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Outcome of Treatment of Uveitic Macular Edema: the Multicenter Uveitis Steroid Treatment (MUST) Trial 2-year Results

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Abstract

Purpose—To evaluate the clinical outcomes of uveitic macular edema through two years of treatment.

Design—Longitudinal follow-up of a randomized cohort.

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Conflict of Interest:

Dr. Lightman received grants and personal fees from Allergan.
Dr. Vitale, consultant to Aciont.
Dr. Holland, medical advisory boards to Genetech, Novartis International AG, Santen and Xoma.
Dr. Jabs, consultant to Santen, and serves on Data and Safety Monitoring Committees for Applied Genetic Technologies Corporation and Novartis Pharmaceutical Corporation.
All other authors have no conflicts of interest to report.

Participants—At baseline, 148 eyes of 117 patients enrolled in the Multicenter Uveitis Steroid Treatment (MUST) Trial had macular edema, and 134 eyes of 108 patients completed two-year follow-up.

Methods—All patients enrolled in the study were randomized to either systemic immunosuppression or intravitreal fluocinolone acetonide implant therapy. Macular edema was defined as thickening of the retina (center point thickness ≥240 μm) on time-domain optical coherence tomography (OCT) of macula.

Main Outcome Measures—Improvement in macular edema (≥20% reduction in central point thickness on OCT), resolution of macular edema (normalization of thickness on OCT) and best-corrected visual acuity (BCVA).

Results—Between randomization and 2-years' follow-up, 62% and 25% of eyes in the systemic and implant groups respectively, received at least one supplemental regional corticosteroid injection. Overall, by 2-years' follow-up, macular edema improved in 71% of eyes and resolved in 60%. There were no differences between treatment groups in the proportion of eyes with macular edema improving (systemic therapy vs. implant, 65% vs. 77%, P=0.20) and resolving (52% vs. 68%, P=0.28). However, on average, eyes randomized to implant had more improvement in macular thickness (median decrease of 180μm vs. 109μm in the systemic therapy group, P=0.04). Eyes with fluorescein angiographic leakage at baseline were more likely to improve in macular thickness than those without (76% vs. 58%, P=0.03). Overall, there was a mean 5-letter (1 line) improvement in BCVA at 2 years. Mean changes in BCVA from baseline at 2 years by macular edema response status were: resolution,+10 letters; improvement without resolution, +10 letters (P=0.92); little to no change, 6 letters (P=0.19); and worsening, −16 letters (worsening acuity, P=0.0003).

Conclusions—About two-thirds of eyes with uveitic macular edema were observed to experience improvement in the edema and visual acuity with implant or systemic treatment. Fluocinolone acetonide implant therapy was associated with a greater quantitative improvement in thickness. Associated leakage on fluorescein angiography at baseline was associated with a greater likelihood of improvement in macular edema.

One of the most common structural complications of the uveitides is macular edema, which is the most frequent cause of both reversible and long-term visual loss in this population.[1–3] Disruption of the inner blood-retinal barrier by inflammatory cytokines leads to leakage of fluid in the extracellular space, which accumulates in the outer plexiform and inner nuclear layers around the fovea. This is manifested as leakage on fluorescein angiography and retinal thickening as measured by optical coherence tomography (OCT).[4] Persistent macular edema may lead to irreversible disruption of the retinal neural network, gliosis or atrophy, and result in permanent vision loss, whereas transient macular edema is more likely to recover and often has a good visual outcome. Management of uveitic macular edema represents a key goal of the treatment of the uveitides, usually using injected or oral corticosteroid therapy.

Approximately 30% to 40% of patients with intermediate uveitis can be managed with occasional regional (periocular or intravitreal) corticosteroid injections, the indication for which usually is macular edema.[5, 6] The remainder of patients with intermediate uveitis, and

most patients with posterior and panuveitis, require long-term suppressive anti-inflammatory treatment with systemic corticosteroids and immunosuppression, alone or on combination.; adjunctive regional corticosteroid injections are used as supplemental therapy as necessary.[7–11] The aim of this approach is to control the intraocular inflammation and thereby attenuate the stimulus for retinal fluid accumulation, allowing for restoration of retinal architecture and improvement in vision.[12–15] An alternative approach is the surgical implantation of the fluocinolone acetonide implant (Retisert, Bausch & Lomb, Rochester, NY, USA), which releases corticosteroid into the vitreous over a 2.5 to 3 year time frame and is effective for management of intermediate, posterior, and panuveitides.[16]

The Multicenter Uveitis Steroid Treatment (MUST) Trial, a randomized, comparative effectiveness clinical trial of the fluocinolone acetonide implant (local therapy) vs. standard systemic therapy with oral corticosteroids and immunosuppression (as needed) for intermediate, posterior or panuveitides for which systemic therapy would be indicated, is following patients under the randomized treatments over time.[17, 18] As part of this trial, data are collected prospectively on uveitic macular edema. Here we examine the clinical outcome of and response to treatment of macular edema and to identify factors related to the outcome in this well-documented cohort.

