METHOTREXATE: AN EMERGING SURGICAL ADJUVANT

This drug is proving useful for improving outcomes in many retinal pathologies.

By Alan J. Franklin, MD, PhD; Lauren Gibson Snellings, MD; Aly Nguyen, MD; and Christopher Riemann, MD

As a resident, I (A.J.F.) assisted Thomas K. Krummenacher, MD, on a proliferative vitreoretinopathy (PVR) case, and he remarked that we were treating a microscopic disease with macroscopic surgical instruments. This statement really resonated with me. Despite the advent of small-gauge, high-speed instruments and improved visualization in the retina OR since that time, instrumentation remains a macroscopic approach to pathologies that have biological processes that drive disease on a microscopic level.

PVR occurs in 5% to 10% of all retinal detachment (RD) surgeries but accounts for 75% of RD surgery failures.[1] Similarly, eyes with significant posterior segment trauma or eyes with advanced proliferative diabetic retinopathy (PDR) are also at significantly higher risk for postoperative PVR and poor outcomes.[2-4]

Until better therapies become available to target these microscopic processes as pharmacosurgical adjuncts, our success as vitreoretinal surgeons will be limited.

A PHARMACOSURGICAL APPROACH ALREADY HERE

Multiple pharmacologic interventions, such as steroids, antineoplastic agents, colchicine, and retinoic acid, have attempted to establish superiority over surgical interventions to manage PVR without convincing results.[5] However, a novel form of intravitreal methotrexate (MTX) showed a reduction in PVR development and its subsequent complications, both in vitro and in vivo.[6,7] A phase 1b trial also demonstrated that the use of postoperative intravitreal MTX was associated with a reduction in recurrent RD in patients who underwent surgical repair due to PVR or trauma.[6] The pivotal phase 3 GUARD trial found that the use of intravitreal MTX reduced the reoperation rate following surgery for rhegmatogenous RD by 35% to 40%.[8]

Thus, intravitreal MTX is becoming an integral part of our surgical armamentarium to treat RD, trauma, and PDR to prevent recurrent fibrotic proliferation in the posterior segment after vitrectomy.[2,3,9]

The safety and efficacy of intraocular MTX (which costs approximately $4 a dose) has been well-established in the treatment of primary intraocular lymphoma and refractory uveitis. Intraocular MTX can be administered as a 200 µg to 400 µg intravitreal injection or an intraoperative infusion of 40 mg in a 500 cc balanced salt solution bottle.

AT A GLANCE

- A novel form of intravitreal methotrexate (MTX) after retinal detachment repair showed a reduction in proliferative vitreoretinopathy development and its subsequent complications.
- The safety and efficacy of intraocular MTX have been well-established in the treatment of primary intraocular lymphoma and refractory uveitis.
- Interim findings from the FIXER trial show that patients receiving both intraoperative MTX infusion and postoperative MTX injections have had no reoperations 3 months postoperatively.

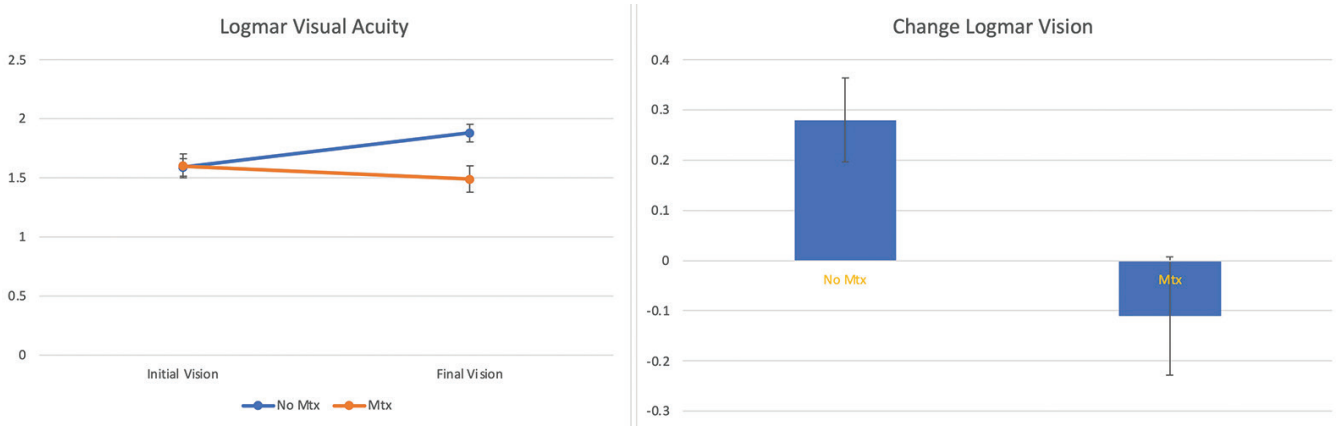

Figure 1. Change in visual acuity after vitrectomy for patients who did or did not receive postoperative MTX. For all patients, the average vision difference was > 3 lines between treated and untreated ($P < .01$).[10]

RECENT MTX DATA

To further explore the utility of MTX in retinal surgery, we performed a retrospective study of 255 patients with complex RDs, either rhegmatogenous RD with large retinal breaks or PVR, as well as patients with advanced PDR or trauma. Our protocol included three to five injections at weeks 1, 2, 4, 7, and 11 postoperatively with a dose of 200 µg. Our primary endpoint was safety, and we also examined the reoperation rate, change in visual acuity, central retinal thickness, and presence of epiretinal membrane.[10]

We found a 57% reduction in the reoperation rate and a 175% higher chance of single-operation success rate for patients who received postoperative MTX injections. Moreover, postoperative MTX led to an average of a 1-line gain in vision compared with an average of 3 lines lost for those who didn't receive injections. Postoperative MTX injections also significantly reduced the risk of a 3-line vision loss, and there was a trend to increase the chance of a 3-line visual recovery. Overall, the injections have been well-tolerated with a less than one in 1,000 risk of post-injection inflammation. In addition, we did not encounter frequent keratopathy as noted with previous studies.[8] Keratopathy incidence was similar in both the study and control eyes.

