parameters using generalized estimating equations (GEE) for quality of life outcomes and the body weight outcome.²⁴ A saturated means model (including indicators for each visit and each visit-by-treatment interaction) adjusting for stratification by uveitis type was used; a Toeplitz, unstructured, or exchangeable covariance structure, depending upon the outcome, accounted for longitudinal and within-eye correlation. All available visit information was incorporated into the model, with missing data indicators used to maintain the data structure. Analyses were conducted by the Statistical Analysis Committee (see Credit Roster, Appendix 1).

Robust standard errors were computed for all models. All reported confidence intervals and p-values are nominal, not adjusted for multiple comparisons. Adjustment of p-values for multiple comparisons was not performed because the emphasis is on the reporting of point estimates and confidence intervals as opposed to p-values, as recommended by Wang, et al.²² 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/>).

Results

During December 2005 through December 2008, 255 patients with active or recently active (within 60 days) intermediate, posterior or panuveitis were enrolled in the MUST Trial and randomized to implant or systemic therapy (479 uveitic eyes). The number of patients in the implant and systemic group under follow-up at 54 months was 110 (85% of those

randomized) implant-assigned patients and 103 (82% of those randomized) systemic-assigned patients), a total of 369 eyes with uveitis (77%). The CONSORT diagram for the 54 month cohort was reported in the accompanying manuscript.¹⁰ In brief, by 54 months, 87% of eyes with uveitis in the implant group received at least one implant (some second eyes not having sufficient uveitis severity to warrant implant placement), and about 20% of implant-assigned patients were receiving systemic therapy. By 54 months, 96% in the systemic group had received systemic therapy at some point during follow-up, of whom 65% were on systemic therapy including 45% receiving immunosuppressive therapy at their 54 month visit (patients were allowed to taper off if therapy was no longer needed). By 54 months, 21% of uveitic eyes in the systemic therapy group had received implants, generally as rescue therapy when inflammation could not be controlled with systemic medication. A total of 266 implants were placed prior to 54 months' follow-up, 226 in the implant group (208 first, 16 second, and 2 third implants) and 40 in the systemic group (all first implants).

Ocular Adverse Outcomes

Similar to our observations through 2 years' follow-up,¹ the risk of elevated IOP-related outcomes was higher in the implant group through 54 months (see Figures 1, 2 and Table 1). The overall 54 month cumulative incidence of starting IOP-lowering medications (77.9% vs 34.0%, hazard ratio (HR)=3.9, 95% confidence interval (CI): 2.6-5.6) was significantly higher in the implant group. The time to first of IOP-lowering surgery was statistically different in the first 24 months of follow-up compared to the remaining years (test of interaction $p = 0.02$). During the first 24 months, the cumulative incidence of IOP-lowering surgery (31.1% vs 4.5%, HR = 8.1, 95% CI: 3.5, 18.5, $p < 0.0001$) was significantly higher in the implant group. The incidence of initial IOP-lowering surgery was not statistically different in the two groups after 24 months (13.9% vs 7.2%, HR = 2.1; 95% CI: 0.9, 4.7; $p = 0.06$). However, 14 of the 22 initial IOP-lowering surgeries in the systemic group were in eyes that had implants and in an analysis based on the treatment received (implant included as a time-varying covariate), the HR of having an IOP-lowering surgery in eyes that had received implant was higher over the course of 54 months (HR = 14.4, 95% CI: 6.4, 32.3; $p < 0.0001$). Multiple IOP-lowering surgeries were required for 28 out of the 112 (25%) eyes that had an IOP surgery. In addition to the timing of the first surgery, the relative rates (implant versus systemic) of IOP surgeries differed quantitatively in the first two years versus the remaining years (treatment by time period interaction $p = 0.049$), although there were significantly more surgeries in the implant group in both time periods. The rate of IOP surgeries was 0.02 / year in the systemic group and 0.15 / year in the implant group during the first 2 years (Adjusted RR: 6.2, 95% CI: 2.9, 13.4; $p < 0.0001$). The rate of IOP surgeries was 0.04 / year in the systemic group and 0.12 / year in the implant group after the first 2 years (Adjusted RR: 2.8, 95% CI: 1.5, 5.2; $p = 0.001$).

Eyes in the implant treatment arm had both a high absolute (26.3% vs 10.2%) and relative (HR=3.0, 95% CI: 1.7, 5.2) risk of glaucoma (assessed annually) during the first 48-months of follow-up as compared to those assigned to receive systemic therapy. While the increased relative risk for glaucoma in the implant group tended to be smaller during the 24-48 month interval after randomization (HR=2.1) than that observed during the first two years (HR = 4.2), the treatment by time period interaction was not statistically significant ($p=0.13$).

