Major review

Management of pseudophakic cystoid macular edema

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A B S T R A C T

Pseudophakic cystoid macular edema (PCME) is a common complication following cataract surgery. Acute PCME may resolve spontaneously, but some patients will develop chronic macular edema that affects vision and is difficult to treat. This disease was described more than 50 years ago, and there are multiple options for clinical management. We discuss mechanisms, clinical efficacy, and adverse effects of these treatment modalities. Topical non-steroidal anti-inflammatory agents and corticosteroids are widely used and, when combined, may have a synergistic effect. Intravitreal corticosteroids and anti-vascular endothelial growth factor (anti-VEGF) agents have shown promise when topical medications either fail or have had limited effects. Randomized clinical studies evaluating anti-VEGF agents are needed to fully evaluate benefits and risks. When PCME is either refractory to medical therapy or is associated with significant vitreous involvement, pars plana vitrectomy has been shown to improve outcomes, though it is associated with additional risks.

1. Introduction

Pseudophakic cystoid macular edema (PCME) was first described in 1953 by A. Ray Irvine, Jr., in patients with unexplained visual loss following intracapsular cataract extraction.64 The cause of the visual loss was later identified by Gass and Norton as marked macular edema with a classic perifoveal petalloid pattern of staining and late leakage from the optic nerve on intravenous fluorescein angiography (IVFA, Fig. 1).46 The incidence of angiographic PCME has decreased with the transition from intracapsular cataract extraction (~60%) to extracapsular cataract surgery (~20%) and again with the development of small-incision phacoemulsification.39,117 An estimated 20–30% of patients undergoing phacoemulsification, however, have PCME on IVFA.50,123 New diagnostic tools such as optical coherence tomography (OCT)
suggest that the rate may be as high as 41%.75 The majority of patients with PCME on imaging do not experience visual disturbances.23,123 The incidence of clinical PCME, defined as symptomatic vision loss 20/40 or worse, is much lower with today’s surgical techniques—approximately 0.1% to 2.35%.57,76

Most patients with PCME have spontaneous resolution of the macular edema within 3–4 months.15 One year after surgery, a small minority of patients (<1%) in the absence of treatment may still have decreased visual acuity from PCME. A better understanding of the condition and its causes, as well as more aggressive treatment of PCME, however, has considerably altered the course of the disease.111

1.1. Pathogenesis

Various factors and many presumed mechanisms may be involved in the pathogenesis of PCME, including the release of mediators of inflammation such as prostaglandins, light toxicity, and mechanical irritation.29,60,106 Inflammatory mediators disrupt the blood–aqueous barrier (BAB) and blood–retinal barrier (BRB), leading to increased vascular permeability resulting in macular edema. Breakdown of the BAB and BRB may be associated with diabetes, glaucoma, and uveitis.134 Surgical manipulation of the anterior segment may lead to the release of arachidonic acid from cell membranes, with production of either leukotrienes via the lipooxygenase pathway or prostaglandins via the cyclooxygenase pathway.29,60 These inflammatory biomarkers result in increased retinal vessel permeability and the development of PCME. Alternatively, contraction of the posterior hyaloid as a result of inflammation may lead to mechanical traction onto the perifoveal retinal capillaries and result in PCME. Irido–vitreal adhesions and traction may contribute to PCME.106

1.2. Incidence and risk factors

Following extracapsular cataract extraction, the incidence of clinical PCME in uncomplicated, low-risk patients varies from 2% to 12%.15 Following phacoemulsification the rate is even lower, ranging from 0.1% to 2.35%.57,76 The incidence of angiographic CME 1–2 months postoperatively is as high as 20% to 30%.126 PCME as seen on OCT after modern phacoemulsification may range from 4% to 11%,12,93 though there may be up to a 41% incidence of subtle macular alterations.75 The peak incidence of PCME occurs at 6 weeks after surgery. Incidence increases in patients with high-risk characteristics—including diabetes mellitus, hypertension, history of central retinal vein occlusion, recent history of uveitis, preexisting epiretinal membrane, or following complicated cataract surgery.29,57 Perioperative glaucoma has been implicated as a risk factor for PCME, though a recent large retrospective study showed no increased incidence of clinical PCME in glaucoma patients undergoing uncomplicated cataract extraction.72 Although that study found no relationship between the use of prostaglandin analogs for the treatment of glaucoma and the development of PCME, other studies have found that prostaglandins, synthesized by the uvea and lens epithelial cells, may be one of the inflammatory mediators associated with PCME.87 Arcieri et al randomized 80 patients and demonstrated glaucoma patients on prostaglandin analogs were more likely to develop PCME (by IVFA) compared with controls.3 Henderson et al also reviewed a series of 1,659 cataract surgeries and demonstrated that prostaglandin analog use was one risk factor for developing PCME. They also correlated the presence of epiretinal membrane and prior history of retinal vein occlusion with an increased risk for PCME.57

1.3. Diagnosis and treatment options

PCME most often develops 4–6 weeks after cataract surgery. Acute PCME occurs within 6 months postoperatively; chronic PCME is present more than 6 months after cataract surgery. PCME is diagnosed by decreased visual acuity, by fluorescein angiography with the classic appearance of perifoveal petalloid staining with or without late leakage from the optic disc, or by OCT. Characteristics of PCME on OCT include macular thickening and cystic spaces in the outer plexiform layer, occasionally with subfoveal fluid (Fig. 2).93,126 Once PCME is confirmed by clinical findings, fluorescein angiography, and/or OCT, initial treatment includes the use of topical nonsteroidal anti-inflammatory medications (NSAIDs), which inhibit the production of prostaglandins via inhibition of the COX pathway. Several studies have documented the use of NSAIDs in the treatment and prophylaxis of PCME, although

![Fig. 1 – Intravenous fluorescein angiography demonstrating classic perifoveal petalloid staining with late leakage from the optic nerve head consistent with pseudophakic cystoid macular edema.](image1)

Fig. 1 – Intravenous fluorescein angiography demonstrating classic perifoveal petalloid staining with late leakage from the optic nerve head consistent with pseudophakic cystoid macular edema.

![Fig. 2 – Characteristic macular thickening and cystic intraretinal spaces typical of PCME on OCT.](image2)

Fig. 2 – Characteristic macular thickening and cystic intraretinal spaces typical of PCME on OCT.
there is no standard dosage schedule for their use in the perioperative period. One recommended approach in the literature is NSAID application for 2 days preoperatively in patients at low risk and for 1 week preoperatively for those at high risk for PCME. This algorithm, however, has yet to be thoroughly tested and remains a topic for debate among cataract surgeons.

