Pharmacotherapy of Proliferative Vitreoretinopathy

IV.F.

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Outline

Keywords
Proliferative vitreoretinopathy • Vitreoretinal scarring • Pharmacologic adjuncts • Corticosteroids • Fluoropyrimidines • Retinoids • Chemotherapy • Immunotoxins • Heparins

Key Concepts

1. Despite numerous preclinical studies demonstrating potential pharmacologic candidates in the treatment of proliferative vitreoretinopathy (PVR), few have translated into clinical research.
2. The presence of PVR at the time of a recurrent detachment is a poor proxy for failing to adequately treat the detached retina at the time of initial surgery. The use of perioperative adjunctive agents may be effective at modifying the vitreoretinal scarring response, but in the presence of an untreated or inadequately treated retinal break, a recurrent detachment is likely to ensue.
3. Exploring new modes of local drug delivery in sustained-release preparations may provide sustained therapeutic levels over the crucial periods of vitreoretinal scarring, although as yet, no clinical trials have investigated this approach.

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I. Introduction

Proliferative vitreoretinopathy (PVR) is the most common cause of late anatomic failure in retinal detachment surgery, with a reported incidence of 5–11 % of all rhegmatogenous retinal detachments [1]. PVR can be considered an exaggerated wound healing response in specialized tissue, resulting in the formation of complex fibrocellular membranes on both surfaces of the retina and the posterior vitreous cortex.

J. Sebag (ed.), *Vitreous: in Health and Disease*,
DOI 10.1007/978-1-4939-1086-1_30,

Contraction of these membranes then distorts the normal retinal architecture with resultant visually detrimental sequelae and/or traction retinal detachment, with re-opening of preexisting retinal breaks or the formation of new ones. Based on the premise that the primary pathology was centered in the vitreous, PVR was previously referred to as massive vitreous retraction syndrome (MVR) or massive preretinal retraction syndrome (MPR). However, to acknowledge the role of periretinal membrane formation and pigment epithelial cell proliferation, PVR later became known as massive periretinal proliferation (MPP) [2]. A unifying classification system was established in 1983 by the Retina Society Terminology Committee [1] coining the phrase proliferative vitreoretinopathy (PVR), which was later updated in 1991 to the current classification system in clinical practice today [3].

As is typical in medicine, the first treatments for PVR were surgical, an approach still practiced today [see chapter V.B.5. Management of PVR. However with expanding knowledge of the cells involved and the cytokine signaling that promotes PVR, surgery will be replaced, or at least augmented, by pharmacotherapy directed to the causative cells as well as the substrate upon which these cells migrate and proliferate – vitreous [see chapter VI.A. Pharmacologic vitreolysis]. Ultimately with sufficient knowledge, PVR will be preventable by pharmacotherapy, as will be described below.

II. Clinical Classification of PVR

Although the current classification system has served to standardize PVR terminology in clinical practice and research, it remains limited. The number, location, and size of retinal breaks are not included, and many clinicians feel that grading the extent of PVR membranes in terms of clock hours limits their description to one circumferential meridian, e.g., when distinguishing linear subretinal bands from confluent sheets (Tables IV.F-1 and IV.F-2).

The following clinical illustrations provide examples of PVR and their corresponding grade: (Figures IV.F-1 and IV.F-2)

The grading of established PVR from photographic images may be limited by the field of exposure; however, below are examples of retinal detachments with Grade C PVR: (Figure IV.F-3)

III. Pathophysiology of PVR

The pathophysiology of PVR is a complex sequence of events that remain incompletely understood. A simplified overview is included in this chapter to aid the reader in identifying potential targets against which pharmacologic agents may be directed. Rhegmatogenous retinal detachment is conventionally viewed as the starting point for PVR development. Vitreoretinal scarring can be considered the result of the following components:

- Blood-retinal barrier (BRB) breakdown
- Cellular accumulation and proliferation [see chapter III.J. Cell proliferation at vitreo-retinal interface in PVR & related disorders]
- Extracellular matrix (ECM) production and fibrin deposition
- Formed membrane contraction

Table IV.F-1 Updated proliferative vitreo-retinopathy grade classification [3]

Grade	Features
A	Vitreous haze, vitreous pigment clumps, pigment clusters on inferior retina
B	Wrinkling of inner retinal surface, retinal stiffness, vessel tortuosity, rolled and irregular edge of retinal break, decreased mobility of vitreous
CP 1–12	Posterior to equator; focal, diffuse, or circumferential full-thickness folds, subretinal strands
CA 1–12	Anterior to equator; focal, diffuse, or circumferential full-thickness folds, subretinal strands, anterior displacement, condensed vitreous strands

Table IV.F-2 Updated proliferative vitreo-retinopathy contraction classification [3]

Type	Location (in relation to equator)	Features
Focal	Posterior	Starfold posterior to vitreous base
Diffuse	Posterior	Confluent starfolds posterior to vitreous base; optic disc may not be visible
Subretinal	Posterior/anterior	Proliferation under the retina; annular strand near disc; linear strands; moth-eaten-appearing sheets
Circumferential	Anterior	Contraction along posterior edge of vitreous base with central displacement of retina; peripheral retina stretched; posterior retina in radial folds
Anterior	Anterior	Vitreous base pulled anteriorly by proliferative tissue; peripheral retinal trough; displaced ciliary processes may be stretched, may be covered by membrane; iris may be retracted