Eleven of the 20 eyes (8 individuals) that developed glaucoma in the systemic therapy arm had received an implant prior to diagnosis with glaucoma. In an analysis based upon treatment received, the hazard of glaucoma among eyes that received an implant versus those that did not receive an implant (including implant as a time-varying covariate) was higher (HR = 6.8, 95% CI: 3.5, 13.5, $p < 0.0001$); the cumulative incidence of glaucoma in implant- and non-implant-treated uveitic eyes by 48 months was 26.3% (95% CI: 20.7%, 33.1%) and 10.2% (95% CI: 6.3%, 16.3%) respectively.

Overall, the risk of cataract and cataract surgery was higher in the implant group, especially in the first two years. The time to first identification of a new cataract, as measured by a MUST clinician without reference to visual acuity at each study visit, was shorter in the implant group (HR=3.0, 95% CI: 1.7, 5.3); both groups had a high absolute risk of clinically diagnosed cataract (98.9% vs. 77.3% by 54 months in the implant and systemic groups respectively). The incidence of cataract surgery among phakic eyes by 54 months was ~4-fold higher in the implant group (HR=3.82, 95% CI: 2.6-5.7) with 87.7% of eyes in the implant group having received surgery by 54 months as compared to 43.0% in the systemic group (Table 1). Most of the surgeries occurred during the first two years of follow-up¹ as compared to the additional 2.5 years of follow-up regardless of treatment assignment (cumulative proportion 80% vs 83% for the implant group and 31% vs 40% for the systemic group, Figure 3). There was a quantitatively large but non-statistically significant difference in the relative hazard of surgery between the two treatment groups for the first 24 months versus the 25-54 months' follow-up interval (interaction $p = 0.17$); the HR in the first 2 years was 4.3 (95% CI: 2.8, 6.5) and after 2 years was 1.7 (95% CI: 0.5, 6.1). Twelve of the 51 cataract surgery events in the systemic group occurred after receiving an implant. As in the report through 24 months,¹ with extended follow-up eyes in the implant group still had a significantly shorter time to the first visit with visual acuity below 20/40 (HR = 1.6, 95% CI: 1.1-2.3), consistent with the higher risk of incident cataract. The time-to-the first visit with visual acuity of 20/200 or worse (HR = 1.6, 95% CI: 0.9-2.8) showed less difference. Nevertheless, average visual acuity (which took into account visual recovery with cataract surgery) was similar over time in the two groups (see companion manuscript).¹⁰

We previously reported that the risk of vitreous hemorrhage was significantly higher in the implant group through 24 months, likely reflecting the impact of implant placement surgery.¹ However, this pattern changed significantly during 25-54 month period of follow-up (test of interaction $p = 0.001$), with vitreous hemorrhage becoming significantly more common in the systemic group during the period after 24 months (HR = 0.10, 95% CI: 0.01, 0.76 versus HR = 3.5, 95% CI: 1.6, 7.9 within the first 24 months). Many (10, 50%) of the eyes (8 individuals) with vitreous hemorrhage in the systemic group had received an implant prior to the vitreous hemorrhage. In the as-treated analysis, the relative hazard of vitreous hemorrhage was 5.2 (95% CI: 2.3, 11.7, $p < 0.001$), a value greater than that observed during the first 24 months before most of the cross-overs occurred. A total of 13 of the 45 eyes with vitreous hemorrhage (29%) experienced multiple vitreous hemorrhages. As was the case in the time to first event analysis, the relative rates (implant versus systemic) of visits at which a vitreous hemorrhage was documented differed qualitatively in the first two years versus the remaining years (treatment by time period interaction $p = 0.001$). The rate of vitreous hemorrhage was 0.006 / visit in the systemic group and 0.032 / visit in the

implant group during the first 2 years (Adjusted RR: 5.1, 95% CI: 1.9, 13.8; $p=0.001$). The rate of vitreous hemorrhage was 0.008 / visit in the systemic group and 0.001 / visit in the implant group after the first 2 years (Adjusted RR: 0.10, 95% CI: 0.01, 0.81; $p=0.03$).