New NSAIDs with greater ocular penetration may have greater potency, although this has not been proven by randomized clinical trials. Combination therapy of ketorolac plus prednisolone has been shown in randomized clinical trials to be better than either ketorolac or prednisolone alone. Alternative treatment approaches included either sub-Tenon’s or intravitreal corticosteroid injection to inhibit arachidonic acid release. There is no randomized clinical trial that determines the better route. More recently, retrospective case series and individual case reports support the use of anti-vascular endothelial growth factors such as bevacizumab.

See Table 1.

2. Corticosteroids

2.1. Topical corticosteroids

2.1.1. Mechanism

Although the precise etiology of PCME remains elusive, it is believed that intraocular surgery initiates a cascade of inflammatory events that lead to the breakdown of the BRB, causing intraretinal edema. The role of corticosteroids in the treatment of PCME is based on inhibition of leukotriene and prostaglandin synthesis. Corticosteroids decrease prostaglandin synthesis by inhibiting phospholipase A2 during the arachidonic acid cascade. In addition to this anti-inflammatory effect, corticosteroids also inhibit macrophage and neutrophil migration, and decrease capillary permeability and vasodilation. Currently, topical corticosteroids are used routinely following cataract surgery.

2.1.2. Clinical effect and indications

There have been several studies comparing the incidence of PCME in patients treated with topical steroids versus non-steroidal agents. Wittpenn et al prospectively randomized low-risk patients undergoing routine cataract surgery to prednisolone acetate 1% QID plus ketorolac tromethamine 0.4% 4 weeks or prednisolone QID alone postoperatively. Their study had 546 patients, 268 in the ketorolac/steroid group and 278 in the steroid monotherapy group. In the ketorolac/steroid group, no patients developed PCME by either biomicroscopic examination or OCT. In the steroid monotherapy group, 1.8% of patients developed clinically apparent PCME, and 2.4% had probable or definite PCME by OCT.

Asano et al compared outcomes in 142 patients treated with dicyclofenac 0.1% or betamethasone 0.1% for 8 weeks following cataract surgery in a double-masked, randomized study. The test drugs were administered to each patient 3 hours, 2 hours, 1 hour, and 30 minutes before surgery and then three times per day for 8 weeks after surgery. Their outcome measures included angiographic PCME and blood-aqueous disruption measured by laser flare-cell photometry.

Among patients treated with dicyclofenac, 18.8% developed PCME determined by fluorescein angiography, compared with 58% of patients in the betamethasone group at 5 weeks postoperatively (P < 0.001). At 1 and 2 weeks following surgery, the dicyclofenac-treated patients had significantly less anterior chamber flare than the betamethasone group (P < 0.05). At all time points (postoperative weeks 1, 2, 5, and 8), however, there was no significant difference in logMAR visual acuity between the two groups. This study would be more informative if the authors supplied data on contrast sensitivity and vision change with FA leakage, as well as incorporated longer follow-up.

Heier et al randomized 28 patients who developed acute clinical PCME (within 21–90 days following cataract surgery) to either topical therapy with ketorolac tromethamine 0.5% (group K), prednisolone acetate 1.0% (group P), or ketorolac and prednisolone combination therapy (group C) four times per day. Improvements in visual acuity, contrast sensitivity, and leakage on fluorescein angiography by group revealed the greatest improvement in group C (89%) compared with group P (50%) and group K (67%). Treatment was continued until CME resolved or for 3 months, whichever occurred first, and was then tapered over 3 weeks. A significant difference in visual acuity was detected in the combination group versus the prednisolone monotherapy group at visits 4 (P = 0.006) and 5 (P = 0.042). There was no significant difference in visual acuity between the combination group and ketorolac monotherapy group. Patients treated with combination therapy or ketorolac alone had a faster treatment response compared with the prednisolone group. Notably, all patients in this study experiencing a two-line gain in visual acuity reported concurrent improvement in contrast sensitivity. Diminished contrast sensitivity can be a persistent cause of visual disturbance in this setting despite good Snellen visual acuity.

2.1.3. Adverse effects

Topical corticosteroids are associated with various adverse side effects, including elevated intraocular pressure, postoperative infection, and impaired wound healing.

2.2. Intravitreal injection of corticosteroids

2.2.1. Mechanism

Intravitreal corticosteroid injection is increasingly used to manage macular edema associated with severe vitreoretinal and inflammatory conditions. Intravitreal triamcinolone acetonide (IVTA) injections are shown to reduce BRB breakdown. These injections enable the delivery of corticosteroids to the retina in higher concentrations, allowing better bioavailability compared with topical administration.

Triamcinolone acetonide is used in a crystalline form, which achieves a long-lasting effect. This corticosteroid has been found in the vitreous up to 1.5 years after injection. Additionally, triamcinolone given by this delivery method was nontoxic in rabbits.

2.2.2. Clinical effect and indications

Jonas et al demonstrated in their small prospective interventional case series that patients with PCME who received an
### Table 1 — Summary of medical and surgical treatments for PCME