Methods

Eligibility, enrolment, treatment, and follow-up procedures for participants in the MUST Trial (Clinical Trials.gov registration number 00132691) have been described previously.[4, 17, 19] In brief, patients with active or recently active, non-infectious, intermediate, posterior, or panuveitis who would be candidates for systemic corticosteroid therapy were enrolled. Randomization was stratified based on the class of uveitis: intermediate uveitis and posterior or panuveitis.[17, 18] At enrollment, patients gave a detailed medical and ophthalmic history and underwent a complete ocular examination including; measurement of best corrected visual acuity using logarithmic visual acuity charts,[20] external and slit lamp examinations, tonometry, and examination of the retina through a dilated pupil. Fluorescein angiography and time-domain OCT (Stratus 3, Carl Zeiss Meditec, Jena, Germany) were also performed.[4] Patients were randomized to receive either the fluocinolone acetonide intraocular implant (Retisert®) in all eyes for which it was indicated (some second eyes had very mild uveitis and did not require implant therapy) or to receive systemic treatment with oral prednisone and immunosuppression as needed. Participants were followed under the trial protocol for 2 years with tests including eye examinations, OCT and fluorescein angiographic imaging. All participating centers, both clinical and resource centers, obtained and maintained investigational review board (IRB) approval throughout the study, and all participants gave written, informed consent. The study and its procedures adhered to the principles of the Declaration of Helsinki.

Optical coherence tomograms and fluorescein angiograms were read by a centralized image Reading Center by graders masked to treatment assignment. For the purposes of this study, macular edema was defined as macular thickening on OCT (center point thickness ≥240 μm).[4, 17] Graders classified macular edema on OCT as diffuse or cystoid based on the absence or presence of cystoid spaces, respectively.[4, 21] Participants with cystoid spaces but

without macular thickening were not included in this analysis as there was no ability to detect normalization of macular thickness on OCT (being normal already), and limited ability to detect visual improvement (median baseline visual acuity was 20/30 in this group). Fluorescein leakage was defined as present if graders found leakage involving > 0.44 disk areas (the size of the Early Treatment of Diabetic Retinopathy Trial central subfield) in the macula on fluorescein angiography.[4] Improvement in macular edema was defined as a ≥20% reduction in or normalization of macular thickness by the OCT.[22] Resolution of macular edema was defined on OCT as a decrease in macular thickness into the normal range (<240 μm), not requiring the resolution of all cystoid spaces. Intraocular pressure was measured at every visit. Ocular hypertension was defined as a measured intraocular pressure ≥24 mmHg, the need for the use of topical pressure lowering agents or a history of glaucoma surgery. Glaucoma was diagnosed based on the consensus of two masked glaucoma specialists taking into account glaucomatous disc changes or glaucomatous visual field loss.[23]

Statistical analysis

Primary analyses were conducted ‘as randomized’. All uveitic eyes with macular edema, defined as retinal thickness at the center point ≥240 mm, at baseline were included in analyses. Comparisons of baseline characteristics and the outcomes by treatment group were performed using generalized estimating equations (GEE) with a logit link and exchangeable covariance structure to account for correlation between eyes within the same participant.[24] GEE functions with an exchangeable covariance structure were also used to fit logistic regression models to assess the association between macular edema response and other eye and person level characteristics. Candidates for the final adjusted model included all variables that were significant at the 10% level in the unadjusted models plus treatment group (implant vs. systemic) and type of macular edema (cystoid vs. diffuse), both of which *a priori* were thought to be associated with macular edema response. The final model was fit through a combination of backwards and forwards selection. For each variable not included in the final model, an adjusted model was fit to show the effect after adjustment for the final model variables. The linear association between change in visual acuity and eye and person level characteristics was modelled similarly using GEE. The final adjusted model and additional adjusted analyses were created as described above. Since the association between macular edema response and change in visual acuity was our primary comparison of interest, we also included the variables that were associated with macular edema response as candidate variables.

