

GUARD AGAINST PVR: METHOTREXATE FOR PROLIFERATIVE VITREORETINOPATHY AFTER RETINAL DETACHMENT SURGERY



The phase 3 GUARD trial is evaluating the safety and efficacy of this innovation.

BY S.K. STEVEN HOUSTON III, MD; AND DAVID R. LALLY, MD

Vitreoretinal surgery has seen tremendous advances in the past few decades. Vitrectomy platforms now offer small-gauge instrumentation (23, 25, and 27 gauge), vitreous cutters operate at 10,000 to 20,000 cuts per minute, and a plethora of advanced surgical instruments (forceps, scissors) and surgical adjuvants (perfluoro-n-octane, gas, silicone oil) are available. Visualization has also seen significant advances in the form of widefield noncontact and contact systems as well as digitally assisted vitrectomy surgery (DAVS) platforms. Despite all of the improved safety and efficacy of modern day vitreoretinal surgery, however, one complication still eludes us: proliferative vitreoretinopathy (PVR).

PVR is a complex disease process that can occur after rhegmatogenous retinal detachment surgery in 5% to 10% of patients.¹ PVR is initiated as a reparative process following a retinal break and retinal detachment. It is characterized by glial cell or retinal pigment epithelium cell migration with resulting proliferation of preretinal or subretinal membranes. Contraction of these membranes after surgical repair is the most common cause for failure of primary retinal detachment surgery. Rates of PVR can increase substantially with retinal detachments secondary to trauma or giant retinal tear. Additionally, several risk factors have been identified that may increase the risk of PVR, including preoperative PVR, extent of retinal detachment, number and extent of retinal breaks, choroidal detachment, vitreous hemorrhage, and duration of retinal detachment.^{2,3}

PVR has been shown to be associated with multiple cytokines, chemokines, and growth factors, as well as other extracellular matrix proteins. This complex pathophysiology

hints at the difficulty of developing pharmaceutical treatments for PVR.

Treatment for retinal redetachment from PVR requires surgery to achieve anatomic stabilization. Preretinal and subretinal membrane peeling, internal limiting membrane peeling, relaxing retinectomy, perfluoro-n-octane liquid, and silicone oil are all elements in our armamentarium for successful treatment of PVR.

Primary prevention of PVR would represent a major breakthrough in vitreoretinal surgery. Many pharmaceutical candidates have been investigated, including corticosteroids,

AT A GLANCE

- PVR occurs in 5% to 10% of patients with retinal detachment. Surgical options are used to address PVR in these cases.
- The GUARD trial will assess whether postoperative administration of ADX-2191 (intravitreal methotrexate 0.8%, Aldeyra Therapeutics) has an effect on rates of redetachment due to PVR that requires surgery.
- Updates on GUARD are expected in the next 1 to 2 years.

GUARD Trial Injection Protocol

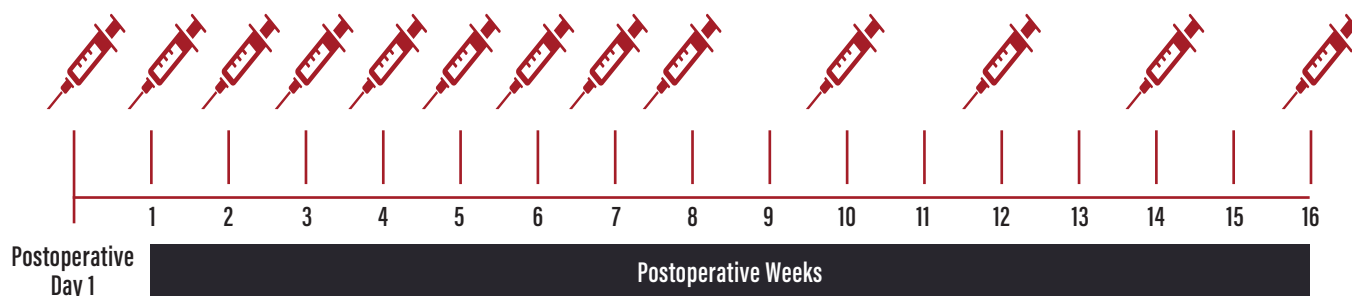


Figure 1. The injection protocol for the GUARD trial requires 13 doses of ADX-2191 over 16 weeks.