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Duration</th>
<th>Main outcome measures</th>
<th>Conclusions</th>
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<tr>
<td><strong>Corticosteroids</strong></td>
<td>Thach et al&lt;sup&gt;121&lt;/sup&gt;</td>
<td>Retrospective Single retrobulbar triamcinolone injection (18 eyes, 40 mg) vs Three biweekly posterior sub-Tenon's triamcinolone injections (31 eyes, 40 mg)</td>
<td>48 (49 eyes)</td>
<td>10–12 mo</td>
<td>BCVA</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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<tr>
<td><strong>Corticosteroids</strong></td>
<td>Boscia et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Prospective IVTA (4 mg)</td>
<td>6 (7 eyes)</td>
<td>11.1 mo</td>
<td>BCVA</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Jonas et al&lt;sup&gt;67&lt;/sup&gt;, Yannuzzi et al&lt;sup&gt;132&lt;/sup&gt;</td>
<td>Randomized Double-masked Indomethacin 25 mg PO TID vs placebo</td>
<td>20 (23 eyes)</td>
<td>-</td>
<td>BCVA</td>
<td>No significant improvement in VA noted in treatment vs placebo</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Burnett et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Prospective fenoprofen 1% tid vs placebo</td>
<td>14</td>
<td>-</td>
<td>BCVA</td>
<td>No significant improvement in VA noted in treatment vs placebo</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Flach et al&lt;sup&gt;40&lt;/sup&gt;, Flach et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Randomized Double-masked ketorolac 0.5% qid vs placebo</td>
<td>26</td>
<td>3 mo</td>
<td>BCVA</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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<tr>
<td><strong>Anti-VEGF</strong></td>
<td>Arevalo et al&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Retrospective Intravitreal bevacizumab (1.25 or 2.5 mg)</td>
<td>31 (36 eyes)</td>
<td>12 mo</td>
<td>BCVA, CMT by OCT</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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<tr>
<td><strong>Anti-VEGF</strong></td>
<td>Arevalo et al&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Retrospective Intravitreal bevacizumab (1.25 or 2.5 mg)</td>
<td>25 (28 eyes)</td>
<td>8 mo</td>
<td>BCVA, CMT by OCT</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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<tr>
<td><strong>Anti-VEGF</strong></td>
<td>Spitzer et al&lt;sup&gt;115&lt;/sup&gt;</td>
<td>Case series Retrospective Intravitreal bevacizumab (1.25 mg)</td>
<td>16 (16 eyes)</td>
<td>3.5–20.5 mo</td>
<td>BCVA, CMT by OCT, Treatment Complications</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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<tr>
<td><strong>Anti-VEGF</strong></td>
<td>Barone et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Case series Retrospective Intravitreal bevacizumab (1.25 mg)</td>
<td>10 (10 eyes)</td>
<td>6 mo</td>
<td>BCVA, CMT by OCT</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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<tr>
<td><strong>Anti-VEGF</strong></td>
<td>Cervera et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Prospective Nonrandomized Pegaptanib</td>
<td>4 (4 eyes)</td>
<td>4 mo</td>
<td>BCVA</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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<tr>
<td><strong>Pars plana vitrectomy</strong></td>
<td>Harbour et al&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Case series Retrospective PPV in the setting of vitreous adhesions or iris capture</td>
<td>24 (24 eyes)</td>
<td>-</td>
<td>BCVA</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
</tr>
<tr>
<td><strong>Pars plana vitrectomy</strong></td>
<td>Pendergast et al&lt;sup&gt;122&lt;/sup&gt;</td>
<td>Case series Retrospective PPV in the absence of vitreous incarceration in wound</td>
<td>23 (23 eyes)</td>
<td>30.2 mo (2–109)</td>
<td>BCVA</td>
<td>Significant improvement in BCVA for posterior sub-Tenon's (P = 0.0001) and retrobulbar (P = 0.035) injection No significant difference between the two groups</td>
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(continued on next page)
intravitreal injection of 25 mg crystalline triamcinolone acetonide transconjunctivally with topical anesthesia had improved visual acuities. Their mean follow-up time was 6.6 ± 4.1 months.66 Benhamou et al administered IVTA to patients with refractory PCME and found decreased macular thickness by OCT; all patients had a recurrence of macular edema within 2 to 4 months, however. This high recurrence rate persisted following repeat injections.13

Conway et al found increased visual acuity, improved macular edema by biomicroscopy, and angiographic improvement in eight eyes with recalcitrant PCME injected with 1 mg IVTA. Eyes received anywhere from two to five injections over the mean observation time of 31 weeks. They observed some acute rises in intraocular pressure (IOP), with a few patients requiring anterior chamber paracentesis. Otherwise, IOPs were well controlled with topical ocular antihypertensives, and there was no change in the number of such medications needed at final follow-up.29

2.2.3. Adverse effects
IVTA injections have some associated risks, most commonly elevated IOP.99 Jonas et al performed a meta-analysis of IOP following IVTA injection. The study included 305 eyes in 272 patients receiving approximately 20 mg crystalline triamcinolone acetonide in 0.2 ml Ringer’s solution. At a mean follow-up of 10.4 months, 112 (41.2%) had recorded at least one IOP measurement greater than 21 mm Hg. Mean IOP increased significantly after the first intravitreal injection from a baseline of 15.3 ± 2.9 mm Hg to a mean maximum of 22.3 ± 7.0 mm Hg (range, 11–64 mm Hg) during follow-up. The rise in mean IOP started one week post-injection and returned to baseline approximately 8–9 months later. A rise in IOP of more than 10 mm Hg occurred in 61 (22.4%), an IOP elevation of more than 15 mm Hg occurred in 30 (11.09%), and a rise in IOP of more than 20 mm Hg in was recorded in 15 (5.5%). Younger age was a risk factor for increased IOP; diabetes was not. The majority of cases were managed with topical glaucoma medications.67

Rhee et al collected a retrospective, consecutive case series of 570 eyes of 536 patients who received a single 4 mg IVTA injection and a second set of 43 eyes of 30 patients who received a second injection. Mean follow-up was 5.67 and 6.41 months, respectively. Of 528 eyes (42 eyes were excluded due to lack of data) receiving a single injection, 281 (57 eyes) had an IOP elevation. A total of 267 eyes (50.6%) experienced an elevation of IOP of at least 30%. An increase of 5 mm Hg or more was seen in 245 (45.8%); an increase of 10 mm Hg or more was observed in 75 (14.2%). They found that baseline IOP greater than 16 mm Hg is a risk factor for post-injection IOP elevation.100 Despite the sixfold difference in IVTA dosage, both of the previous studies reported similar incidence of IOP elevation.

Other complications associated with IVTA include infectious or sterile endophthalmitis, retinal detachment, and vitreous hemorrhage.47,99 There is some evidence that triamcinolone acetonide may be harmful if used after vitrectomy with internal limiting membrane peeling, especially
when TA crystals are in intimate contact with the retinal surface.\textsuperscript{120,133} Thus, it may be wise to avoid IVTA or to use with caution in patients with CME who have undergone vitrectomy with internal limiting membrane peeling. IVTA has also been shown to increase the risk for, and mask symptoms of, endophthalmitis in an experimental model.\textsuperscript{21}

In summary, although topical corticosteroids theoretically act on inflammatory pathways leading to PCME, this treatment alone may be less effective than concomitant therapy with topical nonsteroidal inflammatory agents. There appears to be a synergistic effect of using combined corticosteroid and nonsteroidal topical therapy. IVTA injections may have a useful role in the treatment of refractory PCME. Despite a significant adverse side effect profile, IVTA injections are generally well tolerated.

