Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Major review

Management of pseudophakic cystoid macular edema

Suqin Guo, MD, Shriji Patel, MD, Ben Baumrind, MD, Keegan Johnson, MD, Daniel Levinsohn, MD, Edward Marcus, MD, Brad Tannen, MD, Monique Roy, MD, Neelakshi Bhagat, MD, Marco Zarbin, MD, PhD*

Department of Ophthalmology, The Institute of Ophthalmology and Visual Science, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA

ARTICLE INFO

Article history:
Received 3 April 2014
Received in revised form
24 August 2014
Accepted 26 August 2014
Available online 2 September 2014

Keywords:
pseudophakic cystoid
macular edema
corticosteroids
non-steroidal anti-
inflammatory agents
anti-vascular endothelial
growth factor
pars plana vitrectomy

ABSTRACT

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)

* Corresponding author: Suqin Guo, MD, Associate Professor, Rutgers New Jersey Medical School, Doctors Office Center, Suite 6100, PO Box 1709, Newark, NJ 07101-1709.
E-mail address: guos1@njms.rutgers.edu (S. Guo).
0039-6257/$ – see front matter
http://dx.doi.org/10.1016/j.survophthal.2014.08.005

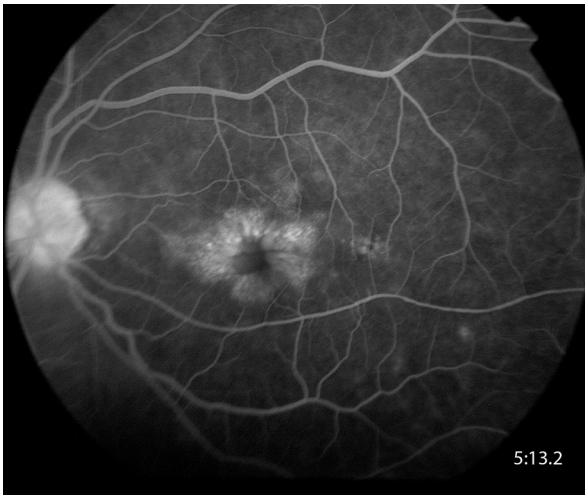

Fig. 1 – Intravenous fluorescein angiography demonstrating classic perifoveal petalloid staining with late leakage from the optic nerve head consistent with pseudophakic cystoid macular edema.

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. Iridovitreal 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.[39,57] 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 disk, 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).[69,134] 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

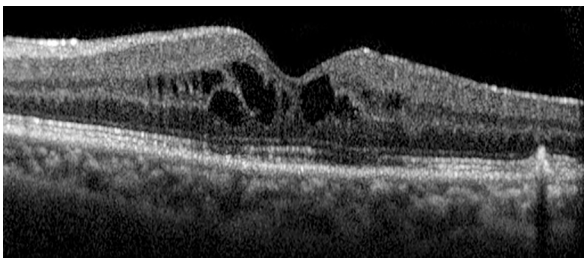

Fig. 2 – Characteristic macular thickening and cystic intraretinal spaces typical of PCME on OCT.

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.[90] 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.[56] 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.[4,5] 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.[129] The role of corticosteroids in the treatment of PCME is based on inhibition of leukotriene and prostaglandin synthesis.[29] 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.[112] 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.[129]

Asano et al compared outcomes in 142 patients treated with diclofenac 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 diclofenac, 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 diclofenac-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.[7] 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.[56] 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.[62]

2.1.3. *Adverse effects*

Topical corticosteroids are associated with various adverse side effects, including elevated intraocular pressure, postoperative infection, and impaired wound healing.[7,112]

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.[135] These injections enable the delivery of corticosteroids to the retina in higher concentrations, allowing better bioavailability compared with topical administration.[13] Triamcinolone acetonide is used in a crystalline form, which achieves a long-lasting effect.[66] This corticosteroid has been found in the vitreous up to 1.5 years after injection.[119] Additionally, triamcinolone given by this delivery method was nontoxic in rabbits.[79]