Results

Of the 255 participants (479 uveitic eyes) enrolled in the trial, 117 had macular thickness ≥240 μm identified on OCT at enrolment, and 108 of these 117 participants completed the 2-year follow-up visit. These participants form the study population for these analyses on uveitic macular edema. Characteristics of the study population are shown as Table 1. Although the MUST Trial did not stratify for macular edema at presentation, of the 117 participants with uveitic macular edema, those randomized to systemic therapy and those randomized to the fluocinolone acetonide implant were reasonably similar with respect to demographic characteristics, duration of uveitis, disease stratum (intermediate vs. posterior

or pan-uveitis), ocular characteristics, and visual acuity. Among the entire population with uveitic macular edema at presentation, 72% had cystoid macular edema and 28% had diffuse macular edema as identified on OCT. The median macular thickness was 367 μm (interquartile range [IQR], 284, 539). Fluorescein angiograms were obtained at enrolment on 83% of participants, and of these, 69% had macular leakage≥0.44 disk diameters. Additionally, epiretinal membranes were identified by OCT on 43% of all those with macular edema.

The outcomes of eyes with uveitic macular edema at the 2-year visit are shown as Table 2. Of the 117 patients with uveitic macular edema at baseline, 108 completed the 2-year follow-up visit. At the 2-year follow-up visit, 32% of those with uveitic macular edema were receiving oral prednisone (57% of those that had been randomized to systemic therapy vs. 9% of those that had been randomized to the fluocinolone acetonide implant) and 34% were receiving systemic immunosuppression (64% of those randomized to systemic therapy vs. 5% of those randomized to the implant). By 2 years, 43% of the total eyes with uveitic macular edema had received at least one supplemental regional corticosteroid injection, 62% and 25% in the systemic and implant groups respectively. The median number of these injections among those randomized to systemic therapy was 1 (75^{th} percentile = 2) and to the implant was 0 (75^{th} percentile = 1).

By 2 years macular thickness on OCT had improved in 71% of participants with uveitic macular edema, and the edema had resolved in 60%. There was no difference by treatment assignment in either improvement (65% of those randomized to systemic therapy vs. 77% of those randomized to implant, P=0.20) or resolution (52% of those randomized to systemic therapy vs. 68% of those randomized to implant, P=0.28). Overall, the median macular thickness on OCT improved to 210 μm, and there was no significant difference between the two treatment groups (236 μm for those randomized to systemic therapy vs. 184 μm for those randomized to implant, P=0.14). While median macular thickness at baseline was similar between those in the implant group and the systemic therapy group (376 μm vs. 348 μm, p=0.44), eyes treated with the implant appeared to have a greater improvement in macular thickness with a median decrease of 180 μm compared to 109 μm in the systemic therapy group (P=0.04); the corresponding percent changes in macular thickness were 58% decrease in the implant group vs. 32% decrease in in the systemic therapy group.

The outcomes of uveitic macular edema at 2 years comparing baseline eye characteristics are shown in Table 3. There were no significant differences in improvement or resolution at 2 years for different types of macular edema (diffuse vs. cystoid). Eyes with fluorescein angiographic leakage at baseline were more likely to show 20% improvement in macular thickness on OCT than those without (76% vs. 58%, P=0.03) but complete resolution of macular edema on the OCT was similar between eyes with and without fluorescein angiographic leakage at baseline (61% vs. 55%, P=0.49). Because 17% of the patients with macular edema were missing a fluorescein angiograms at baseline, a sensitivity analysis was performed with the missing group included, and it did not affect the conclusion that baseline fluorescein angiographic leakage was associated with the likelihood of improvement in the macular edema (data not shown). The presence of an epiretinal membrane at baseline on time-domain OCT did not appear to affect the likelihood of improvement in or resolution of

macular edema at 2 years. An assessment of factors potentially associated with improvement in macular edema is given as Table 4. The only significant factor was the presence of leakage on fluorescein angiography at enrolment, which was associated with a 2.3-fold increased odds of improvement in macular thickness on OCT in the adjusted model (95% CI 1.1, 4.9, P=0.03).

Among 67 eyes with leakage on fluorescein angiogram at baseline and a follow-up angiogram at 2 years, 45% had resolution of the leakage. Among 31 eyes without fluorescein leakage at baseline and a follow-up angiogram at 2 years, 77% had no leakage, and 23% had new-onset leakage by 2 years. The percent of eyes with improvement in macular edema was similar for eyes with leakage at baseline only (30%), both baseline and follow-up (37%) and neither baseline nor follow-up (24%) and was lower for those with new onset leakage (7%). Mean improvements and 95% CIs in visual acuity by fluorescein angiographic results were: resolution of leakage, 8 letters (95% CI 4, 13) and no resolution of leakage, 7 letters (95% CI 3, 11). For those eyes with new onset leakage at 2 years (i.e. no leakage at baseline), the mean change in visual acuity was −16 letters (a loss; 95% CI −35, 0). Among those eyes with no leakage at baseline and at 2 years, the mean change in visual acuity was 6 letters (95% CI −2, 13).