There were no significant differences between groups in the risk of hypotony (cumulative incidence of a semiannual visit with IOP ≤ 6 mmHg within 54 months of 20.2% and 14.0% in the implant and systemic group, $p=0.14$), endophthalmitis (1.3% vs. 0.5%, $p=0.37$), or rhegmatogenous retinal detachment (2.1% vs. 0.4%, $p=0.15$) between the two treatment groups nor was there a difference in the relative hazards observed between the first 24 months of follow-up and months 25-54 for these outcomes. In the systemic group, 8/27 hypotony events, 1/1 retinal detachment and 1/1 endophthalmitis events occurred in eyes that had received implant. Overall, 6 (2.0%) implant extrusions were observed out of 266 (226 in implant group; 40 in systemic group) implants placed, all extrusions occurred in eyes assigned to receive implant.

Systemic Adverse Outcomes

While through 24 months there had been a higher incidence of an elevated blood pressure reading in the systemic group,¹ by 54 months the incidence of an elevated blood pressure reading was similar in the two groups, with a large number of elevated blood pressure readings in both groups (see Table 2). During extended follow-up, as in the first 24 months' follow-up, hypertension requiring treatment tended to be less in the implant group (HR=0.4, 95% CI: 0.2-1.1), but not to a statistically significant degree. The overall 54 month incidences of hyperlipidemia requiring treatment (5.7% vs. 9.8%, HR=0.4, 95% CI: 0.1-1.5) and of diabetes mellitus (2.0% vs. 5.7%, HR=0.4, 95% CI: 0.1-1.8) were low in both groups without statistically significant differences. The 54 month cumulative incidence of osteoporosis was similarly low in both groups (7.8% vs. 16.6%, $p=0.66$). Osteopenia occurred similarly often and frequently in both groups (48.4% vs. 56.4%, $p=0.30$).

Although use of immunosuppressive therapy was much less common in the implant than the systemic group,²³ low hemoglobin, platelets and white blood cell counts and elevation of creatinine >1.5 mg/dL or of liver enzymes to 2-fold higher than the upper limit of normal were seldom observed in either group, without a suggestion of differences in the cumulative incidence between groups (see Table 2). Relative hazard of these events during the 25-48 month interval was similar to during the 0-24 month follow-up interval. The overall incidence rate for infections requiring treatment remained lower in the implant than the systemic group through 54 months (33 events [95% CI: 0.28-0.38] vs 51 events [95% CI: 0.45, 0.58]/100 person-years, $p=0.01$), rates that were similar to those observed during the first 24 months,¹ which were not associated with any lasting consequences in study participants (data not shown). Over the entire 54 months, hospitalization occurred similarly frequently in the two groups (14 events [95% CI: 0.11-0.17 vs 18 events [95% CI: 0.15-0.22]/100 person-years, $p=0.12$; this includes one patient in the systemic group who was electively hospitalized 12 times for chemotherapy). Fractures were not uncommon in both the implant (10%) and the systemic (17%) groups (HR = 0.6, [95% CI: 0.3, 1.2], $p=0.16$). The cumulative 54 month incidences of cancer (0.8% vs 2.5% [excluding non-melanoma skin cancers], $p=0.30$) and death (2.5% vs 3.6%, $p=0.60$) were very low in both groups

without significant differences. Weight remained similar to baseline in both groups throughout follow-up, with similar mean non-significant gains of 0.6 and 1.2 kg by 54 months in the implant and systemic groups, respectively ($p=0.64$, Table 3).

Quality of Life (QoL)

Vision-related (VRQoL) and generic health-related (HRQoL) quality of life and health utility outcomes are summarized in Table 3. On average, both groups presented with and maintained generally favorable health utility and HRQoL outcomes throughout the study. As reported previously,¹ on average, implant-assigned patients reported small, significantly better changes in VRQoL and HRQoL at 12 months across all metrics, a benefit that remained significant or borderline significant at 24 months.¹ However, this difference was no longer evident at 54 months (see Table 3) except in the case of the SF-36 physical component score (difference implant – systemic [I - S]: 3.17, 95% CI: 0.66, 5.68). A mean difference of 3.17 on a scale of 100 is marginal with respect to a reported mean clinically meaningful difference on this scale (mean clinically important difference=3-5 points).¹⁹ This SF-36 Physical Component Score difference was driven by a decline in the scores for patients assigned to systemic therapy versus stable scores in the implant group. The implant group had a consistently larger improvement in EQ-5D health utility (which has a scale of 0.00-1.00) throughout the first 48 months (I – S: 0.05, 95% CI: 0.01 to 0.10, $p = 0.03$ at 48 months), but the absolute difference was small and probably not clinically important.²⁰ By 54 months both treatment arms had a similar (minimal) change in EQ-5D health utility from baseline (I – S: 0.01, 95% CI: -0.03 to 0.06, $p = 0.58$).

