Macular Edema

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Abstract. Macular edema is the final common pathway of many intraocular and systemic insults. It may develop in a diffuse pattern where the macula appears generally thickened or it may acquire the characteristic petaloid appearance referred to as cystoid macular edema. Although macular edema may be associated with protean underlying conditions, it is most commonly seen following intraocular surgery, venous occlusive disease, diabetic retinopathy, and posterior segment inflammatory disease. As well as clinical suspicion, a wide range of investigations may lead to the diagnosis of macular edema. Fluorescein angiography and optical coherence tomography provide enhanced visualization of the geometry and distribution of macular edema. A variety of approaches to the treatment of macular edema have been attempted, with a variable degree of success. These options have included topical and systemic steroids, topical and oral non-steroidal anti-inflammatory agents and laser photocoagulation treatment. More recently other therapeutic modalities, including immunomodulators, intravitreal injection of triamcinolone, and pars plana vitrectomy have also been employed. Clinical trials are currently looking into the use of a steroid slow-release intravitreal device for the management of macular edema secondary to uveitis and diabetes. This article reviews the clinical entity of macular edema focusing on the current therapeutic strategies for its management. (Surv Ophthalmol 49:470–490, 2004. © 2004 Elsevier Inc. All rights reserved.)

Key words. cystoid macular edema • diabetic maculopathy • investigations • pathogenesis • retinal vein occlusion • traction • tumors • uveitis • vitrectomy

I. Introduction

Macular edema represents a common pathologic sequel of the retina associated with a broad spectrum of potential insults. It consists of a localized expansion of the retinal intracellular and/or extracellular space in the macular area. This predilection to the macular region is probably associated with the loose binding of inner connecting fibers in Henle’s layer, allowing accumulation of fluid leaking from perifoveal capillaries. The absence of Müller cells in the foveal region is also a contributing factor. Radially orientated cystoid spaces consisting of ophthalmoscopically clear fluid are often clinically detectable in the macular area. The cysts are characterized by an altered light reflex with a decreased central reflex and a thin, highly reflective edge (Fig. 1). Histological studies show the cysts to be areas of retina in which the cells have been displaced. Recently Antcliff et al15 monitored the hydraulic conductivity of the human retina following progressive ablation of retinal layers performed with the aid of an excimer laser. They concluded that the inner and outer plexiform layers constitute high resistance
barriers to fluid flow through the retina, which accounts for the characteristic distribution of cystoid macular edema (CME) seen in histological specimens and with optical coherence tomography (OCT).

In this review the etiology and investigative methods for the diagnosis and monitoring of macular edema are presented with an emphasis on current therapeutic modalities based on evidence from existing literature.

II. Etiology and Clinical Manifestations

A multitude of underlying conditions may result in macular edema. In this section the most common causes of macular edema are described with reports on its clinical manifestation in different clinical settings.

A. MACULAR EDEMA AND RETINAL VASCULAR DISEASES

1. Diabetes Mellitus

Diabetic macular edema is seen in both type I and II diabetes mellitus and is the most common cause of visual loss in the latter. Macular edema can be divided into two subtypes focal and diffuse. Focal macular edema refers to localized areas of retinal thickening caused primarily by focal leakage from microaneurysms, dilated retinal capillaries, and less commonly from intraretinal microvascular abnormalities. Complete or partial rings of hard exudates often demarcate it. Clusters of microaneurysms are seen in the center of circinate exudates and fundus fluorescein angiography demonstrates both their presence and their abnormal permeability. Infrequently a fibrous plaque may develop beneath the macula, resulting from fibrous metaplasia of the retinal pigment epithelium stimulated by the subretinal exudates.\(^\text{20,24,169}\)

In diffuse macular edema there is generalized leakage from dilated capillaries throughout the posterior pole. Occlusion of a considerable portion of the capillary bed leads to widening of the intercapillary spaces and compensatory dilation of the patent capillaries that tend to leak diffusely and cause edema. Diffuse macular edema is usually symmetric in both eyes and without significant exudation. Systemic and ocular risk factors associated with diffuse macular edema are cardiovascular or renal disease, severe systemic hypertension, adult-onset diabetes mellitus, increasing number of retinal microaneurysms, advanced retinopathy, and vitreomacular traction.\(^\text{106,119}\)