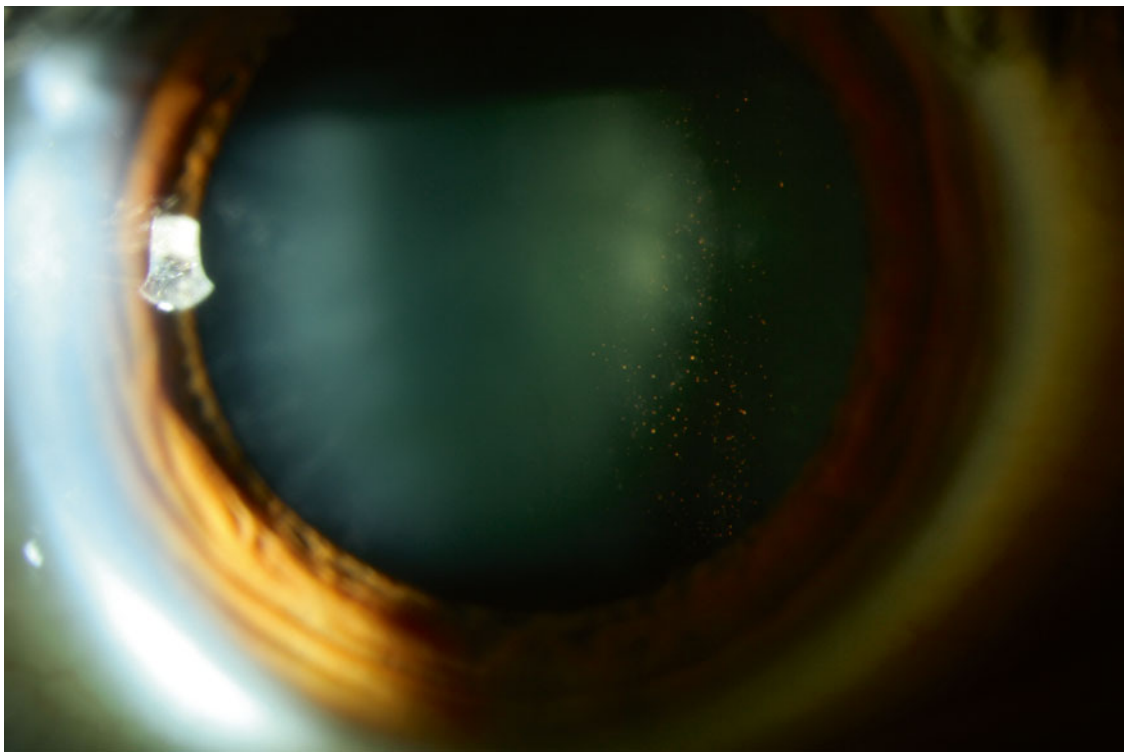

Figure IV.F-1 PVR *Grade A* – pigment clumping in the anterior vitreous

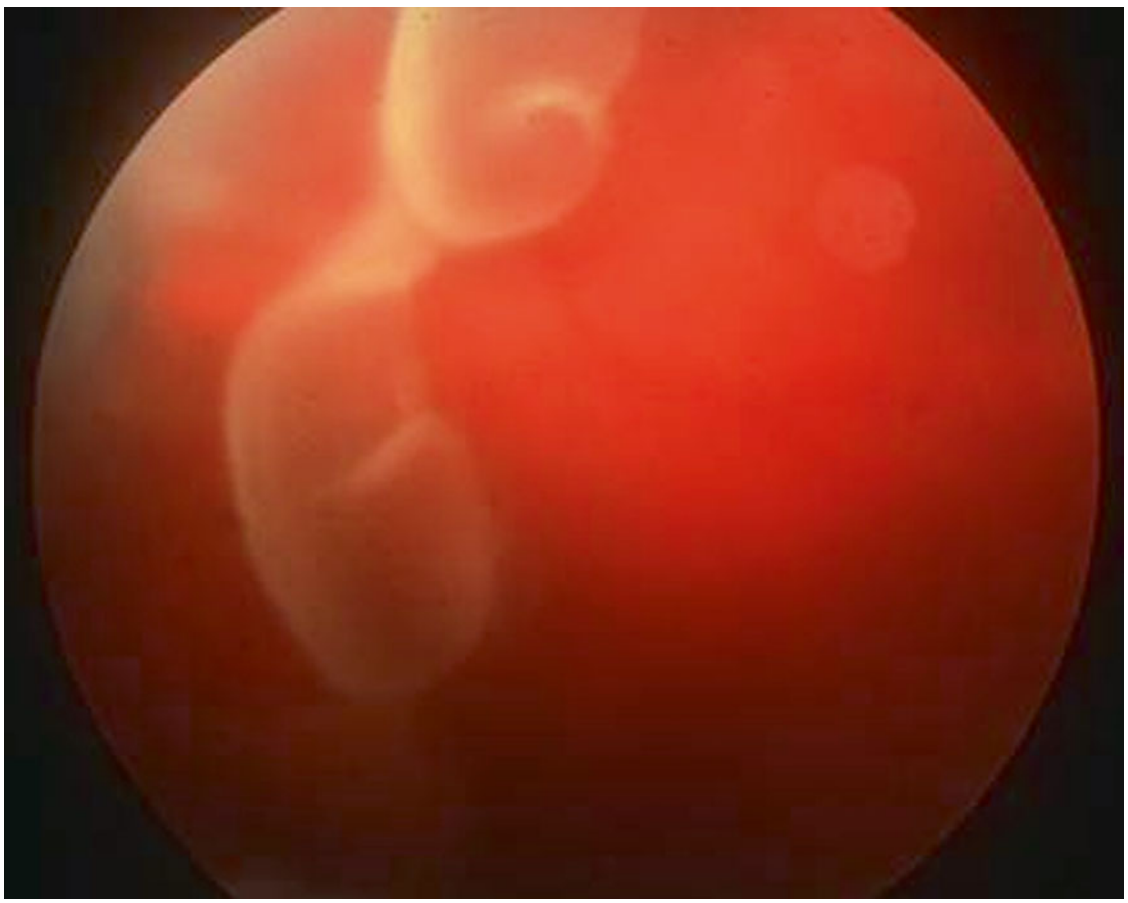

Figure IV.F-2 PVR *Grade B* – a rolled edge to a giant retinal tear (image reproduced courtesy of Lippincott, Williams and Wilkins)