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

	Study	Design	Treatment	No. of patients	Duration	Main outcome measures	Conclusions
Corticosteroids	Thach et al[121]	Retrospective	Single retrobulbar triamcinolone injection (18 eyes, 40 mg) vs Three biweekly posterior sub-Tenon's triamcinolone injections (31 eyes, 40 mg)	48 (49 eyes)	10–12 mo	BCVA	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
	Boscia et al[14]	Prospective	IVTA (4 mg)	6 (7 eyes)	11.1 mo	BCVA CMT on OCT Leakage on FA	Significant improvement in BCVA ($P = 0.019$) Significant improvement in CMT by OCT ($P = 0.0018$) and area of leakage on FA ($P < 0.0001$)
	Jonas et al[67]	Prospective	IVTA (25 mg)	5	6.6 mo	BCVA	Improvement in VA in all patients
NSAIDs	Yannuzzi et al[132]	Randomized Double-masked Prospective	Indomethacin 25 mg PO TID vs placebo	20 (23 eyes)	-	BCVA	No significant improvement in VA noted in treatment vs placebo
	Burnett et al[22]	Randomized Double-masked Prospective	fenoprogen 1% tid vs placebo	14	-	BCVA	No significant improvement in VA noted in treatment vs placebo
	Flach et al[40]	Randomized Double-masked Prospective	ketorolac 0.5% qid vs placebo	26	3 mo	BCVA	Significant improvement in BCVA ($P = 0.005$) in ketorolac 0.5% group vs placebo
	Flach et al[41]	Randomized Double-masked Prospective	ketorolac 0.5% qid vs placebo	120	4 mo	BCVA	Significant improvement in BCVA ($P = 0.008$) in ketorolac 0.5% group vs placebo
	Rho[101]	Randomized Prospective	diclofenac 0.1% qid vs ketorolac 0.5% qid	34	26 weeks	BCVA Severity of CME (contact lens biomicroscopy)	Both treatment methods resulted in a significant reduction in CME and a significant improvement in visual acuity. No difference between the two medications was found.
Anti-VEGF	Arevalo et al[5]	Retrospective Multicenter	Intravitreal bevacizumab (1.25 or 2.5 mg)	31 (36 eyes)	12 mo	BCVA CMT by OCT	Significant improvement in BCVA ($P < 0.0001$) Significant improvement in CMT by OCT ($P < 0.0001$)
	Arevalo et al[4]	Retrospective Multicenter	Intravitreal bevacizumab (1.25 or 2.5 mg)	25 (28 eyes)	8 mo	BCVA CMT by OCT	Significant improvement in BCVA ($P < 0.0001$) Significant improvement in CMT by OCT ($P < 0.0001$)
	Spitzer et al[115]	Case series Retrospective	Intravitreal bevacizumab (1.25 mg)	16 (16 eyes)	3.5–20.5 mo	BCVA CMT by OCT Treatment Complications	No significant change in BCVA Significant improvement in CMT by OCT No significant adverse effects
	Barone et al[10]	Case series Retrospective	Intravitreal bevacizumab (1.25 mg)	10 (10 eyes)	6 mo	BCVA CMT by OCT	Significant improvement in BCVA ($P < 0.0001$) Significant improvement in CMT by OCT ($P < 0.0001$)
	Cervera et al[26]	Prospective Nonrandomized	Pegaptanib	4 (4 eyes)	4 mo	BCVA	Visual improvement in all patients (mean = 17 ETDRS letters)
Pars plana vitrectomy	Harbour et al[51]	Case series Retrospective	PPV in the setting of vitreous adhesions or iris capture	24 (24 eyes)	-	BCVA	Significant improvement in BCVA ($P < 0.0001$)
	Pendergast et al[92]	Case series Retrospective	PPV in the absence of vitreous incarceration in wound	23 (23 eyes)	30.2 mo (2–109)	BCVA	Significant improvement in BCVA ($P < 0.0001$)

(continued on next page)

Table 1 – (continued)

	Study	Design	Treatment	No. of patients	Duration	Main outcome measures	Conclusions
	Patel et al[91]	Case series Retrospective	PPV in aphakia with vitreous incarceration in wound	16 (17 eyes)	20 mo (6–66)	BCVA Improvement in CME	Visual improvement (>2 lines) in 65% of eyes Improvement of CME (FA or fundus biomicroscopy) in 88% of eyes
	Sevim et al[108]	Case series Retrospective	IVTA (20 eyes, 4 mg) vs 23-gauge PPV with ILM peeling (19 eyes)	39	12 mo	Mean foveal thickness Visual Acuity	Significant improvement in BCVA ($P = 0.001$) in both groups Significant improvement in mean foveal thickness ($P = 0.001$) in both groups No significant difference between the two groups at 12 months
Combination therapy	Warren et al[126]	Randomized Investigator-masked Prospective	IVTA (4 mg) + Intravitreal bevacizumab (1.25 mg) at study entry Repeat bevacizumab injection (1.25 mg) at week 4 Randomized to NSAID vs placebo at study entry	39	4 mo	Mean retinal thickness Visual Acuity	IVTA + bevacizumab + nepafenac 0.1% showed reduced MRT versus placebo ($P = 0.0048$) IVT + bevacizumab + nepafenac 0.1% showed improved VA versus placebo ($P = 0.0233$)
	Heier et al[56]	Randomized Double-masked Prospective	Ketorolac 0.5% qid vs Prednisolone 1.0% qid vs Combination therapy	26	3 mo (or until CME resolved)	BCVA Time to recovery Contrast sensitivity	Significant improvement in BCVA with combination therapy over either monotherapy

