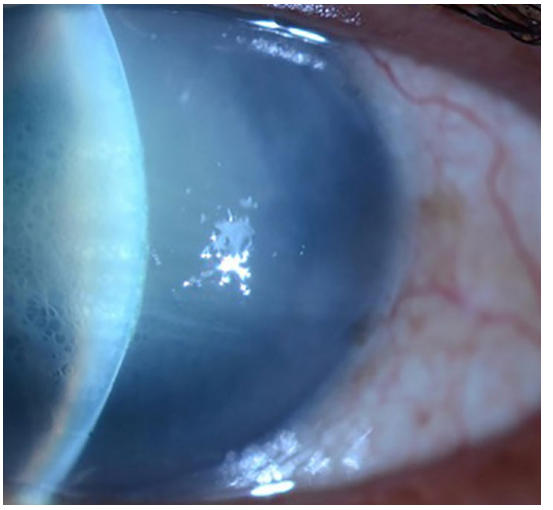
News in Review

COMMENTARY AND PERSPECTIVE



CORNEAL EDEMA. *Reticular corneal epithelial edema in a patient with preexisting corneal haze. The edema developed shortly after the patient began treatment with netarsudil.*

CORNEA

Rho Kinase and Corneal Edema

RESEARCHERS AT MASSACHUSETTS Eye and Ear (MEE) in Boston have added to a small but growing body of case reports in which patients developed reticular corneal epithelial edema following treatment with netarsudil (Rhopressa; Aerie).[1] In keeping with earlier reports, all cases fully resolved after the patient discontinued the topical rho kinase inhibitor, which was approved by the FDA in 2017 for use as an IOP-lowering drug for patients with ocular hypertension and open-angle glaucoma.

This report is the first to provide photographic evidence of how the unique reticular honeycomb pattern of edema resolves over time, as individual bullae become smaller and more widely spaced apart.

Retrospective results. All but one of eight cases of netarsudil-induced edema identified in the MEE database had corneal conditions or procedures that predisposed them to develop the edema, including penetrating keratoplasty (PK), corneal decompensation after trabeculectomy-associated endophthalmitis, and Fuchs endothelial corneal dystrophy undergoing Descemet stripping only.

Onset of most instances of the edema was within weeks after initiating netarsudil. However, the researchers also documented a previously unreported phenomenon in which two patients tolerated the medication for months but then developed the edema on post-op day 1 following diode laser cyclophotocoagulation. In another finding, anterior segment OCT imaging revealed that in eyes with a history of PK, reticular corneal epithelial edema affected both host and donor cornea simultaneously.

The chart review also revealed a paradoxical lowering of IOP after stopping netarsudil.

Clinical implications. The true rate of netarsudil-associated reticular epithelial edema is unknown, but the majority of patients who use netarsudil do not develop the condition, said Michael Lin, MD, and his coauthors.

In addition, although it is known that netarsudil lowers IOP by increasing aqueous outflow through the trabecular meshwork and decreasing episcleral venous pressure, the mechanism behind the development of reticular corneal epithelial edema in patients who use netarsudil remains unclear.

And the study has not significantly affected Dr. Lin's decision to prescribe netarsudil for some glaucoma patients who need lower IOP, he said. "Unless patients have preexisting corneal issues, I am not especially concerned about them developing reticular corneal epithelial edema."

Although insurance coverage initially limited netarsudil to use as a last resort, Dr. Lin said, some ophthalmologists are prescribing the drug earlier in selected cases of glaucoma. This is particularly true for those patients who have difficulty using other medications that require dosing multiple times per day, and for those whose glaucoma is believed to be primarily caused by trabecular meshwork dysfunction.

Advice to clinicians. Dr. Lin reexamines all patients after they've started netarsudil. He also counsels patients about potential conjunctival injection, which may occur with the medication.

He added, "Given the findings of this study and others, ophthalmologists may want to avoid netarsudil in patients with compromised corneas—although they could potentially still try the medication and then stop it if reticular corneal epithelial edema develops."

For his part, Dr. Lin said, if he sees that a patient has developed the condition, "I'll likely stop the netarsudil and expect full recovery." —*Miriam Karmel*

1 Tran JA et al. *Am J Ophthalmol Case Rep.* Published online Jan 20, 2022.

Relevant financial disclosures: Dr. Lin—None.