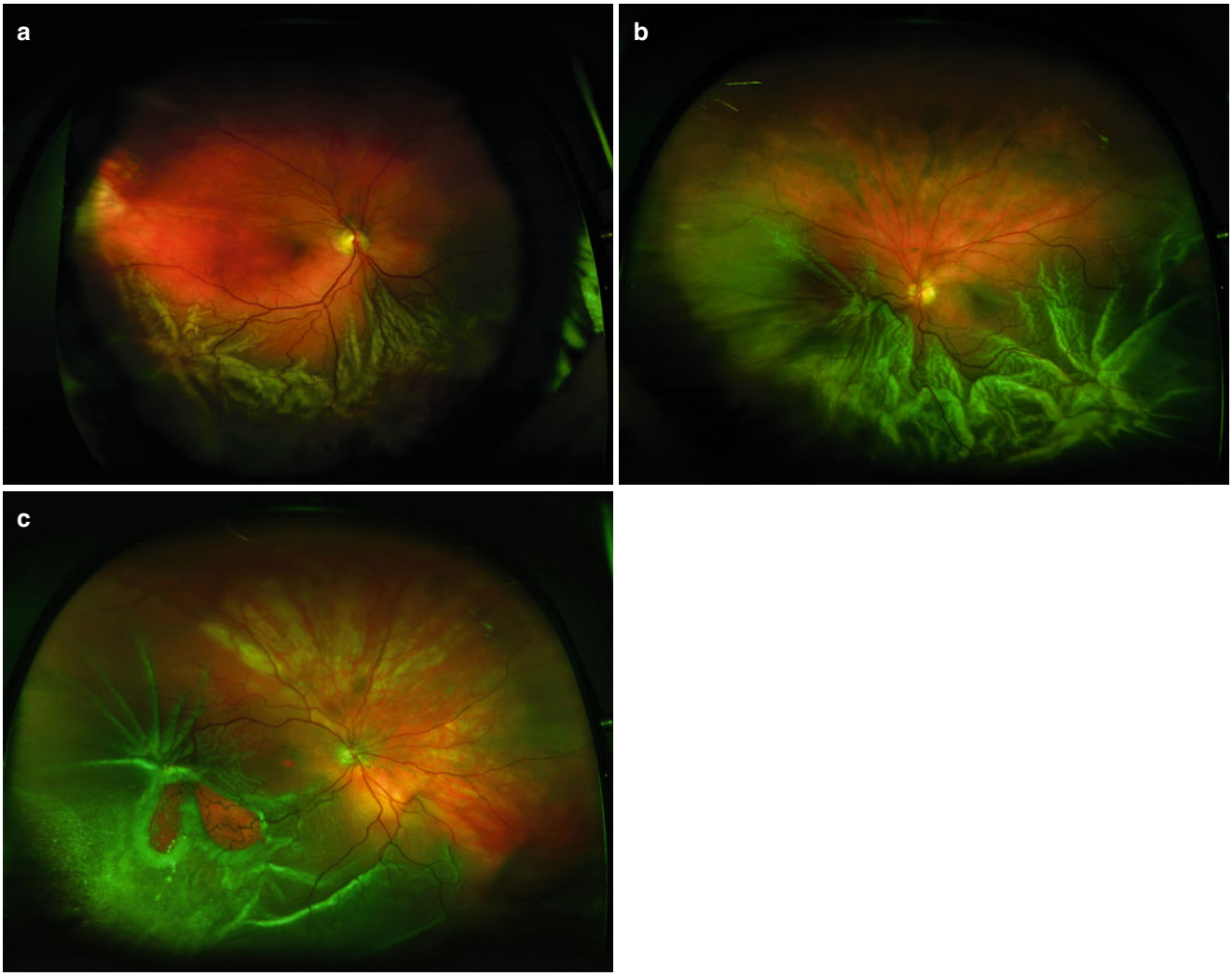

Figure IV.F-3 PVR *Grade C* – (**a**) anterior circumferential contraction with diffuse starfolds extending posteriorly, (**b**) multiple starfolds posterior to the equator with a full-thickness retinal tear temporally at 3 o'clock, and (**c**) a combined schisis-RD with a posterior starfold and inner leaf tear

A. Blood-Retinal Barrier Breakdown

In addition to allowing ingress of liquid vitreous into the subretinal space, a retinal tear results in the dispersion of retinal pigment epithelial (RPE) cells into the vitreous cavity. The blood-retinal barrier (BRB) breakdown which follows retinal detachment appears to have a central role in the dispersion of cells and growth factors which promote the further evolution of PVR [4].

B. Cell Accumulation and Proliferation

Analysis of excised tissue and animal models [see chapter III.J. Cell proliferation at the vitreo-retinal interface in PVR & related disorders] have identified four categories of cells in PVR membranes:

1. Retinal pigment epithelial cells (RPE) [5–14]
2. Glial cells [5, 10–18]
3. Fibroblasts [5–8, 19–23]
4. Inflammatory cells (macrophages [7, 9, 21, 22, 24, 25] and lymphocytes [26–28]

Experimental and clinical studies have identified the importance of RPE cell chemotaxis, proliferation, and metaplastic differentiation into fibroblast morphology under the effect of local growth factors/cytokines. Recent studies have demonstrated a central role of retinal glial cell activation and extension into periretinal membranes [29, 30]. Infiltrating inflammatory cells are also thought to play a role in membrane formation and contraction through growth factor production.