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.[68] 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 (53.2%) 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.[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.[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 prostanoids during the inflammatory process, fulfilling a multitude of biologic roles. Animal models indicate capillary pericyte prostanoid activity results in a potent vasoactive response.[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.[83] 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.[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.[53,126] 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.[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.[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.[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.[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.[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.[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.[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.[132] 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.[22] 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) ($P = 0.005$).[40] 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.[41] 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.[101]

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.[114]

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.[38,128] 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.[95,109,110,113] Punctual plugs may prevent this side effect.[109] 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.[52] 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.[8,45,134]

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, potently increases vascular permeability by causing dysfunction of tight junctions and activating vesicular–vacuolar organelles.[26,35,80,124] Additionally, VEGF up-regulates the formation of plasminogen, which further contributes to increased vascular permeability.[98]

The VEGF family comprises isotypes VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor, and the several splice variants in humans (e.g., VEGF-A 121, VEGF-A 145, VEGF-A 165).[25] 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.[97] 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.[1,2,30,37,74,96,104,127] A number of large studies including ANCHOR,[19] VISION,[48] MARINA,[102] PIER,[20] FOCUS,[54] BRAVO,[24] CRUISE,[16] DRCRnet,[33] GALILEO,[70] and COPERNICUS[17] have clearly shown the benefits of anti-VEGF treatment of retinal edema in these conditions.

Ranibizumab,[32] bevacizumab,[115] pegaptanib,[44] and aflibercept[55] 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,[125] 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 ($P = 0.04$).[65] Additionally, it is well established that diabetes and history of retinal vein occlusion[57] 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 $\geq$ 2 ETDRS lines ($P < 0.0001$), and no eye demonstrated worsening of visual acuity $\geq$2 ETDRS lines. Mean baseline BCVA was 20/200 with average baseline being 10.6 months from onset of symptoms to intravitreal anti-VEGF injection. At 12 months, mean BCVA was 20/80. OCT showed mean CMT at baseline of 499 μm that decreased to a mean of 286 μm at 12 months ($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.[26] 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.[34] 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.[9] 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 (0.01–0.066%), 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%).[6,42,82,131] The Comparison of Age-related Macular Degeneration Treatments (CATT) Trial[49] and the Randomized Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization (IVAN) Trial[63] 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 MARINA[102]

trials, noting that patients receiving bevacizumab were indeed at an increased risk for serious systemic adverse events including venous thrombotic 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 intravitreal 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 ($P = 0.82$)[27]; 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 intravitreal 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; 99% 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 intravitreal 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 comorbid 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)[106] 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.[43] 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 post-vitrectomy 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.[57] 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.[61] Pseudophakic CME has also been noted in the setting of inflammation incited by lens fragments left in the vitreous during complicated cataract extraction.[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[92] 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.[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.[122] Prostaglandins cause disruption of the BAB, which can result in the accumulation of further inflammatory mediators including endotoxin, immune complexes, and cytokines.[83] These inflammatory markers can diffuse into the posterior segment and result in disruption of the BRB,[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.[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[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 vitreofoveal 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.[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.[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 (≥8 days) vitrectomy on visual acuity.

Rossetti et al[103] showed a clear benefit of PPV in reducing inflammation compared with non-vitrectomized eyes in the setting of retained lens material. This prospective, nonrandomized 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 nonvitrectomized 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,[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 nonvitrectomized 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.[92] 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[94] demonstrated a definite benefit of PPV with internal limiting membrane peeling. If PCME has not responded to management with topical and intravitreal pharmaceutical 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 al[118] 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 al[89] 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 al[81] 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.