Michael Lin, MD

RETINA

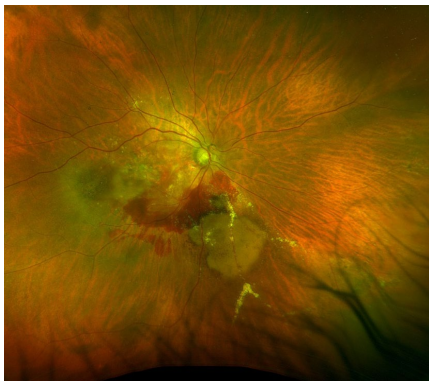
Reducing Errors Related to Intravitreal Injections

HOW OFTEN DO PATIENT SAFETY issues occur with intravitreal injections in your practice? Researchers at the Mayo Clinic in Rochester, Minnesota, set out to determine the root cause of injection-related safety events in their high-volume clinic—and they developed a plan that significantly reduced the risk of these medical errors.[1]

"It's easy to assume errors do not occur in your own practice," said Sanjay V. Patel, MD, FRCOphth, lead author of the study. "But the frequency of events in a practice is probably underestimated until they are actually tracked in a transparent manner."

Tracking errors. For three years, the researchers tracked events in the clinic's database that were documented as "never events" (i.e., medical errors that are clearly identifiable, preventable, and serious) or "near misses." The former included wrong eye, wrong medication, and wrong patient scenarios. The latter occurrences might have resulted in a never event if they had been missed.

Creating a plan. A safety plan was implemented based on the findings. The plan reflected the Mayo Clinic's model, in which the injecting physician usually is not the prescribing physician,



RISK REDUCTION. *Intravitreal injections for conditions such as neovascular age-related macular degeneration (shown here) have become a common ophthalmic procedure. Site marking and dual verification can reduce the risk of injection-related medical errors.*

ONCOLOGY

Predicting Risk of Metastasis in Uveal Melanoma

GENOMIC TESTING FOR COPY NUMBER ABERRATIONS (CNAs) at diagnosis is used to predict the risk of metastasis in patients with uveal melanoma (UM). However, UM is a rare disease, and small cohort sizes hinder the identification of infrequent CNAs that have prognostic ability. Researchers from the University of Pennsylvania performed a large-scale genome-wide analysis of CNAs and identified deletions in chromosomes 1p and 16q as low-frequency CNAs associated with an increased risk of metastasis in patients with UM.[1]

"Our findings suggest that, although 1p and 16q deletions are uncommon, they strongly increase the risk of metastasis in patients with UM," said Arupa Ganguly, PhD. She added that testing for deletions in chromosomes 1p and 16q should be incorporated into clinical practice to identify patients who are at a high risk of metastasis. "Knowing this information is key for optimization of clinical management."

Study rationale. CNAs in chromosomes 1p, 3, 6, and 8 can be used to assess prognosis in patients with UM. However, identifying low-frequency CNAs with prognostic value is challenging because of the rarity of UM. "To identify low-frequency CNAs with prognostic value, we conducted genome-wide CNA profiling of 921 primary tumors and 19 metastatic tumors from patients with UM," Dr. Ganguly said. The patients were referred to the University of Pennsylvania for genetic testing between 2008 and 2016.

Low-frequency prognostic CNAs. "Although aberrations in 16q have been previously reported in UM, their prognostic ability remained unclear," Dr. Ganguly pointed out. "By profiling CNAs in a large cohort of patients, we were able to confirm the prognostic significance of 16q deletion, which was associated with a high risk of metastasis." Although 16q deletion was observed in only 9.3% of patients, patients with this CNA had the worst outcomes.[1]

New molecular subtypes. Traditionally, UMs are classified into four molecular subtypes using standard prognostic CNAs. However, inclusion of chromosome 16q deletion revealed a rare but clinically relevant molecular subtype that cannot be captured by standard CNAs. "Analyzing a large number of tumors enabled us to uncover additional genomic drivers of UM and improve the accuracy of molecular tumor subtypes," Dr. Ganguly said.

Identification of an ultra–high-risk patient group. By analyzing outcomes in a large cohort of patients with UM, the researchers were able to identify a small subgroup of patients who had a very high rate of metastasis, Dr. Ganguly said. Primary tumors from these patients harbored chromosome 3 monosomy, chromosome 8q amplification, and 1p or 16q deletion. "Although this subpopulation of patients represents less than 10% of the entire cohort, the four-year metastasis rate in this group is nearly twice as high as the rate in the second-highest risk group," she said.

Next steps. The findings need to be clinically validated in large multicenter studies, Dr. Ganguly said. "We also plan to conduct mechanistic studies to assess how CNAs contribute to metastasis in UM," she added.

—Christos Evangelou, PhD

1 Lalonde E et al. *Ophthalmol Sci.* 2022;2:100121.

Relevant financial disclosures: Dr. Ganguly—None.

and injections and outpatient retina care are delivered in separate settings.

The plan called for the following: 1) standardized documentation to reduce ambiguity and simplify interpretation of the treatment plan; 2) scheduled time for injecting physicians to review the prescribing physician's treatment plans; and 3) a designated nurse or technician to verify treatment plans and serve as liaison between the retina and injection clinics. The plan also required wristbands to be affixed prior to patient handover for injection.

