REVIEW

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# Intravitreal triamcinolone acetonide and bevacizumab injection as prevention of proliferative vitreoretinopathy in open globe injury

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## ABSTRACT

**Background:** Proliferative vitreoretinopathy (PVR) is common following an open globe injury (OGI) due to aberrant wound healing that can result in retinal detachment or vitreous hemorrhage. Despite the anatomical success, visual acuity improvement remains unsatisfactory. Triamcinolone acetonide (TCA) and Bevacizumab are among these therapies. This study aims to explore the effect of TCA and Bevacizumab intravitreal injection as potential preventive therapies for PVR in OGI.

**Methods:** This literature review compiles and elaborates on previous studies from many authors to support future experimental studies, which will be conducted to evaluate the intravitreal triamcinolone acetonide and bevacizumab injection as prevention of proliferative vitreoretinopathy in open globe injury through several relevant articles.

**Results:** The healing process requires inflammation that stimulates inflammatory cells and mediators, such as transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), interleukin-1 (IL-1), IL-2, IL-3, IL-6, IL-8, and IL-10. Plasminogen activator inhibitor-1 (PAI) is upregulated during inflammation, resulting in continued collagen deposition due to fibrosis. The injection of corticosteroids as immunosuppressants and anti-VEGFs as antiangiogenesis is thought to have a positive impact by reducing inflammation and the development of new blood vessels, thus suppressing fibrosis.

**Conclusion:** TCA injection was associated with improved anatomical and visual acuity in humans, pre-operatively or during pars plana vitrectomy. Anti-VEGFs, such as Bevacizumab, ranibizumab, conbercept, and aflibercept, demonstrated protective effects on the eyes of animal models and showed their ability to reduce VEGF, TGF-β, and PAI-1, thereby inhibiting wound fibrosis.

**Keywords:** Anti-VEGF, Corticosteroid, Preventive Therapy, Retinal Detachment.
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## INTRODUCTION

Traction on the vitreoretinal tissue or Proliferative Vitreoretinopathy (PVR) is a common sequela of Open Globe Injury (OGI), ranging from mild to severe injury, which is frequently followed by retinal detachment (RD) or vitreous hemorrhage (VH). PVR represents the outcome of the wound healing process, particularly in cases of ocular trauma with scleral lacerations. While the incidence of PVR with rhegmatogenous retinal detachment ranges from 5-10% in the general population, this rate can be as high as 50% in patients with OGI. Despite the rapid advances in vitreoretinal surgical techniques, PVR remains a challenge. Despite the anatomical success achieved during surgery, the visual acuity outcome remains unsatisfactory.[1] Currently, research on the use of medical therapy in OGI patients is quite popular. This therapy prevents the formation of PVR in OGI patients. However, to date, no clinically recognized therapy exists.[2]

Proliferative vitreoretinopathy (PVR) is a complex wound-healing process that occurs in response to injury of the vitreoretinal area. Previous studies have suggested that PVR formation is initiated following retinal tear due to Open Globe Injury (OGI), which exposes the retinal pigment epithelium (RPE) to the vitreous cavity.[2] The interaction of RPE cells with immune cells infiltrating the retinal tissue leads to increased production of growth factors and cytokines, ultimately triggering a cellular response in the form of PVR formation.[3]

Various growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and tumor necrosis factor-alpha (TNF-α), are elevated in PVR-affected vitreous samples. Previous studies have investigated the levels of inflammatory mediators in the vitreous and subretinal fluid to determine their potential as predictors of severe PVR development. Therefore, measuring differences in the levels of these biomarkers before and after different intravitreal injection therapies can provide valuable insight into the

effectiveness of each treatment strategy.[1]

Corticosteroids are a drug that has been used for a long time and has an inhibitory effect on the growth of fibroblasts.[4] Anti-vascular endothelial growth factor (anti-VEGF) therapy has recently gained interest for its potential to prevent the development of PVR in OGI patients.[3] In the past, corticosteroids and anti-VEGF have been studied in various diseases such as macular edema, age macular disease (AMD), and retinal vein occlusion (RVO).[4] Intravitreal corticosteroids and anti-VEGF require multiple administrations to maintain therapeutic effects. So the cost per injection per patient is still a concern in Indonesia. Triamcinolone acetonide (Kenalog) is an inexpensive corticosteroid in Indonesia and lower-middle-income countries.[5] The anti-VEGF currently available in Indonesia, such as Bevacizumab, Ranibizumab, and Aflibercept, are often used in Indonesia but are not always available in all parts of Indonesia, and the prices are not affordable for some groups. Anti-VEGF therapy under BPJS coverage only covers patients with neovascular age macular degeneration (nAMD). Based on those mentioned above, this study aims to elaborate on the effect of triamcinolone acetonide and Bevacizumab intravitreal injection as potential prevention therapy of PVR in OGI.

## METHODS

We conducted literature searching from various databases such as PubMed, EBSCOHost, EMBASE, Cochrane, and Google Scholar, using relevant keywords such as "proliferative vitreoretinopathy", "open globe injury", "corticosteroids", "anti-VEGF", "triamcinolone acetonide", and "bevacizumab". The search results were screened based on their title and abstracts. We then retrieved the full text of the related articles for further analysis.

