• Editorial •

What can we learn from negative results in clinical trials for proliferative vitreoretinopathy?

Peter Wiedemann

Medical Faculty, Leipzig University, Leipzig 04103, Germany

Correspondence to: Peter Wiedemann. Medical Faculty, Leipzig University, Leipzig 04103, Germany. P@prwiedemann.de

Received: 2022-07-11 Accepted: 2022-07-20

DOI:10.18240/ijo.2022.09.01

Citation: Wiedemann P. What can we learn from negative results in clinical trials for proliferative vitreoretinopathy? *Int J Ophthalmol* 2022;15(9):1413-1415

INTRODUCTION

Since the beginning of vitreoretinal surgery proliferative vitreoretinopathy (PVR) has been a constant complication. PVR is the major cause for surgical failure after primary rhegmatogenous retinal detachment (RRD) resulting in multiple reoperations and vision loss. So far, there is no proven therapy to treat or prevent PVR. The incidence of PVR is estimated to be between 5% and 10% of all RRD repairs and generally occurs within 8wk of surgery. It often is difficult to predict which patients may develop PVR. A retinal break is a prerequisite for the development and almost all clinical risk factors for PVR are associated either with intravitreal dispersion of retinal pigment epithelial (RPE) cells or the breakdown of the blood-retinal barrier (BRB). Certain risk factors make the development of PVR more likely, such as the presence of intraocular hemorrhage, uveitis, preoperative or postoperative choroidal detachment, size of retinal tears, multiple retinal tears, chronic retinal detachments, and multiple previous surgeries or trauma[1]. Current strategies for PVR prevention are equally focused on timely and successful repair of RRD. The goal of surgical repair is to relieve traction and reattach the retina. To date, surgery remains the only management of PVR. In our current understanding PVR is a cellular reaction molded by many cytokines leading to fibrosis and scarring and redetachment and vision loss. Suitable pharmacological adjuncts moderate inflammation and cellular proliferation, thereby lessening PVR formation. The following trials tried to address the problem.

Daunomycin Trial (1998)[2] The 286 patients/eyes with advanced preoperative PVR in which surgery with silicone oil was planned were recruited in a prospective, randomized, controlled multicenter European clinical trial to assess the efficacy and safety of adjunctive daunorubicin during vitrectomy surgery in eyes with PVR (Grade C or higher). Standardized surgery alone (control) was compared with surgery plus adjunctive daunorubicin perfusion (study treatment). Outcomes appraised were retinal attachment without additional vitreoretinal surgery 6mo after standardized surgery, number of and time of vitreoretinal reoperations, and change in visual acuity. Six months after standardized surgery, complete retinal reattachment without additional vitreoretinal surgery was achieved in 62.7% (89/142) of eyes in the treatment group *vs* 54.1% (73/135) in the control group (P=0.07, one-sided). Although anatomic success rate after 6mo failed to show significance, some benefit of adjunctive daunomycin treatment exists, especially a tendency toward increased rates of reattachment and a significant reduction in the number of reoperations. No severe adverse effect related to daunorubicin was seen.

Ozurdex Slow-Release Dexamethasone Trial (2017)[3] To test the hypothesis that adjunctive slow-release dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA, USA) can improve the outcomes of surgery for established PVR a single center, prospective, masked randomized controlled clinical trial (EudraCT No.2011-004498-96) was performed.

A total of 140 patients requiring vitrectomy with silicone oil for retinal detachment with established PVR (Grade C) were randomized to standard (control) or study treatment (adjunct). Intraoperatively, the adjunct group received an injection of 0.7 mg of slow-release dexamethasone (Ozurdex) at the time of 1) vitrectomy surgery and 2) silicone oil removal. The control group received standard care.

Primary endpoint was the proportion of patients with a stable retinal reattachment with removal of silicone oil without additional vitreoretinal surgical intervention at 6mo. Secondary outcomes included 1) final visual acuity; 2) cystoid macular edema (CME), foveal thickness, and macular volume; 3) development of overt PVR recurrence; 4) complete and posterior retinal reattachment; 5) tractional retinal detachment;

6) hypotony/increased intraocular pressure (IOP); 7) macula pucker/epiretinal membrane; 8) cataract; and 9) quality of life.

