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Review Article

Intravitreal Administration of Corticosteroids and Anti-Vascular Endothelial Growth Factor (Anti-VEGF) Agents to Prevent Proliferative Vitreoretinopathy in Open Globe Injury: A Review

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ABSTRACT

Proliferative vitreoretinopathy (PVR) may occur as a complication in cases of open globe injury (OGI), where full-thickness injuries occur on the cornea or sclera. PVR arises due to excessive healing of vitreoretinal wound, significantly affecting poor visual outcomes. Although there have been advancements in vitreoretinal surgical techniques, effective prevention and management of PVR remain elusive. The use of pharmacological agents, especially intravitreal corticosteroids and anti-vascular endothelial growth factor (anti-VEGF) therapies has gained considerable attention. This article explores the phases of wound healing in OGI, highlighting the role of inflammatory responses in both wound healing and potential complications like PVR. Corticosteroids exhibit anti-inflammatory effects and reduce blood-retinal barrier (BRB) damage. Triamcinolone acetonide (TA), dexamethasone, and fluocinolone are among the most common locally administered corticosteroids. In addition, the role of anti-VEGF agents in PVR prevention is explored. VEGF plays a significant role in angiogenesis and neovascularization, making it a target for intervention. Various anti-VEGF agents, such as bevacizumab, ranibizumab, and aflibercept, are discussed for their potential to inhibit PVR progression. Intravitreal administration of these agents is a strategy to target PVR while minimizing systemic side effects. Even so, further clinical trials to establish the efficacy of intravitreal corticosteroids and anti-VEGF therapies in preventing PVR among OGI patients are still needed. PVR remains a complex challenge, and pharmacological approach is a promising treatment strategy to improve visual outcomes and quality of life for affected individuals.

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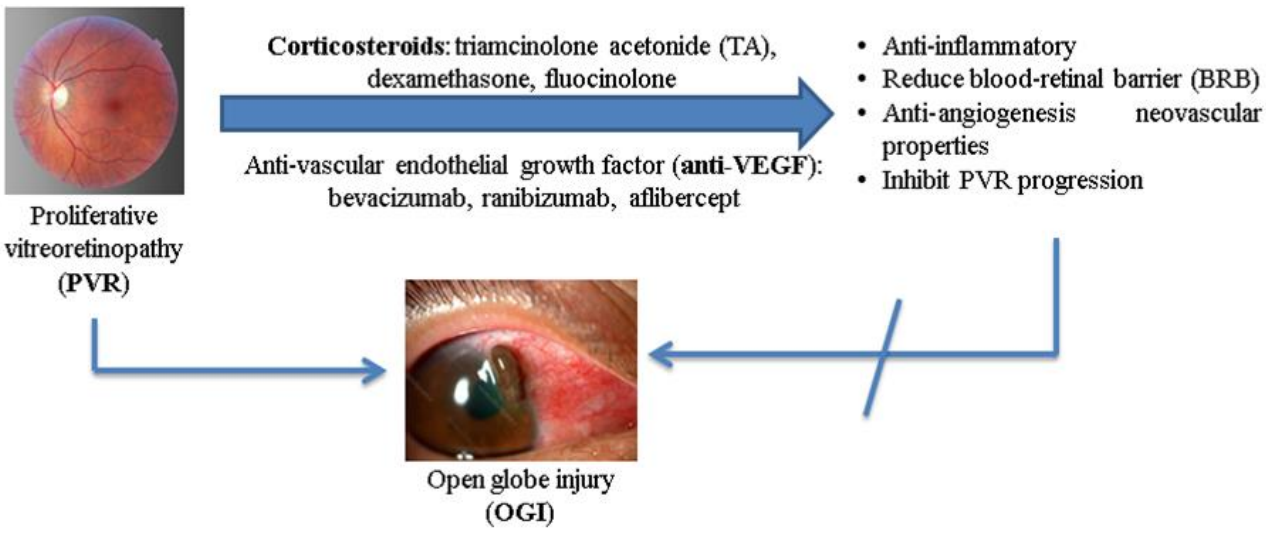
GRAPHICAL ABSTRACT