### 3. Nonsteroidal anti-inflammatory drugs

#### 3.1. Mechanism

The role of inflammation and the prostaglandin pathway is central to the development of PCME. During uncomplicated eye surgery, as with minor trauma, a cascade of inflammatory mediators is secreted into the eye. Arachidonic acid, an essential fatty acid, is converted by the cyclooxygenase (COX) enzyme into prostanooids during the inflammatory process, fulfilling a multitude of biologic roles. Animal models indicate capillary pericyte prostanooid activity results in a potent vasoactive response.\textsuperscript{60} Etiologically, this is believed to direct inflammatory cells to damaged tissue for defense and healing. The transient increase in vascular permeability allows fluid accumulation in the outer plexiform layer, and a cystoid pattern of macula edema develops. This hypothesis is bolstered by studies reporting that the incidence of PCME corresponds with the disruption of the BAB.\textsuperscript{25} As stated previously, even following uncomplicated surgery, the incidence of angiographic CME 1–2 months postoperatively is as high as 20–30%. Although the incidence of chronic, clinical PCME is much less, at 1–3%, the associated vision loss makes it a serious complication.\textsuperscript{126}

The NSAIDs work by inhibiting the COX enzyme. Several ophthalmic preparations exist, with individual characteristics. Nepafenac, a topical NSAID, is converted to the more active metabolite amfenac by intraocular hydrolases in vascular ocular tissue and acts as a potent inhibitor of COX-1 and COX-2 activity.\textsuperscript{123,126} Diclofenac, an NSAID with analgesic effects, has proven to be safe and effective during more than 20 years of use. When diclofenac sodium 0.1% ophthalmic solution was compared with ketorolac tromethamine 0.5% in a randomized prospective study of 34 patients with clinical CME, they were found to be equally effective in reducing the severity and duration of PCME.\textsuperscript{101} Additionally, preparations such as bromfenac offer twice daily dosing.

#### 3.2. Clinical effect and indications

In patients with complicated ocular surgery or patients in high-risk groups such as those with a history of diabetes or topical prostaglandin analog use, encouraging data regarding NSAIDs exist for the prevention of post-surgical macular edema. Miyake published a prospective, randomized study in 1999 that angiographically showed a lower incidence of PCME in patients taking latanoprost prior to cataract surgery when treated with topical diclofenac as compared with those on topical fluorometholone.\textsuperscript{86} Henderson examined 1,659 patients in a retrospective analysis following resident-performed cataract surgery and stratified them to prophylactic regimens including either topical steroid alone, topical NSAID alone, a combination of both, or neither. The NSAIDs used were either diclofenac 0.1% or ketorolac tromethamine 0.5% four times daily. This study found a history of retinal vein occlusion, epiretinal membrane, or prostaglandin analogs to be associated with a higher incidence of PCME following cataract extraction.\textsuperscript{57} They also found the rate of development of PCME in patients who received topical NSAIDs for 3 months after cataract surgery with diabetes, posterior capsule tear, or vitreous loss to be similar to the rate of PCME in groups with no high-risk factors. This supports the use of prophylactic NSAIDs for the first 3 postoperative months following complicated cataract surgery as well as in diabetic patients.

The literature also supports the use of NSAIDs in the treatment and prophylaxis of PCME in uncomplicated surgical cases. Miyake compared patients taking diclofenac 0.1% with patients taking fluorometholone 0.1% and found that reduction of choroidal blood flow, disruption of BAB, and the incidence of PCME in early post-surgical eyes was lower in eyes treated with diclofenac than those treated with fluorometholone. The overall incidence of angiographic CME measured 5 weeks postoperatively was 54.7% in the steroid group and 5.7% in the NSAID group.\textsuperscript{85} Warren examined 15 patients with clinical and angiographic evidence of PCME and a known history of increased IOP following topical corticosteroid application. Although relatively small, this study provided an opportunity to examine patients not treated with steroids. Warren reported a significant benefit in the use of topical nepafenac in PCME.\textsuperscript{126} On NSAIDs alone, patients had a mean improvement in visual acuity compared with baseline at 4 weeks (from 20/64 to 20/36, P < 0.0001) and at 12 weeks (from 20/64 to 20/33, P < 0.001). Retinal thickness measurements significantly improved as well. A retrospective study by Wolf found that, after uneventful cataract surgery, patients treated with topical prednisolone alone had a higher incidence of visually significant PCME than those treated with topical prednisolone and nepafenac.\textsuperscript{130} There were five patients who developed visually significant macular edema in the prednisolone alone group versus none in the prednisolone in combination with nepafenac group (P = 0.0354).

Topical NSAIDs appear beneficial in prevention and management of PCME; nevertheless, discussions among cataract surgeons frequently arise regarding appropriate clinical application of topical NSAIDs. Many studies investigating NSAID use in acute PCME, defined as that occurring within 6 months following surgery, are criticized for having small sample sizes and being insufficiently powered. As previously noted, the Heier et al study reveals an improvement in visual acuity with a combination of topical corticosteroids and ketorolac 0.5% in patients with acute PCME.\textsuperscript{56} Although compelling, a definitive benefit of topical NSAIDs for treating acute PCME has yet to be established.
In contrast, good evidence does exist to support the use of topical NSAIDs for chronic PCME. The classic study conducted by Yanuzzi et al indicates little role for oral indomethacin in chronic PCME management. Several years later, when Burnet et al examined 14 aphakic eyes in a randomized study comparing fenoprofen sodium 1% to placebo for treatment of chronic PCME, a positive, but statistically nonsignificant, effect was observed. Flach showed in two studies a benefit of topical ketorolac 0.5% in the treatment of chronic PCME. The smaller, 1987 study, involving 26 patients, revealed significantly improved distance visual acuity in the ketorolac 0.5% group (8/13 patients) compared with the placebo-treated group (1/13 patients) (P = 0.005). Four years later these results were supported in a multicenter study examining 61 patients in the ketorolac 0.5% group and 59 patients in the placebo group. That study revealed significant improvement in distance visual acuity after 30 days (P = 0.038), 60 days (P = 0.017), and 90 days (P = 0.008) of treatment. Rho found both ketorolac 0.5% and diclofenac 0.1% to be equivalent and efficacious in reducing the severity and duration of chronic CME following uneventful phacoemulsification.