Discussion

These results suggest that the much higher risk of local problems with implant vs. systemic therapy, notably IOP-related events and cataract, continues through 54 months. While the rate of rise in new events in some instances was less dramatic in the implant group after 24 months than in the first 24 months,¹ the absolute risk in eyes free of each event tended to be higher in the implant than the systemic group during the 25-54 month window, and the overall risk of IOP-related events during 54 months after randomization was much higher in the implant group in both an absolute and a relative sense. As-treated analyses showed even greater differences between the two groups, as many of the IOP-related and cataract-related events occurred in the systemic arms in eyes which had crossed over to receive implant therapy. Thus, we conclude that the risk of most such events does not converge during the additional follow-up period, with the exception of IOP-lowering surgery and vitreous hemorrhage, but remains much higher in the implant group, at least through 54 months. Although, the incidence of vitreous hemorrhage was the primary outcome observed more often in the systemic group during the 25-54 months' follow-up period, most vitreous hemorrhages were observed in eyes crossing over to implant therapy as rescue therapy. In the systemic group, cataract and IOP-related outcomes also occurred more often in eyes which had received implant therapy, although the events were encountered fairly often in the systemic group as well. Fortunately endophthalmitis and retinal detachment were rare in both groups, an observation of importance in establishing proof of concept of the potential safety of therapies that suppress inflammation/immunity and require surgical implantation.

In contrast, systemic problems did not markedly differ between groups, even though large differences in the ongoing use of systemic therapies persisted through 54 months in the alternative groups. The risk of hyperlipidemia and hypertension based on protocol-directed measurements was moderate to high in both groups, but despite the large number of events no significant differences between groups were observed. A much smaller number of patients required treatment for hyperlipidemia or hypertension, perhaps because many of the observed elevations of lipids or blood pressure were transient. The number requiring such treatment tended to be more in the systemic group, but the difference was small in absolute magnitude and not statistically significant. Incidence of diabetes mellitus was infrequent in both groups with no significant differences. Neither did the incidence of osteopenia, osteoporosis or fractures differ significantly between groups, even though the incidence of osteoporosis was not uncommon in the cohort. In general, the risk of these classic complications of systemic corticosteroid therapy was slightly higher in the systemic therapy group, but the differences were small and not statistically significant, suggesting that judicious use of systemic corticosteroids in the uveitis setting following expert panel recommendations⁶ is a reasonably safe practice. Another notable finding is that there were neither appreciable differences between groups nor between baseline and follow-up in the weight of study participants, suggesting that substantial changes in weight are not the norm with the study treatments.

Immunosuppressive therapy was used much more widely in the systemic than the implant group through 54 months, in accordance with the study design.^{1;9} Prospective monitoring for potential hematological, liver and renal complications of such therapy found minimal risk of such events in both groups, without any observable tendency for such events to occur more often in one group than the other. These results provide strong evidence that such complications are rarely seen with immunosuppressive therapy administered used in accordance with expert panel recommendations.⁶ Because the study did not require the use of specific immunosuppressive drugs, it is difficult to be sure that differences do not exist between alternative immunosuppressive regimens, but the lack of any appreciable signal in these data suggests that if an excess risk exists, it likely is small at least with the immunosuppressive drugs most commonly used in the study (methotrexate and mycophenolate mofetil). The previously reported observation of a higher risk of being prescribed medication for an infection during the first two years of follow-up persisted through 54 months, as did the lack of any lasting consequences related to these events. The issue of whether unmasked clinicians may have been more likely to prescribe antibiotics for patients taking systemic corticosteroids and immunosuppressive drugs remains relevant to interpreting these results.