Factors predictive of visual acuity improvement among patients with uveitic macular edema are shown in Table 5. In the adjusted model, the presence of macular leakage on the enrolment fluorescein angiogram was associated with 7-letter (1.4 lines) better change in visual acuity at 2 years (95% CI 2, 12 letters, P=0.01). Worsening macular edema on OCT was associated with a 26-letter worse change in visual acuity at 2 years (95% CI −39, −14 letters, P<0.0001). In the adjusted model, the presence of cataract at baseline was associated with a 9-letter better change in visual acuity at 2 years (95% CI 1, 17 letters, P=0.03). Among participants with cataract at enrolment, 76% underwent cataract surgery by 2 years, and the mean improvement in visual acuity among these was 12 letters, whereas among those with cataract at enrolment who did not undergo cataract surgery by 2 years, the mean improvement in visual acuity was 7 letters. Ocular hypertension at enrolment was associated with a 7-letter worse improvement in visual acuity at 2 years in the adjusted model (95% CI −13, −1, P=0.03) but it should be noted that this association was only apparent in the final adjusted model and should be interpreted cautiously. As opposed to the overall use of regional corticosteroid injections of 62% in the systemic group and 25% in the implant group, only 6% in the systemic group and 7% in the implant group with ocular hypertension at enrolment had received at least one regional corticosteroid injection by 2 years.

Discussion

Uveitic macular edema may be identified by either fluorescein angiography, which detects physiological leakage, or by OCT, which measures anatomic thickening. As these modalities measure different manifestations of an underlying inflammatory process, there may be only a moderate correlation between the two, with macular leakage in the absence of retinal thickening and its converse, most often in eyes with good visual acuity.[4] Retinal thickness correlates better with visual acuity than fluorescein leakage, and so, OCT most often is used to document and follow macular edema.[25] In this analysis we chose to use OCT as the

primary measure, as eyes without thickening had good visual acuity at baseline and little to no ability to detect an improvement in acuity or edema. Our results suggest that with treatment, uveitic macular edema improves in ~70% of eyes and resolves in ~60% of eyes, without an evident difference between the implant and systemic therapy-assigned groups in the proportions either improving or resolving at 2 years of follow-up. However, on average, the fluocinolone acetonide implant was associated with a greater reduction in macular thickness on OCT than systemic therapy, suggesting that it may be more efficacious.

Although both treatment approaches result in control of the inflammation in the majority of patients, adjunctive regional corticosteroid injections within two years of randomization were needed for over 60% of eyes in the systemic treatment group and 25% in the implant group, suggesting that the need for adjunctive corticosteroid treatment should be expected in patients with intermediate, posterior and panuveitis and macular edema managed with systemic therapy. This difference is unlikely to reflect a practice pattern alone, given specifications of the protocol, the large number of clinical centers involved, and the very large difference between groups. However, the median number of injections was one, and only 25% of eyes in the systemic therapy group needed more than 2 adjunctive regional corticosteroid injections. Previous work on adjunctive intravitreal corticosteroid injections for uveitic macular edema suggested that in contradistinction to intravitreal corticosteroid therapy alone, those given intravitreal corticosteroid injections in addition to systemic therapy were much less likely to have the edema recur.[11] Our data on the limited need for repetitive injections in the systemic therapy group are consistent with these results.

Our evaluation of factors at presentation predictive of improvement in macular edema found that the only risk factor identified was leakage on the fluorescein angiogram at presentation. In the adjusted model, eyes with fluorescein angiographic leakage above the minimum threshold had 2.3-fold higher odds of experiencing improvement in the macular edema as those without it. The presence of leakage accompanying macular thickening may suggest a more active ongoing pathologic process, which is modifiable with therapy and is associated with a better prognosis. Although those without such leakage were less likely to experience improvement in macular edema, the majority (58%) did improve, suggesting that absence of fluorescein leakage should not dissuade clinicians from a trial of therapy for the macular edema.

Other morphological features of the edema, such as diffuse vs. cystoid edema, and presenting thickness of the macula, were not associated with different odds of improvement in the macular edema. In this study, epiretinal membranes were not associated with any difference in the likelihood of improvement of the macular edema, but the MUST Trial used time-domain OCT. One study of uveitic macular edema using spectral-domain OCT, which allows better resolution of retinal details, suggested that mild epiretinal membranes not associated with distortion of the retinal surface (“wrinkling”) do not affect the outcomes of treatment of uveitic macular edema, whereas membranes that produce such distortion do affect the outcome of medical treatment, suggesting that surgical intervention may be required.[26] The lower resolution of time-domain OCT, while sufficient for accurately determining macular thickness and the presence of cysts, did not permit this level of distinction.