2. Retinal Vein Occlusion

Retinal vein obstructions represent another common retinal vascular cause of CME (Fig. 2). In patients with central retinal vein occlusion or a tributary branch occlusion involving the macula, CME is a major cause of visual loss. This edema, if severe or chronic (>8 months), causes permanent diminution of vision secondary to disruption of the microscopic intraretinal connections and to the intracellular damage suffered by the visual elements.\(^\text{36}\) Persistent CME may be associated with vitreomacular attachment or hyperlipidemia and cardiovascular history, whereas it is inversely correlated to glaucoma.\(^\text{70,83,181}\) Finkelstein et al suggested that ischemic CME following branch retinal vein occlusion is often transient and, compared to perfused CME, has better prognosis for visual acuity.\(^\text{48}\) These results contradict those from the BRVOS group who reported that 37% of
the patients with perfused CME experienced two or more lines spontaneous improvement of their visual acuity after 3-year follow-up.8 Another important sign of CME following obstructive venous retinopathy is the development of fluid blood levels in central cystoid spaces (Fig. 3). Although fluid blood levels can occasionally be seen in diabetic, aphakic, or pseudophakic macular edema its occurrence is significantly more common in retinal vein occlusion. Therefore any diabetic patient displaying such a clinical finding should be suspected of having obstructive venous disease.98,161

3. Radiation Retinopathy

Macular edema is a leading cause of visual loss in patients with radiation retinopathy (Fig. 4). Guyer and colleagues have reported the largest series of patients following irradiation of choroidal melanomas.72 Of 218 patients receiving proton beam therapy for paramacular tumors, the earliest and most common finding was macular edema, which was observed in 87% of patients within 3 years of radiation treatment.

B. MACULAR EDEMA AND OCULAR INFLAMMATORY DISEASES

1. Pars Planitis

Macular edema and consequent loss of vision are the most frequent and serious complications of pars
planitis (Fig. 1). Persistent macular edema for more than 6 to 9 months leads to chronic macular changes, with permanent impairment of central vision; the degree of impairment reflects the severity of the changes. The presence of the pars plana exudate or membrane is more often, but not invariably, associated with more severe vitreous inflammation and CME.

2. HIV and Immune Recovery Uveitis

Although serous macular exudation has been described in patients with AIDS-related cytomegalovirus retinitis, CME is rarely encountered in this clinical setting. However, the introduction of HAART has markedly changed the incidence and the prognosis of cytomegalovirus retinitis-related CME. In some patients the restoration of immune competence is associated with anterior segment and vitreous inflammatory reactions resulting in chronic vision threatening complications including CME.

Other inflammatory conditions in which CME may occur include HLA-B27-associated acute anterior uveitis, sarcoidosis, birdshot retinocchoroidopathy, Behcet’s syndrome, toxoplasmosis, Eales’ disease, idiopathic vitritis, Vogt-Koyanagi-Harada syndrome, and scleritis.

C. POSTOPERATIVE CYSTOID MACULAR EDEMA

1. Cataract Surgery

Cystoid macular edema following cataract surgery was initially reported by Irvine in 1953 and is known as the Irvine-Gass syndrome. Approximately 20% of the patients who undergo uncomplicated phacoemulsification or extracapsular extraction develop angiographically proven CME. However, a clinically significant decrease in visual acuity is seen only in about 1% of these eyes. If cataract extraction is complicated by posterior capsule rupture and vitreous loss, severe iris trauma or vitreous traction at the wound, there is a significantly higher incidence (up to 20%) of clinically apparent CME, which is unrelated to the presence of AC-IOL. Clinically significant CME usually occurs within 3–12 weeks postoperatively, but in some instances its onset may be delayed for months or many years after surgery. Spontaneous resolution of the CME with subsequent visual improvement may occur within 3–12 months in 80% of the patients.

Cataract surgery in diabetic patients may result in a dramatic acceleration of pre-existing diabetic macular edema leading to poor functional visual outcome. This can be prevented provided the severity of the retinopathy is recognized preoperatively and treated appropriately with prompt laser photocoagulation either before surgery, if there is adequate fundal view, or shortly afterward. Dowler et al in a prospective clinical and angiographic study reported that 69% of the eyes in which clinically significant macular edema arose in the first 6 months after cataract surgery showed spontaneous resolution of macular edema. In contrast it persisted in all eyes in which macular edema had been present at the time of surgery (Fig. 5). Studies comparing phacoemulsification versus extracapsular cataract extraction in patients with diabetes revealed no difference in incidence of postoperative clinically significant macular edema between the two techniques emphasizing that early intervention when required is more critical to outcome than choice of surgical technique.

Cystoid macular edema is one of the leading causes of poor postoperative visual acuity after cataract surgery in uveitis patients. Foster et al in a retrospective study of uveitis patients undergoing extracapsular cataract extraction and posterior chamber intraocular lens implantation, reported 46% incidence of postoperative macular edema but in all cases improved or resolved with corticosteroid therapy. It has been suggested that the risk of macular edema is greater in uveitis patients with severe postoperative uveitis and preoperative anterior uveitis.