Introduction

Open globe injury (OGI) is full-thickness injury on the cornea or sclera. Proliferative vitreoretinopathy (PVR) that occurs in OGI is caused by excessive healing of vitreoretinal wound due to retinal tear and inflammatory response to the entrance of retinal pigment epithelium (RPE) inside the vitreous cavity. In the general population, PVR incidence rates vary from 5 to 10%. In OGI, this number may reach 50%. This leads to poor visual outcomes in a quarter of the population, diminishing an individual's quality of life and imposing a significant economic burden [1-4]. Despite rapid development of vitreoretinal surgical techniques, the PVR management still remains a challenge. While successful anatomical outcomes can be achieved in surgery, visual acuity results are still unsatisfactory. Currently, the use of pharmacological agents to prevent PVR formation in OGI patients has gained considerable attention, particularly anti-inflammatories and anti-proliferative agents [5]. Corticosteroids have demonstrated the ability to reduce degradation of blood-retinal barrier, suppress inflammation, and inhibit the generation of vascular endothelial growth factor (VEGF) [6, 7]. Furthermore, utilization of anti-VEGF agents in OGI have demonstrated reduced up-regulation of growth factors and cytokines within the vitreous humor, potentially preventing complications such as PVR [5]. The intravitreal administration of these medications is one important clinical strategy, aiming to enhance drug concentration while minimizing potential systemic side effects [8, 9]. For instance, intravitreal triamcinolone has been used in prevention and management of PVR as well as choroidal and retinal neovascularization [7]. However, up to this point, a clinically established and proven medical therapy for PVR prevention remains elusive. In this review, we aim to summarize the current evidence concerning the use of intravitreal corticosteroids and anti-VEGF therapies in preventing PVR among OGI patients.

Current State of Knowledge

Open globe injury (OGI)

Epidemiologically, the OGI incidence reaches 200.000 every year. OGI is an injury which involves the entire thickness of the ocular wall (cornea and/or sclera) caused by sharp objects (penetration, perforation, or intraocular foreign bodies) or blunt objects (globe rupture). Eyes experiencing OGI, especially the perforating type, are at high risk of severe vision impairment.

Retinal detachment often occurs in OGI cases, which requires multiple surgical procedures. Proliferative vitreoretinopathy (PVR) is the most frequent cause of retinal detachment and vision loss in OGI. It is estimated to occur in approximately 10-45% of all OGI cases [10-12].

Wound healing in open globe injury

The process of wound healing in OGI is a dynamic and complex process which comprises of three phases: inflammation phase, proliferative phase, and remodelling phase. In each step, certain cells, cytokines, and chemokines play dominant roles. While this process is essential for wound healing, under certain conditions, it may occur excessively, resulting in chronic inflammation which damages the eye's structures [13-15].

Inflammatory phase

The inflammatory phase consists of two stages: early inflammation and late inflammation. The main goal of inflammation is to prevent infection since the mechanical barrier as the frontline of defense against microorganisms is compromised due to the injury [16]. Neutrophils are the first cells involved in early inflammatory stage. They are highly motile and enter the wound area within the first 24 hours. The entry of neutrophils in wound area is mediated by various complement cascades, interleukins, and TGF-β, a process known as chemotaxis. There are three main mechanisms by which neutrophils destroy debris and bacteria. First, they engage in phagocytosis, engulfing and destroying foreign particles. Second, neutrophils undergo degranulation, releasing various toxic substances such as lactoferrin, protease, neutrophil elastase, and cathepsin, which will destroy bacteria and tissue debris [17]. Macrophages are phagocytic cells which are much larger and reach their peak concentration in 48-72 hours after injury or during the late inflammatory stage. These macrophages result from the maturation of monocytes that enter the wound area with the help of local cytokines. These cytokines and chemokines are released by platelets and damaged cells. Macrophages have a large reservoir of growth factors, such as TGF-β and EGF, which play a crucial role in regulating the inflammatory response, stimulating angiogenesis, and enhancing the formation of granulation tissue. Moreover, they are involved in eliminating bacterial residues, necrotic tissues, and senescent neutrophils. Lymphocytes appear in the wound area within 72 hours and play a significant role in regulating wound healing by producing extracellular matrix and remodeling collagen. Inhibition of T lymphocytes in experimental studies has shown a decrease in wound strength and abnormal collagen deposition. The inflammatory phase will persist until all bacteria and debris in the wound bed are removed. However, a prolonged inflammatory phase will lead to extensive tissue damage, hindered proliferation, and formation of chronic wounds [17].

