

Topical Bromfenac for Pseudophakic Cystoid Macular Edema – Case Reports

George Voyatzis,¹ Anil Pitalia,² Colin Vize³ and Madhavan Rajan^{1,4}

1. Addenbrooke's Hospital, Cambridge; UK; 2. SpaMedica, Manchester, UK; 3. Hull and East Yorkshire Eye Hospital, Hull, UK;

4. Anglia Ruskin University, Cambridge, UK

Abstract

Cystoid macular edema (CME) is the most common cause of visual loss following uncomplicated cataract surgery and although the condition usually resolves itself within several months, it can result in permanent vision loss in a minority of patients. There is a lack of consensus in diagnostic methods and definition of the condition and as a result, estimates of its incidence vary greatly, ranging from 4 to 41 %. There is also a scarcity of randomised controlled trial data to support the efficacy of ophthalmic agents in the prophylaxis and treatment of CME. However, a growing body of evidence supports the use of topical non-steroidal anti-inflammatory drugs (NSAIDs) both pre-and post-surgery. The importance of the prophylactic use of NSAIDs should be emphasized as many cases of CME are preventable. The combination of corticosteroids and NSAIDs may be more effective than either class of agents alone. The use of bromfenac for the treatment and prevention of CME is growing. Its unique chemical structure makes it highly lipophilic with rapid penetration of ocular tissues; it has sustained anti-inflammatory action and allows less frequent dosing (twice a day as opposed to three or four times a day). This article presents four case studies detailing rapid CME resolution following topical administration of bromfenac.

Keywords

Bromfenac, cataract surgery, cystoid macular edema, non-steroidal anti-inflammatory drugs, phacoemulsification

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Correspondence: Madhavan Rajan, Professor of Ophthalmic and Visual Sciences, Vision and Eye Research Unit, Postgraduate Medical Institute, Anglia Ruskin University, Easting 204, East Road, Cambridge, CB1 1PT, UK. E: madhavan.rajan@addenbrookes.nhs.uk

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Cataract removal is one of the most commonly performed surgeries and in recent years has benefited from advances in technique, lens design and instrumentation.¹ Phacoemulsification surgery via small incisions and implantation of a foldable intraocular lens (IOL) is an effective procedure, and provides good visual outcomes.^{2–5}

Post-operative complications of cataract surgery however, may occur, including cystoid macular edema (CME) which is the most common cause of visual loss following cataract surgery.^{6–8} It is more common in patients with ocular diseases such as uveitis or diabetic retinopathy and after complicated or uncomplicated surgery in patients with otherwise healthy eyes.⁹ The development of small incision cataract surgery and phacoemulsification techniques has lowered the incidence of CME, but the total volume of cataract surgeries makes it a common morbidity. Up to 80 % of symptomatic patients show spontaneous improvement in visual function three to 12 months post surgery. In a minority of patients, CME requires treatment and in some cases, it may be refractory to treatment.¹⁰

Prevention of CME through post-operative use of NSAIDs is now standard of care in the US and increasingly practiced in several other countries around the world. In addition, there have been several clinical studies that support the role of NSAIDs in helping prevent CME.^{8,10–15}

This review considers the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment and prevention of CME with a focus on

bromfenac. Four case reports of rapid CME resolution after topical administration of bromfenac are discussed.

Definition, Incidence and Cost

CME can be detected using either clinical or angiographic methods. Clinical CME is diagnosed using slit-lamp biomicroscopic observation of cystoid abnormalities or angiographic evidence of perifoveal leakage as well as reduced visual acuity (VA). The angiographic CME is diagnosed using fluorescein angiography. The incidence of clinical CME is low, ranging from 0 to 4 %.¹⁶ The incidence of angiographic CME is higher; incidence rates of 19,¹⁵ 22¹⁷ and 9 %¹⁸ have been reported.

