

MUST Beg to Differ

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ABSTRACT: The authors provide a significant interpretation of the National Eye Institute-sponsored Multicenter Uveitis Steroid Treatment study, in which patients with severe, non-infectious intermediate, posterior, or panuveitis were randomly assigned to receive local treatment using the sutured intravitreal fluocinolone acetonide implant or systemic treatment consisting of oral steroids and conventional steroid-sparing immunosuppression, with a primary outcome of visual acuity at 2 years of follow-up. The authors also present evidence-based guidance for the treatment of noninfectious posterior segment involving uveitis.

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In the National Eye Institute-sponsored Multicenter Uveitis Steroid Treatment (MUST) study, patients with severe, non-infectious intermediate, posterior, or panuveitis were randomized to receive local treatment, using the sutured intravitreal fluocinolone acetonide implant (Retisert; Bausch + Lomb, Rochester, NY), or systemic treatment, consisting of oral steroids and conventional steroid-sparing immunosuppression. The primary outcome was visual acuity (VA) at 2 years of follow-up. The study group continued to follow enrolled subjects for a total of 7 years.¹⁻³ The published 7-year follow-up study concluded that systemic treatment was superior in efficacy and safety compared to the implant. However, there remain some significant considerations that weaken this conclusion and support the continued use of the implant in many patients. Although the study suggests that the implant be used as a second-line treatment, there is a substantial case to be made that, given the available data, the implant is still a reasonable option for first-line therapy. Individual patient features and circumstances may make the implant a better choice, such as potential side-effects of systemic therapy, patient desire for pregnancy, patient prejudice against systemic therapy, and the complexity and number of systemic agents required to control a particular patient's ocular inflammation.

The sutured fluocinolone implant was U.S. Food and Drug Administration-approved for the treatment of non-infectious intermediate, posterior, and panuveitis in 2005. It was designed to release a steady concentration of fluocinolone

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acetonide into the eye for up to 36 months.⁴ Although it was predictable that the implant would exhibit the anticipated complications of local steroids (ie, cataract, ocular hypertension and glaucoma), it was not clear whether sustained local steroid delivery would be as effective as systemic immunosuppression in preserving vision and decreasing inflammation.

The MUST study was groundbreaking as it was the largest prospective uveitis comparative study that included an arm with standard real-world treatment and was designed to answer an important question in the management of uveitis patients: “Is there a significant difference in VA with long-term follow-up of treatment with an [intravitreal] fluocinolone acetonide implant or systemic anti-inflammatory therapy for severe intermediate, posterior, or panuveitis”?¹ The methodology planned a 2-year study end-point² with VA as the primary outcome measure. The study was powered to see a 7 ETDRS letter difference in the primary outcome at 2 years. Several secondary efficacy outcome measures including uveitis activity and macular edema were also reported. The primary study outcome at 2 years, published in 2011, reported no significant difference in VA or quality of life or systemic safety between the two arms.³ Uveitis activity was higher in the systemic arm than in the implant arm at year 2 (33.7% active in the systemic arm vs. 13.7% active in the implant arm; $P < .001$). There was a tendency for better control of macular edema in the implant arm, but this advantage did not reach statistical significance. Local safety, especially the risk of cataracts and ocular hypertension, strongly favored systemic therapy. The authors insightfully recommended that the treatment should be tailored to the patient and circumstances. Although systemic therapy remained the primary treatment modality for most patients with uveitis with posterior segment involvement, the implant seemed to provide an equally effective therapeutic option for patients who failed and/or were intolerant of systemic therapy.

Subjects from the primary 2-year study were later followed in an observational study, and the 4.5-year efficacy and safety data were published in 2015 that supported the initial study results.⁵ In 2017, the MUST study group published a non-prespecified 7-year observational follow-up study that differed from the prespecified study outcome conclusions with the authors reporting, “after 7 years, systemic corticosteroids and immunosuppressive therapy was associated with better VA compared with the fluocinolone acetonide implant.”¹

The MUST study was not designed to evaluate 7-year outcomes. Scheduled reimplantation of the fluocinolone delivery system beyond the projected drug delivery duration (ie, 36 months) was not predetermined.

Clinicians decided when and if a second implant needed to be placed. At the conclusion of the extended 7-year follow-up period, subjects randomized to receive systemic therapy had 7 ETDRS letters better VA and better inflammatory control than those randomized to receive the fluocinolone acetonide implant. However, very few of the participants in the implant arm of the 7-year observational MUST study had a second implant placed, even though the implant delivers drug, on average, for approximately 3 years.⁶ At year 2, the majority of eyes randomized to the implant arm (85%) had an implant placed within 3 years (ie, an implant that was likely releasing steroid). By contrast, at 4.5 and 7 years, only 15% and 27%, respectively, of eyes in the implant arm had an implant placed in the preceding 3 years. Consequently, a significant majority of implants were likely not releasing corticosteroid in the second half of the 7-year study. At 7 years, in the systemic treatment arm, 64% of patients had received some form of treatment in the preceding 6 months, and there were increasing numbers of systemic-therapy-assigned eyes requiring implants during the 7 years presumably due to need for improved local control of inflammation (five eyes required two implants in the systemic arm); on the other hand, only 27% of patients in the implant arm had received an implant in the preceding 3 years, and additional systemic treatment in the implant group typically began only after around 5 years.

Why did patients in the implant arm not receive a second implant after the first implant was no longer functioning? One possibility is that they were free from inflammatory activity and did not require a second implant for the duration of the 7-year observational study. This appears to be the case for some implant patients at 54 months, but by years 6 and 7, the percentage of eyes in the implant arm with VA worse than 20/200, uveitis activity, and/or macular edema greatly increases. Alternative hypotheses include the following: practical barriers to payment for the implant restricted its use, surgeons and/or patients did not feel comfortable placing a second implant, and/or removing the first implant, until it was absolutely necessary. According to the MUST study protocol, the implant was not replaced until there was reactivation, however, it may be this period of active inflammation that resulted in irreversible vision loss.