2. Laser Procedures

Cystoid macular edema following Nd:YAG capsulotomy develops in 0–2.5% of the cases but the incidence increases if the laser is performed within the first 3 postoperative months. It occasionally occurs as a complication of panretinal photocoagulation (PRP) for diabetic retinopathy, usually in type II diabetics, probably caused by increased macular
blood flow and inflammation induced by the laser
treatment. When the clinical situation allows, pre-
extisting macular edema should be treated prior to or
concurrent with PRP. It is also helpful if the panretinal
ablation can be divided into several sessions.

D. INHERITED DYSTROPHIES

Deutman et al have described pedigrees with au-
tosomal dominant CME. In this clinical entity visual
loss is the result of extensive leakage of macular reti-
nal capillaries. Cystoid macular edema may also complicate retini-
tis pigmentosa (RP). The incidence of CME is be-
tween 3% and 15%, and it is probably more common
in younger patients with minimal retinal pigment
epithelium disturbances and with a family history
of such occurrence. Subclinical, angiographic
CME is typically asymptomatic but by the time cysts
become biomicroscopically visible, visual acuity is usu-
ally 20/40 or less. Nevertheless, some patients with
chronic CME retain good vision for many years. Cys-
toid macular edema is frequently associated with mild
to moderate vitreous activity. Pinckers et al studied the
effect of CME on color vision and concluded that in
RP patients it mainly affects visual acuity and not
color vision.

E. TUMORS

Cystoid macular edema is an infrequent clinical
feature in some of the intraocular tumors. Wolter de-
scribed three main types of CME, which have been
seen to occur in association with choroidal melanomas:
1) direct involvement in cases where the neoplasm is
located under the fovea, 2) indirect involvement due to a subfoveal exudate in choroidal melanomas distant to the fovea, and 3) indirect foveo-
lar involvement without associated subfoveal tumor
or exudates. Cystoid macular edema can be the
initial finding in patients with choroidal melanoma
located in the equatorial region of the globe without
any evidence of serous detachment of the macula.
The cause of this edema is probably a chronic inflam-
atory cell infiltration within the choroid adjacent to the melanoma and retinal vasculitis.
Cystoid macular edema may also occur in retinal capillary or choroidal hemangiomas.

F. DRUG-INDUCED MACULAR EDEMA

Occurrence of CME following administration of
several therapeutic agents is a well-known pheno-
menon. Use of topical epinephrine-like antiglaucoma
drops in aphakic or phakic patients may cause break-
down of the blood-retinal barrier (BRB) leading to
CME. Prolonged use of tamoxifen may also potentially result in macular edema, which tends
to disappear after cessation of treatment. A differ-
tent type of CME with characteristic absence of late
leakage on fundus fluorescein angiography may
develop following high doses of nicotinic acid or
its derivatives.

Latanoprost, a prostaglandin analog, has been
widely used lately for the treatment of glaucoma.
There is evidence that latanoprost in the early postop-
errative pseudophakias or aphakias is associated with
increased destruction of the blood-aqueous barrier (BAB) and higher incidence of angiographic
CME. Although latanoprost itself is not known
to be vasoactive or to affect vascular permeability,
recent studies have shown that it stimulates endoge-
nous synthesis of prostaglandins, which mediate
inflammation, resulting in BAB breakdown. However,
these phenomena are transient and sub-
clinical. Warwar et al in a retrospective review re-
ported 1.2% incidence of CME associated with
latanoprost therapy, but other studies support that
coeexisting ocular conditions may have placed these
eyes at risk for prostaglandin-mediated BAB vascular
insufficiency. Generally it seems unlikely that topi-
cal latanoprost induces CME, in glaucomatous eyes
with a normally functioning blood–ocular barrier.

Recently it has been proposed that timolol and
its preservative, benzalkonium chloride, can cause
disruption of the BAB in early postoperative pseudophakia with an increased incidence of angiog-
rophic CME. The authors suggest concurrent
administration of NSAID in order to prevent these
adverse reactions without interfering with the desir-
able effect of timolol on the intraocular pressure.

G. MACULAR EDEMA AND TRACTIONAL
DISORDERS

1. Epiretinal Membrane

Macular epiretinal membrane, whether idiopathic
or secondary to vitreo-retinal pathology, may result
in the development of CME. The disturbance of mac-
ular microcirculation in eyes with epiretinal mem-
brane has been proven by means of scanning laser
ophthalmoscope (SLO) fluorescein angiography
showing significantly reduced capillary blood flow
velocity, which may lead to macular edema. Sponta-
aneous peeling of the epiretinal membrane may oc-
casionally occur, but if central visual acuity declines
to the 20/60 to 20/80 level, surgical intervention
should be considered in order to prevent irreversible
macular changes.