### Retina and Cavum Vitreous Anatomy

The retina is a structurally complex part of the human eye located at the posterior segment, consisting of 10 well-organized layers with distinct functional roles. Its primary function is to receive and transmit visual signals to the brain via a series of interconnected neural networks. The layers include: the internal limiting membrane (ILM); the nerve fiber layer (NFL), composed of axons from the ganglion cell layer; the ganglion cell layer (GCL); the inner plexiform layer (IPL), consisting of the junctions between ganglion, bipolar, and amacrine cells; the inner nuclear layer (INL), containing bipolar, amacrine, and horizontal cell bodies; the middle limiting membrane; the outer plexiform layer (OPL), which includes junctions between horizontal, bipolar cells and photoreceptors; the outer nuclear layer, consisting of photoreceptor cell nuclei; the external limiting membrane; the inner and outer photoreceptor layers of rods and cones cells; and the retinal pigment epithelium (RPE).[6–8]

The vitreous cavity, comprising 80% or 4/5 of the volume of the eyeball, is a transparent gelatinous body that primarily consists of water, type III collagen, and hyaluronic acid. It plays a vital role in regulating the metabolism of the surrounding intraocular tissues, including the lens, ciliary body, and retina. The volume of the vitreous is approximately 4 ml and is composed of 98% water, 0.15% macromolecules (collagen, hyaluronic acid, and water-soluble proteins), and has a viscosity that is twice that of water due to its mucopolysaccharide content. The vitreous is surrounded by a hyaloid membrane that typically comes into contact with the posterior lens capsule, zonular fibers, macula, retinal vessels, optic nerve papilla, and peripheral retina at its base, with peripheral attachments extending up to 2 mm anteriorly and 4 mm posterior to the ora serrata. The vitreous contains several important substances: glucose, galactose, maltose, fructose, glucuronic acid, and glucosamine. Unlike retinal tissue, the vitreous does not possess blood vessels or cells.[6,7]

Retinal detachment (RD) is a serious condition in which the layers of rods and cones detach from the retinal pigment epithelium (RPE), leading to the degeneration of photoreceptors and eventual loss of vision. The initial symptom of RD is typically the perception of flashes of light and floaters in the affected eye. Focal laser therapy around the detached retina aims to reattach it. Other treatments, such as vitrectomy or the vitreous replacement with silicon oil, may also press the retina into its original position. Common causes of RD include trauma, hypertension, and diabetic retinopathy.[9]

### Ocular Trauma

Ocular trauma is a broad spectrum of injuries that affect ocular tissue, including the globe, optic nerve, and adnexa. It can result in various outcomes, from mild visual acuity reduction to vision-threatening conditions. Prior to the publication of standardized terminology by Kuhn et al. in 2008, inconsistencies in terminology posed challenges for developing ocular trauma scores, designing clinical trials, and communicating among ophthalmologists and other healthcare professionals. In 1998, ocular trauma was estimated to affect up to 19 million people globally, with 2.3 million experiencing bilateral visual impairment and 19 million experiencing unilateral vision loss. In the United States, eye trauma is estimated at 2.5 million annually, of which 40,000 result in permanent visual impairment.[10]

Epidemiological data on ocular trauma events are often lacking, particularly in low-income countries. However, a study conducted in Malawi reported an incidence of ocular trauma of up to 5.6% of all eye cases. The incidence of eye trauma can vary widely depending on social and geographic factors. Several risk factors for eye trauma have been identified, including age, gender, and socioeconomic status. Multiple studies have shown that men are more likely to experience ocular trauma, with rates ranging from 75% to 91.2%, with the highest incidence observed in the productive age group, which is thought to be due to their involvement in more manual labor and hazardous activities compared to women.[10–14]

One of the standardized terminologies currently used for trauma to the eyeball is The Birmingham Eye Trauma Terminology (BETT), which has gained recognition from various organizations.[12] BETT categorizes eye trauma as shown in Figure 1, dividing it into closed-globe and open-globe injuries. Closed-globe injuries are further classified into contusions and lamellar lacerations, while open-globe injuries are classified into lacerations and ruptures. Laceration

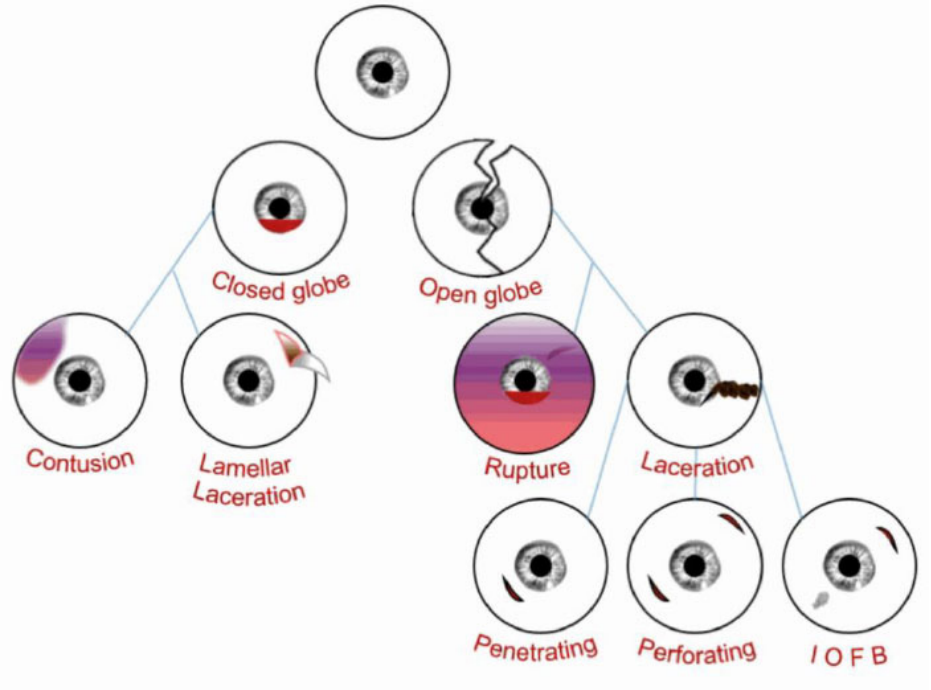


**Figure 1.** The division of the BETT trauma classification into two major clinical diagnoses, closed-globe and open-globe.[10]