Soheilian et al reported a pilot study of intravitreal injection of diclofenac (500 µg/0.1 mL), treating 10 eyes with macular edema of various etiologies including PCME. Their study showed the improvement of visual acuity in 7 of 10 eyes at 8 weeks after treatment without adverse effects, although there was no significant decrease in central macular thickness.

3.3. Adverse effects

Topical NSAIDs are generally well tolerated. The main side effects are burning, conjunctival hyperemia, keratitis, corneal infiltrates, and corneal lesions similar to those observed with other topical preparations and likely related to preservatives. Systemic side effects result from drainage into the nasolacrimal duct and entry into circulation. Several instances of asthma exacerbation occurred in patients with a history of NSAID hypersensitivity or asthma. Punctual plugs may prevent this side effect. With the introduction of generic diclofenac in 1998, an increase in serious adverse events, particularly corneal melt, occurred, which prompted a recall of the formulation. Although both preparations contained diclofenac 0.1%, the adverse effect may be the result of different suspension buffers and their effect on matrix metalloproteinases and wound healing rather than a direct effect of the diclofenac. Patients with preexisting ocular surface conditions such as Sjögren syndrome, rheumatoid arthritis, or chronic ocular surface disease should avoid generic diclofenac.

Based on reported data in the literature, ocular NSAIDs are an important and evolving tool in the prevention and treatment of PCME. In a review of available data, Bromday (bromfenac 0.09%, ISTA Pharmaceuticals, Inc., Irvine, CA), Voltaren (diclofenac 0.1%, Novartis Ophthalmics, East Hanover, NJ) and Acular (ketorolac 0.5%, Allergan, Irvine, CA) have been used for cases of acute and chronic PCME and for prophylaxis in patients with known risk factors for the development of PCME. There are very little data that compare the efficacy of different brands of NSAIDs in treating PCME. Both bromfenac and a recently available newer NSAID, Nevanac (nepafenac 0.1%, Alcon, Fort Worth, TX) are found in rabbit retina after topical application, suggesting their utility in both anterior and posterior segment inflammatory conditions, though their clinical value in PCME is not proven.

As topical NSAIDs are relatively safe, and there is a dearth of data defining their role in acute PCME, treatment initiated on an individual basis is reasonable until better evidence exists. At this time, there is no standard protocol.

4. Anti-vascular endothelial growth factor

4.1. Mechanism

Vascular endothelial growth factor (VEGF), besides being a key mediator of vasculogenesis and angiogenesis, potentially increases vascular permeability by causing dysfunction of tight junctions and activating vesicular–vacuolar organelles. Additionally, VEGF up-regulates the formation of plasminogen, which further contributes to increased vascular permeability.

The VEGF family comprises isotypes VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor, and several splice variants in humans (e.g., VEGF-A 121, VEGF-A 145, VEGF-A 165). Overexpression of VEGF occurs in some cancers, in rheumatoid arthritis as a response to tumor necrosis factor-alpha, in age-related macular degeneration (AMD)-associated choroidal neovascularization, and in macular edema associated with diabetic retinopathy or retinal vein occlusions. Anti-VEGF agents restore the occludin proteins in tight junctions, which are needed to fortify the BRB. They have been used effectively in AMD-, diabetic-, and vein occlusion-associated CME. They function to reduce edema as well as to restore the BRB. A number of large studies including ANCHOR, VISION, MARINA, PIER, FOCUS, BRAVO, CRUISE, DRCRnet, GALILEO, and COPERNICUS have clearly shown the benefits of anti-VEGF treatment of retinal edema in these conditions.

Ranibizumab, bevacizumab, pegaptanib, and aflibercept are treatment options in CME. Although we will provide some clinical evidence for the use of such treatments, no study thus far has shown increased ocular VEGF levels in patients with PCME in the absence of ischemic ocular disease. One postmortem study demonstrated elevated human VEGF levels in eyes with aphakic and pseudophakic CME, although the status of concurrent ischemic ocular diseases (including diabetic retinopathy, vein occlusion, etc.) was not accounted for in these specimens. Of note, some data indicate that peripheral ischemia elevates the risk for PCME. A retrospective study carried out on 177 consecutive patients (252 eyes) found that there was an elevated risk of ischemic heart disease in those patient who experienced visually significant and angiographically evident PCME (P = 0.04). Additionally, it is well established that diabetes and history of retinal vein occlusion are high-risk characteristics for the development of PCME.

4.2. Clinical effect and indications

No studies have clearly shown that VEGF levels are increased in the vitreous in pseudophakic and aphakic eyes in the absence of ischemic ocular diseases. The studies that have
been published are focused on treating refractory PCME after other options have failed. PCME typically resolves with time, which makes the evaluation of any treatment modality difficult.73

One of the largest recent trials involves a multicenter, interventional, retrospective pilot study from the Pan-American Collaborative Retina Study Group. Thirty-six eyes of 31 patients (mean age, 68 years) with refractory CME after cataract surgery were chosen for intravitreal injection of 1.25 mg or 2.5 mg bevacizumab. Exclusion criteria included a history of other intraocular surgery, administration of intravitreal triamcinolone, CME due to other cause(s), or the presence of vitreoretinal pathology. In addition, the study excluded eyes with structural changes such as an epiretinal membrane or anterior segment changes including vitreous or iris to the wound, broken posterior capsule, sulcus-fixated intraocular lens (IOL), and iris–IOL contact. Main outcome measures were best-corrected visual acuity (BCVA) and central macular thickness (CMT) by OCT. Seventy-two percent (72%) of patients demonstrated improvement in BCVA ≥ 2 ETDRS lines (P < 0.001), and no eye demonstrated worsening of visual acuity ≥ 2 ETDRS lines. Mean baseline BCVA was 20/200 with average baseline being 10.6 months from onset of symptoms to intravitreal anti-VEGF injection. At 12 months, mean BCVA was 20/80. OCT showed mean CMT at baseline of 499 μm that decreased to a mean of 286 μm at 12 months (P < 0.0001). The number of injections varied from 2 to 6, with a mean of 2.7 and a mean interval between injections of 15 weeks. No adverse events were reported.5 Although this study represents a relatively large group with significant follow-up, the variability in injection number (2–6) and dose of bevacizumab (1.25–2.5 mg), as well as it not being a randomized double-blind placebo trial limit the generalizability of the findings.