Proliferative phase

The formation of granulation tissue is a hallmark of this stage. Moreover, in the proliferation phase, angiogenesis, collagen deposition, epithelialization, and wound contraction occur simultaneously. This phase lasts for 2-10 days after the injury, during which fibroblasts and endothelial cells are the last cells to penetrate. Subsequently, fibroblasts will secrete extracellular matrix (ECM) proteins and ground substance components. Fibroblasts function as regulators of collagen, glycosaminoglycans, proteoglycans, fibronectin, and elastin as components of the ECM. Various factors are identified in this stage, such as blood components, PDGF, TGF-β, monocyte chemoattractant protein-1 (MCP1), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), connective tissue growth factor (CTGF) and VEGF [18]. VEGF is found in the proliferation phase as a mediator of cellular proliferation and vascular permeability. It stimulates proliferation and migration in ocular wound healing, promoting angiogenesis [19, 20]. Elevated levels of VEGF are detected in patients with PVR, making it a target for PVR control therapy. VEGF is secreted by retinal pigment epithelium (RPE) cells and glia, acting as autocrine and paracrine stimulators. They

contribute to the progression of fibro-vascular membrane formation, neovascularization of the peripheral retina, cilliary body, and anterior segment [21].

Remodelling phase

The remodeling phase starts around 2-3 weeks after the injury and continues for one year or longer. During the final stage of wound healing, immature fibro-vascular tissue undergoes reformation and remodeling into mature fibrovascular tissue. This stage also shows decreased proliferation and inflammation, reorganization of the ECM, and regression of newly formed capillaries. Balance between synthesis and degradation is crucial for this phase. ECM comprises collagen, glycoproteins, glycosaminoglycans, and proteoglycans. Plasminogen activator and matrix metalloproteinase (MMP) mediate ECM degradation by mobilizing hyaluronan and fibronectin. Certain inflammatory cells (including fibroblasts, neutrophils, and macrophages) can synthesize MMPs at the wound site. MMPs form collagenase and gelatinase enzymes, regulated by tissue inhibitors of metalloproteinases (TIMPs). Proteoglycans are deposited and collagen type III is replaced by collagen type I as fibroblasts decrease. Collagen becomes cross-linked, dehydrates, and transforms into a dense, hypocellular scar tissue. Myofibroblast is reduced through apoptosis [14, 15]. In PVR, ECM remodelling through contraction of the fibrocellular membrane creates pulling forces, leading to wrinkles in the retinal layer, star-fold formation, and tractional retinal detachment. In PVR membranes, detected ECM components include structural proteins, adhesive proteins, and anti-adhesive proteins.

The balance between MMP and TIMP regulates ECM turnover and tissue remodeling associated with PVR. Cellular components synthesizing MMPs are RPE cells, glial cells, and fibroblasts. Moreover, MMP activation is necessary for ECM contraction. Given the diverse cellular and soluble factors involved in PVR formation, therapy based on inhibiting any single factor or phenomenon remains sceptical. Vitrectomy surgery, as a definitive surgery for PVR therapy, is required to eliminate activated cells and membranes [22, 23].