Optical coherence tomography (OCT) is a sensitive technique for high-resolution cross-sectional imaging that directly measures macular thickness and has been increasingly used to assess CME after cataract surgery.¹⁶ Its sensitivity allows the detection of macular thickening in the absence of cysts or any obvious visual impairment. However, it is not performed routinely after cataract surgery. Recent studies have suggested that the peak incidence of CME, as detected by OCT, occurs about four weeks after cataract surgery, whereas most literature reports state that postoperative CME does not begin until six weeks after surgery.¹⁶ Because of the lack of a clear definition for CME and the presence of retinal thickening, a broad range of incidences have been reported. Incidences of CME following phacoemulsification, as identified by OCT, have varied from 4–11 %.^{10,19,20} In a study of

Table 1: Use of Bromfenac for Post-operative Cystoid Macular Edema⁶⁷⁻⁷⁰

	Case 1 ⁶⁷	Case 2 ⁶⁸	Case 3 ^{69,70}	Case 4 ^{69,70}
Demographics	Male, 76 years old	Male, 54 years old	Female, 84 years old	Male, 63 years old
Complicated or Uncomplicated Surgery	Uncomplicated	Uncomplicated	Uncomplicated	Posterior capsule tear without vitreous loss
Previous Ocular Co-morbidity (DME/Uveitis)	Previous history of diabetes Drusen both eyes No previous history of uveitis	No previous history of diabetes or uveitis	None	Diabetes
Time of Diagnosis of CME	4 weeks post operation, 2 weeks after surgery on left eye	1/12 post operation	4/52 following surgery	3/52 following surgery
VA at Diagnosis of CME	6/18	6/9	6/18	6/36
Medication Used Post-diagnosis	Bromfenac	Bromfenac Post-operative Tobradex 3/52, Yellox 1/52 Initially – ‘rebound’ CME	Bromfenac and topical dexamethasone	Bromfenac and topical dexamethasone
Adverse Events from Use of Bromfenac	None reported	None	None	None
Time to Resolution	2 weeks	6/52, subjective	4/52	8/52
VA at Resolution	VAR 6/12 UA, 6/9 PH VAL 6/12 UA, 6/12 PH	6/7.5, aim -1.00 for monovision, N5	BCVA: 6/6 Near vision: N5	BCVA: 6/9 Near vision: N5

CME = cystoid macular edema; DME = diabetic macular edema; VA = visual acuity.

32 patients, increases in retinal thickness were observed in 41 % of patients.²¹ However, again, the definitions of CME differed greatly in these studies.

CME is associated with substantial costs. In an analysis of payments to Medicare recipients who had undergone cataract surgery, total annual ophthalmic claims were 41 % higher for patients who developed CME than for controls.²² However, there is currently no validated or universally accepted definition of CME. Published studies use varying diagnostic methodologies, including clinical observation of cystoid changes, leakage shown by fluorescein angiography and increased thickness shown by OCT, along with some degree of visual impairment.²³ Contrast sensitivity may have clinical value in the assessment of retinal disease and visual function;²⁴ however, contrast sensitivity testing is not performed routinely and abnormalities are commonly missed with standard vision evaluations.

Pathogenesis

Clinical observations and experimental studies suggest that the pathophysiology of post-surgical CME is multifactorial. Many aetiological factors have been proposed, but the major cause is inflammation.^{15,25-28} As a result of surgical trauma to the cornea, secondary inflammatory mediators – mostly prostaglandins – are produced.²⁹ Inflammation breaks down the blood–aqueous and blood–retinal barriers, which leads to increased vascular permeability.²⁵ Eosinophilic transudate accumulates in the outer plexiform and inner nuclear layers of the retina, leading to the formation of cystic spaces that coalesce to form larger pockets of fluid.²⁸ Excessive leakage occurs in certain conditions which may cause a severe and permanent impairment of VA. The various amounts of leakage explain the higher incidence of CME detected by angiography and by OCT compared with clinically identified CME.¹⁸