Cervera and coworkers described four patients with refractory PCME who were treated with pegaptanib sodium and had improvement in visual acuity and CMT as measured with OCT.72 Two patients in this group had previously undergone intravitreal injections with triamcinolone, and one patient underwent vitrectomy after vitreous traction on the macula was noted on OCT. A case study from Spain describes a 71-year-old man who presented with refractory PCME 16 months after receiving two intravitreal injections of triamcinolone. He was treated with intravitreal bevacizumab, and 3 months later, his BCVA had improved from 20/200 to 20/40, and his OCT showed a significant decrease in CMT.74 The status of concurrent ocular ischemic disease was not described in these two reports. A case report by Barone et al documented significant improvement in vision and complete resolution of PCME 3 months following intravitreal injection of 1.25 mg bevacizumab.7 Subsequently, Barone et al published similar results in a series of 10 patients with PCME. Mean baseline visual acuity was 20/80, and mean final visual acuity was 20/32 (P < 0.0001). Follow-up was 6 months, and each patient received at least one intravitreal injection of 1.25 mg bevacizumab. The mean baseline CMT was 546 μm, which decreased to 228 μm by the end of follow-up (P < 0.0001). All patients showed improvement of visual acuity with no adverse effects. Exclusion criteria included a history of other intraocular surgery, administration of intravitreal triamcinolone, non-CME uveitis, and vitreoretinal pathology such as diabetic maculopathy or proliferative diabetic retinopathy, neovascular AMD, and retinal vein occlusion.10

In a retrospective case series of 16 patients with PCME unresponsive to medical treatment for a median duration of 14 weeks (range, 3–84 weeks) received intravitreal injections of 1.25 mg bevacizumab. Although significant decreases in CMT occurred, there was no significant visual improvement in 15 of 16 patients, and repeat injections of bevacizumab did not improve visual outcomes. This may have been the result of two factors: significant residual macular edema present despite multiple intravitreal injections and the chronicity of the macular edema. Mild ocular irritation was the only adverse effect.115 This study excluded patients with visually significant preoperative coexisting ocular pathology such as uveitis not related to cataract surgery, diabetic maculopathy, neovascular AMD, advanced glaucoma, proliferative diabetic retinopathy, and retinal vein occlusion.

4.3. Adverse effects

The risks of intravitreal anti-VEGF injections include endophthalmitis (0.01–0.06%), central retinal artery occlusion (0.01%), retinal tear (0.3–0.5%) and retinal detachment (0.04–0.18%). Others are damage to crystalline lens (0.009–0.01%), uveitis (0.09%), subconjunctival hemorrhage (0.03%), and mild surface discomfort (0.14%).5,6,42,82,131 The Comparison of Age-related Macular Degeneration Treatments Trial49 and the Randomized Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization (IVAN) Trial63 provide data regarding systemic side effects of intravitreal anti-VEGF agents. The CATT was a multicenter randomized clinical trial of 1,107 patients treated with either ranibizumab or bevacizumab for AMD-associated choroidal new vessels. Side effects of intravitreal ranibizumab versus bevacizumab, respectively, included arteriothrombotic events (4.7 vs 5.0%), venous thrombotic events (0.5% vs 1.7%), and hypertension (0.5% vs 0.7%). There were no differences in rates of all-cause mortality between the bevacizumab-treated group (5.3%) and the ranibizumab-treated group (6.1%) at 2 years (P = 0.62). The proportion of patients with arteriothrombotic events was similar in the bevacizumab-treated group (5.0%) and the ranibizumab-treated group (4.7%) at 2 years (P = 0.89). One or more serious systemic adverse events occurred in 190 (31.7%) of 599 ranibizumab-treated patients and 234 (39.9%) of 586 bevacizumab-treated patients. The proportion of patients with one or more systemic serious adverse events was significantly higher in the bevacizumab cohort than in the ranibizumab cohort (P = 0.004). After adjustment for demographic features and coexisting illness at baseline, the risk ratio for all systemic serious adverse events within 2 years for bevacizumab vs ranibizumab was 1.30 (95% confidence interval, 1.07–1.57, P = 0.009).28 Because there is no placebo-treated control group in the CATT trial, we cannot determine whether the incidence of arteriothrombotic events, venous thrombotic events, and/or hypertension was increased as a result of intravitreal injection of these agents. The interpretation of the CATT data is intensely debated. Beaumont analyzed the data from multiple large trials including the CATT, ANCHOR,18 and MARINA102.
trials, noting that patients receiving bevacizumab were indeed at an increased risk for serious systemic adverse events including venous thromboembolic events (P < 0.02), gastrointestinal tract ulceration or hemorrhage (P < 0.03), and bacterial infections (P < 0.01).11

IVAN is a multicenter randomized noninferiority trial studying the treatment effects and adverse effects of intraocular bevacizumab and ranibizumab for AMD-associated choroidal new vessels. At year 2, this study, which was smaller than CATT with 610 patients, also demonstrated no significant difference in the rate of death (P = 0.91), arteriothrombotic events, or hospital admission for heart failure (P = 0.16) in the ranibizumab cohort when compared to the bevacizumab cohort. No significant difference was found in the frequency of systemic serious adverse effects (P = 0.82)19; it should be noted, however, that neither the CATT nor the IVAN trials were intentionally powered to detect differences in adverse side effects. A meta-analysis of both trials did not detect a difference in rate of mortality or arterial thrombotic events between ranibizumab and bevacizumab groups after 2 years, although a significant 24% higher risk of serious systemic adverse events was seen in the bevacizumab cohort versus the ranibizumab cohort.27 Moreover, the IVAN trial demonstrated a substantial, statistically significant reduction in systemic VEGF levels among patients treated with intraocular bevacizumab but not among patients treated with ranibizumab.27,63

Curtis et al studied risks of all-cause mortality, incident myocardial infarction, bleeding, and incident stroke in a large retrospective cohort study of 146,942 Medicare beneficiaries 65 years or older who received treatment for AMD with either photodynamic therapy, pegaptanib, bevacizumab, or ranibizumab.31 Mortality was significantly lower with ranibizumab therapy than with photodynamic therapy (hazard ratio, 0.85; 95% confidence interval, 0.75–0.95) or pegaptanib use (0.84; 0.74–0.95). Myocardial infarction was significantly lower with ranibizumab use than with photodynamic therapy (0.73; 0.58–0.92). Analyses directly comparing only ranibizumab and bevacizumab were performed (n = 40,841). This included 19,026 patients receiving ranibizumab and 21,815 patients receiving bevacizumab as first-line therapy. These secondary analyses were subgroup analyses that applied only to ranibizumab and bevacizumab. Similar to the primary analyses, data from this secondary analysis were based on a 12-month follow-up period. The secondary analysis showed there was a significantly lower risk of death and stroke with ranibizumab versus bevacizumab. The adjusted analysis suggested a 0.86 (0.75–0.98) hazard ratio for death, which may be interpreted to mean a 14% significantly lower risk of death with ranibizumab. The hazard ratio for stroke was 0.78 (0.64–0.98), suggesting a 22% significantly lower risk with ranibizumab. This study demonstrated that there was a significantly increased risk of arteriothrombotic events in patients using intraocular bevacizumab versus ranibizumab.