Proliferative Vitreoretinopathy (PVR)

Pathogenesis of PVR

PVR is a multifactorial disease which is considered as an abnormal wound healing process, characterized by abnormal growth and contraction of cellular membranes within the vitreous cavity and on the retinal surface. This can occur as a complication of rhegmatogenous retinal detachment (RRD), surgical interventions, and trauma. PVR is a membrane which develops on detached retinal surface and posterior hyaloid. Posterior contraction of these membranes leads to retinal distortion and further progression into tractional retinal detachment (TRD). PVR is the most common cause of failure after RRD repair, accounting for about 50-75% of cases. Clinically, PVR presents as rigid and folded retina, later worsening into funnel-shaped or non-mobile retinal detachment [24-27]. In cases of ocular injury, the retinal tissue initiates wound healing. Ischemia of the outer retinal layers also occurs, leading to cell death through apoptosis and necroptosis pathways. This process typically results in non-functional scar tissue, leading to poor visual outcomes without treatment. The pathogenesis of PVR is divided into several stages: 1) cell migration, especially RPE and glial cells; 2) proliferation of migrating cells; 3) membrane formation; 4) contraction of cellular membranes; 5) production of extracellular collagen; and 6) formation of rigid folds on the retina [28-31].

A hallmark of PVR is the formation of fibrocellular membranes and intraretinal fibrosis. These membranes result from the interaction between retinal and extra-retinal cells with ECM components. Various cells contribute to this membrane, including retinal glial cells (Muller cells, microglia, and astrocytes), epithelial cells from RPE and the ciliary body, hyalocytes, immune cells from blood components (macrophages, lymphocytes, and neutrophils), fibroblasts, and myofibroblasts.

These cells are induced by the separation of the neuroretina from the RPE. Glial cells undergo hypertrophy and initiate nonspecific tissue repair, resulting in retinal remodelling. However, if this process becomes excessive, it can lead to replacement of neuron cells by glial tissue and shortening of retinal photoreceptor cells. Meanwhile, RPE cells differentiate into cells with fibroblast- and macrophage-like morphology. This process is also known as epithelial-mesenchymal transition (EMT). In fibro-proliferative membranes like PVR, glial cells, RPE cells, and fibroblasts transform into contractile myofibroblasts, expressing contractile protein α-SMA and vimentin, generating contractile forces. This is one reason why immunohistochemical examination does not just find a few glial and pigmented epithelial cells in the periretinal membrane. These membranes obstruct the retina's reattachment process [31].

Although the role of RPE cells has been reviewed in various literatures of the last three decades, the contribution of glial cells to PVR pathogenesis has recently gained our attention. Glial cells, particularly Muller cells, play a crucial role in normal retinal physiology. Muller cells, radial glia extending through the entire thickness of the retina from the subretinal space to the vitreous surface, along with astrocytes, are collectively known as macroglial cells. Macroglial and microglial cells in the retina function as immune cells. Furthermore, macroglial cells also support the function and metabolism of retinal neurons. In PVR, changes in Muller cells can be observed within a day after injury. On the third day, Muller cell bodies would migrate to the outer nuclear and outer plexiform layers, filling the spaces left by dead photoreceptors and extending their processes into the subretinal space. The hypertrophy of these Muller cells leads to reactive gliosis, creating massive and long-lasting cellular proliferation. In experimental studies, this process persists as long as the retina is still detached. Moreover, these activated Muller cells modulate immune and inflammatory processes by producing pro-inflammatory cytokines [32]. The blood-retinal barrier (BRB) damage leads to the migration of microglia and macrophages to the subretinal area, and the vitreous cavity.

Upon encountering vitreous tissue, macrophages release pro-inflammatory cytokines that stimulate cell migration and proliferation. Fibrocytes and macrophages function as precursor cells for myofibroblasts in PVR membranes. Recently, several techniques for managing PVR have been rapidly developed, providing good anatomical improvements, such as pars plana vitrectomy (PPV) combined with retinotomy around the entry wound, as studied by Victor *et al.* [33]. However, under certain conditions, functional improvement remains less satisfactory, prompting on-going research into adjunctive therapies [33].