We also evaluated factors associated with improvement in visual acuity among eyes with uveitic macular edema two years after randomization. These included improvement or resolution of the macular edema and the baseline factors of fluorescein leakage, presence of a cataract, and a lack of ocular hypertension. The resolution or worsening of macular edema is presumed to be directly related to the direct effects of macular edema itself on visual function, which is well-known to be the leading cause of visual impairment in uveitiscases.[1, 2] The presence of fluorescein leakage at baseline is consistent with its association with inflammatory macular edema, and in this study, the likelihood of improvement in the macular edema. However, even after adjusting for macular edema resolution or worsening, baseline fluorescein leakage was associated with a greater degree of improvement, suggesting that the physiological disorder leading to leakage may further amplify the effect of the macular edema process on vision, and is susceptible to improvement with treatment. In the adjusted model, eyes with a cataract at enrolment had a mean 9 letter better visual improvement at 2 years, likely due to the improvement seen with cataract surgery, as 76% of these eyes underwent cataract surgery by 2 years. The association of ocular hypertension at baseline with a poorer outcome may represent less aggressive use of injected corticosteroid therapy in this group so as to avoid corticosteroid-induced exacerbation of intraocular pressure elevation. The use of regional corticosteroid injections was not directly associated with visual outcome after adjustment, suggesting that its benefits on vision may have been mediated through its benefits on macular edema.

Strengths of the study include prospective collection of data as part of a randomized, comparative effectiveness trial, in which uveitic macular edema was an outcome of interest and there was planned, prospective OCT imaging at defined time points graded in a masked fashion by a reading center according to a well-defined protocol.[27] Limitations include a lack of stratification by macular edema status, such that imbalances in unknown variables in the two treatment groups could have confounded the comparative results. Nevertheless, the baseline characteristics between the two groups were similar, indicating that balance was achieved by randomization of recognized potentially associated factors, and in a study of this size, unknown confounders most likely would be balanced as well. The study has moderate power as some cells in the subgroup analyses are relatively small, resulting in relatively large confidence intervals in these analyses. As such modest risk factors could have been missed. Nevertheless, the analyses identified clinically important risk factors for improvement in macular edema and vision among participants presenting with macular edema at baseline. The analysis of the effect of fluorescein angiographic leakage was subject ot 17% missing data; however a sensitivity analysis did not alter the conclusion that it was related to the likelihood of improvement in macular edema on OCT. Finally the use of time-domain OCT, which was the “state-of-the art” at the start of the trial may, as noted above, missed differences identifiable with spectral-domain OCT, which is now in widespread use. Nevertheless, aside from potential difficulties in assessing the effect of associated epiretinal membrane on macular edema outcome, the primary outcomes of interest (macular thickening and the presence of cysts) are well-documented on time-domain OCT. [27]

In conclusion, our data suggest that the majority of eyes with uveitic macular edema will experience improvement in the edema with treatment and that the proportion of eyes with improvement in or resolution of the edema will be similar between those treated with

systemic therapy and those treated with the fluocinolone acetonide implant. The implant does appear to result in a bigger improvement in terms of reduction of the macular thickness. For eyes treated with systemic therapy, the majority will require adjunctive regional corticosteroid injections (which in this protocol would have been indicated for macular edema), but typically only one or two such injections. More than minimal fluorescein angiographic leakage at presentation is associated with a greater likelihood of improvement in the macular edema and improved visual outcome, but even without such leakage, the majority of eyes will experience improvement in the macular edema and in visual acuity with treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the Study Population of Cases of Intermediate, Posterior or Panuveitis with Uveitic Macular Edema from the Multicenter Uveitis Steroid Treatment (MUST) Trial at Baseline