**Table 1.** ***PVR classification based on Retina Society 1983.***[36]

| Grade | Criteria | Clinical sign |
|---|---|---|
| A | Minimal | Vitreous haze and pigment clumps |
| B | Moderate | Surface retinal wrinkling, rolled edges of the retinal, retinal stiffness, and vessel tortuosity |
| C | Marked | Full-thickness retinal folds in<br>C-1 one quadrant<br>C-2 two quadrants<br>C-3 three quadrants |
| D | Massive | Fixed retinal folds in four quadrants that result in<br>D-1 is a wide funnel shape<br>D-2 is a narrow funnel shape<br>D-3 closed funnel without a view of the optic disc |

**Table 2.** **PVR classification based on Retinal Society 1991.**[36]

| Grade | Clinical sign |
|---|---|
| A | Vitreous haze, pigment clumps, and pigment clusters on the inferior retina |
| B | Surface retinal wrinkling rolled and irregular edges of a retinal break, retinal stiffness, and vessel tortuosity, decreased mobility of vitreous |
| CP 1-12 | Posterior to the equator: focal, diffuse, or circumferential full-thickness fold, subretinal strands |
| CA 1-12 | Anterior to the equator: focal, diffuse, or circumferential full-thickness fold, subretinal strands, anterior displacement, condensed vitreous with strands |

wounds are subdivided into penetrating wounds, intraocular foreign body (IOFB), and perforated wounds. Several studies have demonstrated that the prevalence of closed and open-globe injuries varies by region. For example, Zungu et al. found that closed-globe injuries accounted for 60.8% of ocular trauma in Malawi.[14] In contrast, previous studies found that open-globe injuries accounted for 62.5% of ocular trauma in China.[15-20] However, in previous studies, both types of injuries were reported at similar proportions.[15-35]

## Proliferative Vitreoretinopathy

Proliferative Vitreoretinopathy (PVR) is a pathological process that occurs due to abnormal wound healing leading to excessive growth and contraction of cellular membranes on the vitreous body and retinal surface after disruption of the integrity of the vitreous body caused by OGI or complications RRD. In 2016, Di Lauro et al. conducted a detailed analysis of the terminology still used in the PVR classification, first listed by the Retina Society Terminology Committee in 1983 in Table 1 as a complication of RRD.[36] The clinical severity of PVR is classified into four groups, namely A (minimal), B, C, and D (massive), and the initial terminology regarding PVR is still used in several studies today. The Retina Society Terminology Committee updated this terminology in 1991, retaining grades A and B but modifying grade C and eliminating grade D. Additionally, the Silicone Study Classification, as shown in Table 2, provides a more detailed description of PVR grade C (posterior and anterior) by including the type of pull and direction of the pull, which is described using the clock direction according to the location of the pull.[36–41]

The membrane observed in PVR comprises a cellular component derived from glial and retinal pigment epithelium (RPE) cells, a macrophage component, and a collagen component. The proliferation and separation of RPE cells from exposed pigment epithelial cells combine with proliferating glial cells to produce contracted collagen membranes that cover the surface of the retina and vitreous matrix, leading to the formation of funnel-shaped retinal detachment, which is a severe consequence of PVR. PVR is the most frequent cause of failure after RRD repair, with a failure rate ranging from 50-75%. Clinically, PVR appears as a rigid and folded retina (as outlined in Table 1), which then deteriorates into a funnel-shaped or immobile RD. The incidence of PVR in RRD is observed in 5-10% of cases preoperatively and 4-34% postoperatively. However, in patients with OGI, the incidence of PVR is increased by up to 50% and can lead to RRD.[4,26,42]

In the case of sharp injury to the eye, the retinal tissue undergoes wound healing, often resulting in scar tissue that does not function properly, leading to a decline in visual acuity if left untreated. PVR pathogenesis is a multistage

process, which involves: 1) migration of cells, particularly RPE and glial cells; 2) proliferation of migrating cells; 3) formation of membranes; 4) contraction of cellular membranes; 5) production of extracellular collagen; and 6) development of rigid folds in the retina (As illustrated in Figure 2).[24,25,37,38,43]