2. Vitreomacular Traction Syndrome (Fig. 6)

The vitreomacular traction syndrome is a rare
entity in which partial posterior vitreous detach-
ment is combined with persistent macular adherence and
Macular edema. In case vitreomacular adhesion is sufficiently dense, prolonged traction may cause CME, degeneration, and detachment of the macula. Hikichi et al. reported 81% incidence of CME at the diagnostic examination in eyes with vitreomacular traction syndrome. Complete vitreomacular separation, which occurs infrequently in eyes with the disorder, allows resolution of cystoid changes and improvement of visual acuity. Vitrectomy for separation of the vitreomacular attachment may be required to reattach the macula with moderately good visual prognosis.

III. Investigations

Slit-lamp examination with contact or non-contact lens, makes it possible to detect retinal thickening, localized or extending to the posterior pole. The use of a narrow slit beam is useful in detecting cystoid spaces. Clinical suspicion of macular edema can be confirmed with the aid of a wide variety of investigations (Table 1). Tests may be grouped into three categories according to whether one is analyzing the underlying pathogenesis, the effect of the macular edema on the retina, or its impact on visual function.

A. TESTS DETECTING DISTURBANCES IN THE BLOOD RETINAL BARRIER

Macular edema may result from the breakdown of the BRB. This may occur at the level of the retinal pigment epithelium or the capillary endothelial cells. Various methods of investigation are utilized to detect disruption of the BRB in order to determine the presence and the extent of macular edema.

The fundus fluorescein angiogram is clinically the most widely available and useful test. It permits study of the circulation of the retina and choroid in normal and diseased states. The amount of fluorescein leakage depends on the dysfunction of the retinal vascular endothelium. Although there is a significant correlation between visual acuity and the area covered by these cystoid changes, there is no relation between visual acuity and distance of cysts from the foveal avascular zone. Fundus fluorescein angiography, apart from being a significant diagnostic modality also improves the accuracy of planning treatment for macular edema. Late-phase stereoscopic pairs are useful in estimating the retinal thickness, the level of the leakage and the location and extent of cystic spaces.

Other tests that evaluate the BRB/BAB are not commonly used in clinical practice and are predominantly research tools.

Vitreous fluorophotometry is a technique used to quantify fluorescein leakage with the aid of a slit-lamp fluorophotometer. Normally only small amounts of fluorescein enter the vitreous due to the presence of the BRB. With disruption of the barrier, increased fluorescein leakage may be detected. The fluorometer is capable of scanning small volumes of the vitreous cavity and converting the fluorescence measurements to concentrations, so that it is possible to plot concentration of fluorescein as a function of location within the vitreous, and also as a function of time. Formulas may be used that permit calculation of BRB permeability to fluorescein and a diffusion coefficient for fluorescein in the vitreous body. However, due to inconsistent results and the fact that vitreous fluorophotometry is abnormal in any instance of retinal vascular incompetence, the technique is not usually clinically helpful.

B. TESTS DETECTING RETINAL TISSUE THICKNESS

Assessment of retinal thickness can be useful in the treatment and follow-up of macular edema. Retinal thickness at the posterior pole can be assessed by several methods. Because slit-lamp biomicroscopy and stereoscopic fundus photography are to some extent subjective, new imaging techniques for objective measurement of retinal thickness have been introduced to clinical use. The two most commonly used techniques are the OCT and the retinal thickness analyzer (RTA).

Optical coherence tomography is a non-invasive device that obtains cross-sectional, high-resolution images of the retina and thus may detect retinal thickening. Microstructural features are determined by measuring the ‘echo’ time it takes for the light to reflect from the different structures at varying distances, analogous to A-scan ultrasonography. As the OCT operates with a near-infrared wavelength (about 840 nm), the examination is of minimal discomfort for the patient. Optical coherence tomography examination is possibly indicated in the early detection and follow-up of patients with macular edema. It has been shown to produce highly reproducible measurements and it is as effective at detecting macular edema as fluorescein angiography, but is superior at demonstrating axial distribution of the fluid. The RTA is a rapid screening instrument that generates a detailed map of retinal thickness. Multiple cross sectional imaging generates a 3D reconstruction of the retina. The major advantage of the RTA is the option to scan a relatively wide area of the retina in a short acquisition time. It has been shown that RTA is a useful and sensitive tool, which
### TABLE 1