Characteristic	Overall	Systemic Therapy	Implant therapy	P-value
Number patients	117	57	60	
Age (years)				0.76
Median	53	53	54	
25th, 75th percentile	40, 62	44,60	39, 66	
Gender (%)				0.10
Men	28	21	35	
Women	72	79	65	
Race/ethnicity				0.77
White, non-Hispanic	63	60	67	
African American	21	23	20	
Hispanic	10	11	10	
Other	5	7	3	
Smoking status (%)				0.55
Current	30	32	28	
Former	27	30	23	
Non-smoker	44	39	48	
Uveitis class stratum (%)				0.57
Intermediate uveitis	42	39	45	
Posterior uveitis/panuveitis	58	61	55	
Uveitis duration (years)				0.72
Median	4.4	4.0	4.4	
25th, 75th percentile	1.4, 9.9	1.3, 9.9	2.2, 9.8	
Bilateral macular edema (%)	27	26	28	0.84
Visual acuity (%)				
Bilateral worse than 20/40	41	44	38	0.58
Bilateral 20/200 or worse	5	5	5	1.00
Ocular characteristics				
Number eyes	148	71	77	
Macular edema type (%)				0.64
Cystoid macular edema	72	75	70	
Diffuse macular edema	28	25	30	
Center point macular thickness (μm)				0.44
Median	367	348	376	
25th, 75th percentile	284, 539	272, 503	289, 540	
Leakage on fluorescein angiogram (%)				0.42

Characteristic	Overall	Systemic Therapy	Implant therapy	P-value
Yes	57	62	52	
No	26	27	25	
Missing	17	11	23	
Epiretinal membrane on OCT (%)*	43	32	53	0.07
Lens status (%)				0.75
Phakic, clear	11	10	12	
Phakic, cataract	34	32	36	
Pseudophakic	53	55	51	
Aphakic	2	3	1	
Intraocular pressure (%)				
Ocular hypertension†	20	23	18	0.63
Glaucoma§	2	2	3	0.76
Visual acuity				
Median (letters)	63	63	62	0.35
Median (Snellen equivalent)	20/56	20/56	20/54	
25^{th}, 75^{th} percentile (letters)	45, 71	49, 70	40, 74	
Worse than 20/40 (%)	68	73	62	0.29
20/200 or worse (%)	15	13	17	0.55

*OCT = optical coherence tomography.

†Ocular hypertension = intraocular pressure ≥24 mm Hg or use of topical anti-glaucoma medications or prior glaucoma surgery.

§Glaucoma = presence or history of ocular hypertension and either glaucomatous disc changes or visual field loss.

Table 2

Outcomes of Uveitic Macular Edema at Two Years' Follow-up in the Multicenter Uveitis Steroid Treatment (MUST) Trial

Outcome	Overall	Systemic Therapy	Implant Therapy	P-value
Number patients	108	53	55	
Current therapy at 2 year visit				
Prednisone therapy (%)	32	57	9	<0.001
Prednisone median dose (mg/day)	0	4.5	0	<0.001
25th, 75th percentile prednisone dose	0, 5	0, 10	0, 0	
Immunosuppression (%)	34	64	5	<0.001
Implant in either eye (% patients)	53	11	93	<0.001
Regional corticosteroid injection in either eye since last visit (% patients)*	10	16	5	0.05
Visual acuity (%)				
Bilateral worse than 20/40	33	31	35	0.68
Bilateral 20/200 or worse	5	6	4	0.67
Ocular characteristics				
Number eyes	134	64	70	
Macular edema				
Improved (%)†	71	65	77	0.20
Resolved (%)‡	60	52	68	0.28
Improved, but not resolved (%)	11	13	9	
Persistent and not improved (%)	29	35	23	
Center point macular thickness (μm)				0.14
Median	210	236	184	
25th, 75th percentile	140, 313	167, 349	134, 263	
Change in center point thickness (μm)				0.04
Median	−125	−109	−180	
25th, 75th percentile	−312, −18	−211, −10	−384, −27	
Change in center point thickness (%)				
Median	−37	−32	−58	
25th, 75th percentile	−68, −6	−51, −4	−72, −11	
Leakage on fluorescein angiogram (%)				0.12
Yes	34	48	21	
No	45	31	58	
Missing	21	21	21	
Epiretinal membrane (%)	54	48	52	0.34
Lens status (%)				
Phakic, clear	2	5	0	

Outcome	Overall	Systemic Therapy	Implant Therapy	P-value
Phakic, cataract	12	20	4	
Pseudophakic	83	73	93	
Aphakic	2	2	3	
Intraocular pressure (%)				
Ocular hypertension§ during follow-up	45	32	56	0.05
Glaucoma¶	13	8	18	0.36
Glaucoma surgery	15	8	21	0.18
Visual acuity				
Median (letters)	68	67	68	0.86
Median (Snellen equivalent)	20/46	20/48	20/46	
25th, 75th percentile	53, 78	52, 78	56, 78	
Regional corticosteroid injections*				
Eyes with ≥ 1 injection (%)	43	62	25	0.07
Number injections				
Median	0	1	0	
25th, 75th percentile	0, 1	0, 2	0, 0.5	

*Regional corticosteroid injections include periocular (either by the posterior superior sub-Tenon's or orbital floor/retrobulbar route) or intravitreal (either triamcinolone or dexamethasone) injections.