The detachment of the outer and inner layers of the retina initiates cell migration. The ischemia in the outer layer leads to photoreceptor apoptosis and subsequent cell death. In response to neuronal death, retinal glial cells undergo hypertrophy, which triggers the remodeling of the retinal lining. However, excessive remodeling can lead to the replacement of neuron cells by glial tissue and the shortening of retinal photoreceptor cells. Damage to the blood-retinal barrier (BRB) causes the migration of microglia and macrophages to the subretinal area, which then migrate to the vitreous cavity. When macrophages encounter the vitreous, they release inflammatory cytokines that stimulate cell migration and proliferation. Recent studies have shown that inflammatory mediators, such as growth factors and cytokines, present in the vitreous or subretinal fluid play a critical role in developing PVR. While various inflammatory mediators have been proposed to cause PVR, only a few have clinical relevance, including transforming growth factor-β (TGF-β), PDGF, basic fibroblast growth factor (bFGF), VEGF, interleukin-1 alpha (IL-1α), IL-1β, IL-2, IL-3, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1), chemokine ligands CCL2, CCL11, CCL17, CCL18, CCL19, CCL22, CXC Motif Chemokine Ligand 8 (CXCL8), CXCL9, and CXCL10, as well as several other proteins.[26,37,38,41]

Retinal detachment (RD) is a triggering event that can initiate a cascade of pathophysiological processes leading to Proliferative Vitreoretinopathy (PVR) and subsequent retinal re-detachment. The initial insult of RD can cause damage to the blood-retinal barrier, inflammation, activation of glial and retinal pigment epithelial (RPE) cells, and hypoxia in retinal tissue. This, in turn, results in the release of various cytokines, growth factors, and chemokines that facilitate RPE cell migration, proliferation, and epithelial-mesenchymal transition. These fibrotic cells migrate into the vitreous body and begin laying down membranes on the retina's surface, which subsequently contract and cause recurrent retinal detachment. Additionally, ischemia of the outer retina leads to cell death of retinal photoreceptors and the development of intraretinal fibrosis, ultimately resulting in retinal ossification.[44-46]

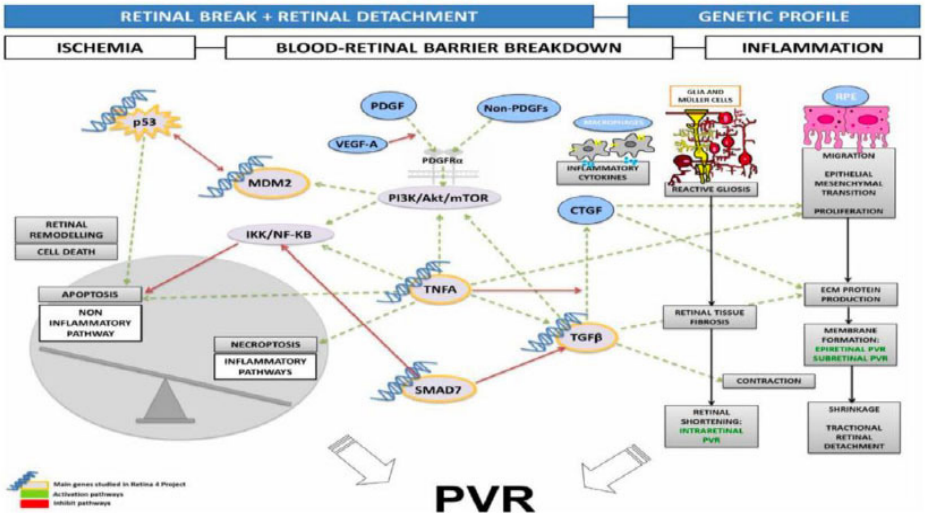


**Figure 2.** Graphic of PVR pathogenesis based on genetic findings and the relation between tissue change and cell death mechanism.[37]

## TGF-β Role on PVR

TGF-β is a multifunctional cytokine that exerts diverse effects on various physiological processes such as immune response regulation, cellular migration, proliferation and differentiation, vascular homeostasis, wound healing, fibrosis, motility, adhesion, extracellular matrix protein synthesis, cancer metastasis, and apoptosis. Within the eye, TGF-β is a crucial modulator of cellular behavior in different tissues. Generally, TGF-β enhances extracellular matrix production, inhibits cell proliferation, and activates multiple growth factors, including CTGF, PDGF, VEGF, and FGF. Moreover, TGF-β triggers intracellular signaling cascades involving Smad and mitogen-activated protein kinase (MAPK) proteins. As a fibrogenic cytokine, TGF-β is involved in the epithelial-mesenchymal transition (EMT) process and contributes to the transformation of fibroblasts into myofibroblasts.[47-50]

The aqueous and vitreous humors in the eye harbor various cytokines and growth factors also present in the corneal endothelium, iris, lens, trabecular meshwork, and retina. Among these, TGF-β, particularly TGF-β2, is the predominant cytokine in ocular tissue. The concentration of TGF-β varies in the progression of ocular diseases. For instance, in proliferative vitreoretinopathy (PVR), TGF-β2 concentration in the vitreous humor rises proportionally with the severity of PVR. TGF-β2 levels are also elevated in conditions such as diabetic retinopathy and open-angle glaucoma. Elevated TGF-β levels base the pathogenesis of fibrotic eye diseases,

**Table 3. Notable characteristics of corticosteroids used in ophthalmology.**[8]

| Characteristics | Dexamethasone | Fluocinolone | Triamcinolone |
|---|---|---|---|
| Molecular weight (kDa) | 0.392 | 0.452 | 0.394 |
| Affinity bond (nmol) | 5.4 | 2.0 | 1.5 |
| Intravitreal half-life | 5.5 hours | Unknown | 18 days (crystalline) |
| Relative potency (cortisol = 1) | 25 | 25 | 5 |

which can affect visual acuity and eye homeostasis.[25,48-50]