retinoic acid, 5-fluorouracil, platelet-derived growth factor, VEGF, heparin, and others, with varied responses. Despite some evidence of efficacy for some of these agents, the evidence has not been sufficient to lead to widespread adoption of any treatment.

THE GUARD TRIAL

In 2011, a phase 1b, investigator-initiated clinical trial was conducted at Mass Eye and Ear by Dean Elliott, MD, and Tomasz Strykowski, MD, to determine the safety and tolerability of administering repeated, weekly intravitreal injections of methotrexate into eyes at high risk for the development of PVR after retinal detachment repair.

The rationale for use of intravitreal methotrexate for treatment of PVR is based on its mechanism of action. Methotrexate suppresses inflammation and inhibits cellular replication, both of which are key in the pathogenesis of PVR. PVR typically manifests weeks to months after surgical repair, so the treatment is given repeatedly throughout the entire risk period rather than as a single injection at the time of surgery.

In December 2019, enrollment began in the Gain Understanding Against Retinal Detachment (GUARD) trial, a two-part multicenter, randomized, controlled, adaptive phase 3 clinical trial investigating the efficacy of ADX-2191 (intravitreal methotrexate 0.8%, Aldeyra

Therapeutics) for the prevention of recurrent retinal detachment due to PVR.^{4,5} ADX-2191 has received orphan drug and fast track designations from the US FDA.

Inclusion and Exclusion Criteria

The GUARD trial is recruiting patients undergoing vitrectomy for recurrent retinal detachment due to PVR with star folds in at least 3 cumulative clock hours documented on retinal imaging, or for retinal detachment associated with open globe injury.

Exclusion criteria include no light perception vision, pre-phthisis, severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy, severe dry eye or corneal disease, previous incisional glaucoma surgery, a history of intraocular inflammation, sensitivity to methotrexate, and being 17 years old or younger. In addition, a history of more than six retinal detachments in the study eye is exclusionary.

Study Protocol

Patients are randomly assigned 1:1 intraoperatively to ADX-2191 or control. Part 1 of the study will enroll approximately 100 patients. The results of part 1 will be used to power part 2 of the study, which will enroll an additional 100 to 360 individuals.

Study participants in the treatment arm receive intravitreal ADX-2191 at the

conclusion of surgery or on postoperative day 1, and then weekly for 8 weeks, followed by every-other-week treatment through postoperative week 16. Thus, a total of 13 ADX-2191 injections are administered over 16 weeks (Figure 1). Neither the surgeon nor the patient is masked to treatment.

Significant membranes, including epiretinal, subretinal, and epipilary, are all surgically removed to the extent possible. Use of intravitreal dyes, scleral buckle, relaxing retinectomy, and perfluorocarbon liquid are allowed at the discretion of the investigator. Retinal breaks are sealed using moderate to intense white laser retinopexy burns, and then all eyes receive 1,000 or 5,000 centistoke silicone oil tamponade. Subconjunctival, peribulbar, intravenous, oral, or sustained-release intraocular steroids are prohibited.

The individual is enrolled at the end of the surgery only after successful reattachment is confirmed by the investigator. All participants receiving the investigational product are required to use lubricating drops or ointment at least four times daily postoperatively. Maintaining a well-lubricated cornea is crucial to reduce the risk of epithelial defects and other forms of keratopathy, that may occur during repeated intravitreal injections of methotrexate. Silicone oil may be removed after week 24.