C. Extracellular Matrix Production and Fibrin Deposition

Collagen (predominantly types I and III) and fibronectin (a cell attachment protein), derived from RPE and glial cells, are key components in PVR membrane formation [9, 10, 31].

Fibrin deposition in the early phase of BRB breakdown may also provide a scaffold upon which complex fibrocellular PVR membranes may form [32].

D. Formed Membrane Contraction

Contraction of complex periretinal and vitreous membranes is responsible for the clinical picture of PVR. Membrane shortening may be mediated by intrinsic fibroblastic cells, some of which have been demonstrated to contain myofilaments [6, 8, 20]. However, alternative explanations suggest an RPE-collagen interaction via fibronectin bridges [33].

IV. Adjunctive Agents and Target

A wide variety of agents have been identified as potential adjuncts to modify the scarring response. Agents may either target a specific stage of the pathway or multiple stages, with the latter offering the advantage of monotherapy, where the former may require a combination of agents. The following section aims to provide an overview of the pharmacological agents that have been tested experimentally and is subdivided by their primary therapeutic target (summarized in Table IV.F-3). Selected agents which have been tested in clinical trials will be discussed in more detail thereafter under their relevant section (summarized in Table IV.F-4).

Table IV.F-3 Targets for adjunctive treatment

Pathological process	Strategy
Blood-retinal barrier breakdown	Anti-inflammatory treatment
Cellular activation	Antiproliferatives, growth factor manipulation
Cellular proliferation	Antiproliferatives – (a) cell specific (b) nonspecific
Fibrin formation	Decrease production/increase breakdown
Extracellular matrix formation	Inhibition of cellular activation, MMP/TIMP manipulation
Membrane contraction	Contraction inhibition

Table IV.F-4 Summary of adjunctive agents which have been investigated in clinical trials

Adjunct	Regime	Target	Study Population	Treatment Allocation	Outcome
Triamcinolone Acetonide [49]	4mg into oil filled eye at end of procedure	BRB breakdown, cellular proliferation, growth factors	75 eyes with established PVR undergoing vitrectomy with oil	38 patients adjunct 37 patients standard care	No difference in primary anatomical success, final VA or PVR recurrence
Prednisolone [50]	100mg PO od tapering to 12.5mg od for 15 days postoperatively	BRB breakdown, cellular proliferation, growth factors	220 consecutive patients with primary RD undergoing scleral buckle surgery	110 patients adjunct 110 patients placebo	Reduced cellophane maculopathy in steroid group (27%, 24%, 20% vs 42%, 47%, 39% control group at 1, 3,6 months, respectively.
5FU and LMWH [70]	20ug/mL of 5FU with 5IU/mL of LMWH as 1hour intraoperative vitrectomy solution infusion	5FU – Cellular proliferation LMWH – Fibrin, fibronectin, cellular proliferation, growth factors	174 patients at high risk of PVR	87 patients adjunct 87 patients placebo	Reduction in postop PVR (12.6% treatment vs 26.4% control
5FU and LMWH [71]			157 patients with established PVR undergoing vitrectomy surgery with oil	73 patients adjunct 84 patients placebo	No difference in primary anatomical success (56% treatment vs 51% control) No difference in secondary outcome measures
5FU and LMWH [72]			641 consecutive unselected cases with primary RD undergoing vitrectomy surgery with gas tamponade	342 patients adjunct 299 patients placebo	No difference in primary anatomical success at 6 months (82.3% treatment vs 86.8% controls). Significantly worse final VA in patients with macula sparing RDs in treatment group
Daunorubicin [88]	7.5ug/mL of daunorubicin as 10 minute vitrectomy solution infusion upon retinal attachment	Cellular proliferation and migration	286 patients with established PVR undergoing vitrectomy with oil	145 patients adjunct 141 patients standard care	No difference in primary anatomical success at 6 months (62.7% treatment vs 54.1% controls). Significantly fewer reoperations in treatment group
13-cis-retinoic acid [100]	10mg oral 13-cis-retinoic acid bd for 8 weeks postoperatively	Cellular proliferation	35 patients with established PVR undergoing vitrectomy Surgery with oil	16 patients adjunct 19 patients standard care	Improved final reattachment rate at 1 year (93.8% treatment vs 63.2% controls). Reduced macula pucker 18.8% vs 78.9%) Greater rate of ambulatory VA (56.3% vs 10.5%
Colchicine [116]	0.6mg daily for 2weeks then 1.2mg daily of oral colchicine	Cellular proliferation and contractility	22 patients with PVR secondary to trauma or vascular disease	11 patients adjunct 11 patients standard care	No difference in reduction of PVR

A. Anti-inflammatory Agents

1. Corticosteroids

Corticosteroids emerged as the first pharmacological agent to be employed as an adjunctive agent to target the scarring response. Their anti-inflammatory properties and secondary reduction in blood-ocular barrier breakdown target a key component in the PVR process. A variety of modes of corticosteroid administration have been investigated: systemic (oral), periocular, and intraocular (by direct injection or via the infusate).