<table>
<thead>
<tr>
<th>Technique</th>
<th>Principle</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein angiography</td>
<td>Leakage of dye from capillaries via damaged endothelial cells and/or Leakage associated with breakdown of the tight junctions between adjacent retinal pigment epithelium cells</td>
<td>Allows visualization of area covered by cystoid formations Correlates well with acuity</td>
<td>Small risk to patient</td>
<td>Qualitative Invasive</td>
</tr>
<tr>
<td>Vitreous fluorophotometry</td>
<td>Slit-lamp fluorophotometer</td>
<td>Quantifies fluorescein leakage Inconsistent results Non-specific</td>
<td>Qualitative Quantitative</td>
<td>Non-invasive</td>
</tr>
<tr>
<td>Laser flare cell photometer</td>
<td>Alteration in Blood-Aqueous barrier</td>
<td>Quantifies blood–aqueous disruption Role in monitoring macular edema</td>
<td>Non-specific</td>
<td>Quantitative Non-invasive</td>
</tr>
<tr>
<td>Ocular coherence tomography</td>
<td>Visible light interference</td>
<td>Quantification of retinal thickness Visualization of undisturbed retinal structure</td>
<td>Poorer resolution than high microscopy Depends on processing algorithms which may misrepresent retina surface contours Requires clear media</td>
<td>Quantitative Non-invasive</td>
</tr>
<tr>
<td>Retinal thickness analyzer</td>
<td>Laser projected at oblique angle to retina</td>
<td>Retinal thickness $\alpha$ to acuity Affected by clarity of media</td>
<td>Quantitative Non-invasive</td>
<td></td>
</tr>
<tr>
<td>Scanning laser ophthalmoscope</td>
<td>Scans small focused spot to provide high contrast image</td>
<td>Able to image through small pupils and hazy media Affected by optics of eye</td>
<td>Quantitative Non-invasive</td>
<td></td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>Small letter contrast Sensitivity varied</td>
<td>More sensitive than Snellen to macular edema Unreliable</td>
<td>Qualitative Non-invasive</td>
<td></td>
</tr>
<tr>
<td>Electro diagnostics</td>
<td>Stimulates foveal cones only</td>
<td>Amplitude correlates well with acuity</td>
<td>Qualitative Non-invasive</td>
<td></td>
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</tbody>
</table>

provides objective measurement of the retinal thickness, facilitating the diagnosis and follow-up of diabetic macular edema, as well as evaluation of the efficacy of laser treatment in this condition.\textsuperscript{148,189} It has also been suggested that estimation of retinal thickness has a more reliable correlation with visual acuity than fluorescein leakage since angiographic leakage is not always accompanied by retinal thickening.\textsuperscript{144}

The SLO has also been utilized in order to quantify retinal thickness by ophthalmoscopy and retinal topography.\textsuperscript{121} It is a rapid and non-invasive imaging method that provides quantitative analysis of macular cysts in addition to qualitative information not seen clinically.\textsuperscript{17} The chief advantage of the SLO is scanning a small focused spot to generate an image, (rather than illuminating a large area), which provides a high contrast image. The infrared imaging of the SLO offers advantages over current imaging techniques by minimizing light scatter through cloudy media. Additional advantages include the ability to image through small pupils, retinal hyperpigmentation, blood, heavy exudation, or subretinal fluid. Scanning laser ophthalmoscope has been used to assess photoreceptor function in various stages of macular edema.\textsuperscript{114} Recent studies have reported that
the results of SLO measurements were related to Snellen visual acuity and to findings using fluorescein angiography.114

C. TESTS ASSESSING RETINAL FUNCTION

Macular edema may potentially affect macular function as far as visual acuity and contrast sensitivity are concerned. Tests assessing macular function may be used indirectly to detect the effects of macular edema and follow up its treatment. Contrast sensitivity charts and electroretinography are both clinical and experimental tools.

Contrast sensitivity has been documented as suffering specific changes in CME as well as other localized and generalized retinal disorders.67,170 Ibanez et al in a prospective comparative study evaluated the effect of pseudophakic CME on contrast sensitivity. They reported a statistically significant decrease in contrast sensitivity for patients who developed transient or persistent pseudophakic CME for all spatial frequencies studied at two months and for higher frequencies at 8.5 months following surgery, as opposed to no CME group. Reduction in contrast sensitivity may account for persistent difficulties experienced by patients despite good Snellen acuity.88

Electroretinography may also be utilized to follow up the treatment of macular edema. The focal electroretinogram (ERG) is the response evoked by the foveal cones of the retina to a brief flash of light focused on the fovea.137,165,190 The foveal ERG provides objective information on the presence or absence of organic disease at the macula. The mean implicit time is significantly longer in eyes with clinically significant macular edema as compared to normals. The amplitudes are directly correlated with the best corrected Snellen visual acuity. This tends to support the role of outer retinal dysfunction in eyes with macular edema.190 Generally the focal ERG will vary depending on the severity and stage of macular edema.137

IV. Treatment

A. MEDICAL

The challenge concerning the management of macular edema arises in the chronic and persistent case, for which a stepwise therapeutic approach is optimal. The clinician must always be alert to the possible side effects of the many effective, but potentially toxic, pharmaceutical agents used to treat this entity. Additionally, surgical management should be considered for unremitting cases of CME (Table 2).