These data may have been affected by potential treatment selection bias related to the higher coinsurance required of patients receiving ranibizumab over bevacizumab. The same authors conducted a smaller, secondary analysis attempting to address this bias related to socioeconomic status. This analysis did not reproduce the increased risks associated with bevacizumab use. Note, however, that the authors identify statistically significant differences in the prevalence of co-morbid conditions (e.g., cancer, renal disease, P = 0.003) in the bevacizumab cohort, hindering interpretation of the results.

Data from the RISE and RIDE trials indicate that, among patients with CME due to diabetes mellitus, there is an increased risk of death and stroke after intravitreal ranibizumab injection, even at doses as low as 0.3 mg. The incidence of systemic adverse events in the 0.5 mg ranibizumab cohort was 19.7%. The incidence in the 0.3 mg cohort was 16.8%. Rates of stroke over 3 years in the 0.5 mg and 0.3 mg cohorts were 4.8% and 2.0%, respectively. Rates of myocardial infarction during this time in the 0.5 mg and 0.3 mg cohorts were 3.6% and 7.2%, respectively.

In summary, although the biological basis for the use of anti-VEGF agents in PCME is not established, there are some studies indicating potential benefit of intravitreal anti-VEGF therapy. The natural history of the disease, however, combined with study design limitations pointed out herein make it difficult to be confident that there is a true treatment benefit.

On the other hand, data from large randomized clinical trials indicate that there is a risk of systemic toxicity with intravitreal anti-VEGF agents, including stroke and death. Thus, we approach the use of these agents for PCME at this time with caution, particularly in extreme elderly patients, in patients with a recent history of stroke, or in patients with a history of gastrointestinal bleeding. More rigorously designed clinical trials are needed to establish the safety and efficacy of these agents for PCME.

5. Surgical treatment: pars plana vitrectomy

Pars plana vitrectomy (PPV) may be considered for chronic cases of PCME associated with vitreoretinal traction or retained lens fragments. Additionally, a few studies have shown that PPV can resolve chronic CME in some eyes even in the absence of vitreoretinal abnormalities.

5.1. Mechanism

PCME has been seen with vitreomacular traction (VMT)126 and extrafoveal vitreo-retinal traction.78 The Vitrectomy-Aphakic Cystoid Macular Edema Study Group observed vitreomacular traction in 3.7% of surgically aphakic patients with chronic CME.63 Vitreous incarceration in the cataract wound is associated with release of inflammatory factors that lead to increased vascular permeability and, ultimately, edema. Miyake et al investigated the effect of PPV in nine patients with intracapsular cataract extraction with vitreous loss, vitreous incarceration in the wound, and severe CME. Aqueous prostaglandin levels were markedly elevated preoperatively and showed significant reduction following vitrectomy. Fundus fluorescein angiography showed improvement postvitrectomy in those patients with CME of short duration; chronic CME did not respond similarly.84

A history of an epiretinal membrane has been linked to postoperative cystoid macular edema.77 PCME has been documented in patients after cataract extraction despite a previous history of PPV with internal limiting membrane or
epiretinal membrane peeling, suggesting that vitreoretinal traction is not involved in all cases of PCME.\textsuperscript{61} Pseudophakic CME has also been noted in the setting of inflammation incited by lens fragments left in the vitreous during complicated cataract extraction.\textsuperscript{58,77,88}

Some eyes with chronic PCME but without identifiable anterior or posterior vitreoretinal adhesions or retained lens fragments may respond favorably to PPV. One possible explanation discussed by Pendergast et al\textsuperscript{99} is that cataract surgery, even without complications, induces intraocular inflammation and vitreous disturbance by altering anterior chamber anatomy. Prostaglandins are released into the aqueous by intraocular surgery.\textsuperscript{71} Normal vitreous prostaglandin levels (100 pg/mL) are present in patients following routine cataract extraction; elevated vitreous prostaglandin levels (up to 10,000 pg/mL) occur postoperatively in cases involving significant iris/vitreous adhesions.\textsuperscript{122} Prostaglandins cause disruption of the BAB, which can result in the accumulation of further inflammatory mediators including endotoxin, immune complexes, and cytokines.\textsuperscript{83} These inflammatory markers can diffuse into the posterior segment and result in disruption of the BRB,\textsuperscript{84} in turn leading to postoperative CME. The removal of vitreous in these cases can prevent the accumulation of inflammatory factors that exacerbate macular edema even without any clear VMT.

5.2. Clinical effect and indications

5.2.1. Vitreomacular traction

PPV may be indicated in cases with clear evidence of VMT and chronic PCME. Harbour et al demonstrated beneficial effects of PPV in eyes with chronic PCME and VMT.\textsuperscript{51} All 24 patients in that study had some element of persistent VMT associated with vitreous adhesions to the anterior segment. The visual acuity improved an average of 4.7 Snellen lines following PPV in these cases ($P < 0.0001$). Although visual acuity improved, no angiographic studies were performed to confirm resolution of the edema. Spectral domain OCT can be very helpful in diagnosing PCME due to VMT. A small retrospective study by Martinez et al\textsuperscript{78} to evaluate OCT as a diagnostic tool in PCME with VMT demonstrated the presence of extrafoveal VMT in three patients with chronic PCME. That retrospective study, albeit small, is the first to document an association of chronic macular edema of pseudophakic origin and extrafoveal vitreoretinal traction. No intervention was described. In some cases (e.g., focal vitreosfoveal adhesion <1,500 μm diameter), intravitreal injection of ocriplasmin could be considered before the patient undergoes PPV for VMT, although patients with PCME were not enrolled in the randomized trial in which ocriplasmin’s efficacy at relieving VMT was demonstrated.\textsuperscript{116} To date, no studies have examined the role of ocriplasmin in pseudophakic cystoid macular edema.