REFERENCES

1. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994;331:1480–7
2. Andreoli CM, Miller JW. Anti-vascular endothelial growth factor therapy for ocular neovascular disease. Curr Opin Ophthalmol. 2007;18:502–8
3. Arcieri ES, Santana A, Rocha FN, et al. Blood-aqueous barrier changes after the use of prostaglandin analogues in patients with pseudophakia and aphakia: a 6-month randomized trial. Arch Ophthalmol. 2005;123:186–92
4. Arevalo JF, Garcia-Amaris RA, Roca JA, et al. Primary intravitreal bevacizumab for the management of pseudophakic cystoid macular edema: pilot study of the Pan-American Collaborative Retina Study Group. J Cataract Refract Surg. 2007;33:2098–105
5. Arevalo JF, Maia M, Garcia-Amaris RA, et al. Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. Ophthalmology. 2009;116:1481–7, 1487.e1
6. Artunay O, Yuzbasioglu E, Rasier R, et al. Incidence and management of acute endophthalmitis after intravitreal bevacizumab (Avastin) injection. Eye (Lond). 2009;23:2187–93
7. Asano S, Miyake K, Ota I, et al. Reducing angiographic cystoid macular edema and blood-aqueous barrier disruption after small-incision phacoemulsification and foldable intraocular lens implantation: multicenter prospective randomized comparison of topical diclofenac 0.1% and betamethasone 0.1%. J Cataract Refract Surg. 2008;34:57–63
8. Baklayan GA, Patterson HM, Song CK, et al. 24-hour evaluation of the ocular distribution of C-labeled bromfenac following topical instillation into the eyes of New Zealand White rabbits. J Ocul Pharmacol Ther. 2008;24:392–8
9. Barone A, Prascina F, Russo V, et al. Successful treatment of pseudophakic cystoid macular edema with intravitreal bevacizumab. J Cataract Refract Surg. 2008;34:1210–2
10. Barone A, Russo V, Prascina F, et al. Short-term safety and efficacy of intravitreal bevacizumab for pseudophakic cystoid macular edema. Retina. 2009;29:33–7
11. Beaumont P. Bevacizumab: not as good with more adverse reactions? Clin Experiment Ophthalmol. 2011;39:588–90