## The Role of Corticosteroids in PVR Therapy

There have been various attempts to find effective drugs and drug delivery methods for treating PVR. However, no standard therapy is currently available for preventing or treating PVR in clinical stages. Researchers are exploring several drugs, including anti-inflammatory, anti-proliferative, antineoplastic, anti-growth factor, and antioxidant agents, through in vitro and in vivo studies, also randomized controlled trials (RCT).[37,51]

Corticosteroids provide anti-inflammatory and immunosuppressive effects. Glucocorticoids are a subgroup of steroids widely used to treat eye diseases. It can be administered locally (topical: sub-conjunctiva, periocular: sub-Tenon, peribulbar, and intravitreal) or systemically. Local administration is preferred as it can penetrate the blood-retinal barrier, thus increasing drug concentration in the target area and minimizing systemic side effects.[28,52]

PVR can trigger retinal abnormalities and corticosteroids are believed to prevent this condition by inhibiting blood-retina barrier (BRB) damage as well as reducing inflammatory cytokines. Triamcinolone acetonide, dexamethasone, and fluocinolone are some glucocorticoids without mineralocorticoid activity commonly used locally. Triamcinolone acetonide (TCA) is a highly potent steroid, 15 times stronger than cortisone, with a half-life of 18 to 36 hours. Due to its insoluble nature in water, it acts as a depot in the vitreous cavity.[5,28,53,54]

## Triamcinolone Acetonide (TCA) as Potential PVR Therapy

Triamcinolone Acetonide (TCA) is a synthetic steroid belonging to the glucocorticoid family, with a fluorine atom replacing a hydrogen atom in the ninth position. TCA is available in various forms, such as esters, alcohol, and a chloroform-soluble white powder, as indicated in Table 3. In an in vivo model of rat eye vitreous, Oishi et al. reported a half-life of 6.08 days for TCA.[56] However, the mean half-life was 18.6 days in eyes that had not undergone vitrectomy and significantly reduced to 3.2 days in vitrectomized eyes. The level of TCA in aqueous humor ranges between 2.15 – 7.20 mg/mL and is found to be higher after intravitreal injection compared to sub-tenon injection. Banerjee et al. conducted a randomized trial on human subjects and found that intravitreal and subconjunctival TCA injection, either pre-operative or during pars plana vitrectomy (PPV), resulted in better anatomical improvement and visual acuity.[23] An intravitreal injection of 4 mg/0.1 mL TCA is effective for 2-4 months.[23,55,56]

Intravitreal TCA injection (TCA IVIT) is generally well-tolerated and has a favorable safety profile. Multiple studies have shown that the most common complication associated with TCA IVIT is increased intraocular pressure, which can be managed by administering topical anti-glaucoma medication. Other potential complications that may arise from TCA IVIT include post-injection endophthalmitis, post-injection cataracts, rhegmatogenous retinal detachment (RRD), central serous chorioretinopathy, and systemic TCA toxicity.[15,52,57]

## The Role of Anti-VEGF in PVR Therapy

Vascular Endothelial Growth Factor (VEGF) is a crucial factor in stimulating angiogenesis, which is the formation of new blood vessels by endothelial cells during the proliferative phase of wound healing. However, excessive stimulation of VEGF can lead to pathological angiogenesis. While angiogenesis is normal during childhood, it can also appear later in life during various pathological conditions. Maintaining a balance between angiostatic conditions and angiogenesis in the ocular vascular system is critical to prevent pathological vessel growth. Ischemia is one of the triggers of neovascularization in eye diseases. In ischemic neovascularization, new capillaries grow and branch from retinal arteries, which can be vulnerable to retinal hemorrhage and may trigger retinal detachment.[32,38]

Angiogenesis is a complex process heavily reliant on VEGF, a derivate from platelet-derived growth factor (PDGF) that stimulates the growth and proliferation of new blood vessels and influences vascular permeability. VEGF-A has been identified as a crucial factor in this process. Research studies have demonstrated that blocking the activity of VEGF-A through the use of anti-VEGF agents can result in a reduction of PVR bioactivity in the vitreous. Consequently, several therapeutic strategies aimed at inhibiting VEGF activity are still being investigated.[8,32,38,58–60]

Anti-VEGF therapies, which are derived from humanized monoclonal antibodies, have demonstrated efficacy in inhibiting the progression of several retinal diseases, including age-related macular degeneration (AMD), diabetic retinopathy, choroidal neovascularization in pathologic myopia, and congenital disorders. However, the need for serial injections every few months remains a significant healthcare burden. To address this issue, ongoing research is focused on developing new anti-VEGF agents that offer longer-lasting effects, such as slow-release systems, genetic therapy, and angiogenesis molecular target therapy.[27,61–65]

Pegaptanib is the first identified and discontinued anti-VEGF agent, a small RNA fragment with a molecular weight of 5 kDa. It selectively binds to the VEGF165 isoform, thus interfering with its interaction with receptors on endothelial cells. The second anti-VEGF agent discovered is Bevacizumab, a monoclonal antibody that targets the VEGF-A receptor. While approved by the FDA for systemic cancer therapy, it is used off-label for treating eye disorders due to its cost-effectiveness compared to other anti-VEGF agents. Ranibizumab is a recombinant humanized immunoglobulin G1k antibody fragment with a molecular weight of 48 kDa. It can bind to all isoforms of VEGF-A and has a shorter half-life, approximately 75% of Bevacizumab's, attributed to its smaller molecular weight. The latest anti-VEGF agent approved for ocular use in Europe and America is Aflibercept. Aflibercept is a fusion protein (115 kDa) consisting of the second immunoglobulin receptor domain of vascular endothelial growth factor receptor-1 (VEGF-R1) and the third domain of human VEGF-R2, along with a portion of the human Fc IgG1 region. Aflibercept has a higher competitive

inhibitory binding affinity to VEGF-A when compared to ranibizumab and Bevacizumab.[58,66,67]