1. Non Steroidal Anti-inflammatory Agents (NSAIDs)

Commercially available NSAIDs consist of a chemically heterogeneous group of compounds, which may be divided into six different classes: alicylicates, fenamates, indoles, phenylalkanoic acids, phenylacetic acids, and pyralozones. Salicylates, fenamates, and pyralozones are too toxic for topical preparations or too unstable in solution for commercial formulation as eye drops, hence currently used topical ophthalmic preparations are from the indoles, phenylalkanoic acids, and phenylacetic acids.52

In aphakic or pseudophakic CME, the occurrence of intraocular inflammation with synthesis of prostaglandins results in disruption of the tight junctions of the perifoveal retinal capillaries. NSAIDs are useful as they inhibit the enzyme cyclooxygenase, which is required for the production of the prostaglandinas a degradation product of arachidonic acid. There is evidence that some NSAIDs may also act on other mediators. Experimental data showed that diclofenac at high concentrations inhibits the formation of lipoxigenase products (5-hydroxyeicosatetraenoic acid, leukotrienes) suggesting an additional regulatory role in the lipoxigenase pathway. However, the clinical relevance of the above property is still to be determined.52,110,195

Topical NSAIDs, including ketorolac tromethamine 0.5%, indomethacin 1%, and diclofenac 1%, are available and have been used either for treatment of macular edema following cataract surgery29,53,132,156 or prophylactically to prevent angiographic edema.35,133,134 Although there is a multiplicity of studies addressing the issue of topical administration of NSAIDs for the prophylaxis or treatment of postoperative CME, the majority of them have not been randomized, or have had inadequate controls. In addition there is a diversity of final outcomes as some of the authors evaluate angiographic macular edema and others clinically significant CME, whereas most relevant outcomes such as visual acuity have been used only in a few studies.

The Italian Diclofenac Study Group, in a randomized, controlled study, reported that diclofenac sodium had a protective effect on the development of angiographic CME following extracapsular cataract surgery. They found that after 140 days, the incidence of CME was almost three times lower than in the control group.1 However, this study, as well as most of the other trials assessing the efficacy of topical NSAIDs in preventing postoperative CME, included concurrent use of corticosteroids, introducing bias to the results. Flach et al in a randomized, placebo-controlled, double-masked study of prophylaxis of CME using NSAIDs as a single agent, reported less postoperative
<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary Site of Pathology</th>
<th>Proposed Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>Capillary endothelial cells</td>
<td>Grid focal photocoagulation, ? intraocular steroid implants, ? pars plana vitrectomy</td>
</tr>
<tr>
<td>BRVO/CRVO</td>
<td>Capillary endothelial cells</td>
<td>Grid focal photocoagulation (BRVO), ? pars plana vitrectomy with adventitial sheathotomy (BRVO), ? Hyperbaric oxygen</td>
</tr>
<tr>
<td>Radiation retinopathy</td>
<td>Capillary endothelial cells</td>
<td>Grid focal photocoagulation</td>
</tr>
<tr>
<td>Acquired Retinal macroaneurysm</td>
<td>Retinal anteriole</td>
<td>Photocoagulation to or surrounding the macroaneurysm</td>
</tr>
<tr>
<td>Inflammatory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitic syndromes</td>
<td>Capillary endothelial cells</td>
<td>Oral/periocular steroids, Steroid intraocular implants, ? intravitreal steroids, immunoinsuppressive agents, Acetazolamide, ? pars plana vitrectomy</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irvine-Gass</td>
<td>Capillary endothelial cells</td>
<td>Topical steroids/NSAIDs, Acetazolamide</td>
</tr>
<tr>
<td>Inherited</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>Retinal pigment epithelium</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Tumors</td>
<td>Direct involvement/vascular leakage</td>
<td>Treat primary cause</td>
</tr>
<tr>
<td>Drug induced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine/nicotinic acid, etc.</td>
<td>Capillary endothelial cells</td>
<td>Discontinuation of drug NSAIDs</td>
</tr>
<tr>
<td>Tractional disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated vitreous strand</td>
<td>Vitreous traction on macula</td>
<td>Nd:YAG vitreolysis</td>
</tr>
<tr>
<td>Pupillary distortion from iris strands</td>
<td>Vitreous traction on macula</td>
<td>Interior vitrectomy</td>
</tr>
<tr>
<td>Vitreomacular adhesion</td>
<td>Vitreous traction/epiretinal membrane on macula</td>
<td>Pars plana vitrectomy</td>
</tr>
</tbody>
</table>