Anatomic success between the 2 groups was similar (49.3% *vs* 46.3%, adjunct *vs* control). Secondary anatomic outcomes (vision, complete/posterior reattachment rates and PVR recurrence) were comparable between the 2 groups. At 6mo, fewer dexamethasone patients had CME (42.7%) or an increased foveal thickness (47.6%) compared with controls (67.2% and 67.7%, respectively).

A slow-release dexamethasone implant did therefore not improve the anatomic success rate in eyes undergoing vitrectomy surgery with silicone oil for PVR.

PRIVENT Trial (Prophylactic Intravitreal 5-Fluorouracil and Heparin to Prevent PVR in High-risk Patients with Retinal Detachment (2022)[4] The objective of this randomized, controlled, double-blind, multicenter, interventional trial with one interim analysis in Germany was to examine the effect of adjuvant intravitreal therapy with 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH), compared with placebo, on the incidence of PVR. Patients with primary RRD and preoperative elevated aqueous flare measurements as an indication of blood retinal barrier breakdown were considered high-risk for PVR and were included. Patients were randomized 1:1 to Verum (200 mg/mL 5-FU and 5 IU/mL Dalteparin) or placebo (balanced salt solution). These solutions were intravitreally applied during routine vitrectomy.

The primary outcome was the development of PVR grade CP (full-thickness retinal folds or subretinal strands in clock hours located posterior to equator) within 12wk after surgery. Secondary endpoints included re-detachment rate and best-corrected visual acuity.

A total of 325 subjects in 13 German trial sites had been randomized (Verum: *n*=163; placebo: *n*=162). There was no significant difference in PVR rate (Verum: 28% *vs* placebo: 23%). None of the secondary endpoints showed a significant difference between treatment groups. No relevant safety risks were observed.

GUARD (Gain Understanding Against Retinal Detachment) Trial Methotrexate (2023)[5-6] The rationale for use of intravitreal methotrexate for treatment of PVR is based on its property to suppress inflammation and inhibit cellular replication, both of which are key factors in the pathogenesis of PVR. In December 2019, enrollment began in the GUARD trial, a two-part multicenter, randomized, controlled, adaptive phase 3 clinical trial in the United States investigating the efficacy of ADX-2191 (intravitreal methotrexate 0.8%, Aldeyra Therapeutics) for the prevention of PVR-associated retinal redetachment. Only PVR eyes that achieve successful retinal reattachment are randomized into the GUARD trial, with a ratio of 1:1 intraoperatively between methotrexate or control, which is standard surgery. ADX-2191 has received orphan drug designation from the US FDA. Because the PVR life cycle lasts for several weeks, the GUARD trial involves serial injections of intravitreal methotrexate throughout the entire risk period rather than as a single injection at the time of surgery. Results from part 1 of the GUARD trial is expected in the second half of 2022.

Timely diagnosis, a thoughtful surgical approach and careful postoperative management are key to successful retinal reattachment and vision preservation. Despite all the refinement and improved efficacy and safety of modern-day vitreoretinal surgery this complication still eludes us and only modest progress in the treatment of PVR has been achieved. The most important step forward was the capacity to remove quite completely the vitreous, not done and not possible at the time of the daunomycin trial.

Substantial advances have been made in understanding critical molecular and cellular mechanisms driving PVR. These findings have led to the discovery of a variety of molecular targets. The verdict is still out on whether intravitreal drugs will be a definitive therapeutic modality for treatment and/or primary prevention of PVR.

What can we learn from the negative results of the above trials?

I believe there are three points:

1) Anecdotal reports and small investigator-initiated trials have shown favorable results in preventing progression of PVR for all mentioned drugs (daunomycin, dexamethasone, fluorouracil, methotrexate). In the randomized clinical trial, the results were different.

In the therapeutic daunomycin trial against established PVR anatomic success rate after 6mo failed to show significance. Primary outcome assessment in the therapeutic dexamethasone trial showed similar results in anatomic success between the 2 groups.