a. Preclinical Evidence

Intravitreal injection of corticosteroid was first reported to significantly reduce experimental PVR in rabbits by Tano et al. in 1980. Traction retinal detachment (TRD) in rabbits was significantly reduced from 57 to 24 % and from 84 to 34 % after a single injection of 1 mg dexamethasone or triamcinolone acetonide, respectively [34, 35]. This effect was later confirmed using 2 mg of intravitreal triamcinolone acetonide in a refined experimental PVR rabbit model, with a reduction in TRD rate from 90 to 56 % [36]. Periocular administration of methylprednisolone (10 mg) was shown to reduce experimental complicated RD from 87 to 14 %, also showing a reduction in cell proliferation within the vitreous microenvironment [37]. More recently, this antiproliferative effect has been confirmed by a significant reduction in human retinal pigment epithelial cell proliferation *in vitro* following a dose-dependent treatment of unpreserved triamcinolone acetonide [38].

b. Clinical Evidence

The clinical application of corticosteroids as adjuncts to vitreoretinal surgery was first reported by Koerner et al. in 1982 who concluded that the systemic effects of oral prednisolone on postoperative retinal fibrosis did not match that of experimental intravitreal triamcinolone [39]. An infusate containing dexamethasone showed a trend toward a reduction in PVR reproliferation and a reduction in hypotony, but did not achieve statistical significance. Subconjunctival dexamethasone (10 mg) injected 5–6 h prior to scleral buckle surgery was reported to reduce blood-ocular barrier breakdown, postoperatively, as measured by laser flare photometry, but has not been investigated as an adjunctive agent in patients with PVR [40].

Jonas et al. opened the door to the clinical investigation of intravitreal triamcinolone in 2000 by reporting it to be nontoxic and of potential benefit through a reduction in postoperative intraocular inflammation [41], and this has since become the most widely clinically investigated adjunctive corticosteroid. Its clinical safety profile has been subsequently confirmed although its therapeutic benefit has yet to be consistently proven. Reduction in blood-ocular barrier breakdown [42] and a proposed benefit in established PVR have been reported [43–46] although these studies were either retrospective or non-comparative. A large multicenter, prospective, quasi-randomized controlled trial investigating the use of varying doses of intravitreal triamcinolone acetonide as an adjunctive surgical tool to aid vitreous visualization showed a significant reduction in intraoperative complications [47] with fewer retinal breaks and intraoperative retinal detachments. However, 1-year follow-up failed to show a statistical difference in visual acuity or reoperation rate [48]. The absence of any long-term positive effect may be explained by its use as a surgical tool rather than as a therapeutic injection, as it is likely that negligible corticosteroid concentrations would have remained at the end of the procedure following its removal. To date, only one prospective randomized controlled clinical trial investigating the use of triamcinolone acetonide in the eyes with established PVR (Grade C) undergoing pars plana vitrectomy with silicone oil has been reported [49]. 75 eyes divided into two groups with a 1:1 treatment allocation ratio were investigated. The treatment group received 4 mg of intravitreal triamcinolone into the oil-filled eye at the end of the procedure. No statistical difference in primary anatomical success at 6 months was noted (84 and 78 % in the adjunct and control groups, respectively). Neither was there any statistical difference in any of the investigated secondary outcomes (visual acuity, reoperation rate, PVR recurrence, macula pucker, IOP rise). The authors acknowledge that a positive treatment effect may have been masked by a higher than expected primary success rate in the control group and a resultant underpowered study.

More recently, Koerner et al. have published earlier work on the use of systemic oral prednisolone [50] and its effect on cellophane maculopathy in 220 consecutive eyes undergoing scleral buckle surgery for primary RRD. They reported significantly fewer cases of cellophane maculopathy in the steroid group 27, 24, and 20 % compared with 42, 47, and 39 % in the control group at 1, 3, and 6 months, respectively. They concluded that oral corticosteroids have a prophylactic effect against the early stages of PVR, but affirm the need for larger randomized and controlled trials to confirm whether this effect is extended to advanced PVR. It should be noted, however, that local corticosteroid administration is preferable over systemic use, as it achieves significantly higher intraocular concentrations [51] and avoids systemic side effects. It is possible that previous clinical studies have been limited by the duration of action of the corticosteroid and that future success may be achieved by local slow release agents, thereby adequately covering the active PVR period, in addition to avoiding systemic side effects.

2. Nonsteroidal Anti-inflammatory Agents

Nonsteroidal agents, like corticosteroids, are of therapeutic value in vitreoretinal scarring through their anti-inflammatory

properties and subsequent reduction in blood-ocular barrier breakdown. They have been less widely investigated than corticosteroids due to their reduced potency.

a. Preclinical Evidence

Meclofenamate and indomethacin were first shown to inhibit cell proliferation in cell culture in 1984 [52], but were not subsequently investigated as single therapeutic agents, presumably due to their inability to compete with corticosteroids as realistic treatment options. However, in combination with 5-FU in a sustained-release preparation, a significant benefit was reported in posttraumatic experimental PVR in rabbits. A significant reduction in both the presence and severity of PVR was found in animals treated with the co-drug preparation [53].

b. Clinical Evidence

Topical indomethacin in combination with routine peroperative corticosteroids was found to significantly reduce blood-aqueous barrier breakdown in patients undergoing extracapsular cataract surgery [54] as well as decrease postoperative inflammation [55]. However, no clinical trials have investigated the use of nonsteroidal anti-inflammatory agents in patients with PVR.