angiographic CME in the group treated with ketorolac 0.5% as compared to the placebo group.\(^{55}\) Two double-masked, placebo-controlled studies in which corticosteroids were not used demonstrated that ketorolac 0.5% ophthalmic solution, administered for up to 3 months, improves vision in some patients with chronic CME after cataract surgery.\(^{53,54}\) Weisz et al suggested that topical ketorolac can be used with satisfactory results even for the treatment of chronic pseudophakic CME identified more than 24 months after cataract surgery.\(^{191}\) Nevertheless, this requires persistent use of ketorolac as recurrence of macular edema follows discontinuation of the treatment (“on-off” phenomenon).\(^{54,191}\)

Despite the absence of FDA-approved therapy for the prophylaxis or treatment of postoperative CME and the often conflicting reports regarding the effect of NSAIDs on visual acuity, a recently undertaken meta-analysis of the results from randomized controlled trials suggest that medical prophylaxis for aphakic and pseudophakic CME and medical treatment for chronic CME is beneficial.\(^{164}\)

More recently it has been supported that treatment of acute, visually significant pseudophakic CME with topical ketorolac and prednisolone combination therapy appears to offer benefits over monotherapy with either agent alone, as their synergic activity results in more rapid resolution of symptomatic CME.\(^{78}\)

Complications of NSAID use include ocular irritation, conjunctival injection, punctate keratopathy, and mydriasis. Recently, reports of corneal melting following administration of topical diclofenac have
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also been described. However, microbiologic and immunohistologic analysis attribute the toxic effect to the preservative/solubilizer of the preparation rather than the active ingredient.

2. Carbonic Anhydrase Inhibitors

Medical treatment of CME with carbonic anhydrase inhibitors (CAIs) has been known for over a decade. Initial observations were based on experimental data, which suggested that acetazolamide can increase fluid absorption across the retinal pigment epithelium. Carbonic anhydrase inhibitors may alter the polarity of the ionic transport systems in the retinal pigment epithelium through the inhibition of carbonic anhydrase and γ-glutamyl transferase. As a result there is increased fluid transport across the retinal pigment epithelium from the sub-retinal space to the choroid with reduction of the edema. Carbonic anhydrase inhibitors have also been shown to have other direct effects both on retinal and retinal pigment epithelial cell function by inducing an acidification of the sub-retinal space, a decrease of the standing potential as well as an increase in retinal adhesiveness. Carbonic anhydrase inhibitors tend to be more effective in disorders where the retinal pigment epithelium is at fault as opposed to the retinal capillaries. This may be due to the modulation of membrane-bound carbonic anhydrase IV in the retinal pigment epithelium, which may have lost its polarized distribution in the presence of macular edema.

Acetazolamide and other CAIs may reduce macular edema due to pseudophakia, diabetes mellitus, uveitis, and epiretinal membranes. Although there is enough evidence to support the beneficial effect of CAIs in RP patients, administration in uveitic and pseudophakic CME remains controversial. Use of acetazolamide for treatment of CME of other cause is largely based upon brief reports and uncontrolled studies with limited number of patients. Cox et al, in a prospective, cross-over study of 41 patients with chronic macular edema of various causes and durations, who were treated with oral acetazolamide reported that the latter had no effect on macular edema due to primary retinal vascular disease. In contrast, a large proportion of patients with inflammatory or inherited outer retinal disorders showed reproducible positive response to acetazolamide therapy.

Acetazolamide appears to be a particularly useful therapeutic agent in the management of macular edema due to RP. A randomized crossover study reported improvement of visual acuity in more than 80% of all patients who received acetazolamide. The therapeutic effect may be independent of the reduction of macular edema, as judged by fluorescein angiography. Rebound of CME in this group of patients may occur if methazolamide is used despite continuing treatment.

Conflicting reports have been published regarding inflammatory CME. Farber et al studied 30 patients with CME secondary to chronic iridocyclitis and reported statistically significant improvement of visual acuity in the group treated with acetazolamide. The response to treatment was more favorable in younger (under the age of 55 years) than older individuals. Conversely, Whitcup et al demonstrated that a 4-week course of acetazolamide in patients with chronic uveitis resulted in approximately 25% decrease in CME, as measured by fluorescein angiography, although it failed to improve the visual acuity.