The Cincinnati Eye Institute had a similar positive experience with MTX and has been using MTX in the setting of PVR as an intraocular infusion since 2006 and as postoperative injections since 2008. Although multiple other groups have reported favorable experiences with MTX for PVR, level one evidence supporting these almost universally positive clinical impressions is lacking.[11,12]

FINDING THE RIGHT PROTOCOL

Given these positive findings, two critical questions remain: 1) Is the best dosing strategy intraoperative MTX infusions, postoperative MTX injections, or both? and 2) Can this drug prevent PVR by administering it in the setting of primary RD repair?

To answer these questions, we initiated the Prevention of ProliFerative Vitreoretinopathy with Intravitreal MethotreXate in Primary Retinal DEtachment Repair (FIXER) trial (NCT06541574). This prospective, multicenter, double-masked phase 2b/3a study is being conducted at three sites in the Cincinnati area. We are randomizing patients with primary RD of less than 6 weeks duration into four arms: 1) intraoperative MTX infusions; 2) postoperative MTX injections on weeks 1, 3, 6, and 10; 3) both intraoperative MTX infusions and postoperative MTX injections; and 4) neither. The primary endpoints at 12 months include the attachment rate at 6 months, the reoperation rate, visual acuity at 12 months, the incidence of epiretinal membrane (ERM), and the incidence of grade C PVR.

Reoperations for missed or new breaks are managed with the same randomization strategy. Reoperations due to PVR were given with MTX rescue therapy.

We have randomized 177 patients to date with excellent follow-up and very little dropout. We recently performed a preplanned safety analysis on the first 107 patients to have reached the 3-month follow-up (Figures 1 and 2). This was first presented at the 2025 annual meeting of the American Society of Retina Specialists in Long Beach, California.[13] Demographics, preoperative examination findings, and surgical details were well-balanced across all groups. Looking at the whole cohort, RD, PVR, and ERM increased over time as expected. Currently, patients receiving combined MTX infusions and MTX injections are doing much better than patients receiving either intervention alone, and all patients who are receiving any intervention are doing better than controls. This correlates to an impressive difference in reoperation rates; in fact, patients receiving both intraoperative MTX infusion and postoperative MTX injections have had no reoperations.

So far, this retrospective study suggests three to five intravitreal MTX injections benefit patients after vitrectomy for advanced PDR, trauma, or complex RD in terms of both anatomic and functional biomarkers.

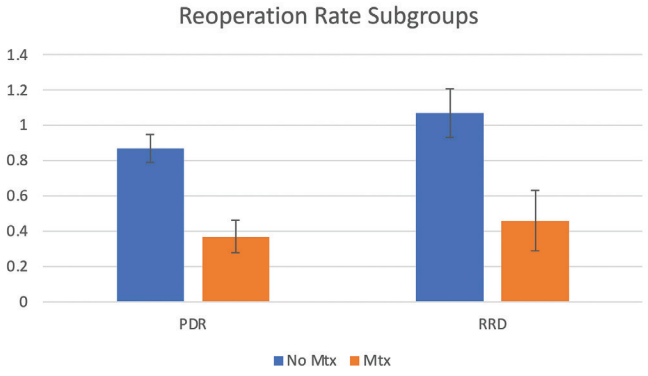

Figure 2. The number of reoperations was reduced by 57% in patients who received postoperative MTX injections compared with those who did not ($P < .01$). This reduction was similar for patients with both PDR and rhegmatogenous RD ($P < .01$). Patients who received MTX injections had a 72% chance of requiring only one operation compared with a 41% single-operation rate for those who did not receive injections ($P < .01$).[10]

THE CHANGING WINDS OF PHARMACOSURGICAL APPROACHES

Many other adjunctive therapies are being developed that include acetyl-salicyclic acid, colchicine, corticosteroids, daunorubicin, 5-fluorouracil, heparin, infliximab, and retinoic acid.[14] The multitude of treatments under investigation underscores the current unmet need for improving surgical outcomes and signals the progress and interest in emerging pharmacosurgical approaches. Research continues to support intravitreal MTX injections as a surgical adjuvant that can positively influence our surgical outcomes.

More than 20 years ago, we could only treat neovascular ocular disease with destructive laser. Anti-VEGF therapy targeting a biochemical pathway represented a monumental change in our ability to influence these pathologies. Intravitreal pharmacosurgical adjuvant therapy is now at a similar stage and is poised to change the treatment paradigm for surgical retinal diseases. ■

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INTRAVITREAL METHOTREXATE IS BECOMING AN INTEGRAL PART OF OUR SURGICAL ARMAMENTARIUM TO TREAT RD, TRAUMA, AND PDR.

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