Before and after. At baseline, the rate of all events was 0.1% (28 of 27,400 intravitreal injections; 9.3 events per year). Three were never events that involved the wrong eye; the remaining 25 were near misses related to laterality (n = 11), medication (n = 10), and timing of injection (n = 4). No events were associated with patient harm.

After plan implementation, the rate of all events dropped to 0.01% (1 of 9,375 intravitreal injections). While the baseline frequency may appear low, it amounted to almost one event per year, said Dr. Patel. Although most of these events were near misses, Dr. Patel noted that low frequency events can still translate into high absolute numbers for high volume procedures.

Safety tips. Dr. Patel acknowledged that most practices administer injections as they see patients in outpatient clinics. Thus, there may be minimal gap between decision-making and the procedure. Still, he said, every practice can require site marking as well as dual verification of the treatment plan. This is especially true if there's a gap, no matter how small, between the physician making the treatment decision and the one performing the procedure, he said.

At a minimum, Dr. Patel advised simply addressing the topic. "All practices should discuss the potential for errors with injections to raise awareness and promote a culture of safety."

—Miriam Karmel

1 Patel SV et al. *Ophthalmol Retina.* Published online Feb. 10, 2022.

Relevant financial disclosures: Dr. Patel—None.

UVEITIS

Chronic Macular Edema: FAST Study Update

THE ANTIMETABOLITE DRUGS METH-otrexate (MTX) and mycophenolate mofetil (MMF) are commonly used as corticosteroid-sparing treatments for uveitic macular edema. But how do these treatments compare—and are they adequately effective? A clinical trial and subanalysis led by researchers at the University of California, San Francisco (UCSF) may help to answer these questions.

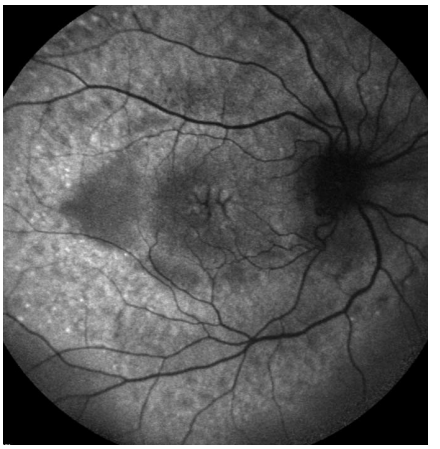
The head-to-head FAST (First-line Antimetabolites as Steroid-sparing Treatment) study found MTX and MMF to be similarly effective in the treatment of uveitis and uveitic macular edema.[1] However, a recent subanalysis of FAST data has found that about half of all patients still had macular edema after 12 months.[2]

"We found comparable improvement and resolution of macular edema and improvement in visual acuity in both treatment groups, but approximately half of the patients had persistent edema after treatment," said Nisha R. Acharya, MD, MS, at UCSF.

FAST basics. The multicenter FAST study was conducted to compare the efficacy of MTX versus MMF in uveitis. The researchers enrolled 216 patients who had noninfectious intermediate uveitis, posterior uveitis, or panuveitis. Patients were randomized to receive 25 mg of MTX weekly or 1.5 g of MMF twice daily for 12 months. A corticosteroid taper also was used.

All patients were assessed regularly using OCT and clinical exams. At six months, patients who achieved treatment success continued the same treatment, and those who failed treatment were switched to the other antimetabolite.

Subanalysis: A troubling surprise. At 12 months, median macular thickness in patients who stayed on the same treatment decreased from baseline by 23 µm in those treated with MTX and 18 µm in those who received MMF (p = .76). Resolution of macular edema was observed in 37% of eyes in the MTX group, versus 60% of eyes in the MMF group at 12 months (p = .10). Of those who switched treatments after six months, 47% of eyes on MTX and 55% of eyes on MMF had improvement of their macular edema at 12 months (p = .92).



PERSISTENT. *Macular edema in the right eye of a 17-year-old boy with chronic intermediate uveitis.*

"I expected both treatments would lead to improvement in macular edema and vision, and we found that. However, the finding that approximately 50% of patients had persistent edema was striking," Dr. Acharya noted.

Bottom line. Dr. Acharya emphasized the importance of treating macular edema effectively, as it is a frequent cause of vision loss in uveitis patients. And the FAST results, as well as those from other research, suggest that "we may need to escalate or use additional adjunctive treatments to fully treat uveitic macular edema," she said. Of note, she also recommended using OCT in the clinic to both detect and monitor macular edema in patients with uveitis.

—Patricia Weiser, PharmD

1 Rathinam SR et al, for the FAST Research Group. *JAMA.* 2019;322(10):936-945.

2 Tsui E et al, for the FAST Research Group. *Ophthalmology.* Published online Feb. 8, 2022.

Relevant financial disclosures: Dr Acharya—NEI: S.

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.