12. Belair ML, Kim SJ, Thorne JE, et al. Incidence of cystoid macular edema after cataract surgery in patients with and without uveitis using optical coherence tomography. Am J Ophthalmol. 2009;148:128–35.e122
13. Benhamou N, Massin P, Haouchine B, et al. Intravitreal triamcinolone for refractory pseudophakic macular edema. Am J Ophthalmol. 2003;135:246–9
14. Boscia F, Furino C, Dammacco R, et al. Intravitreal triamcinolone acetonide in refractory pseudophakic cystoid macular edema: functional and anatomic results. Eur J Ophthalmol. 2005;15:89–95
15. Bradford JD, Wilkinson CP, Bradford RH Jr. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. Retina. 1988;8:161–4
16. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117:1104–12.e1
17. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol. 2013;155:429–37.e7
18. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1432–44
19. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology. 2009;116:57–65.e5
20. Brown DM, Tuomi L, Shapiro H, et al. Anatomical measures as predictors of visual outcomes in ranibizumab-treated eyes with neovascular age-related macular degeneration. Retina. 2013;33:23–34
21. Bucher RS, Hall E, Reed DM, et al. Effect of intravitreal triamcinolone acetonide on susceptibility to experimental bacterial endophthalmitis and subsequent response to treatment. Arch Ophthalmol. 2005;123:649–53
22. Burnett J, Tessler H, Isenberg S, et al. Double-masked trial of fenoprofen sodium: treatment of chronic aphakic cystoid macular edema. Ophthalmic Surg. 1983;14:150–2
23. Cagini C, Fiore T, Iaccheri B, et al. Macular thickness measured by optical coherence tomography in a healthy population before and after uncomplicated cataract phacoemulsification surgery. Curr Eye Res. 2009;34:1036–41
24. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117:1102–12.e1
25. Cebe Suarez S, Pieren M, Cariolato L, et al. A VEGF-A splice variant defective for heparan sulfate and neuropilin-1 binding shows attenuated signaling through VEGFR-2. Cell Mol Life Sci. 2006;63:2067–77
26. Cervera E, Diaz-Llopis M, Udaondo P, et al. Intravitreal pegaptanib sodium for refractory pseudophakic macular oedema. Eye (Lond). 2008;22:1180–2
27. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013;382:1258–67
28. Comparison of Age-related Macular Degeneration Treatments Trials Research GroupMartin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119:1388–98
29. Conway MD, Canakis C, Livir-Rallatos C, et al. Intravitreal triamcinolone acetonide for refractory chronic pseudophakic cystoid macular edema. J Cataract Refract Surg. 2003;29:27–33
30. Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology. 2005;112:1747–57
31. Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. 2010;128:1273–9
32. Demirel S, Batioglu F, Ozmert E. Intravitreal ranibizumab for the treatment of cystoid macular edema in Irvine-Gass syndrome. J Ocul Pharmacol Ther. 2012;28:636–9
33. Diabetic Retinopathy Clinical Research NetworkElman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology. 2012;119:2312–8
34. Diaz-Llopis M, Amselem L, Cervera E, et al. [Intravitreal injection of bevacizumab for pseudophakic cystoid macular edema resistant to steroids]. Arch Soc Esp Oftalmol. 2007;82:447–50
35. Dvorak HF, Brown LF, Detmar M, et al. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol. 1995;146:1029–39
36. Eifrig CW, Scott IU, Flynn HW Jr, et al. Endophthalmitis after pars plana vitrectomy: Incidence, causative organisms, and visual acuity outcomes. Am J Ophthalmol. 2004;138:799–802
37. Fine HF, Baffi J, Reed GF, et al. Aqueous humor and plasma vascular endothelial growth factor in uveitis-associated cystoid macular edema. Am J Ophthalmol. 2001;132:794–6
38. Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. Surv Ophthalmol. 1992;36:259–84
39. Flach AJ. The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. Trans Am Ophthalmol Soc. 1998;96:557–634
40. Flach AJ, Dolan BJ, Irvine AR. Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. Am J Ophthalmol. 1987;103:479–86
41. Flach AJ, Jampol LM, Weinberg D, et al. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. Am J Ophthalmol. 1991;112:514–9
42. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. Br J Ophthalmol. 2006;90:1344–9
43. Fung WE. Vitrectomy for chronic aphakic cystoid macular edema. Results of a national, collaborative, prospective, randomized investigation. Ophthalmology. 1985;92:1102–11
44. Gallego-Pinazo R, Arevalo JF, Udaondo P, et al. Prophylaxis of pseudophakic cystoid macular edema with intraoperative pegaptanib. J Ocul Pharmacol Ther. 2012;28:65–8
45. Gamache DA, Graff G, Brady MT, et al. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: I. Assessment of anti-inflammatory efficacy. Inflammation. 2000;24:357–70
46. Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. Arch Ophthalmol. 1966;76:646–61
47. Gillies MC, Simpson JM, Billson FA, et al. Safety of an intravitreal injection of triamcinolone: results from a