B. Inhibitors of Cell Proliferation

1. Fluoropyrimidines

The fluoropyrimidines are a family of antimetabolites which modify protein synthesis by (a) binding to and inhibiting the enzyme thymidylate synthetase and (b) incorporation into RNA causing coding errors in protein translation, thus inhibiting cell proliferation. They are more commonly used as a chemotherapeutic agent in solid tumors, particularly of the gastrointestinal tract.

a. Preclinical Evidence

5-Fluorouracil (5-FU) was first reported to reduce experimental traction retinal detachment (TRD) in rabbits in 1982. In non-vitrectomized eyes, a TRD rate of 73.6 % in control animals was reduced to 31.5 % following a single intravitreal injection of 5-FU [56]. This effect was replicated in vitrectomized eyes with repeated daily intraocular injections 0.5 mg for 7 days [57] and found to be nontoxic at this dosing regimen [58] following initial toxicity concerns [59]. 5-FU may be converted to 5-fluorourudine (5-FUR), the latter offering the advantage of anti-contractile properties [60] and increased potency with a greater antiproliferative effect [61, 62]. However, 5-FUR was found to be significantly more toxic to retinal cells [63] and efforts to translate laboratory work to clinical trials have favored 5-FU. Use of a sustained-release preparation containing 1 mg of 5-FU was associated with a reduction in TRD rates from 89 % in controls to 11 % in treated animals, in an experimental PVR model [64]. Sustained intravitreal concentrations of 5-FU of between 1 and 13 mg/L for at least 14 days were reported, with concentrations remaining above 0.3 microgram/mL for almost 21 days. No toxic effects were observed. Co-drug preparations containing 5-FU and either dexamethasone or triamcinolone have also been shown to reduce the severity and progression of experimental PVR in non-vitrectomized rabbits [65, 66]. When a co-drug containing 5-FU and fluocinolone was injected into the gas-filled eyes, intravitreal concentrations of the drug were unaffected, when compared with controls [67].

b. Clinical Evidence

In 1984, a prospective non-comparative pilot study was conducted in 22 patients undergoing surgery for established PVR who were treated intraoperatively with additional intraocular and periocular 5-FU. A final reattachment rate of 60 % was achieved at 6 months. The therapy was considered to be well tolerated, nontoxic, and superior to reported standard care at the time [68]. This was confirmed in a prospective randomized controlled trial using 10 mg of intravitreal 5-FU on completion of vitrectomy surgery [69]. A trend toward better vision was observed in the treatment group compared with controls, but with a lower macula reattachment rate (60 % vs 77 %). More recently, 5-fluorouracil has been investigated in combination with low molecular weight heparin in three prospective randomized controlled clinical trials [70–72]. These trials will be discussed in detail below.

2. Daunorubicin

Daunorubicin, or daunomycin, is a chemotherapeutic agent of the anthracycline family which was most commonly used in combination therapy to treat hematological malignancies. It inhibits cellular proliferation by inhibiting DNA replication.

a. Preclinical Evidence

Daunomycin was first tried intravitreally in experimental PVR in 1983, where it was shown to reduce dermal fibroblastic proliferation [73], and after initial concerns regarding its narrow safety margin [74], it later showed promise as a potential nontoxic and therapeutic adjunct [75–79]. The mode of administration of daunomycin has also been investigated, through drug delivery systems, and reports suggested a reduction in toxicity [80–83]; however, these preparations have yet to be tried clinically. In a staggered regime with intravitreal triamcinolone, it has been shown to significantly reduce experimental TRD in rabbits, with rates of 83.3 % in controls compared to 8.3 % in animals treated with combination therapy. This staggered combination was also found to be superior to monotherapy, with TRD rates of 33.3 and 16.1 %, in the eyes treated with only daunomycin or

triamcinolone, respectively. Human multidrug-resistant cells, via P-glycoprotein induction, have been found in excised premacular membranes, in the eyes treated with daunomycin, pushing it further down the list of preferred adjunctive agents [84]. More recently, doxorubicin, a close relative to daunorubicin, has been shown in addition to its antiproliferative properties, to attenuate the glial cell response and reduce the severity of experimental PVR [85], and may form the basis of future studies, either as a single agent or in combination therapy.

b. Clinical Evidence

Intravitreal daunorubicin was first shown to be safe and well tolerated when administered as a 7.5ug/ml intravitreal 10 minute infusion in 15 posttraumatic eyes with PVR, prior to silicone oil injection [86]. A larger non-comparative study of 68 eyes with advanced PVR reported an eventual anatomic success rate of 73 % at 18 months, with 89 % achieving a final visual acuity of >20/800 [87]. A multicenter, prospective, randomized, controlled clinical trial studied 286 eyes of patients with PVR Grade C2 or greater undergoing vitrectomy and silicone oil exchange. Patients were randomized to treatment with or without a 10-minute intraoperative infusion of daunorubicin (7.5 μg/mL). The primary outcome measure used was primary anatomical success, with a rate of 62.7 % in the treatment group compared to 54.1 % in controls. It marginally failed to reach significance ($P=0.07$); however, the trial did demonstrate a statistically significant reduction in the number of vitreoretinal reoperations within 1 year ($P=0.005$) [88]. Further small-scale studies have since suggested a benefit [89], but daunorubicin has, like many other adjuncts, failed to gain widespread clinical acceptance.