Because death and cancer incidence were extremely rare in both groups, the study has modest power to assess these highly important events. However, a recent publication with only slightly more follow-up (median of 7 years) than in this study suggested a higher risk of malignancies (whether including or not including non-melanoma skin cancers) in patients treated with immunosuppressive drugs versus those treated with systemic corticosteroids and followed.²⁴ Although that manuscript lumped all immunosuppressive drugs together (including alkylating agents and Tumor Necrosis Factor inhibitors), methotrexate and mycophenolate mofetil were the immunosuppressive drugs most commonly used. Through

our shorter 54 months' follow-up, also using a heterogeneous group of immunosuppressive drugs (most commonly methotrexate and mycophenolate mofetil), we have not observed a pattern of this nature; rather we have observed a small number of incident malignancies occurring with similar frequency in both groups. Data from other disease conditions suggest that the immunosuppressive drugs most commonly used for ocular inflammatory diseases (methotrexate and mycophenolate mofetil) probably do not convey a clinically important degree of increased cancer risk when used as indicated for ocular inflammatory diseases,²⁵ although data from other disease settings (mostly transplantation) have been interpreted as indicating that azathioprine and especially cyclosporine are human carcinogens.²⁶ Both overall and cancer-specific mortality risk have been reported to be similar with and without treatment in a large cohort of ocular inflammation patients treated with the immunosuppressive drugs methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine and with systemic corticosteroids.²⁷ Additional data from the MUST Trial will be valuable to further address the issue of carcinogenicity with immunosuppression.

Despite substantial differences in the risk of local problems, the lack of large differences between groups in quality of life indices supports an interpretation that these effects have a limited impact on the patient's experience, at least through 54 months. This pattern may reflect the reversibility of cataract with surgery in most cases, and the limited detectable effect of all but the most advanced glaucoma on central vision. (In this study, the frequent incidence of glaucoma still was not sufficient to effect a difference in the visual field's mean deviation between treatment groups.)

Nevertheless, the difference in glaucoma between the two groups is compelling, given that the problem potentially could be avoided by rapidly controlling intraocular pressure. Implant patients frequently experience large upward excursions of intraocular pressure without having accompanying symptoms, and might indeed have substantial improvement in symptoms due to control of uveitis—often for the first time in years. It is easy for such patients to neglect follow-up, which nevertheless should be aggressively enforced. Given the high risk of glaucoma, careful monitoring at least quarterly and perhaps every six weeks in the first 2 years after implant placement is warranted, and aggressive interventions are warranted when large changes in intraocular pressure are detected. Given that a high proportion will require surgical intervention, and that patients of black race, those with active uveitis and those already using IOP-lowering therapy at the time of randomization have a substantial elevation in the already high risk of glaucoma,¹¹ early surgical interventions often will be warranted.

Limitations of the study include the lack of a strict treatment protocol after completion of the MUST Trial portion of the study, which was required so as to allow subjects to reconsider their treatment options in light of the primary study results. However, much of the follow-up through 54 months took place under the clinical trial portion of the study, and relatively few patients crossed over after results were revealed. The degree of crossovers observed were not unusually high, and given the strong differences in local side effect risk and the lack of differences in the other outcomes, these crossovers are unlikely to have affected the study conclusions, as is further argued by similar conclusions based on analyses “as treated.” Follow-up of the cohort was reasonably complete, and key outcomes were measured

prospectively under a common protocol following relevant practice guidelines whenever possible. Quality of life self-reports used validated instruments, and the results showed face validity in their general similarity to other disease outcomes measured in the study. Lack of masking, which was required for ethical reasons, might have led to overestimation of the infectious risks with systemic therapy, as discussed above.

In conclusion, fluocinolone acetonide implant therapy is associated with a clinically important excess risk of local side effects with respect to systemic therapy. In contrast, the risk of systemic potential side effects of corticosteroids and immunosuppression is similar with the two treatment approaches through 54 months, and self-reported quality of life outcomes also are similar. Given that implant therapy is substantially more expensive for bilateral disease²⁸ and has more risks, systemic therapy may be the preferred initial treatment for a number of patients. Given the superior control of inflammation with implant therapy,¹⁰ implant therapy will continue to have a role for selected cases. Further research is needed to clarify whether these findings diverge over longer term follow-up, and whether alternative local or systemic therapy approaches offer improvements over the current state of the art for management of non-infectious intermediate, posterior, and panuveitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Distribution of intraocular pressure at selected study visits by treatment assignment group, uveitic eyes of Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study participants. Systemic therapy (systemic corticosteroids plus immunosuppression when indicated) is given in gray, fluocinolone acetonide implant therapy is given in white.

Figure 2. Proportion undergoing surgery to control intraocular pressure (IOP) over time among uveitic eyes of Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study participants.

Figure 3.

Proportion undergoing cataract surgery over time among uveitic eyes of Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study participants.