†Improved macular edema = ≥20% decrease in or normalization of center point macular thickness.

‡Resolved macular edema = normalization of center point macular thickness (to less than 240 μm).

§Ocular hypertension = intraocular pressure ≥24 mm Hg or use of topical anti-glaucoma medications or prior glaucoma surgery.

¶Glaucoma = presence or history of ocular hypertension and either glaucomatous disc changes or visual field loss.

Table 3

Macular Edema Response among Cases of Uveitic Macular Edema in the Multicenter Uveitis Steroid Treatment (MUST) Trial, by Macular Edema Baseline Characteristics

Characteristic	Number	Improved (%)*	P-value	Resolved (%)†	P-value
Number patients	124				
Macular edema type			0.70		0.33
Diffuse	92	75		60	
Cystoid	32	59		59	
Fluorescein angiographic leakage			0.03		0.49
Yes	72	76		61	
No	33	58		55	
Epiretinal membrane on OCT			0.21		0.54
Present	52	69		56	
Absent	72	72		63	

*Improved macular edema = ≥20% decrease in or normalization of macular thickness.

†Resolution of macular edema = decrease in macular thickness to <240μm.[22]

Table 4

Factors Associated with Improvement in Macular Edema among Eyes with Uveitic Macular Edema in the Multicenter Uveitis Steroid Treatment (MUST) Trial

		Improved (%)*	Unadjusted			Adjusted††		
Risk factor	**Number**		**HR†**	**95% CI‡**	**P-value**	**HR†**	**95%CI‡**	**P-value**
Overall	124	71						
Age(years)								
<53	66	65	Ref**			Ref		
≥53	58	78	1.6	0.7, 3.8	0.30	2.2	0.8, 5.8	0.12
Gender								
Men	30	67	Ref			Ref		
Women	94	72	1.3	0.5, 3.5	0.53	1.4	0.5, 3.8	0.53
Race/ethnicity								
White, non-Hispanic	78	72	Ref			Ref		
African-American	24	71	0.9	0.3, 2.7	0.88	0.6	0.2, 2.2	0.49
Hispanic	15	67	0.6	0.2, 2.4	0.49	0.5	0.1, 2.1	0.33
Other	7	71	0.6	0.1, 3.6	0.54	1.1	0.1, 13.5	0.95
Smoking status								
Current	36	69	Ref			Ref		
Former	34	79	1.6	0.5, 5.2	0.47	1.3	0.3, 4.9	0.72
Non-smoker	67	67	1.0	0.4, 2.6	0.96	0.8	0.2, 2.8	0.75
Uveitis class stratum								
Intermediate uveitis	55	76	Ref			Ref		
Posterior /panuveitis	69	67	0.6	0.3, 1.5	0.28	0.9	0.3, 2.3	0.77
Treatment assignment								
Systemic therapy	62	65	Ref			Ref		
Implant therapy	62	77	2.0	0.8, 4.8	0.12	1.7	0.7, 4.4	0.27
Regional corticosteroids								
No injections	74	72	Ref			Ref		

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Risk factor	Number	Improved (%)*	Unadjusted			Adjusted††		
			HR†	95% CI‡	P-value	HR†	95%CI‡	P-value
≥1 injection	50	58	0.5	0.1, 2.1	0.38	0.5	0.1, 2.2	0.37
Macular edema type								
Diffuse	32	59	Ref			Ref		
Cystoid	92	75	1.2	0.5, 2.8	0.71	0.8	0.3, 2.5	0.76
Macular thickness								
<370 μm	65	65	Ref			Ref		
≥370 μm	59	78	1.6	0.7, 3.3	0.25	0.8	0.3, 2.2	0.71
Baseline fluorescein leakage								
No	33	58	Ref			Ref		
Yes	72	76	2.3	1.1, 4.9	0.03	2.3	1.1, 4.9	0.03
Epiretinal membrane								
Absent on OCT§	72	72	Ref			Ref		
Present on OCT	52	69	0.9	0.4, 2.1	0.75	0.8	0.3, 2.1	0.65
Lens status at enrollment								
Pseudophakic/Aphakic	69	75	Ref			Ref		
Phakic, clear	14	86	1.8	0.4, 9.2	0.46	1,5	0.3, 8.0	0.60
Phakic, cataract	41	59	0.5	0.2, 1.2	0.11	0.5	0.2, 1.3	0.16
Enrolment intraocular pressure								
Normal	95	69	Ref			Ref		
Ocular hypertension¶	28	75	1.4	0.6, 3.3	0.45	1.5	0.6, 3.8	0.42

*Improved macular edema = 20% decrease in or normalization of central subfield thickness.