## Bevacizumab as Potential PVR Therapy

Bevacizumab is a non-selective intact monoclonal antibody against VEGF of the immunoglobulin G1 (IgG) class. It inhibits the proliferation of fibroblasts mediated by the VEGF-A isoform by binding to the VEGF receptor, inhibiting proangiogenic signals. While Bevacizumab is widely recognized for its anti-neovascular properties and approved by the US Food and Drug Administration (FDA) as intravenous adjuvant therapy in metastatic colorectal cancer patients, several studies have shown that it may also have antifibrotic effects for ocular diseases. In 2004, it was used in neovascular age-related macular degeneration (AMD) patients. Although not yet officially approved, the use of Bevacizumab as an off-label therapy for other ocular neovascular diseases such as diabetic retinopathy, retinal vein occlusion (RVO), retinopathy of prematurity (ROP), and other ocular neovascular disorders has been reported.[40,68–70]

Bevacizumab is a fully intact antibody with a molecular weight of 149 kDa, which is larger than other anti-VEGF agents such as ranibizumab, aflibercept, pegaptanib, and conbercept, resulting in a shorter half-life in the vitreous cavity and slower absorption by retinal tissue. Numerous pharmacokinetic studies have been conducted to determine the efficacy of anti-VEGF agents in clinical settings. An animal study conducted by Zhao et al. investigating the effects of anti-VEGF agents, such as ranibizumab and conbercept, has shown their ability to reduce the levels of growth factors and cytokines, especially VEGF, PDGF, TGF-β, and PAI-1. Inhibiting wound fibrosis was found to be more effective in conbercept than ranibizumab. Aflibercept, on the other hand, demonstrated a protective effect on the eye of the rabbit model of PVR by neutralizing VEGF, according to a study by Pennock et al.[1–3,27,38,71]

Anti-VEGF drugs, including pegaptanib, ranibizumab, and Bevacizumab, are contraindicated for pregnant patients due to their potential teratogenic effects in animal studies. While ranibizumab and Bevacizumab are labeled as category C drugs for pregnancy, their safety in pregnant women has not been established. Furthermore, using Bevacizumab during pregnancy has been linked to spontaneous miscarriage in diabetic macular edema (DME) patients. Pregnant women should avoid Bevacizumab and other anti-VEGF drugs because angiogenesis is crucial for fetal growth and development. Patients with cardiovascular disease, a history of stroke, or peripheral vascular disease should also avoid Bevacizumab due to its potential to cause thromboembolism and worsen their condition.[8,67]

In 2006, the International Intravitreal Bevacizumab Survey conducted research to evaluate the safety profile of 70 service centers in 12 countries, involving 7,113 injections in 5,228 patients with various eye diseases. The reports were categorized into procedure-related and drug-related side effects. The drug-related side effects were further classified as ocular and systemic side effects. Corneal abrasion (0.15%) was the most frequently reported side effect across all categories. Mild grittiness (0.14%), retinal detachment (0.04%), subconjunctival hemorrhage (0.03%), lens injury (0.01%), and endophthalmitis (0.01%) were among the procedure-related events reported. Ocular adverse events were inflammation or uveitis (0.14%) and acute vision loss (0.07%). Additionally, an increase in blood pressure was reported at 0.21%. Cox et al. identified three types of inflammation side effects in their review: sterile intraocular inflammation (SII), brolucizumab-associated retinal vasculitis (BARV), and infectious endophthalmitis.[58,61,62,67]

## Open-globe injury in New Zealand Rabbits (*Oryctolagus cuniculus*) Model

Experimental animal models are essential research tools used to investigate and find treatments for various eye diseases that may cause visual impairment and blindness in humans. Common eye diseases such as dry eye syndrome, age-related macular degeneration (AMD), glaucoma, and uveitis require thorough research on etiology, pathogenesis, and disease progression. However, experimental animal models in a controlled environment are often required due to the high variability of human diseases. Obtaining human retinal tissue for pre- and post-intervention comparisons is challenging, making animal models an attractive option. The literature mentions several animals, including monkeys, horses, pigs, dogs, cats, rabbits, and rats, as models for ocular disease. Although primates are the most representative, their breeding and facility requirements make them inaccessible to most researchers. Dogs and cats are also unsuitable due to their aggressive nature. Rats and rabbits are widely used due to their accessibility, ease of breeding, and economic feasibility. However, mice are considered less suitable for experimental eye studies due to their smaller eye volume than rabbits (50 – 55 mL vs. 1.15 – 1.7 mL), which restricts their manipulation in these studies.[72–76]

Rabbits are a commonly used experimental animal model for ocular research due to their ease of care, rapid breeding, and cost-effectiveness. Regarding anatomy, rabbits possess relatively large eyeballs that share many characteristics with human eyes, including similar eyeball size, internal structure, optical system, biomechanics, biochemistry, and conjunctival cavity. Notable differences in rabbit eyes include a larger anterior segment, a Hardarian gland that allows rabbits to hold their blinks longer, and a thin and fragile retinal layer. Additionally, rabbits lack a macula but possess a visual streak, with the highest photoreceptor and ganglion cell activity. Despite these similarities, it is important to note that rabbit eyes do not fully resemble human eyes, and researchers must understand this limitation when interpreting their experimental results. Nonetheless, rabbit eyes remain a valuable and accessible tool for ocular research for most researchers.[76,77]

Los et al.[78] conducted a study comparing the vitreous matrix in humans and rabbits. The study revealed similarities between the differentiation and degeneration processes of the vitreous matrix in both humans and rabbits. Based on these findings, it can be concluded that rabbits are a viable animal model for research requiring the manipulation of the vitreous. This

study provides valuable insights into the similarities between the vitreous matrix in humans and rabbits, which may aid in developing novel treatments for various vitreous-related diseases.