5.2.2. Retained lens fragments

Margherio and coworkers demonstrated improved visual acuity following PPV to remove retained lens fragments from the vitreous.\textsuperscript{77} They studied 126 consecutive eyes of 126 patients with dislocated lens fragments after phacoemulsification managed with PPV. The mean pre-vitrectomy visual acuity was 20/278; mean post-vitrectomy visual acuity was 20/40 ($P < 0.0001$) after an average follow-up of 18.9 months. The final outcome depended on factors such as type of IOL used and presence of corneal edema, retinal detachment, glaucoma, or endophthalmitis. There was no statistically significant difference between early ($<7$ days) and delayed ($\geq8$ days) vitrectomy on visual acuity.

Rossetti et al\textsuperscript{105} showed a clear benefit of PPV in reducing inflammation compared with non-vitrectomized eyes in the setting of retained lens material. This prospective, non-randomized study analyzed 36 eyes with retained lens fragments, half of which underwent PPV. At month 3, the vitrectomized eyes had a significantly lower frequency of fundoscopically evident CME when compared to the non-vitrectomized eyes. This trend persisted at 6-month follow-up. While slit-lamp biomicroscopy has its limitations in the detection and quantification of macular edema as compared to OCT,\textsuperscript{105} this study demonstrates the utility of PPV in reduction of PCME in the setting of retained lens material. The vitrectomized eyes recovered vision more quickly than non-vitrectomized eyes, but the eventual visual outcomes were not significantly different at final follow-up of 6 months.

5.2.3. Absence of vitreoretinal adhesions

We note that no large scale studies have been published that evaluate the effect of PPV in eyes with chronic PCME in absence of clear vitreous incarceration in the anterior segment wound, VMT, or retained lens material. A retrospective study by Pendergast examined 23 patients with persistent CME after cataract surgery and IOL placement refractory to maximal medical management.\textsuperscript{95} These patients were treated with pars plana vitrectomy despite showing no evidence of vitreous adhesion to the cornea or cataract incision; 18 of 23 patients had a total posterior vitreous detachment present at baseline examination. The results were encouraging as median preoperative visual acuity improved from 20/200 preoperatively to 20/60 ($P < 0.0001$) after a mean follow-up of 30.2 months. There was a trend toward better final visual acuity in eyes receiving PPV within one year of cataract extraction versus delayed intervention ($P = 0.069$). Biomicroscopic fundoscopy documented resolution of CME in all eyes postoperatively; 12 of 23 eyes showed vitreous or anterior hyaloid adhesions to iris, IOL haptic, or both. Additionally, four eyes in this study had VMT prior to vitrectomy. These results suggest the utility of PPV in cases of chronic PCME previously resistant to medical management, even in the absence of vitreous incarceration to the cataract incision or vitreous disturbances.

In two eyes with PCME that had failed medical management and with absence of clear VMT, Peyman et al\textsuperscript{94} demonstrated a definite benefit of PPV with internal limiting membrane peeling. If PCME has not responded to management with topical and intravitreal pharmacological therapy, and even if vitreoretinal abnormalities are not noted, PPV may be considered; the risks of surgery should be considered before proceeding, however, especially given the possibility of no visual recovery with treatment.

5.3. Adverse effects

Surgical treatment of PCME carries significant risk compared with more conservative therapies. The major risks associated
with PPV include retinal tear, retinal detachment, suprachoroidal hemorrhage, and endophthalmitis. The reported incidence of endophthalmitis ranges from 0% to 0.82%.36,59,107 Stein et al118 assessed the overall risk of complications of PPV in Medicare patients as approximately 5%. In that study, the incidence of rhegmatogenous retinal detachment ranged from 4.0–4.6% from 1994–2005. Less visually threatening complications such as glaucoma, vitreous hemorrhage, retinal tear, and corneal pathology affected 14.8–20% of patients. The risk of retinal detachment in eyes undergoing PPV for removal of retained lens fragments, where the indication for PPV is fairly strong, is somewhat higher. Moore et al19 published a large retrospective study in which the rate of retinal detachment after PPV in this setting was 5.5%. Additionally, the rate of retinal detachment before or during PPV for retained lens fragment was 7.3%. Merani et al16 also found an increased risk of retinal detachment after PPV for retained lens fragments. In a large retrospective study, retinal detachment occurred in 9% (20 of 223), with 11 diagnosed before or during vitrectomy and 9 occurring after vitrectomy. Patients with severe refractory PCME or those in whom surgery can clearly address a specific cause such as vitreous incarceration in the wound or macular traction and edema are probably best suited for surgery.

6. Conclusion

Despite significant evolution in the technique and precision of cataract surgery, PCME remains an important cause of suboptimal postoperative vision. The vast majority of cases will resolve without intervention. Recalcitrant cases of PCME can pose a therapeutic dilemma. The development and accessibility of high-resolution, spectral domain OCT has dramatically improved the diagnosis and monitoring of macular edema following cataract surgery. Disease management options, however, have remained relatively unchanged. Topical NSAIDs remain the mainstay in prevention and management of PCME. Topical, periocular, and intraocular corticosteroids also serve a useful role both as monotherapy as well as an adjunct alongside NSAIDs. The present literature does not provide robust support for the use of anti-VEGF treatments. Although there have been some positive results in recent studies looking at anti-VEGF use in PCME, a lack of randomized double-blind placebo trials limit the generalizability of these data, and there are concerns regarding systemic toxicity in vulnerable patient populations following intravitreal anti-VEGF injection. Surgical intervention can be effective in the presence of certain conditions, namely, vitreomacular traction or retained lens nuclear material. Presently, there is no uniform or standard algorithm for the prevention and treatment of pseudophakic cystoid macular edema. Prospective, randomized clinical trials comparing various treatments are needed.

7. Method of literature search

This review was prepared using articles identified by searching the Medline database from 1950–2013. The following key words were used: pseudophakic cystoid macular edema, macular edema, pseudophakia, topical corticosteroids, intravitreal corticosteroid injection, intravitreal triamcinolone injection, non-steroidal anti-inflammatory agents, anti-VEGF agents, and pars plana vitrectomy. Other articles were identified from the bibliographies of the articles produced by the Medline search. Relevant articles written in other languages were included if an English translation of the abstracts was available.

8. Disclosure

Marco Zarbin is a consultant to Calhoun Vision, Inc., Genentech, Imagen Biotech, Helios KK, Novartis, Pfizer, and Roche. All other authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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