

Today's Perspective on Proliferative Vitreoretinopathy



This complication continues to plague retina surgery, but new techniques and treatments are helping to reduce its incidence.

**A DISCUSSION WITH DEAN ELIOTT, MD; AVNI P. FINN, MD, MBA; AJAY E. KURIYAN, MD, MS; AND M. ALI KHAN, MD
MODERATED BY ALLEN C. HO, MD, AND ROBERT L. AVERY, MD**



Our patients remind us of significant opportunities for improvement of retinal detachment (RD) repair—for example, poor vision despite anatomic retina reattachment and the need for repeat RD surgery most commonly due to proliferative vitreoretinopathy (PVR). Perhaps neuroprotective agents in early clinical trials will improve visual outcomes via photoreceptor protection from cell death pathways activated by detachment. There is a long history of failed agents for PVR prevention after RD repair, but there may be hope on the horizon. With improved tools and techniques, we are better at addressing PVR surgically, but we must find ways to attack this problem systematically. We sat down with colleagues to discuss the recent research and latest surgical techniques for tackling PVR in the OR.

- Allen C. Ho, MD, and Robert L. Avery, MD

ALLEN C. HO, MD: WHAT ARE SOME MAJOR KNOWLEDGE GAPS REGARDING PVR DEVELOPMENT?

M. Ali Khan, MD: Generally, we have conceptualized PVR as a cytokine-driven process in the vitreous that allows for the abnormal proliferation of retinal pigment epithelium (RPE) cells, leading to clinical PVR. Many molecular targets have been identified to inhibit that cytokine-driven cascade, but no specific agent has proven effective at treating or preventing PVR to date.

We don't fully understand the pathophysiology, and

it's likely more complex than we have simplified. We have animal models of PVR, but we do not know how accurate those models are in predicting human disease. Studying the disease in humans is difficult, and there hasn't been many powered clinical trials evaluating therapeutics for PVR. Hopefully, some current trials will fill in some gaps and encourage larger studies.

AT A GLANCE

- Certain patient factors can increase the risk of proliferative vitreoretinopathy (PVR), including younger age, ocular trauma history, and smoking.
- Many are hoping the GUARD trial evaluating intravitreal methotrexate will be successful, as it would be a promising, local treatment for patients with established PVR.
- One of the potential reasons for PVR, even with today's advanced techniques, is that surgeons are leaving a residual layer of anterior or posterior cortical vitreous that they don't recognize.

ROBERT L. AVERY, MD: WHAT ARE THE OCULAR AND SURGICAL RISK FACTORS FOR PVR?

Avni P. Finn, MD, MBA: Certain patient factors can increase the risk of PVR and redetachment, including younger age, a history of ocular trauma, and smoking. As for clinical history, a patient with a history of chronic RD or vision loss for a longer period may be at an increased risk for PVR, which takes about 4 to 6 weeks to develop.

During the preoperative examination, it is important to note any vitreous hemorrhage, giant retinal tears, choroidal detachments, hypotony, or uveitis, all of which predispose a patient to PVR or redetachment.

When I see any of these, I counsel my patients about the fact that they may be at a higher risk for scar tissue forming (that's the word I use when I talk about PVR) and that they may be at heightened risk for a redetachment as well.

DR. HO: WHAT'S THE PERCENTAGE YOU QUOTE THAT THERE'S A CHANCE OF PVR AND/OR REDETACHMENT?

Dr. Finn: I usually tell patients that 90% of the time RDs are fixed with the first surgery, and that's variable across surgeons. That's a reasonable number that falls within the data from large retrospective series for primary RDs.

Dr. Ho: I tend to be a little more conservative and usually say 85%. In that, I am including anything that would require a second surgery.

Dr. Avery: I usually tell patients 95%, because we reviewed nearly 1,000 of our cases, and we had close to a 97% success rate with vitrectomy or scleral buckle/vitrectomy surgery when we excluded cases with preexisting PVR. Of course, if a patient is at high risk for PVR, I reduce that dramatically.

Dean Elliott, MD: I tell patients roughly 90%, and I may tweak it by saying, "You have a straightforward RD with one small retinal break, and your odds are probably a bit better than that." I worry that if you say 95% or 97%, the patient assumes it won't happen to them, which may defeat the purpose of telling them that there's a probability of failure.

Dr. Khan: Patients can understand that they have a one in 10 chance of failure. If they have high-risk features, you need to set them up to understand that the opportunity exists for PVR to develop. Patients who are told that there's a chance of it beforehand aren't so disappointed if it happens. But patients who are never told there was a chance of failure are really upset about what happened during the surgery.