Risk Factors

Risk factors for CME comprise three groups relating to patient characteristics, surgical technique and intra-operative complications, and post-operative treatment of the patient. The first group includes diabetic maculopathy.^{22,30,31} CME can be hard to differentiate from development of diabetic macular edema (DME). Cataract surgery

has been previously considered to exacerbate diabetic retinopathy, however, latest trials may not corroborate this hypothesis.^{32,33} Post-operative CME is a frequent occurrence in those with a history of DME and is unlikely to resolve spontaneously. DME should be treated pre-surgery.^{34,35}

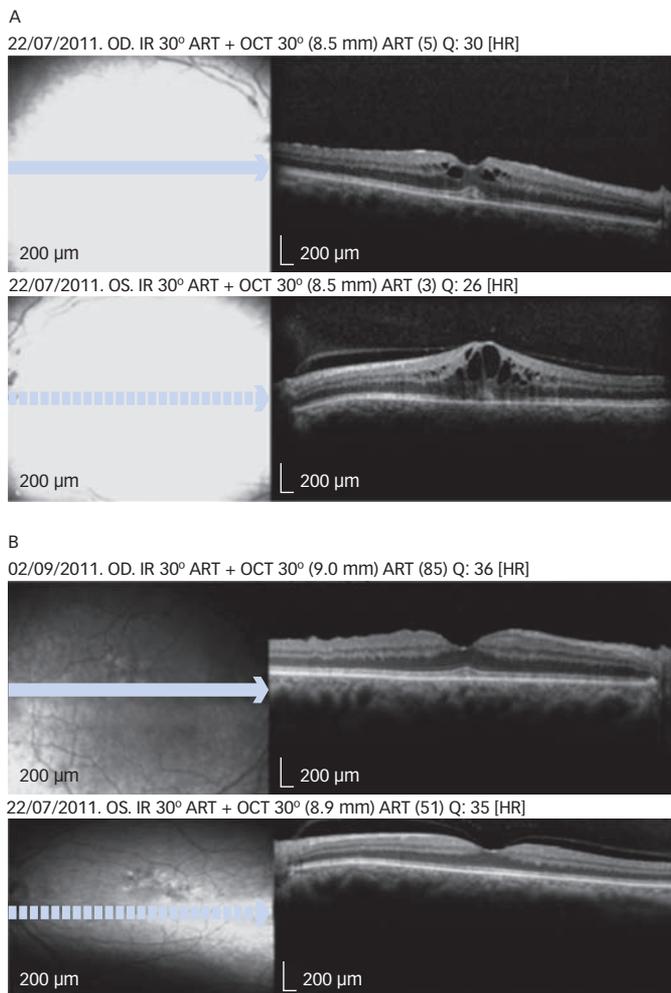
Uveitis predisposes eyes to cataract development and cataract removal in patients with this condition carries greater risk of complications. Such patients commonly develop CME, and it is the most frequent reason for poor results of cataract surgery in these patients.³⁶ A retrospective study of 108 eyes with uveitis found a CME incidence of 21 %.³⁷ A prospective cohort of 41 eyes with uveitis and 52 without uveitis showed an incidence of CME on OCT at three months postoperatively of 8 and 0 %, respectively (p=0.08).¹⁹ Development of CME has been associated with the use of prostaglandin analogues for glaucoma³⁸ although a large retrospective study found no statistically significant difference in the prevalence of clinical CME after phacoemulsification cataract surgery between patients with and without glaucoma.³⁹ The results may have differed if angiographic CME had been the endpoint. A history of retinal vein occlusion (RVO) and epiretinal membrane (ERM) have also been associated with an increased risk for pseudophakic CME.⁴⁰

Surgical risk factors for CME include iris trauma, iris-fixated or anterior chamber IOLs, early post-operative capsulotomy, IOL dislocation, posterior capsule rupture, vitreous traction at incision sites, vitreous loss and vitrectomy for retained lens fragments.^{28,41,42} In one study, CME occurred in 70 % of patients with iris trauma and 20.5 % of patients without it.⁴² Protracted exposure to light from operating microscopes during surgery involving pars plana vitrectomy is also associated with increased CME incidence.^{43,44}

Diagnosis

Signs and symptoms of clinically significant CME develop 4–12 weeks after surgery and reach a peak at 4–6 weeks postoperatively. Surgeons are frequently not even aware of the condition as by that stage patients would have returned to their general ophthalmologist. Presenting symptoms may include reduced VA, decreased contrast sensitivity, central scotoma or metamorphopsia.