In the preventive PRIVENT trial the rate of PVR did not differ between adjuvant therapy with 5-FU and LMWH and placebo treatment in eyes with RRD considered at high PVR risk.

Larger study might have had the statistical power to detect a smaller benefit. However, a too small benefit may not be clinically relevant. Some benefit of the adjunctive treatment for existing PVR exists, however: 1) a tendency toward increased rate of reattachment and a significant reduction in the number of reoperations for daunomycin and a greater reduction in CME for dexamethasone. 2) None of the treatments had major side effects, tolerable ocular concentrations can be determined. *This shows that human PVR should be in principle amenable to pharmacologic treatment.*

2) The Daunomycin and Dexamethasone study treated established PVR by a single infusion during surgery or one-time repeated injection (slow release), the Privent trial tried prevention with a single perfusion. The Guard trial intends to prevent recurrence of PVR with serial injections. This may be a better approach to effectively prevent recurrent PVR. Repeated injections are no problem today but were not even thought of 30 years ago.

Therefore, pharmacokinetic refinements for longer-lasting therapeutic drug levels which comply with the course of PVR will be necessary to achieve better study results.

3) The results of the above studies suggest that we do not understand the basic pathobiology of the PVR as well as we thought. It is important to recognize that the efficacy of intravitreal drugs for treatment and prevention has not been established to date. However, the publication of initial treatment negative results is very important because it is this information which helps in designing newer studies attempting to treat the same condition with similar or other pharmaceutical agents.

We need to re-examine our assumptions about why some eyes demonstrate PVR after otherwise uncomplicated retinal detachment repair. It is not clear whether it is better to prevent development or to treat established PVR for longer period. There is a clear need for identification and validation of diagnostic, prognostic, and predictive biomarkers to help accelerate new treatments. As our understanding of the underlying molecular mechanisms in PVR pathogenesis continues to expand, so too is the list of novel drug targets.

We very much hope that the Guard trial will show significance. But it is good to know that several phase 2 trials are ongoing[7]. *The need for clinical trials to improve anatomic and visual outcomes in these eyes will remain.*

ACKNOWLEDGEMENTS

Conflicts of Interest: Wiedemann P, None.

REFERENCES

1 Wiedemann P, Yandiev Y, Prigliger S, Hui Y. Pathogenesis of proliferative vitreoretinopathy. In: Sadda SR, ed. *Ryan's Retina*, 7th edition. Elsevier Health Sciences 2023;1978-1289.

2 Wiedemann P, Hilgers RD, Bauer P, Heimann K. Adjunctive daunorubicin in the treatment of proliferative vitreoretinopathy: results of a multicenter clinical trial. Daunomycin Study Group. *Am J Ophthalmol* 1998;126(4):550-559.

3 Banerjee PJ, Quartilho A, Bunce C, Xing W, Zvobgo TM, Harris N, Charteris DG. Slow-release dexamethasone in proliferative vitreoretinopathy. *Ophthalmology* 2017;124(6):757-767.

4 Schaub F, Schiller P, Hoerster R, *et al*, PRIVENT Study Group. Intravitreal 5-fluorouracil and heparin to prevent proliferative vitreoretinopathy: results from a randomized clinical trial. *Ophthalmology* 2022;S0161-6420(22)00413-4. Epub ahead of print.

5 Eliott D, Stryjewski TP. Methotrexate for proliferative vitreoretinopathy. US Patent 2017. https://patents.google.com/patent/US10098884B2/en$ Accessed on July 7, 2022.

6 The GUARD Trial part 1: a phase 3 clinical trial for prevention of proliferative vitreoretinopathy. Clinicaltrials.gov identifier NCT04136366. https://clinicaltrials.gov/ct2/show/NCT04136366. Accessed on July 7, 2022.

7 Clinical trials on proliferative vitreoretinopathy. https://ichgcp.net/clinical-trials-registry/research/list?cond=Vitreoretinopathy%252C%2BProliferative#google_vignette. Accessed on July 7, 2022.