3. Retinoids

Retinoids, or vitamin A compounds, have important roles in regulating the cell proliferation and differentiation of multiple cell types throughout the body by mediating gene transcription. They have been shown experimentally to inhibit RPE cell proliferation, as well as modify ECM and cell-mediated contraction.

a. Preclinical Evidence

Retinoic acid first emerged as a potential pharmacologic agent to prevent vitreoretinal scarring in 1991. Human RPE cell proliferation was significantly reduced when grown in the presence of 1 μm of retinoic acid. Cells were also found to maintain mature RPE cell morphology, rather than undergo the phenotypic changes associated with PVR retinal detachments [90]. This inhibitory effect on cell proliferation was subsequently confirmed [91], in addition to a reduction in cell-mediated contraction. Sustained drug delivery systems containing all-trans retinoic acid have been shown to reduce experimental PVR from 100 to 36 % in rabbit models [92], but an associated foreign body reaction was reported. Doses of 605 micrograms and 1070 micrograms have since been found to be therapeutic and nontoxic [93, 94]. In an experimental PVR model in rabbits using silicone oil and heavy silicone oil, all-trans retinoic acid significantly reduced the severity of traction RDs at concentrations of 15 micrograms/ml and 10 micrograms/ml, respectively [95]. This was later confirmed with 13-cis-retinoic acid [96]. Both isomers of retinoic acid were shown to reduce proliferation of PVR membrane-derived human RPE cells [97]. This response was dose dependent at a variety of concentrations and found to be nontoxic. More recently, all-trans retinoic acid has been shown to significantly inhibit RPE cell extracellular matrix production (particularly laminin beta-1) and thereby reduce cell-mediated collagen contractility [98]. It therefore offers the advantage as a single therapeutic agent active against multiple steps in the PVR process.

b. Clinical Evidence

A small retrospective study compared the outcomes of 10 patients undergoing surgery for PVR who were additionally treated with 40 mg of oral 13-cis-retinoic acid twice daily for 4 weeks postoperatively, with 10 control patients. A trend toward a benefit was noted in the treatment group by a reduction in PVR recurrence, with anatomical success in 9 out of 10 patients at 8 months compared with 4 out of 10 in the control group ($P=0.061$) at 9 months [99]. A prospective randomized controlled clinical trial of 35 patients undergoing surgery for PVR compared the use of 20 mg of oral 13-cis-retinoic acid twice daily postoperatively for 8 weeks (16 patients) with no additional treatment (19 patients) [100]. Both anatomical and visual outcomes were superior in the treatment arm compared with the control arm, with reported final anatomical success rates of 93.8 and 63.2 % ($P=0.047$), respectively. Ambulatory vision was achieved in 56.3 % of patients in the treatment group, compared with only 10.5 % in the control arm ($P=0.009$). Fewer patients in the treatment group developed macula pucker (18.8 %) compared with the control group (78.9 %) ($P=0.001$). Despite this positive treatment effect, retinoic acid has not been universally adopted clinically. This may be due to the small sample size and lack of statistical power, in addition to concerns regarding systemic side effects of the treatment.

4. Immunotoxins

Immunotoxins are chimeric proteins consisting of a modified antibody or antibody fragment attached to a biological toxin fragment with its natural binding domain removed. The antibody is cell specific and hence, upon binding to its target, allows intracellular incorporation of the toxin and a resultant cytotoxic effect. Actively dividing RPE cells have been shown to abundantly express transferrin receptors and are thus targets for antiproliferative therapy [101, 102].

a. Preclinical Evidence

Transferrin ricin-A (Tfr-rRA) is an immunotoxin comprised of an antibody to the RPE transferrin receptor which is linked with the A chain of ricin, a potent toxin. It has been shown to significantly inhibit both RPE cell [103–105] and fibroblast proliferation [105, 106]. In an experimental PVR model in rabbits, only 10 % of the eyes developed traction retinal detachments when treated with an intravitreal injection of 2,000 ng of Tfr-rRA compared with 78 % of controls [107]. The VEGF receptors expressed by RPE cells have also been targeted using a combination of VEGF 165 and the diphtheria toxin (DT390-VEGF165). RPE cell survival was reduced when co-cultured with this immunotoxin in a dose-dependent response [108]. To date, no clinical studies have been conducted to investigate the use of immunotoxins as therapies for PVR.

5. Colchicine

Colchicine is a natural product sourced from the autumn crocus plant (*Colchicum autumnale*). Its use has been traced back to ancient Egypt when it may have been employed to treat rheumatism as early as 1500 BC. Today, it remains an alternative therapeutic agent in the treatment of gout, although its narrow therapeutic window limits its use. Colchicine prevents cell proliferation by inhibiting microtubule polymerization with a resultant inhibition of mitosis.

a. Preclinical Evidence

In 1985, colchicine was first shown to inhibit fibroblast growth in an experimental model *in vitro* [109] and later shown to be a potent inhibitor of RPE cell chemotaxis [110]. Its antiproliferative effects were subsequently confirmed in animal models, with inhibition of astrocyte and fibroblast and RPE cell proliferation and migration at concentrations well below levels of ocular toxicity [111] in cell culture. Experimental TRDs in rabbits was shown to be reduced from 74 to 29.6 % at 5 weeks in animals treated with oral colchicine [112]. In addition to its effect on proliferation, colchicine has also been shown to reduce RPE cell-mediated collagen gel contraction when human RPE cells were treated with 0.01–1 μm of colchicine [113]. More recently, therapies where colchicine has been combined with both methylprednisolone and sodium diclofenac [114] or 5-FU [115] have shown a significant reduction in experimental TRD rate and an inhibition of human glial cell proliferation, respectively.

b. Clinical Evidence

A small prospective controlled study in patients with PVR secondary to trauma or proliferative vascular disease compared the use of oral colchicine (1.2 mg daily) with controls (vitamin C 250 mg daily). It was concluded that the safe therapeutic dose of colchicine does not inhibit PVR [116]. No further clinical studies have been conducted since.

C. ECM Modifiers

Collagen (types 1 and 3), fibronectin, and deposited fibrin form key components to the extracellular matrix found in PVR membranes. Thus, drugs that affect their production, attachment, or contraction offer potential benefit as therapeutic agents against vitreoretinal scarring.