Figure 1: Cystoid Macular Edema in a 76-year-old Man (Case 1) with Diabetes following Cataract Surgery and Intraocular Lens Implants Diagnosed by Optical Coherence Tomography



A: Before bromfenac treatment (22 July 2011); B: after bromfenac treatment (2 September 2011).⁶⁷

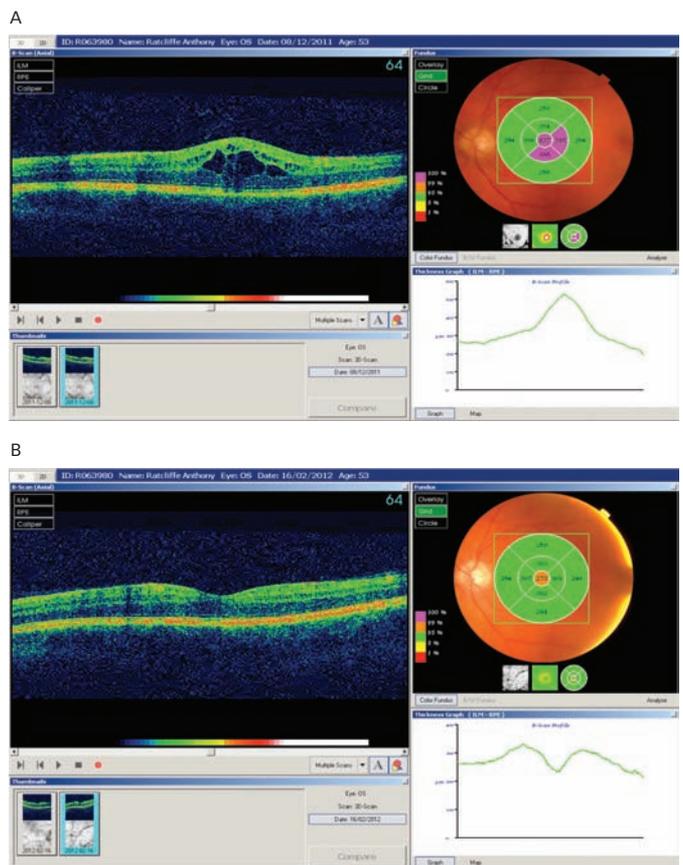
Decreased contrast sensitivity may occur in cases with normal VA and is a useful early sign.⁴⁵ Patients with a change of as little as 10 microns in retinal thickness may experience changes in contrast sensitivity.⁴⁶ Clinical examination may reveal limbal ciliary flush, mild iritis and vitritis. A common sign is the absence of the foveal light reflex and a yellowish spot in the retina. In severe cases, intraretinal cystoid spaces surrounding the fovea may be detected.^{8,28,45,47}

Fluorescence angiography and biomicroscopic findings have until recently been the diagnostic procedures of choice to detect CME.^{45,48} However, OCT offers several advantages over fluorescence angiography in terms of safety, ease of use, and patient comfort. Furthermore, OCT allows quantitative evaluation of disease progression and treatment efficacy.²³ OCT allows the detection of minimal increases in perifoveal retinal thickness even six months after cataract surgery.⁴⁹ A statistically significant increase in macular thickness has been detected using OCT after the first week following uncomplicated cataract surgery.²⁰

Treatment and Prophylaxis

The treatment of CME with bromfenac may be illustrated by the following case studies.