Role of VEGF in PVR

The process of angiogenesis is mediated by growth factors such as VEGF, TGF, and PDGF. VEGF-A is an important growth factor involved in vasculogenesis and angiogenesis. VEGF-A activity occurs in most endothelial cells of blood vessels, stimulating migration of monocytes/macrophages, neurons, cancer cells, and kidney epithelial cells. In in vitro studies, VEGF-A stimulates endothelial cell mitogenesis and migration. VEGF-A also acts as vasodilator and increases micro-vascular permeability. Meanwhile, VEGF-B is a mitogenic factor for human endothelial cells. Elevated levels of VEGF-B are found especially in neural tissues (retina, brain, and spinal cord), myocardium, skeletal muscle, pancreas, and prostate [34]. Angiogenesis is the process by which new blood vessels form from pre-existing ones, expanding the vascular network [35, 36].

The newly formed blood vessels act as chemotactic agents and sources of blood cells such as monocytes and lymphocytes. VEGF is a major angiogenic factor in rabbit eyes, where anti-VEGF antibodies have been proven to block vascular proliferation [37, 38]. Currently, there are three known classes of growth factors in vitreous related to PVR: PDGF, non-PDGF/other PDGFs outside the PDGF family, and VEGF. All of these activate PDGFR, which downregulates TP53 and initiates PVR. Some reports suggest that VEGF-A can induce PDGFR activation through a non-PDGF-dependent pathway by antagonizing

PDGFR dimerization mediated by PDGF. Because VEGF is pivotal in PVR formation, various studies aim to halt or control it in animal models [4, 21].

Role of TNF-α in PVR

TNF-α is a pleiotropic pro-inflammatory cytokine found during infections, immune reactions, toxicity, trauma, and ischemia in the central nervous system. In various ocular diseases, TNF-α is identified as a key cytokine, such as in uveitis, exudative age-related macular degeneration (AMD), PVR, and diabetic retinopathy (DR). The immune privilege of the posterior eye is maintained by the RPE layer, which also functions as the BRB. TNF-α is primarily produced by macrophages activated by T lymphocytes as pro-TNF protein. This protein is then expressed on the plasma membrane and binds to MMP, transforming into a soluble form found in the extracellular space. Apart from macrophages, TNF-α is also produced by mast cells, B lymphocytes, natural killer cells, neutrophils, endothelial cells, smooth muscle cells, fibroblasts, and osteoclasts [39, 40]. TNF-α plays a role in the production and secretion of soluble tumor necrosis factor receptor I (sTNF-RI) and sTNF-RII receptors found in most nucleated cells. Both receptors bind to MMP and exist in soluble form in the serum. This binding is believed to neutralize the inflammatory effects of TNF-α *in vitro* and *in vivo*, making it a potential marker. TNF-α can disrupt the defense function of RPE, allowing RPE to adopt a pro-inflammatory phenotype, and increase levels of IL-6, IL-1β, IL-8, intercellular adhesion molecule 1 (ICAM-1), MCP-1, VEGF, and CXCL1, which attract neutrophils to participate in damage of epithelial defense [2-3,39].

Under normal conditions, TNF-α is not present in tissues. However, TNF-α levels increase both in the serum and tissues which undergo inflammation and infection. In RRD without PVR, TNF-α increases in the vitreous, insignificantly. This suggests that TNF-α does not play a significant role in acute and uncomplicated RRD. However, in patients with RRD accompanied by PVR, elevated levels of TNF-α are found in the vitreous. A similar phenomenon is also observed in patients with OGI that develops PVR [25, 41].