In animal model studies, research on PVR's pathogenesis after OGI events have been explored using various induction methods. For instance, PVR induction in human eyes has been achieved by injecting cells or factors present in PVR analysis, such as fibroblasts from skin cultures, RPE cells, activated macrophages, or platelet-rich plasma (PRP). Mechanical manipulation methods have also been used, such as posterior penetrating wound creation 6-8 mm from the posterior limbus, lensectomy, and vitrectomy. However, the cells injected in these studies differ significantly from those found in human PVR. While these methods represent the human condition, the model depends on the type of cells injected rather than the RPE or glial cells that transform into fibroblasts in human PVR. Moreover, these methods occur within a relatively short time frame and do not accurately replicate the progression of PVR in human eyes. In a study conducted by Moon et al., VEGF and Matrigel injections were administered, resulting in gradual progression to late-onset PVR.[2,37,40,77,79,80]

Rabbits are commonly used as animal models in preliminary studies related to the eye. Unlike humans, rabbits have almost no pars plana, and the ora serrata is located 3 mm posterior to the limbus. Additionally, the vascularization of the rabbit's retina follows a merangiotic pattern, in which the vascularization of the retina is limited to a part of the retina, in contrast to the holoangiotic pattern observed in primates. The rabbit's retinal layer is thinner and more delicate due to low vascularization, and part of the retinal layer is covered with oligodendrocytes. These differences in anatomy and vascularization are some of the factors that may contribute to variations in the rabbit's eye response to retinal trauma as compared to the human eye.[37,79]

PVR is an abnormal wound-healing process characterized by the formation of fibrous tissue, which can lead to vision loss and negative surgical outcomes. In a rabbit model study, fibrosis was observed in the posterior penetrating injury model on day 14, and more severe fibrosis was found on day 28. Fibrosis biomarkers, such as alpha-smooth muscle actin (α-SMA) and collagen type-1 (Col-1), were identified by Greene et al. in the rabbit eye. The results of this study are consistent with Zhao et al.[1,80]

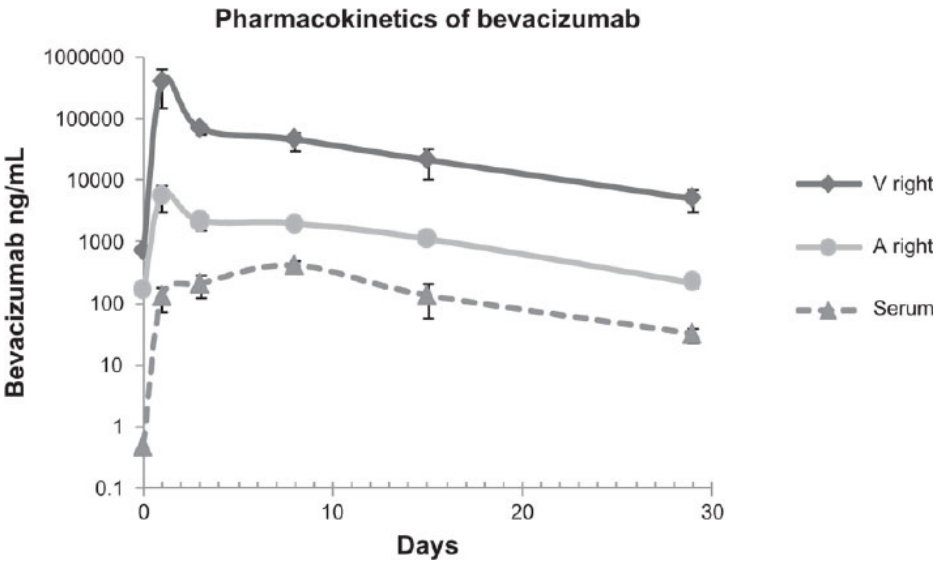


**Figure 3.** The concentration of Bevacizumab in the right vitreous (v), aqueous humor (a), and serum following administration of 1.25 mg/50 mL intravitreal bevacizumab injection to the right eye.[81]

## Intravitreal injection as PVR prevention therapy in OGI eye model

Various routes of drug administration to the eyeball have been investigated in rabbit eyes as a model for various diseases, including OGI. The goal is to increase drug concentrations while suppressing systemic absorption. Intracameral or intravitreal injections can be administered to the rabbit eye using a 26 G – 30 G needle. The pars plana, which lacks vascularization, is the expected location for intravitreal administration. This location can be reached by inserting the needle 2-4 mm posterior to the limbus in any quadrant, although the superior quadrant is commonly preferred due to easy accessibility. In assessing drug effectiveness, histopathological analysis, immunoassay of drug concentration in each eye compartment, and pharmacokinetics based on half-life or highest drug concentration can be carried out.[1,2,73,81]