Table 1
Incidence of Ocular Problems in Uveitic Eyes of MUST Trial and Follow-up Study Participants Randomized to Implant or Systemic Therapy

Glaucoma and IOP events							
IOP	30 mmHg	234	40.9 (34.1, 48.6)	229	9.8 (6.1, 15.7)	5.6 (3.3, 9.5)	<.0001
IOP	24 mmHg	234	61.6 (54.3, 69.0)	228	23.1 (16.9, 31.1)	3.7 (2.5, 5.4)	<.0001
IOP	10 mmHg increase from baseline	235	62.4 (54.9, 69.8)	230	19.6 (14.4, 26.3)	4.3 (2.9, 6.4)	<.0001
Glaucoma**		220	26.3 (20.7, 33.1)	212	10.2 (6.3, 16.3)	3.0 (1.7, 5.2)	0.0002
Use of any IOP-lowering therapy		196	77.9 (69.3, 85.4)	202	34.0 (25.7, 44.0)	3.9 (2.6, 5.6)	<.0001
IOP-lowering surgery†							
	Before 2 years	233	31.1 (24.4, 39.1)	226	4.5 (2.1, 9.6)	8.1 (3.5, 18.5)	<0.0001
	After 2 years	151	13.9 (9.1, 20.9)	200	7.2 (3.8, 13.4)	2.1 (0.9, 4.7)	0.06
Cataract events							
	Incident cataract	54	98.9 (96.7, 99.7)	49	77.3 (61.9, 89.7)	3.0 (1.7, 5.3)	0.0001
	Cataract surgery	140	87.7 (81.1, 92.9)	125	43.0 (32.8, 54.8)	3.8 (2.6, 5.7)	<.0001
Potential complications of implant surgery							
IOP	6 mmHg (hypotony)	226	20.2 (14.5, 27.6)	218	14.0 (9.1, 21.3)	1.5 (0.9, 2.8)	0.14
Vitreous hemorrhage†							
	Before 2 years	236	15.6 (11.2, 21.6)	230	4.9 (2.4, 9.8)	3.5 (1.6, 7.9)	0.002
	After 2 years	189	1.7 (0.0, 11.3)	208	10.1 (3.7, 26.2)	0.1 (0.0, 0.8)	0.03
	Endophthalmitis	237	1.3 (0.4, 4.0)	230	0.5 (0.1, 3.5)	2.9 (0.3, 28.4)	0.37
	Rhegmatogenous retinal detachment	236	2.1 (0.9, 5.0)	230	0.4 (0.1, 3.1)	4.9 (0.6, 42.6)	0.15

CI, confidence interval. IOP, intraocular pressure.

* Including eyes with uveitis. Eyes with prevalent complications or missing data at enrollment were excluded from the risk set.

Hazard ratios (HR) are adjusted for uveitis stratum (intermediate vs. posterior or panuveitis).

** Measured yearly, the cumulative % and hazard ratio are for events by the 4 year visit

[†] Significant change in HR before versus after 2 years. IOP surgery interaction p-value = 0.02. Vitreous hemorrhage interaction p-value = 0.001.

Table 2
Incidence of Systemic Problems in Multicenter Uveitis Steroid Treatment Trial and Follow-up Study Participants through 54 months