Corticosteroids as pharmacological therapy to prevent development of PVR

Various drugs and drug delivery systems have been attempted for PVR management, but as of now, there is no standardized therapy available for preventing or treating PVR in clinical stages. Drugs that have been the target of advanced research, both *in vitro*, *in vivo*, and randomized controlled trials (RCTs), include anti-inflammatory agents, anti-proliferative agents, antineoplastic agents, anti-growth factors, and antioxidants [21, 31]. Steroids are organic compounds with a 17-carbon core structure fused with three cyclohexane rings and one cyclopentane ring. Further, steroids are divided into two major groups: corticosteroids and hormonal steroids. With anti-inflammatory and immunosuppressive effects, glucocorticoid is commonly used in the field of ophthalmology. Since their introduction in the 1950s by McLean, the use of corticosteroids has been applied both locally (topical; subconjunctival, periocular: sub-Tenon, orbital floor, and peribulbar; as well as intravitreal) and systemically. Local administration is intended to penetrate the BRB, increasing drug concentration in the ocular area while minimizing systemic side effects [42-44]. Corticosteroids induce specific effects on lymphocytes, macrophages, polymorphonuclear leukocytes, endothelial cells of blood vessels, and fibroblasts [45].

At the tissue level, corticosteroids suppress hyperemia, vascular congestion, edema, and pain as responses to early inflammation. Meanwhile, in later stages, they also inhibit capillary and fibroblast proliferation, collagen accumulation, and scar tissue formation in the inflammatory response. Specifically, in PVR, corticosteroids are believed to inhibit BRB damage and reduce inflammatory cytokines [46-48]. Triamcinolone acetonide (TA), dexamethasone, and fluocinolone are some glucocorticoids without mineralocorticoid activity which are commonly used locally [49, 50].

TA can be used for ocular diseases and is said to be 15 times more potent than cortisone, has a long duration of action ranging from 18 to 36 hours, and is not water-soluble but lipid-soluble, acting as a depot within the vitreous. Currently, TA is available in the form of an ester, a white powder that is insoluble in water but soluble in alcohol and chloroform. The half-life of TA was described in an in-vivo model of the rat vitreous humor by Oishi et al., which was approximately 6.08 days [51]. In patients' eyes that have not undergone vitrectomy, the average half-life is 18.6 days, but in vitrectomized eyes, it decreases drastically to 3.2 days. The concentration in the aqueous humor ranges from 2.15 to 7.20 µg/mL. Concentrations after intravitreal injection are found to be higher compared to sub-Tenon administration. Regarding the TA effectiveness in humans, an RCT study conducted by Banarjee *et al.* regarding the use of TA intravitreal or subconjunctival administration showed favourable results both preoperatively and during PPV based on improvements in anatomical outcomes as well as visual acuity [11]. Intravitreal TA at a dose of 4 mg/0.1 mL has a duration of effect between two to four months [52-54]. Several studies have demonstrated the effects of intravitreal dexamethasone on inflammatory substances. Kuo *et al.* showed that administration of Ozurdex in a rabbit model of PVR can decrease the expression of TNF-α and IL-6 [55]. Meanwhile, a study by Villaneuva et al. demonstrated that dexamethasone reduces the expression of inflammatory cytokines (IL-1β**,** IL-6, IL-10, IL-1RA, TNF-α, and IFN-γ), chemokines, lipocortin, and metalloproteases (MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13), and TIMP-1. In addition, inhibition of BRB damage through decreased VEGF levels and inflammation via the NF-κB and mitogen-activated protein kinases (MAPK) pathways were also detected with dexamethasone administration (Table 1) [56].

Table 1: Characteristics of corticosteroids used in ophtamology [57]

Characteristics	Dexamethasone	Fluociolone	Triamcinolone
Molecular weight (kDa)	0.392	0.452	0.394
Binding affinity (nmol)	5.4	2.0	1.5
Intravitreal half life	5.5 hours	Unknown	18 days (crystalline)
Relative potency (cortisol = 1)	25	25	5

Table 2: Characteristics of anti-VGF agents used in humans [68-70]

Characteristics	Pegatanib	Bevacizumab	Ranibizumab	Aflibercept
Description	Pegylated aptamer	Full-length monoclonal antibody	Recombinant monoclonal antibody fragment	Fusion protein with receptor and Fc fragment of IgG
Molecular weight (kDa)	50	149	48	115
Clinical dosage (mg)	0.3	1.25	0.5	2
Intravitreal half-life (days)	7	9.8	7.1	9