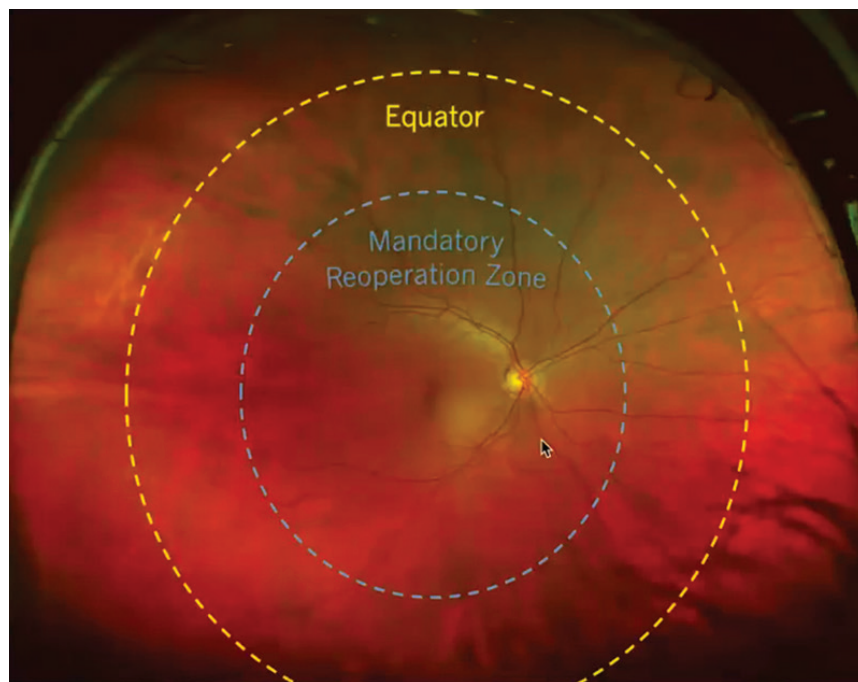


Figure 2. The primary endpoint of recurrent retinal detachment is defined as a retinal detachment that has progressed posterior to the mandatory reoperation zone, as defined by Standardized Study Figure 2, which depicts a circle centered on the fovea that is located halfway between the arcades and the equator (Source: Aldeyra Therapeutics).

Outcome Measures

The primary outcome is the rate of retinal redetachment due to PVR requiring reoperation within 24 weeks of randomization. Retinal redetachment requiring reoperation is defined as either spectral-domain OCT demonstrating a fovea-off retinal detachment with subretinal fluid that is contiguous with a peripheral detachment, or color wide-field imaging documenting a recurrent detachment in the mandatory reoperation zone. The *mandatory reoperation zone* is defined as a redetachment that has progressed posterior to Standardized Study Figure 2 (Figure 2). The secondary endpoint is BCVA change from preoperative examination to week 24.

Protocol Regarding Lens Status

The vitrectomy surgery is performed using a small-gauge system (23, 25, or 27 gauge). If the eye is phakic with a clear lens, the lens may be preserved. If there is a cataract, lensectomy with removal of the entire capsule may be performed at the discretion of the investigator. Cataract extraction with

implantation of a posterior chamber IOL is allowed. If the eye is pseudophakic, the IOL can be left or removed at the discretion of the investigator. If the eye is aphakic, secondary IOL implantation is not permitted.

FINAL THOUGHTS

PVR plagues surgeons and patients as the main cause for failure of primary retinal detachment surgery. The pathophysiology of PVR is complex, with multiple targets contributing to its development and progression. Initial studies of intravitreal methotrexate for PVR have led to the initiation of the phase 3 GUARD trial. We anticipate that the results of this trial will illuminate the efficacy of this potential treatment for patients with rhegmatogenous retinal detachments secondary to advanced PVR or open-globe injuries.

Although the treatment burden of 13 injections over the course of 16 weeks is intense, proof of concept in this study would likely lead to development of slow-release implants or other sustained-release drug delivery

approaches. We look forward to updates on this exciting study over the next 1 to 2 years. ■

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