Rabbits have been extensively utilized in pharmacokinetic studies of intravitreal drugs, including moxifloxacin, etanercept, triamcinolone acetonide, and Bevacizumab. In intravitreal drug studies, the key anatomical differences between rabbit and human eyes are the relatively smaller vitreous cavity in rabbits (1.5 mL vs. 4.5 mL in humans), the smaller serum compartment, and the less densely vascularized retina. Researchers must also consider the use of rabbit species, where pigmented rabbits are preferred if the goal is to evaluate the effects of drugs on the human eye. This preference arises from drug interactions with eye pigments more representative of the human eye in pigmented rabbits. On the other hand, albino rabbits are more recommended for examining drug pharmacokinetics, as this interaction could be a confounder in the case of pigmented rabbits.[73,77,81]

PVR is a common side effect of OGI, characterized by excessive fibrosis formation during intraocular wound healing. Despite advances in vitreoretinal surgical techniques, the impact of PVR on poor visual acuity outcomes following pars plana vitrectomy (PPV) has not been fully eliminated. Therefore, preoperative and intraoperative interventions to prevent PVR are still being developed. The intravitreal injection has been extensively investigated, as previously mentioned. Thus, this study focused on reviewing the effects of intravitreal injection of triamcinolone acetonide (TCA) and Bevacizumab following OGI events to

prevent PVR.[1,2,40]

TCA IVIT has been tested in several preclinical researches. Animal model studies have generally not shown significant intraocular toxicity effects for TCA. For example, Kim et al. observed the administration of 4 mg of preservative-free TCA in the eyes of New Zealand albino rabbits that lasted for up to 24 days, while 4 mg of Kenalog lasted for 23 days.[52,82]

The most concerning adverse reaction of TCA containing the preservative benzyl alcohol is the development of sterile endophthalmitis. In a study by Dierks et al., three groups of rabbits were given commercial TCA injection, supernatant, and TCA reconstituted with BSS solution. No toxic effects were observed via clinical examination, histopathology, and electroretinography (ERG) within seven days. Similar findings were observed in other animal model studies with longer follow-up periods, such as the study by Albini et al. that observed rabbits for up to 12 weeks. These results suggest that differences in retinal vascularization between humans and rabbits may contribute to the different absorption effects of TCA in rabbits compared to humans.[55,82–84]

The pharmacodynamics of intravitreal Bevacizumab in rabbit eyes at a dose of 1.25 mg/50 µL was studied by Sinapis et al.[81] The study revealed variations of bevacizumab concentrations in the anterior chamber, blood serum, and contralateral eye post-injection. This is the most common dosage used in animal models and clinical trials. The highest concentration of Bevacizumab was observed on the first day of injection (406.25 µg/mL) with a half-life of 6.61 days. The drug concentration remained stable at 5.17 µg/mL for 29 days. On the other hand, the concentration of Bevacizumab in the aqueous humor was about 1/8 of the vitreous and decreased successively in blood serum, left eye aqueous humor, and left eye vitreous (Figure 3). The study by Ye et al.[85] reported a shorter vitreous half-life of 3.91 days. The prepared bevacizumab-poly (L-lactic-co-glycolic acid) (PLGA) microspheres or sustained bevacizumab release can increase the concentration almost threefold, i.e., up to 9.6 days.[2,73,77,81,85]

The study conducted by Dinc et al. revealed a decrease in anti-VEGF levels in rabbits on the eighth day following injection.[69] In contrast, several clinical studies have reported a rapid decrease in anti-VEGF levels in humans on the first day after injection. This difference may be attributed to the slower absorption rate of the retina in rabbits compared to humans, despite the high drug concentration. Intravitreal administration of Bevacizumab also detected trace amounts of the drug in distal organs, such as the brain, heart, liver, and colon. It is hypothesized that the drug crosses the retinal-ocular barrier and enters the systemic circulation, necessitating further investigation into the potential effects of Bevacizumab on other organs.[2,69,77,81,85]

Injection of intravitreal triamcinolone acetonide and Bevacizumab in the OGI eye has been found to have low levels of toxicity in various in vivo studies. However, the doses utilized varied among studies, and the correlation between drug dosage, its efficacy, and side effects was not extensively explored. While higher doses may result in better outcomes, they are also associated with more serious adverse events.[86-89] On the other hand, the effects of both TCA and Bevacizumab on inflammation and wound healing biomarkers such as TNF-α, interleukins, VEGF, PDGF, TGF-β, and PAI-1 were not adequately elucidated in previous OGI eye model studies. Thus, further research is required to determine the most effective dose to prevent PVR while minimizing toxicity. Such research should focus on the effect of a range of drug doses on measurable outcomes such as the inflammation and wound healing markers before stepping up to clinical trials.

## CONCLUSION

Triamcinolone acetonide (TCA) and Bevacizumab are two commonly used therapies that have shown promise in preventing PVR by reducing inflammation and suppressing fibrosis. However, several adverse events have been reported following TCA or bevacizumab administration, indicating a need for further research to assess their safety and efficacy. Overall, preventing PVR is crucial to maintain good visual acuity and quality of life in patients who have suffered an OGI.

## CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

## ETHICAL CONSIDERATION

Not applicable as this in a review article.

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## AUTHOR'S CONTRIBUTION

All authors contributed equally to this review article from the conceptual framework, data acquisition, and data analysis until reporting the study results through publication.

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