Anti-VEGF as pharmacological therapy to prevent development of PVR

One of the most important aspects of the proliferation phase of wound healing is the formation of new blood vessels by endothelial cells (angiogenesis) [58, 59]. Normal angiogenesis is generally completed during childhood and re-emerges in later stages of life under certain pathological conditions. If angiostatic and angiogenic conditions can be maintained by the ocular vascular system, this can be prevented. Blood vessels are one of the angiostatic factors, and if there is instability, damaged cells will release angiogenic factors. Ischemia is one of the triggers of neovascularization in eye diseases. In ischemic neovascularization, new capillaries grow and branch from retinal arteries [21, 37]. Angiogenesis is highly dependent on VEGF [58]. VEGF is a form of PDGF that stimulates angiogenesis and affects vascular permeability.

The VEGF family of molecules consists of various ligands such as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placenta growth factor (PIGF). VEGF-A is the dominant mediator of pro-angiogenic signaling in ocular angiogenesis and has several isoforms with varying amino acid chain lengths (amino acids 121, 145, 165, 189, and 206), with VEGF165 being the predominant isoform in the neovascularization process. *In vitro* studies have also shown that VEGF, along with other factors, stimulate fibroblast proliferation in the vitreous. Several studies have also shown that inhibition of VEGF-A reduces the bioactivity of PVR in the vitreous. Therefore, various therapies targeting VEGF and other pathways are continuously under research [60-62]. Currently, anti-VEGF agents produced from humanized monoclonal antibodies have been shown to inhibit the progression of several diseases such as AMD, diabetic retinopathy, choroidal neovascularization in pathologic myopia, and congenital abnormalities. Although anti-VEGF provides favorable effects on visual acuity outcomes, there are gaps in real-world needs. Intravitreal injections require regular and often frequent evaluations, especially during the first two years. Furthermore, the currently available therapies are short-lasting. Thirdly, even though patients can achieve good vision, nearly 30% will experience vision loss due to inadequate anti-neovascular effects, progressive atrophy or subretinal fibrosis, and scar formation. Despite being an effective and beneficial therapy for various retinal diseases, serial monthly or bimonthly injections place a burden on healthcare costs. Ongoing investigations are currently being conducted to discover new, longer-lasting anti-VEGF agents, such as slow-release systems, gene therapy, and molecular angiogenesis-targeted therapy [63-68]. Some of the published and clinically used anti-VEGF agents are presented in Table 2.

Pegaptanib, currently no longer in use, is a small RNA fragment with a molecular weight of 5 kDa that can only bind to the VEGF165 isoform, thereby blocking its interaction with receptors on endothelial cells. Ranibizumab is a fragment of a humanized recombinant immunoglobulin G1 antibody with a molecular weight of 48 kDa and can bind to all isoforms of VEGF-A. Ranibizumab, with a molecular weight three times smaller than bevacizumab, maintains a faster half-life of approximately 75% compared to bevacizumab. The latest anti-VEGF approved for ocular use by Europe and America is aflibercept. Aflibercept is a fusion protein (115 kDa) composed of the second immunoglobulin domain receptor of VEGF-R1 and the third domain of human VEGF-R2, with the Fc region of human IgG1. This medication has a higher binding affinity through competitive inhibition to VEGF-A compared to ranibizumab and bevacizumab [69]. Bevacizumab is a non-selective whole monoclonal IgG VEGF antibody with a molecular weight of 149 kDa. It inhibits fibroblast proliferation mediated by the VEGF-A isoform by binding to the VEGF receptor, thereby disrupting pro-angiogenic signalling. Bevacizumab is commonly recognized for its anti-neovascular properties and is FDA-approved for intravenous adjunctive therapy in patients with metastatic colorectal cancer. However, some studies suggest that it also has anti-fibrotic effects for ocular diseases. In December 2004, its use was introduced for patients with neovascular AMD. While not officially recognized, Bevacizumab is used off-label for ocular conditions such as AMD, DR, retinal vein occlusion (RVO), retinopathy of prematurity (ROP), and other neovascular eye diseases, as well as for preventing post-operative fibrosis in the field of ophthalmology [70-74].