Smaller, long-term series of eyes treated with the fluocinolone acetonide implant suggested recurrences often occur after 3 years, when the implant is no longer releasing steroid.⁶ An interpretation of the observational 7-year MUST data is that when the implant stops releasing steroid, patients may flare and have a worse outcome. Back to the original question, “Is there a significant difference in VA with long-term follow-up of treatment

with [intravitreal] fluocinolone acetonide implant or systemic anti-inflammatory therapy for severe intermediate, posterior or panuveitis?” Yes, at 7 years after only a single 3-year implant in 75% of eyes in the implant arm, the systemic therapy arm does better. Should eyes be reimplanted more frequently? This question remains unanswered. The observational MUST study unfortunately cannot evaluate how these eyes would have done had the eyes received regular, scheduled implantation to maintain functioning implants. Only the 2-year primary study endpoint truly addresses this question and thus should remain the conclusion of the MUST study.

The totality of the efficacy data available from the MUST study should be interpreted with perspective. On the one hand, the implant performed as well as systemic therapy in the first 2 years; there was no difference in the primary outcome at 2 years between those receiving systemic therapy and those who received an implant. On the other hand, when the intent-to-treat groups were followed out to 7 years, the VA among eyes in the systemic arm group was 7 ETDRS letters better. Should the finding at 7 years overturn the finding of the primary outcome? The reasons for prespecifying a clinical trial’s primary outcome are well understood; however, the value of examination of secondary outcomes is also recognized.⁷ Multiple observational data analyses, as were performed in the MUST study at years 4.5 and 7, can lead to chance findings of significance. However, we do not believe that the highly significant result found by the MUST investigators at the 7-year outcome, in contrast to the prespecified 2-year outcome, is a matter of multiple testing or type I error. Rather, we believe that the superiority of systemic therapy found at year 7 is a consequence of the inability of the MUST protocol to determine the efficacy of re-implantation with the fluocinolone implant after the initial study implant ceased releasing drug. Pre-emptive reimplantation may have had better results.

The 7-year follow-up had impressive enrollment and retention. Approximately 70% for each arm completed the 7-year follow-up. The study also offers an important perspective on the complexity of managing uveitis patients and the difficulty of real-world implant use. As for safety, both the 2-year data and the 7-year observational data demonstrate the safety of appropriately used systemic immunosuppression: other than a higher number of infections requiring antibiotic prescriptions in the systemic arm, no more adverse effects such as hypertension, hyperlipidemia, and fractures were observed in the systemic arm as compared to the implant arm. In contrast, the implant had more local complications that were vision-threatening and required secondary interventions, most notably, cataract and ocular hypertension. The 7-year efficacy and safety data on the systemic treatment of posterior segment noninfectious

uveitis are invaluable because they mirror closely what is done in the “real world.” When electing to undergo local treatment patients and physicians need to consider the potential practical hurdles and surgical risks involved with implant exchange or reimplantation. Failure to treat after the implant ceases to release drug may lead to poor outcomes.

When reviewing this publication, we “MUST” beg to differ with the conclusions drawn in the observational follow-up MUST study. The 7-year observational study is perhaps better-suited to generate hypotheses than to overturn the primary finding of the original 2-year study, and the observational study was not designed to answer the question of whether 7-year treatment with functioning implants is better than 7 years of systemic therapy. The implant had similar visual outcomes and better control of inflammation in the first 2 years, with significantly worse local complications. Thus, the 7-year data unfortunately are much harder to interpret. Scheduled implant replacement would have better answered the study question than a replace-after-reactivation strategy. Clinicians who treat posterior segment involving noninfectious uveitis are justified in considering a sustained release fluocinolone implant as an option in selected patients based on the primary outcomes at 2 years. The extended observational data suggest that sustained treatment, whether local or systemic, may be required to preserve early VA gains. Future local therapeutic options will hopefully improve on efficacy and safety.

REFERENCES

1. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group, Kempen JH, Altaweel MM, et al. Association between long-lasting intravitreal fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. *JAMA*. 2017;317(19):1993-2005.
2. Multicenter Uveitis Steroid Treatment Trial Research (MUST) Group, Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: Rationale, design, and baseline characteristics. *Am J Ophthalmol*. 2010;149(4):550-561.e10.
3. Multicenter Uveitis Steroid Treatment Trial (MUST) Research Group, Kempen JH, Altaweel MM, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: The multicenter uveitis steroid treatment trial. *Ophthalmology*. 2011;118(10):1916-1926.
4. Jaffe GJ, Yang CH, Guo H, Denny JP, Lima C, Ashton P. Safety and pharmacokinetics of an intraocular fluocinolone acetonide sustained delivery device. *Invest Ophthalmol Vis Sci*. 2000;41(11):3569-3575.
5. Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group, Kempen JH, Altaweel MM, et al. Benefits of systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate uveitis, posterior uveitis, and panuveitis: Fifty-four-month results of the Multicenter Uveitis Steroid Treatment (MUST) trial and follow-up study. *Ophthalmology*. 2015;122(10):1967-1975.
6. Jaffe GJ. Reimplantation of a fluocinolone acetonide sustained drug delivery implant for chronic uveitis. *Am J Ophthalmol*. 2008;145(4):667-675.
7. SJ Pocock, GW Stone. The Primary Outcome Fails – What Next? *N Engl J Med*. 2016; 375:861-870.