randomized clinical trial. Arch Ophthalmol. 2004;122:336–40
48. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. 2004;351:2805–16
49. Group CR, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897–908
50. Gulkilik G, Kocabora S, Taskapili M, et al. Cystoid macular edema after phacoemulsification: risk factors and effect on visual acuity. Can J Ophthalmol. 2006;41:699–703
51. Harbour JW, Smiddy WE, Rubsamen PE, et al. Pars plana vitrectomy for chronic pseudophakic cystoid macular edema. Am J Ophthalmol. 1995;120:302–7
52. Hargrave SL, Jung JC, Fini ME, et al. Possible role of the vitamin E solubilizer in topical diclofenac on matrix metalloproteinase expression in corneal melting: an analysis of postoperative keratolysis. Ophthalmology. 2002;109:343–50
53. Hariprasad SM, Akduman L, Clever JA, et al. Treatment of cystoid macular edema with the new-generation NSAID nepafenac 0.1%. Clin Ophthalmol. 2009;3:147–54
54. Heier JS, Boyer DS, Ciulla TA, et al. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. Arch Ophthalmol. 2006;124:1532–42
55. Heier JS, Clark WL, Boyer DS, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS Study. Ophthalmology. 2014;121:1414–20.e1
56. Heier JS, Topping TM, Baumann W, et al. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. Ophthalmology. 2000;107:2034–8, discussion 2039.
57. Henderson BA, Kim JY, Ament CS, et al. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg. 2007;33:1550–8
58. Holekamp NM. Treatment of pseudophakic CME. Ocul Immunol Inflamm. 1998;6:121–3
59. Hu AY, Bourges JL, Shah SP, et al. Endophthalmitis after pars plana vitrectomy a 20- and 25-gauge comparison. Ophthalmology. 2009;116:1360–5
60. Hudes GR, Li WY, Rockey JH, et al. Prostacyclin is the major prostaglandin synthesized by bovine retinal capillary pericytes in culture. Invest Ophthalmol Vis Sci. 1988;29:1511–6
61. Huynh TH, Johnson MW. The behavior of surgically repaired idiopathic macular holes in the setting of subsequent cystoid macular edema. Retina. 2007;27:759–63
62. Ibanez HE, Lesher MP, Singerman LJ, et al. Prospective evaluation of the effect of pseudophakic cystoid macula edema on contrast sensitivity. Arch Ophthalmol. 1993;111:1635–9
63. Investigators IVAN Study, Chakravarthy U, Harding SP, Harding SP, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology. 2012;119:1399–411
64. Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol. 1953;36:599–619
65. Jain R, Stevens JD, Bunce CV, et al. Ischaemic heart disease may predispose to pseudophakic cystoid macular oedema. Eye (Lond). 2001;15(Pt 1):34–8
66. Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. Ophthalmic Res. 2006;38:218–45
67. Jonas JB, Degenring RF, Kreissig I, et al. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology. 2005;112:593–8
68. Jonas JB, Kreissig I, Degenring RF. Intravitreal triamcinolone acetonide for pseudophakic cystoid macular edema. Am J Ophthalmol. 2003;136:384–6
69. Kim SJ, Belair ML, Bressler NM, et al. A method of reporting macular edema after cataract surgery using optical coherence tomography. Retina. 2008;28:870–6
70. Korobelnik JF, Holz FG, Roider J, et al. Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: one-year results of the Phase 3 GALILEO Study. Ophthalmology. 2013;121:202–8
71. Kremer M, Baikoff G, Charbonnel B. The release of prostaglandins in human aqueous humour following intraocular surgery. Effect of indomethacin. Prostaglandins. 1982;23:695–702
72. Law SK, Kim E, Yu F, et al. Clinical cystoid macular edema after cataract surgery in glaucoma patients. J Glaucoma. 2010;19:100–4
73. Levin DS, Lim JI. Update on pseudophakic cystoid macular edema treatment options. Ophthalmol Clin North Am. 2002;15:467–72
74. Lim JW, Han JR. Aqueous humour levels of vascular endothelial growth factor and erythropoietin in patients with diabetic macular oedema before and after intravitreal erythropoietin injection. Clin Experiment Ophthalmol. 2011;39:537–44
75. Lobo CL, Faria PM, Soares MA, et al. Macular alterations after small-incision cataract surgery. J Cataract Refract Surg. 2004;30:752–60
76. Loewenstein A, Zur D. Postsurgical cystoid macular edema. Dev Ophthalmol. 2010;47:148–59
77. Margherio RR, Margherio AR, Pendergast SD, et al. Vitrectomy for retained lens fragments after phacoemulsification. Ophthalmology. 1997;104:1426–32
78. Martinez MR, Ophir A. Pseudophakic cystoid macular edema associated with extrafoveal vitreoretinal traction. Open Ophthalmol J. 2011;5:35–41
79. McCuen BW 2nd, Bessler M, Tano Y, et al. The lack of toxicity of intravitreally administered triamcinolone acetonide. Am J Ophthalmol. 1981;91:785–8
80. Mehta D, Malik AB. Signaling mechanisms regulating endothelial permeability. Physiol Rev. 2006;86:279–367
81. Merani R, Hunyor AP, Playfair TJ, et al. Pars plana vitrectomy for the management of retained lens material after cataract surgery. Am J Ophthalmol. 2007;144:364–70
82. Meyer CH, Rodrigues EB, Michels S, et al. Incidence of damage to the crystalline lens during intravitreal injections. J Ocul Pharmacol Ther. 2010;26:491–5
83. Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. Surv Ophthalmol. 2002;47(Suppl 1):S203–18
84. Miyake K, Masuda K, Shirato S, et al. Comparison of diclofenac and fluorometholone in preventing cystoid macular edema after small incision cataract surgery: a multicentered prospective trial. Jpn J Ophthalmol. 2000;44:58–67
85. Miyake K, Nishimura K, Harino S, et al. The effect of topical diclofenac on choroidal blood flow in early postoperative pseudophakias with regard to cystoid macular edema formation. Invest Ophthalmol Vis Sci. 2007;48:5647–52
86. Miyake K, Ota I, Maekubo K, et al. Latanoprost accelerates disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema in early postoperative pseudophakias. Arch Ophthalmol. 1999;117:34–40
87. Miyake K, Sugiyama S, Norimatsu I, et al. Prevention of cystoid macular edema after lens extraction by topical