Systemic Problems	Implant Group		Systemic Group		Hazard Ratio*	
	No. of Patients at Risk [†]	Cumulative % with Event by 54 Months (95% Confidence Interval)	No. of Patients at risk [‡]	Cumulative % with Event by 54 Months (95% Confidence Interval)	Implant/Systemic (95% Confidence Interval)	P Value
Potential complications of corticosteroid therapy						
Hyperlipidemia (LDL 160 mg/ml) [‡]	95	18.7 (11.5–29.5)	102	15.4 (8.7–26.5)	1.4 (0.6–2.9)	0.41
Hyperlipidemia diagnosis requiring treatment	90	5.7 (2.1–15.1)	86	9.8 (5.0–18.7)	0.4 (0.1–1.5)	0.19
Hypertension (measured SBP 160 mmHg and/or DBP 100 mmHg)	115	26.6 (18.5–37.4)	115	31.7 (23.9–41.4)	0.7 (0.4–1.2)	0.18
Hypertension (measured SBP 140 mmHg and/or DBP 90 mmHg)	85	53.1 (42.0–65.1)	94	61.7 (51.5–72.1)	0.7 (0.5–1.1)	0.14
Hypertension diagnosis requiring treatment	88	7.1 (3.2–15.1)	88	15.6 (9.3–25.4)	0.4 (0.2–1.1)	0.08
Diabetes mellitus	105	2.0 (0.5–7.9)	114	5.7 (2.6–12.3)	0.4 (0.1–1.8)	0.20
Osteopenia	56	48.4 (25.4–77.6)	69	56.4 (27.8–88.0)	1.3 (0.7–2.6)	0.42
Osteoporosis	110	7.8 (3.6–16.4)	109	16.6 (5.7–43.1)	0.8 (0.3–2.3)	0.74
Fractures	125	10.3 (6.0–17.5)	124	17.1 (11.2–25.6)	0.6 (0.3–1.2)	0.13
Potential complications of immunosuppressive therapy						
White blood cell count 2500 cells/ μ l [‡]	122	0.8 (0.1–5.7)	119	3.5 (1.3–9.0)	0.2 (0.0–2.3)	0.20
Platelet count 100 000 / μ l [‡]	120	6.2 (2.8–13.7)	118	2.4 (0.6–9.8)	2.9 (0.6–14.3)	0.19
Hemoglobin 10 g/dl [‡]	122	1.7 (0.4–6.7)	117	3.1 (1.0–9.5)	0.6 (0.1–3.7)	0.60
Elevated liver enzymes [‡]	118	5.2 (2.4–11.2)	116	3.2 (1.0–9.6)	2.0 (0.5–8.0)	0.33
Elevated creatinine [‡]	118	7.9 (4.2–14.6)	117	6.0 (2.7–13.2)	1.5 (0.5–4.3)	0.43
Cancer diagnosis [§]	126	0.8 (0.1–5.5)	124	2.5 (0.8–7.5)	0.3 (0.0–3.2)	0.34
Death [§]	126	2.5 (0.8–7.6)	124	3.6 (1.4–9.3)	0.7 (0.2–3.3)	0.69

DBP = diastolic blood pressure; LDL = low density lipoprotein; SBP = systolic blood pressure.

* Adjusted for uveitis stratum (intermediate vs. posterior or panuveitis).

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

[‡] Measured yearly, the cumulative percent and hazard ratio are for events by the 4-year visit.

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The cancer diagnoses were brain (implant); myeloma (2 cases), and lung (systemic). The known causes of death were brain tumor, brain swelling, and sepsis (implant); lung cancer, complications of multiple sclerosis (systemic). Two deaths (systemic) were discovered in a death index search and the cause is unknown.[§]

Change in Measures of Self-reported Quality of Life and Weight Over Time in MUST Trial and Follow-up Study Subjects

Table 3

		Estimated Mean (SE)		Estimated Mean Change from Enrollment (SE)		Estimated Treatment Effect [†] (95% CI)		p value
		Implant	Systemic	Implant	Systemic	Implant	Systemic	
Vision-related QoL								
VFQ-25 (Overall Composite) Minimum Clinically Important Difference: 4-6 points ²¹								
Enrollment	255	61.17 (2.41)	65.45 (2.47)					
12 months	235	73.39 (2.45)	70.32 (2.48)	12.22 (1.60)	4.87 (1.37)	7.35	(3.22, 11.49)	<0.01
24 months	232	72.61 (2.43)	72.19 (2.58)	11.44 (1.66)	6.74 (1.58)	4.70	(0.20, 9.20)	0.04
36 months	218	73.08 (2.40)	74.43 (2.49)	11.91 (1.67)	8.98 (1.67)	2.93	(-1.69, 7.56)	0.21
48 months	208	70.51 (2.43)	73.87 (2.62)	9.34 (1.50)	8.42 (1.81)	0.92	(-3.70, 5.53)	0.70
54 months	197	69.96 (2.54)	75.28 (2.61)	8.79 (1.59)	9.83 (1.83)	-1.04	(-5.79, 3.71)	0.67
Generic health-related QoL								
SF-36 (Mental Component Summary) Minimum Clinically Important Difference: 3-5 points ¹⁹								
Enrollment	255	47.75 (1.31)	48.58 (1.20)					
12 months	234	51.30 (1.13)	46.81 (1.33)	3.55 (1.05)	-1.77 (1.11)	5.32	(2.33, 8.31)	<0.01
24 months	232	50.20 (1.18)	47.49 (1.34)	2.45 (1.10)	-1.09 (1.14)	3.54	(0.43, 6.65)	0.03
36 months	217	50.46 (1.19)	48.43 (1.23)	2.70 (1.06)	-0.15 (1.05)	2.86	(-0.06, 5.78)	0.06
48 months	207	49.63 (1.21)	49.44 (1.26)	1.88 (1.14)	0.86 (1.19)	1.01	(-2.22, 4.25)	0.54
54 months	197	50.48 (1.29)	49.84 (1.33)	2.73 (1.06)	1.26 (1.17)	1.46	(-1.63, 4.56)	0.35
SF-36 (Physical Component Summary) Minimum Clinically Important Difference: 3-5 points ¹⁹								
Enrollment	255	46.16 (1.18)	48.09 (1.13)					
12 months	234	47.26 (1.22)	46.18 (1.15)	1.10 (0.77)	-1.91 (0.87)	3.01	(0.75, 5.28)	0.01
24 months	232	47.26 (1.21)	46.37 (1.18)	1.10 (0.83)	-1.72 (0.89)	2.82	(0.43, 5.21)	0.02
36 months	217	47.26 (1.17)	46.68 (1.19)	1.10 (0.85)	-1.40 (0.92)	2.50	(0.06, 4.95)	0.05
48 months	207	46.47 (1.21)	46.89 (1.12)	0.31 (0.77)	-1.20 (0.93)	1.51	(-0.86, 3.87)	0.21
54 months	197	46.33 (1.15)	45.09 (1.27)	0.17 (0.81)	-3.00 (1.00)	3.17	(0.66, 5.68)	0.01
Health utility								
EuroQoL (Visual analog) Minimum Clinically Important Difference: 7 points ²⁰								
Enrollment	253	72.87 (1.96)	74.48 (2.03)					
12 months	234	77.61 (1.88)	71.42 (2.15)	4.75 (1.36)	-3.07 (1.78)	7.81	(3.43, 12.19)	<0.01