Figure 2: Cystoid Macular Edema in a 53-year-old Man (Case 2) after Uncomplicated Left Phacoemulsification and Intraocular Lens Implant Visualised using Optical Coherence Tomography



A: Thickness graph at diagnosis; B: thickness graph at resolution.⁶⁸

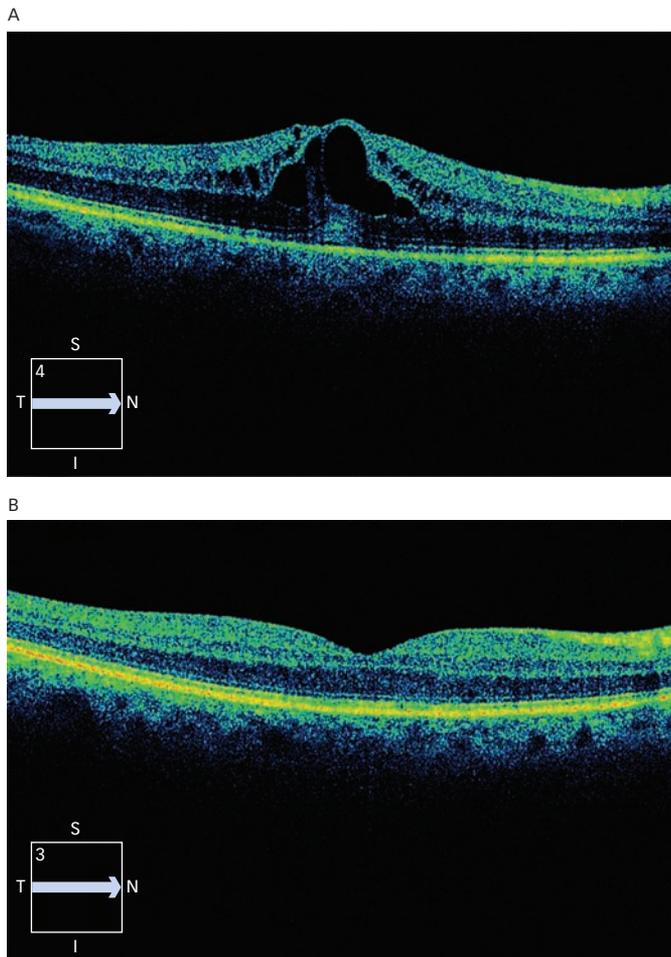
A 76-year-old man with diabetes presented four weeks after uneventful bilateral cataract surgery and IOL implants with decreased vision and CME, diagnosed by OCT. Bromfenac was topically administered and monitored. Resolution was noted after two weeks of therapy with improved VA. No side effects from bromfenac use were reported (see *Table 1* and *Figure 1*).⁶⁷

A 54-year-old man presented one month after uncomplicated left eye phacoemulsification and IOL implant with limbal relaxing incisions and decreased vision. A diagnosis of CME was confirmed by OCT. Bromfenac was topically administered twice daily. After six weeks of therapy, his VA improved, the CME resolved clinically and bromfenac was well tolerated (see *Figure 2*).⁶⁸

An 84-year-old woman presented four weeks after uneventful cataract surgery with decreased vision and CME. A post-operative regimen of bromfenac and topical dexamethasone was administered. Resolution was noted after four weeks of topical therapy with improvement in VA and near vision. No side effects associated with the medication used were reported (see *Figure 3*).^{69,70}

A 63-year-old man with a history of diabetes presented three weeks after cataract surgery, complicated by posterior capsule tear without vitreous loss, with decreased vision and CME. A post-operative regimen of bromfenac and topical dexamethasone was administered. After eight weeks of therapy, his VA improved,

Figure 3: Cystoid Macular Edema in an 84-year-old Woman (Case 3) after Uneventful Cataract Surgery Visualised using Optical Coherence Tomography