1. Cis-hydroxyproline

Hydroxyproline is a major constituent of collagen stability, and its synthesis can be inhibited by a proline analogue, cis-4-hydroxyproline.

a. Preclinical Evidence

Cis-hydroxyproline was shown to inhibit bovine RPE cell proliferation, collagen synthesis, attachment, and migration *in vitro*, in a dose-dependent manner [117]. More recently, when two sustained-release scleral implants were used in an experimental model of PVR, TRD were reduced from 89 % in controls to 57 % in treated animals at 1 month [118]. This adjunct has yet to be investigated clinically.

2. Matrix Metalloproteinases

Turnover and remodeling of extracellular matrix is regulated by a group of proteolytic enzymes known as matrix metalloproteinases (MMPs) and their natural inhibitors, tissue inhibitors of metalloproteinases (TIMPs). MMPs 1, 2, 3, and 9 and TIMPs 1, 2, and 3 have been demonstrated to be present in PVR membranes [119, 120]; thus it is reasonable to attempt modulating these factors.

a. Preclinical Evidence

Prinomastat (AG3340) is a synthetic inhibitor of MMPs that has been shown experimentally to reduce PVR in a rabbit model [121] and in posttraumatic rabbit eyes [122]. It has also been shown to reduce premacular membrane formation in rat eyes [123]. This treatment has yet to be investigated clinically in patients with PVR.

3. Heparin/Low Molecular Weight Heparin (LMWH)

Heparin has multiple cellular effects that can potentially inhibit PVR development. It inactivates thrombin by binding to antithrombin, promoting thrombin-antithrombin complex formation. In preclinical studies heparin has been shown to reduce fibrin formation and interfere with cell-substrate adhesion by binding fibronectin. It also binds fibrogenic growth factors (FGF, EGF, and PDGF) and inhibits cell proliferation, including scleral fibroblasts and RPE cells [124]. A prospective, randomized, controlled trial investigating the effect of heparin in the infusate on postoperative fibrin formation showed a positive effect using concentrations of 10 IU/ml, but a greater tendency to intraocular hemorrhage.

Lower concentrations were ineffective at reducing fibrin formation [125]. Combined heparin and dexamethasone in the infusate suggested a trend toward a reduction in postoperative PVR in treated patients, but again higher rates of intraocular hemorrhage were reported [126].

The low molecular weight fragments of heparin (LMWH) have less effect on the coagulation cascade or platelet function and thus reduce the risk of hemorrhagic complications compared with heparin but produce a comparable antithrombotic effect [124]. Intraocular fibrin formation was markedly reduced using an infusate containing LMWH in vitrectomy/lensectomy surgery in rabbits [127].

a. Clinical Evidence

The potential synergistic effect of combining LMWH with 5-FU to modify PVR development in eyes undergoing vitrectomy surgery has been investigated in three large prospective clinical trials [70–72]. The same adjunctive medication regime was used in the treatment arm of all three trials. An intraoperative vitrectomy infusion solution of Hartmann containing 5-FU at a concentration of *200ug*/ml and LMWH at a concentration of 5 IU/ml was used for 1 h. Control patients received plain Hartmann's solution as a placebo. The three studies investigated (i) high-risk retinal detachments undergoing vitrectomy and gas exchange [70], (ii) established PVR undergoing vitrectomy and silicone oil exchange [71], and (iii) unselected primary retinal detachments undergoing vitrectomy and gas exchange [72].

i. High-Risk Retinal Detachments

High-risk cases were identified using a previously published regression formula based in PVR risk factors [128]. 174 patients were studied, with PVR recurrence rates significantly lower in the treatment group at 12.6 % compared with 26.4 % in controls and fewer reoperations. In patients who developed recurrent PVR, visual outcomes were significantly better in the treatment group.

ii. Established PVR

A total of 157 patients with established PVR (Grade C) undergoing vitrectomy surgery with silicone oil tamponade were randomized to either receive the adjunctive regime or placebo in a 1:1 treatment allocation ratio. No benefit in primary anatomical success was found, and neither were there any significant differences in secondary outcome measures reported (complete or posterior retinal reattachment, visual acuity, hypotony, cataract, keratopathy).

iii. Unselected Primary Retinal Detachments

A total of 641 patients of unselected patients undergoing vitrectomy with gas tamponade were studied in a 1:1 treatment to control allocation ratio. No statistical difference was noted in primary anatomical success at 6 months with rates of 82.3 and 86.8 % in the treatment and control groups, respectively. There was no significant difference in the proportion of patients who required reoperations due to PVR with 7.0 % in the treatment group, compared with 4.9 % of controls. However, patients with macula-sparing retinal detachments were found to have a significantly worse visual outcome at 6 months, thus raising concerns regarding toxicity.

Abbreviations

5-FU	5–Fluorouracil
5-FUR	5-Fluorourudine
BRB	Blood-retinal barrier
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
IOP	Intraocular pressure
LMWH	Low molecular weight heparin
LWW	Lippincott, Williams and Wilkins
MMP	Matrix metalloproteinases
MPP	Massive periretinal proliferation
MPR	Massive preretinal retraction
MVR	Massive vitreous retraction
PDGF	Platelet-derived growth factor
PVR	Proliferative vitreo-retinopathy
RD	Retinal detachment
RNA	Ribonucleic acid
RPE	Retinal pigment epithelium
RRD	Rhegmatogenous retinal detachment
TIMPS	Tissue inhibitors of metalloproteinases
TRD	Tractional retinal detachment
VEGF	Vascular endothelial growth factor

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