†HR = hazard ratio.

‡95% CI = 95% confidence interval.

§OCT = optical coherence tomography.

¶Ocular hypertension = intraocular pressure ≥24 mm Hg or use of topical anti-glaucoma medications or previous glaucoma surgery, and includes those with disc changes or visual field loss.

**Ref = reference.

†† Adjusted models include control for leakage covariate.

Table 5

Factors Associated with Improvement in Visual Acuity among Eyes with Uveitic Macular Edema in the Multicenter Uveitis Steroid Treatment (MUST) Trial

		Unadjusted			Adjusted[¶]		
Risk factor	**Mean change in vision (letters)**	**Difference in change in vision (letters)**	**95% CI***	**P-value**	**Difference in change in vision (letters)**	**95%CI***	**P-value**
Overall	5		2, 9				
Age(years)							
<53	4	Reference			Reference		
≥53	6	2	−5, 9	0.62	2	−5, 9	0.53
Gender							
Men	7	Reference			Reference		
Women	4	−3	−10, 4	0.45	−3	−11, 5	0.50
Race/ethnicity							
White, non-Hispanic	5	Reference			Reference		
African-American	4	1	−9, 11	0.88	5	−2, 12	0.19
Hispanic	8	4	−3, 10	0.29	5	−1, 11	0.12
Other	8	4	−5, 12	0.40	2	−14, 18	0.80
Smoking status							
Current	10	Reference			Reference		
Former	6	−5	−15, 5	0.36	−5	−12, 2	0.20
Non-smoker	1	−9	−16, −2	0.02	−4	−15, 6	0.40
Uveitis class stratum							
Intermediate uveitis	9	Reference			Reference		
Posterior/panuveitis	2	−6	−13, 1	0.08	−4	−11, 3	0.26
Treatment assignment							
Systemic therapy	4	Reference			Reference		
Implant therapy	7	3	−4, 10	0.34	2	−5, 8	0.67
Regional corticosteroids							

		Unadjusted			Adjusted[¶]		
Risk factor	**Mean change in vision (letters)**	**Difference in change in vision (letters)**	**95% CI[*]**	**P-value**	**Difference in change in vision (letters)**	**95%CI[*]**	**P-value**
No injections	6	Reference			Reference		
≥1 injection	3	−3	−11, 6	0.53	−4	−11, 3	0.22
Macular edema type							
Diffuse	−1	Reference			Reference		
Cystoid	7	6	−2, 15	0.12	4	−3, 10	0.27
Baseline macular thickness							
<370 μm	3	Reference			Reference		
≥370 μm	8	5	−0.3, 11	0.07	−1	−6, 4	0.78
Baseline fluorescein leakage							
No	0	Reference			Reference		
Yes	6	6	−2, 14	0.12	7	2, 12	0.01
Baseline epiretinal membrane							
Present on OCT[†]	5	Reference			Reference		
Absent on OCT	5	0	−6, 7	0.99	0	−4, 5	0.85
Macular edema response[‡]							
Resolved	10	Reference			Reference		
Improved, not resolved	10	0	−9, 8	0.92	0	−8, 8	0.99
Little to no change	6	−4	−10, 2	0.19	−1	−8, 5	0.67
Worsened	−16	−26	−40, −12	0.0003	−26	−39, −14	<0.0001
Baseline lens status							
Pseudophakic/aphakic	2	Reference			Reference		
Phakic, clear	15	13	1, 24	0.04	6	−3, 15	0.17
Phakic, cataract	7	5	−4, 14	0.29	9	1, 16	0.03
Baseline ocular pressure status							
Normal	7	Reference			Reference		
Ocular hypertension[§]	5	−2	−8, 5	0.63	−7	−13, −1	0.03

[*] 95% CI = 95% confidence interval.

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[†] OCT = optical coherence tomography.

[‡] Resolved = normalization of central subfield thickness (≤240 μm). Improved, not resolved = ≥20% decrease in central subfield thickness but persistently abnormal central subfield thickness. Little or no change = <20% decrease or increase in central subfield thickness. Worse = ≥20% increase in central subfield thickness.

[§] Ocular hypertension = intraocular pressure ≥24 mm Hg or use of topical anti-glaucoma medications or history of glaucoma surgery.

[¶] Adjusted models include controlling for macular edema resolution category, cataract surgery, and leakage covariates.