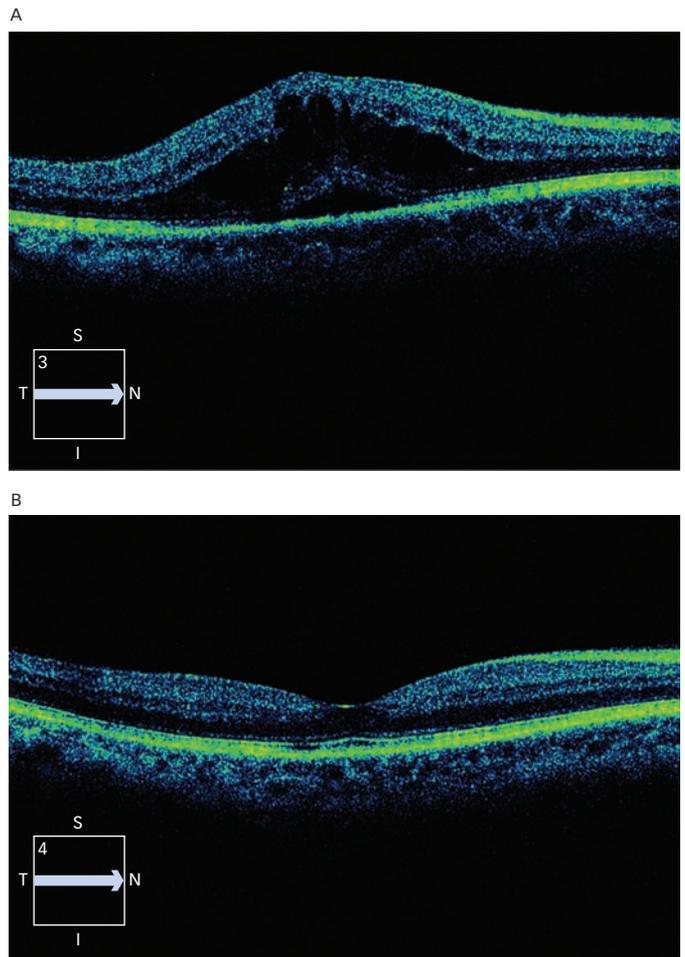
A: At presentation; B: at resolution.^{69,70}

the CME resolved clinically, and no side effects were reported (see Figure 4).^{69,70}

While the efficacy of NSAIDs in the treatment of CME is well-established, there is no standardised therapy or prophylactic protocol for CME owing to the lack of well-designed large randomised controlled trials (RCTs) with long-term follow up.¹⁰ However, the prophylactic use of NSAIDs with steroids after surgery to prevent CME is standard of care in the US and very common in other countries throughout the world.⁵⁰⁻⁵²

An increasing body of data supports the need to undertake prophylactic protocols, as many cases of CME are preventable. Several clinical trials have established the efficacy of NSAIDs in the prophylaxis of CME. A randomised, double-masked, vehicle-controlled trial for six months consisting of 681 patients found that the incidence of angiographic CME in patients treated with one of two NSAIDs (16.8 % with flurbiprofen, 12.4 % with indomethacin) was significantly lower than in the vehicle group (32.2 %).⁵³ A study of 50 patients undergoing cataract surgery showed that patients treated preoperatively with fluorometholone were more likely to develop angiographic CME than those treated with diclofenac ($p=0.08$ at two weeks, $p=0.001$ at five weeks).⁵⁴ A study of 46 patients with mild nonproliferative- or nondiabetic retinopathy found that neither topical diclofenac nor betamethasone fully prevented post-operative

Figure 4: Cystoid Macular Edema in a 63-year-old Man (Case 4) after Cataract Surgery Visualised using Optical Coherence Tomography



A: At presentation; B: at resolution.^{69,70}

macular thickening following cataract surgery. However, diclofenac protected against an early event of post-operative CME.⁵⁵ In a study involving 189 patients following uneventful phacoemulsification surgery, the incidence of angiographic CME was 15.0 % in the group receiving post-operative indomethacin and 32.8 % in the control group ($p<.001$).⁵⁶

Data also exist that support combination therapy employing NSAIDs and corticosteroids in the prophylaxis of CME. In a small RCT of 28 patients who developed acute CME within 21–90 days following cataract surgery, topical ketorolac and prednisolone combination therapy resulted in superior VA outcomes compared with monotherapy of either agent alone.⁵¹ A masked multicentre RCT showed that after four weeks of treatment, clinical/OCT CME developed in five of 278 patients receiving peri-operative prednisolone and in none of the 268 patients who also received ketorolac ($p=0.032$).⁵² However, in a much smaller prospective double-masked RCT ($n=10$), no statistically significant difference was seen between patients who received ketorolac and those who received ketorolac plus prednisolone for the treatment of acute or chronic CME.⁵⁷