DR. HO: WHAT ARE SOME OF THE THINGS WE CAN DO, PHARMACOLOGICALLY, TO MODIFY THE RISK OF PVR?

Ajay Kuriyan, MD, MS: We are excited to have an ongoing trial investigating the use of intravitreal methotrexate

SIDELINED THERAPEUTICS

Many trials have been conducted to try to inhibit proliferative vitreoretinopathy, none of which have succeeded so far.

- Broad antiinflammatory agents such as the dexamethasone implant, triamcinolone, and systemic prednisone
- Antiproliferative agents (liposome-encapsulated 5-fluorouracil, colchicine, daunorubicin, low molecular weight heparin, retinoic acid, and ribozyme-proliferating cell nuclear antigen)
- Anti-VEGF agents for patients with PVR

(Aldeyra Therapeutics), and we are eager for the results.¹ It certainly looks promising, based on my experience with it through the study.

Other than that, we don't have anything to treat patients who already have PVR. Dr. Khan is working on a study investigating the use of anti-VEGF agents, which target the non-canonical platelet-derived growth factor pathway, to prevent PVR.² That approach may allow us to identify patients who are at a high risk for developing PVR and prevent it from happening.

Dr. Elliott also did some great work to identify smoking as a risk factor for PVR formation.³ We don't quite know if smoking cessation at the time of repair modifies your risk for developing PVR later, but I always use it as a great opportunity to do smoking cessation counseling.

DR. AVERY: THE METHOTREXATE TRIAL INCLUDES 13 TREATMENTS INSTEAD OF 10, WHICH WAS THE CASE 5 YEARS AGO. WHY THE CHANGE AND THE NEED FOR PROTRACTED INTERVENTION?

Dr. Elliott: In the phase 1 study, we gave one injection of methotrexate at the end of surgery, eight weekly injections, and one more at week 12. One of the patients in the study had a 13 mm open-globe injury and developed a total RD with retinal incarceration in the scleral wound. We repaired the RD with retinectomy and oil and followed the study protocol using 10 methotrexate injections. At 12 weeks the patient looked good, but at the 16-week visit, he had a massive amount of pigment cells in the oil, a striking difference from 4 weeks prior. Soon thereafter he developed explosive PVR and ended up with light perception visual acuity.

Usually, PVR develops in a month or two following an open-globe injury, and it was unusual for this patient to have no evidence of PVR for 3 months (during the injection period), and then to suddenly develop severe PVR at 4 months. This patient must have had a very high stimulus for PVR development, so we thought that increasing the number of injections to extend the treatment period might be beneficial in some patients. The GUARD study includes 13 injections, which may be overkill in many patients (assuming the drug proves useful for the treatment of PVR).¹

DR. AVERY: AS FOR THE SURGERY ITSELF, ARE THERE ANY MANEUVERS THAT HELP TO PREVENT HYPOTONY, ONE OF THE PROBLEMS WITH PVR?

Dr. Finn: No PVR surgery is ever easy, and you can't approach all of them with the same methodology. But, among the first things I consider is putting a buckle on an eye with severe PVR if there's not already one present and I'm not planning on doing a 360° retinectomy. I also consider visualization during the case. If there is a cataract, I perform a lensectomy because you always need an excellent view to address the PVR.

When it comes to the vitrectomy, we all know that an incompletely removed hyaloid can lead to PVR and membrane formation; thus, it is important to stain and make sure that you are peeling posterior membranes that have grown on the scaffold of the posterior hyaloid.

I use perfluoro-n-octane to start stabilizing and flattening the retina after I've removed those posterior membranes, then I make my way out more peripherally. The MaxGrip forceps (Alcon) and a lighted pick are my go-to instruments. When I don't have an assistant, I use a chandelier so that I can use a bimanual technique.

When you're finishing up the case, especially if you've performed a retinectomy, good hemostasis is crucial to prevent further PVR and redetachment because hemorrhage can be a problem. In these cases, I also choose a long-acting tamponade such as C₃F₈ gas or silicone oil.

DR. AVERY: WHEN SHOULD WE USE A SCLERAL BUCKLE IN THE ABSENCE OF THE 360° RETINECTOMY?

Dr. Elliott: I like to have a buckle in PVR cases. There are two instances when I wouldn't put one on: when I perform a 360° retinectomy, and when the patient has had prior extensive 360° peripheral laser.

But in other cases, I believe that a buckle helps. I know it is controversial, and I may not be right, but I err on the side of doing too much rather than too little. I like to use a buckle even when I have a 180° inferior retinectomy.

Dr. Khan: It's probably 50/50 for me. With many cases of 180° retinectomy, I don't put on a buckle. There are surgeon-specific factors, and everybody figures out what works best in their own hands and experience. We don't have great evidence that adding a buckle really affects the outcomes. That's partially why PVR is so frustrating because it doesn't always make sense.