Estimated Mean (SE)			Estimated Mean Change from Enrollment (SE)			Estimated Treatment Effect [†] (95% CI)		
	Implant	Systemic		Implant	Systemic		Implant: Systemic	p value
24 months	232	78.21 (1.87)	73.60 (1.91)	5.35 (1.27)	-0.88 (1.80)	6.23	(1.90, 10.56)	<0.01
36 months	212	77.37 (2.15)	77.68 (1.81)	4.50 (1.45)	3.20 (1.76)	1.30	(-3.16, 5.77)	0.57
48 months	204	75.73 (2.17)	75.87 (1.80)	2.87 (1.47)	1.38 (1.71)	1.49	(-2.93, 5.90)	0.51
54 months	195	76.49 (2.17)	74.33 (2.08)	3.63 (1.50)	-0.15 (1.94)	3.78	(-1.02, 8.58)	0.12
EuroQol (EQ-5D Health Utility Index) Minimum Clinically Important Difference: 0.06-0.07 points ²⁰								
Enrollment	254	0.81 (0.02)	0.83 (0.02)					
12 months	235	0.83 (0.02)	0.80 (0.02)	0.02 (0.02)	-0.03 (0.02)	0.05	(0.00, 0.09)	0.04
24 months	232	0.83 (0.02)	0.81 (0.02)	0.02 (0.02)	-0.02 (0.02)	0.04	(0.00, 0.08)	0.07
36 months	216	0.83 (0.02)	0.81 (0.02)	0.02 (0.02)	-0.02 (0.02)	0.04	(-0.01, 0.08)	0.13
48 months	207	0.84 (0.02)	0.81 (0.02)	0.03 (0.01)	-0.02 (0.02)	0.05	(0.01, 0.10)	0.03
54 months	198	0.82 (0.02)	0.82 (0.02)	0.01 (0.02)	-0.01 (0.02)	0.01	(-0.03, 0.06)	0.58
Weight (kg)								
Enrollment	255	88.08 (2.64)	86.37 (2.73)					
12 months	229	87.80 (2.72)	86.68 (2.76)	-0.28 (0.71)	0.31 (0.82)	-0.59	(-2.71, 1.53)	0.59
24 months	229	87.81 (2.75)	86.61 (2.84)	-0.27 (0.81)	0.24 (0.86)	-0.51	(-2.83, 1.82)	0.67
36 months	217	88.49 (2.78)	87.64 (2.86)	0.41 (0.78)	1.27 (0.99)	-0.86	(-3.34, 1.62)	0.50
48 months	203	88.74 (2.85)	87.09 (2.75)	0.66 (0.83)	0.72 (1.01)	-0.06	(-2.62, 2.50)	0.96
54 months	196	89.28 (2.84)	86.99 (2.70)	1.20 (0.77)	0.62 (1.01)	0.59	(-1.90, 3.08)	0.64

CI = 95% confidence interval; SE = standard error; QoL = quality of life.

* Sample size: the number of individuals (N) with data available at each visit.

[†] 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).