



PVR Pipeline Roundup

At ASRS 2023, experts discussed two medical therapies under investigation.

BY ALEX BRODIN, ASSOCIATE EDITOR

Proliferative vitreoretinopathy (PVR) is a well-known vision-threatening complication of rhegmatogenous retinal detachment (RRD) and a common cause of RRD repair failure. The incidence of PVR in all cases of RD is estimated to be between 5% and 10%,¹ and it is implicated in 50% to 75% of cases of redetachment after surgery.² These data underscore a serious unmet clinical need to appropriately treat this condition; however, research is still ongoing as far as the best way to prevent and manage PVR. To further heighten this sense of urgency, visual outcomes with PVR can be quite poor, even with anatomic success.³ Standard PVR treatment typically involves performing additional surgery. Although multiple adjunctive therapies have been used to try to prevent or treat PVR, there is still no FDA-approved medication for the management of this condition.

This year at the American Society of Retina Specialists (ASRS) annual meeting, speakers shared clinical trial updates on two therapeutics used in combination with surgical intervention that are attempting to address this unmet need. This article highlights the findings and takeaways shared at the meeting.

METHOTREXATE

Christina J. Flaxel, MD, presented results from the randomized, multicenter phase 3 GUARD trial (NCT04136366) evaluating the safety and efficacy of an intravitreal injection of 0.8% methotrexate (ADX-2191, Aldeyra Therapeutics) for the treatment of PVR (Video).

Methotrexate has already been proven effective at treating a variety of conditions, including ocular inflammatory diseases. The specific formulation of the drug used in this study (0.8%) is distinct from compounded methotrexate with a 2-year shelf life, among other properties.

Study Design

Patients eligible for inclusion in this trial had recurrent RD due to PVR with greater than 3 clock hours of starfolds (81%) or open-globe injury (19%). The initial study design

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Video. Methotrexate Shows Promise for Preventing PVR

randomized patients into either an intervention group (routine surgery plus methotrexate injection; $n = 68$) or a control group (routine surgery alone; $n = 38$). However, some researchers were hesitant to withhold the drug from those in the control group, and the design was modified so that all patients in the trial received treatment with methotrexate.

AT A GLANCE

- Proliferative vitreoretinopathy is implicated in 50% to 75% of cases of redetachment after retinal detachment repair surgery.
- In the GUARD trial, 24% of patients treated with methotrexate experienced recurring retinal detachment requiring reoperation within 6 months compared with 39% in the historical control group.
- In the FIXER trial of infliximab, final BCVA was significantly better in the treatment group by approximately 2 ETDRS letters.



PVR IS A FRUSTRATING AND ELUSIVE CONDITION THAT DOES NOT YET HAVE A SUITABLE SOLUTION BEYOND REOPERATION.

A total of 13 injections were given over a 4-month period; the first injection was given in the OR, the next eight were given weekly, and the last four were given every other week. The primary endpoint was recurrent RD requiring reoperation within 6 months compared with a designated historical control group ($n = 292$).

Results and Key Takeaways

The primary endpoint of this study was achieved; of the patients in the intervention group, 24% experienced recurring RD requiring reoperation within 6 months compared with 39% in the historical control group ($P = .024$).

The most common adverse event was punctate keratitis (16%; $n = 16$). Of the patients affected, none had severe reactions; nine cases were mild, and two were moderate.

INFLIXIMAB

Ayman Elnahry, MD, PhD, shared updates on the FIXER phase 2 randomized, controlled clinical trial of infliximab for the treatment of PVR (NCT04891991). Infliximab is a chimeric monoclonal antibody that inhibits tumor necrosis factor- α , an inflammatory cytokine and mediator of ocular inflammation that plays an important role in the development of PVR.

Infliximab has previously been studied in the treatment of other systemic and ocular conditions with good results. For example, researchers have evaluated it as a treatment for patients with wet AMD who did not respond to ranibizumab (Lucentis, Genentech/Roche), and it has been shown to help reduce intraocular inflammation in cases of noninfectious uveitis.⁴ Specific to the treatment of PVR, a study by Savur et al used an experimental dispase-induced PVR animal model to determine that injection with infliximab effectively inhibited the development of PVR by reducing cytokine levels compared with sham.⁵

The FIXER phase 2 trial is the first-in-human study designed to evaluate a tumor necrosis factor- α inhibitor for the treatment of PVR due to RRD.

Study Design

The goal of this trial was to evaluate the safety and efficacy of infliximab when administered intravitreally upon completion of vitrectomy for RRD repair. Inclusion criteria were patients at least 18 years of age with primary RRD and PVR of grade C or higher, according to the Updated Retina Society Classification.⁶ Those with a globe injury, recurrent RRD, other retinal disease, pregnancy or breastfeeding

status, or history of tuberculosis were excluded.

Patients were randomly assigned to vitrectomy with complete membrane peeling and silicone oil tamponade either with ($n = 33$) or without ($n = 35$) infliximab injection; surgeons were masked to the treatment allocation until completion of surgery. Silicone oil was removed 3 months postoperatively. At 3 months, patients who experienced recurrent RD repeated the same protocol as the initial randomization.

The primary endpoint was anatomic success, defined as complete retinal reattachment without tamponade at 6 months after silicone oil removal. Secondary endpoints included final visual acuity; single-operation success rate; rate of recurrent RD; and macular thickness, function, and vascular density.

Results and Key Takeaways

Of the 68 patients enrolled, 60 were included in the final analysis (30 in each group); the remaining eight were lost to follow-up. Statistical analysis revealed that 30 eyes in the infliximab group experienced final anatomic success versus 29 eyes that underwent surgery alone. The single-operation success rate was higher in the treatment group (86.7%) compared with controls (76.7%), although this result was not statistically significant ($P = .317$).

Final BCVA was found to be significantly better in the treatment group by approximately 2 ETDRS letters ($P = .044$), and no differences were noted in IOP or macular findings. The researchers suggest that the 2-letter improvement in BCVA could be due to the lower rate of recurrent RD in the infliximab group.

GETTING CLOSER

PVR remains a frustrating and elusive condition that does not yet have a suitable solution beyond reoperation. However, the findings presented at ASRS 2023 offer hope that an adjunctive medical therapy will soon be available to more effectively treat—and, better yet, prevent—this serious complication. ■

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