indomethacin (III) radioimmunoassay measurement of prostaglandins in the aqueous during and after lens extraction procedures. Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1978;209:83–8
88. Moisseiev E, Kinori M, Glovinsky Y, et al. Retained lens fragments: nucleus fragments are associated with worse prognosis than cortex or epinucleus fragments. Eur J Ophthalmol. 2011;21:741–7
89. Moore JK, Scott IU, Flynn HW Jr, et al. Retinal detachment in eyes undergoing pars plana vitrectomy for removal of retained lens fragments. Ophthalmology. 2003;110:709–13, discussion 713–704.
90. O'Brien TP. Emerging guidelines for use of NSAID therapy to optimize cataract surgery patient care. Curr Med Res Opin. 2005;21:1131–7
91. Patel A, de Bustros S, Michels RG. Pars plana vitrectomy for aphakic cystoid macular edema. Retina. 1985;5:11–5
92. Pendergast SD, Margherio RR, Williams GA, et al. Vitrectomy for chronic pseudophakic cystoid macular edema. Am J Ophthalmol. 1999;128:317–23
93. Perente I, Utine CA, Ozturker C, et al. Evaluation of macular changes after uncomplicated phacoemulsification surgery by optical coherence tomography. Curr Eye Res. 2007;32:241–7
94. Peyman GA, Canakis C, Livir-Rallatos C, et al. The effect of internal limiting membrane peeling on chronic recalcitrant pseudophakic cystoid macular edema: a report of two cases. Am J Ophthalmol. 2002;133:571–2
95. Polachek J, Shvartzman P. Acute bronchial asthma associated with the administration of ophthalmic indomethacin. Isr J Med Sci. 1996;32:1107–9
96. Querques G, Bux AV, Martinelli D, et al. Intravitreal pegaptanib sodium (Macugen) for diabetic macular oedema. Acta Ophthalmol. 2009;87:623–30
97. Rang HP. Pharmacology. New York, Churchill Livingstone; 2001
98. Ratnoff OD. Increased vascular permeability induced by human plasmin. J Exp Med. 1965;122:905–21
99. Reichle ML. Complications of intravitreal steroid injections. Optometry. 2005;76:450–60
100. Rhee DJ, Peck RE, Belmont J, et al. Intraocular pressure alterations following intravitreal triamcinolone acetonide. Br J Ophthalmol. 2006;90:999–1003
101. Rho DS. Treatment of acute pseudophakic cystoid macular edema: diclofenac versus ketorolac. J Cataract Refract Surg. 2003;29:2378–84
102. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419–31
103. Rossetti A, Doro D. Retained intravitreal lens fragments after phacoemulsification: complications and visual outcome in vitrectomized and nonvitrectomized eyes. J Cataract Refract Surg. 2002;28:310–5
104. Salam A, Mathew R, Sivaprasad S. Treatment of proliferative diabetic retinopathy with anti-VEGF agents. Acta Ophthalmol. 2011;89:405–11
105. Sanchez-Tocino H, Alvarez-Vidal A, Maldonado MJ, et al. Retinal thickness study with optical coherence tomography in patients with diabetes. Invest Ophthalmol Vis Sci. 2002;43:1588–94
106. Schubert HD. Cystoid macular edema: the apparent role of mechanical factors. Prog Clin Biol Res. 1989;312:277–91
107. Scott IU, Flynn HW Jr, Dev S, et al. Endophthalmitis after 25-gauge and 20-gauge pars plana vitrectomy: incidence and outcomes. Retina. 2008;28:138–42
108. Sevim MS, Sanisoglu H, Turkyilmaz K. Intravitreal triamcinolone acetonide versus pars plana vitrectomy for pseudophakic cystoid macular edema. Curr Eye Res. 2012;37:1165–70
109. Sharir M. Exacerbation of asthma by topical diclofenac. Arch Ophthalmol. 1997;115:294–5
110. Sheehan GJ, Kutzner MR, Chin WD. Acute asthma attack due to ophthalmic indomethacin. Ann Intern Med. 1989;111:337–8
111. Shelsta HN, Jampol LM. Pharmacologic therapy of pseudophakic cystoid macular edema: 2010 update. Retina. 2011;31:4–12
112. Simone JN, Whitacre MM. Effects of anti-inflammatory drugs following cataract extraction. Curr Opin Ophthalmol. 2001;12:63–7