The most recently developed topical NSAIDs are nepafenac and bromfenac. A comparative review of 450 patients found no patients

who had received nepafenac prophylaxis developed clinical CME versus five in the control group ($p=0.0354$).⁵⁸ Additional studies and case reports have also shown the efficacy of this drug in the management of CME.^{59,60} In a recent randomised double-masked single-centre clinical trial ($n=59$), nepafenac was found to be more effective than fluorometholone in preventing angiographic CME.⁶¹

Bromfenac is a brominated form of amfenac. Bromination increases the lipophilicity of the drug, causing enhanced penetration through the cornea and ocular tissues.^{62,63} Furthermore, bromination increases the duration of the analgesic and anti-inflammatory activity. This agent is also a potent inhibitor of the enzyme cyclo-oxygenase-2, which is believed to be the primary mediator of ocular inflammation. These properties allow for enhanced patient tolerability.⁴⁶ Although no large RCTs have yet been conducted to assess the efficacy of bromfenac in the treatment and prevention of pseudophakic CME, evidence exists to support its use for the condition. Comparison of bromfenac with diclofenac and ketorolac for the treatment of acute CME showed a greater visual improvement in the bromfenac group. Bromfenac also allows a reduced dosing schedule; twice-daily bromfenac was as effective as diclofenac or ketorolac dosed four times daily.⁶⁴ In a prospective study involving 62 patients, bromfenac was found to be superior to betamethasone and fluorometholone in the prophylaxis of CME.⁶⁵

The off-label use of NSAIDs for CME prophylaxis has been widely implemented on the basis of such data but the longest follow-up period in clinical trials to date is three months; no follow-up data beyond a year is available.^{10,66} It is not known whether CME prophylaxis prevents chronic or late onset CME, and whether it confers any long-term visual benefits.

Discussion

In light of the advances to cataract procedures in recent years, post-surgical complications may still occur, including CME which is the most common cause of visual loss following cataract surgery. While incidence of clinical CME is low (estimated between 0 and 4 %),

incidences of angiographic CME (from 9 to 19 %) and CME as identified by OCT (up to 41 %) are much higher.

When clinical CME does occur, ocular NSAIDs and ocular corticosteroids are currently first-line therapy modalities and data exist to support their efficacy. The use of the NSAID bromfenac has become widespread as a result of its effectiveness, potency and penetration. The four cases presented in this review included patients with CME and decreased vision and demonstrate bromfenac's ability to treat clinical disease. VA was improved in all four patients after topical administration of bromfenac for 2–8 weeks and the CME resolved rapidly with few, if any, side effects.

There is also mounting evidence that NSAIDs are an effective prophylactic treatment for the prevention of CME. While further larger scale trials are needed, prophylactic treatment of CME with NSAIDs has become the standard of care in the US and in many other countries throughout the world. It is important that physicians be aware that CME is preventable and understand the utility of prophylactic NSAID treatment.

Future Developments

In future there is likely to be continued research effort aimed at improving the understanding of CME pathogenesis. CME incidence is increasing largely as a result of the greater volume of cataract surgeries needed by ageing populations worldwide. Improved pathological knowledge of CME is therefore increasingly important and may enable the development of more targeted treatment approaches. Future research should focus on the prophylactic use of NSAIDs. There is also a need for new intravitreal therapies to combat refractory CME, for data on the long-term outcomes of CME prophylaxis using NSAIDs and for well-designed trials comparing the efficacy of different NSAIDs. In addition, standardisation of the definition of CME would be useful when designing future trials. The increasing use of bromfenac justifies further clinical trials to investigate its use in a range of clinical settings including acute and chronic pseudophakic CME. ■

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