But I stain with ICG, especially if the PVR is more posterior, and try to peel from the internal limiting membrane and the macula as far out as I can.

Dr. Ho: We do more retinectomies now, and although we may not have good data on it, the surgeons in our department know that you must do a significant retinectomy if

you're going to do an inferior retinectomy at all. You should think twice about doing a retinectomy less than 120°, because it is going to fail.

When you go more than 120°, and typically I'm at 180° or greater for a bad case, the need for a buckle is obviated. I do a lot of scleral buckles on RD surgery, but when you start, just like in a giant retinal tear, I don't see the sense of putting a scleral buckle on a lot of those cases.

One of the main reasons for PVR, even with today's advanced techniques, is that we're leaving a residual layer of anterior and posterior cortical vitreous that we don't recognize. I perform vitreous base shaving, which includes depression with particles like triamcinolone to identify that layer. You must take the time to remove the gel that straddles the pars plana and ora serrata that will contract either with gas compression or silicone oil and lead to anterior loop proliferation. Also, removing that posterior gel may be helpful to reduce the incidence of PVR, and we need data on this clinical impression.

Dr. Elliott: For PVR surgery, in my opinion, you should be more of a maximalist than you are with other diseases such as retinopathy of prematurity, where it's better to be a minimalist (so you don't make a retinal break). In PVR cases, I like to remove everything—vitreous and membranes—as much as possible.

DR. HO: WHAT ARE YOU MOST EXCITED ABOUT FOR THE TREATMENT OR PREVENTION OF PVR?

Dr. Khan: I think many are hoping the GUARD trial evaluating intravitreal methotrexate will be successful, as it would be a promising, local treatment for patients with established PVR.¹ Isotretinoin has had promising data in prior studies, but it is difficult to prescribe with many potential systemic side effects.

I'm also interested in homing in on what is characterized as a 'high-risk' eye to better understand which primary RDs may be the best candidates for preventative treatment options. We need clinical trials on high-risk primary RDs, not just patients with advanced, grade C PVR.

It's going to take a lot of people working on this together because doing prospective clinical trials alone is difficult and doing it in surgery is even harder.

Dr. Kuriyan: Methotrexate is the closest option we may have, but there's a lot of exciting preclinical work for other agents. Leo A. Kim, MD, PhD, at Massachusetts Eye and Ear in Boston, has done some great work looking at runt-related transcription factor 1 inhibitors and working toward a study of rho-kinase inhibition, both of which are exciting.^{4,5}

We have some work in our lab looking at soluble amniotic membrane and a compound with salinomycin, which has been found to reverse some of the scar phenotype.⁶⁻⁸

DR. HO: WHAT'S THE LATEST WITH THE GUARD TRIAL?

Dr. Elliott: The GUARD trial's goal was to enroll up to 100 patients, and at first patients were randomly assigned to either standard-of-care, which is surgery alone, or standard-of-care with methotrexate. At some point the protocol was altered to put all patients into the standard-of-care surgery plus methotrexate arm. Enrollment should be completed soon, and then we'll be able to evaluate the effect.

Keep in mind that the power to detect a difference in this study is relatively low due to the small number of patients. As with all surgical studies, it faces some difficulties with surgeon variability. It is very difficult to do a surgical study and ensure that all variables are the same except for the drug. Nevertheless, we will get some answer whether there's a signal that the drug might work.

It's an exciting time, but there are some challenges ahead.

DR. HO: ANY FINAL THOUGHTS ON WHERE WE STAND WITH PVR?

Dr. Finn: Rare surgical diseases, like PVR, don't get as much attention as more common medical diseases such as AMD and diabetic retinopathy. We are looking at a very small percentage of our overall patient population, but it is something that haunts all of us as surgeons. I'm excited to be on the precipice of, hopefully, new discoveries in terms of the pathophysiology, and also potential adjuncts outside of surgery to add to our toolbox.

Dr. Khan: We have a lot of preclinical work and active clinical trials, and we need to continue to evaluate our own surgical techniques to see if there's something iatrogenic that could be worsening PVR. I think for a while we as a retina community lost interest in PVR because nothing was working, but the interest is certainly back. Hopefully the momentum keeps going.

Dr. Kuriyan: With all of the advancements in genetic and single-cell analyses, we can revisit older studies that weren't fruitful to better understand the pathophysiology and then work toward developing more pharmacologic agents.

Dr. Avery: It's nice to finally be bringing pharmacotherapy to this important topic. This is an exciting topic now because of these advances, and I want to thank you all for sharing your expertise with us today. ■

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