113. Sitenga GL, Ing EB, Van Dellen RG, et al. Asthma caused by topical application of ketorolac. Ophthalmology. 1996;103:890–2
114. Soheilian M, Karimi S, Ramezani A, et al. Pilot study of intravitreal injection of diclofenac for treatment of macular edema of various etiologies. Retina. 2010;30:509–15
115. Spitzer MS, Ziemssen F, Yoeruek E, et al. Efficacy of intravitreal bevacizumab in treating postoperative pseudophakic cystoid macular edema. J Cataract Refract Surg. 2008;34:70–5
116. Stalmans P, Benz MS, Gandorfer A, et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med. 2012;367:606–15
117. Stark WJ Jr, Maumenee AE, Fagadau W, et al. Cystoid macular edema in pseudophakia. Surv Ophthalmol. 1984;28(Suppl):442–51
118. Stein JD, Zacks DN, Grossman D, et al. Adverse events after pars plana vitrectomy among medicare beneficiaries. Arch Ophthalmol. 2009;127:1656–63
119. Suh LH, Yoo SH, Deobhakta A, et al. Complications of Descemet's stripping with automated endothelial keratoplasty: survey of 118 eyes at One Institute. Ophthalmology. 2008;115:1517–24
120. Szurman P, Sierra A, Kaczmarek R, et al. Different biocompatibility of crystalline triamcinolone deposits on retinal cells in vitro and in vivo. Exp Eye Res. 2007;85:44–53
121. Thach AB, Dugel PU, Flindall RJ, et al. A comparison of retrobulbar versus sub-Tenon's corticosteroid therapy for cystoid macular edema refractory to topical medications. Ophthalmology. 1997;104:2004–8
122. Thomas MA, O'Grady GE, Swartz SL. Prostaglandin levels in human vitreous. Br J Ophthalmol. 1985;69:275–9
123. Ursell PG, Spalton DJ, Whitcup SM, et al. Cystoid macular edema after phacoemulsification: relationship to blood-aqueous barrier damage and visual acuity. J Cataract Refract Surg. 1999;25:1492–7
124. Vinores SA, Derevjanik NL, Ozaki H, et al. Cellular mechanisms of blood-retinal barrier dysfunction in macular edema. Doc Ophthalmol. 1999;97:217–28
125. Vinores SA, Youssri AI, Luna JD, et al. Upregulation of vascular endothelial growth factor in ischemic and non-ischemic human and experimental retinal disease. Histol Histopathol. 1997;12:99–109
126. Warren KA, Fox JE. Topical nepafenac as an alternate treatment for cystoid macular edema in steroid responsive patients. Retina. 2008;28:1427–34
127. Weiss K, Steinbrugger I, Weger M, et al. Intravitreal VEGF levels in uveitis patients and treatment of uveitic macular oedema with intravitreal bevacizumab. Eye (Lond). 2009;23:1812–8
128. Wilson FM 2nd. Adverse external ocular effects of topical ophthalmic therapy: an epidemiologic, laboratory, and clinical study. Trans Am Ophthalmol Soc. 1983;81:854–965

129. Wittpenn JR, Silverstein S, Heier J, et al. A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. Am J Ophthalmol. 2008;146:554–60
130. Wolf EJ, Braunstein A, Shih C, et al. Incidence of visually significant pseudophakic macular edema after uneventful phacoemulsification in patients treated with nepafenac. J Cataract Refract Surg. 2007;33:1546–9
131. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol. 2008;246:81–7
132. Yannuzzi LA, Klein RM, Wallyn RH, et al. Ineffectiveness of indomethacin in the treatment of chronic cystoid macular edema. Am J Ophthalmol. 1977;84:517–9
133. Yeung CK, Chan KP, Chiang SW, et al. The toxic and stress responses of cultured human retinal pigment epithelium (ARPE19) and human glial cells (SVG) in the presence of triamcinolone. Invest Ophthalmol Vis Sci. 2003;44:5293–300
134. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol. 2012;23:26–32
135. Zhang X, Bao S, Lai D, et al. Intravitreal triamcinolone acetonide inhibits breakdown of the blood-retinal barrier through differential regulation of VEGF-A and its receptors in early diabetic rat retinas. Diabetes. 2008;57:1026–33