Intravitreal Injection for PVR Prevention in OGI

Local drug administration in the eye, such as subconjunctival, subtenon, and intravitreal routes, has been studied in rabbit eyes as a model for various diseases, including OGI. The aim is to achieve higher drug concentrations while minimizing systemic absorption.

Needles 26G to 30G of size are used for intracameral and intravitreal injections. In intravitreal injections, the desired location is the avascular pars plana. This location can be accessed by inserting the needle 2 to 4 mm posterior to the limbus, with the superior quadrant commonly preferred for ease of access. To assess the drug's effectiveness, examinations

such as histopathological analysis, immunoassay of drug concentrations in various eye compartments, and pharmacokinetic evaluations based on half-life and peak drug concentration can be performed [75-77].

Rabbits have been utilized in various pharmacokinetic studies of intravitreal drugs, such as moxifloxacin, etanercept, triamcinolone acetonide, and bevacizumab. The most fundamental anatomical differences between rabbit and human eyes in intravitreal drug studies include the smaller vitreous cavity in rabbits (1.5 mL compared to 4.5 mL in humans), smaller serum compartments, and lower vascular density of the retina. The choice of rabbit type should also be taken into consideration. To observe drug effects on human eyes, pigmented rabbits are recommended. This is because pigmented rabbits exhibit drug interactions with ocular pigments that are more representative of human eyes. Conversely, investigating drug pharmacokinetics is the main goal, this interaction could be a confounder, and the use of albino rabbits is advised [78].

A study by Sinapis *et al.* that investigated the pharmacodynamics of intravitreal bevacizumab at a dose of 1.25 mg/50 µL in rabbit eyes found differences in bevacizumab concentrations in the intravitreal space, anterior chamber, blood serum, and contralateral eye following injection. This dose is commonly used in animal models and clinical trials [38]. The highest concentration was observed on the first day after injection (406.25 µg/mL) with a half-life of 6.61 days. The drug concentration could be maintained for 29 days, stabilizing at 5.17 µg/mL. Meanwhile, the concentration in the aqueous humor was about 18% of the vitreous concentration and subsequently smaller in blood serum, aqueous humor of the right eye, and vitreous of the right eye. A shorter vitreous half-life of 3.91 days was found in the study by Ye *et al.* [79]. This concentration could be increased by using prepared bevacizumab PLGA microspheres or sustained release bevacizumab, nearly tripling to 9.6 days [75, 79].

Findings by Dinc *et al.* demonstrated that anti-VEGF levels in rabbits began to decline on the eighth day [70]. In contrast, in clinical studies, anti-VEGF levels in humans decreased immediately on the first day. This difference could be attributed to slower drug absorption by the rabbit retina compared to humans, despite the high drug concentration. After intravitreal bevacizumab injection, traces of bevacizumab were also found in distant organs such as the brain, heart, liver, and colon. It is suspected that the drug passes through the retinal-ocular barrier and enters the bloodstream [78, 79]. Further research is needed to understand the drug's impact on other organs.

Conclusion

In conclusion, OGI presents a significant challenge, especially when complicated by PVR which arises from excessive healing of vitreoretinal wounds, significantly compromising visual outcomes. The emergence of pharmacological agents, particularly anti-inflammatories and anti-proliferative agents, has garnered significant attention as potential therapies to prevent PVR formation in OGI patients. Corticosteroids exhibit the ability to suppress inflammatory response, inhibit BRB damage, and reduce inflammatory cytokines. Therapies targeting VEGF have demonstrated bioactivity of PVR in the vitreous. Intravitreal administration of these agents allows for targeted drug delivery while minimizing systemic side effects. Despite these advancements, further clinical trials are still necessary to establish clinical evidence on the utility of these medical therapies for PVR prevention in OGI.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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