The authors suggested that acetazolamide might have a more limited clinical benefit in patients with long-standing CME associated with chronic uveitis.

A recently introduced topical CAI (dorzolamide) has also been used for the treatment of chronic CME due to RP. Although dorzolamide may provide improvement of macular edema on fluorescein angiograms and subjective improvement of visual function in some patients, no significant improvement in visual acuity has been shown with this preparation. Grover et al, in a double-masked, crossover study reported that oral acetazolamide administered in five patients with RP was more effective than dorzolamide in managing chronic macular edema and improving visual acuity.

A suggested treatment protocol includes a normal starting dose of CAI of 500 mg/day, which should be continued for at least 1 month to see an effect. The patients may reduce this dose over the course of therapy according to the subjective impression of treatment response. Metaphylaxis to the drug may occur with a rebound of the edema despite continuation of treatment.

Unfortunately the clinical use of CAI is limited by frequent and bothersome side effects, including paraesthesias, which occur almost universally, nausea, and dizziness. If long-term administration of CAI is planned, regular renal function monitoring should be carried out and daily supplementation with potassium chloride is advisable to counteract the excessive loss of potassium.

3. Steroids

Steroids also inhibit the production of prostaglandins, but at a higher level in the biochemical pathway, by inhibiting the enzyme phospholipase A2, which catalyses the conversion of membrane lipids to arachidonic acid. By this process, steroids inhibit
the formation of both prostaglandins and leukotrienes. Locally their vasoconstrictive properties decrease intracellular and extracellular edema, suppress macrophage activity, and decrease lymphokine production.

Corticosteroids may be administered topically, by periorcular injection, orally and parenterally. Topical corticosteroids penetrate the corneal epithelium and reach the anterior chamber. Ointments yield a more prolonged release of steroid, although peak concentrations in the eye are less compared with drops. The anti-inflammatory properties of topical corticosteroids can be potentially helpful in treating CME caused by chronic iritis or iridocyclitis. Occasionally CME attributable to intermediate uveitis may also respond to topical corticosteroids. There is evidence that combination therapy with both topical steroids and NSAIDs appears to offer benefits over monotherapy with either agent alone. Significant potential complications of topical steroid use include glaucoma, posterior subcapsular cataracts, exacerbations of infections, and recurrence of herpetic keratitis.

Periocular injections may be delivered via posterior sub-Tenon’s or peribulbar routes. They have advantages over topical application as they allow administration of a large bolus of drug while minimizing the systemic side effects and also allow a more sustained release of the drug. They exert a maximal, long-lasting response at the site of injection. However there is a risk of inadvertent globe penetration, elevation of intraocular pressure, and cataract formation. The mechanism of penetration of corticosteroids into the eye after periocular injection is most likely to be trans-scleral. McCartney et al used autoradiography to examine the steroid penetration following subconjunctival injection. The results showed that penetration into inflamed eyes is much faster than into normal eyes and consequently recommended that steroids should be injected immediately adjacent to the site of inflammation, rather than in a nonspecific fashion. Posterior sub-Tenon’s as opposed to orbital floor injections are in theory more efficacious as they deliver the steroids closer to the macula, although there are no published data to support this assumption (Fig. 8).

Systemic corticosteroids are very useful for the treatment of inflammatory CME predominantly in bilateral or resistant cases. Initial high doses, to achieve control of the inflammatory process, followed by a slow taper, in an attempt to prevent recurrences, are usually needed in the treatment of macular edema. In certain cases a combination of systemic

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**Fig. 6.** OCTs illustrating four cases of CME secondary to vitreomacular traction syndrome (Courtesy of G. Duguid MD, FRCS).

**Fig. 7.** OCTs showing macular edema of different causes. **Top left:** Pseudophacic CME 4 weeks following phacoemulsification cataract surgery. **Top right:** CME in a patient with retinitis pigmentosa. **Bottom left and right:** Diabetic macular edema (Courtesy of G. Duguid MD, FRCS).

**Fig. 8.** Left: OCT demonstrating macular edema in pars planitis. Right: significant reduction of macular edema as revealed by OCT 6 weeks following posterior sub-Tenon’s injection of triamcinolone acetonide (Courtesy of G. Duguid MD, FRCS).
steroid and posterior sub-Tenon’s injection of corticosteroids can be given for additive effect. A wide spectrum of significant ophthalmic and systemic side effects are common following systemic administration of steroids including peptic ulceration, osteoporosis, exacerbation of diabetes and hypertension, Cushingoid state, and adrenal suppression. Due to these potentially severe systemic complications, oral steroids should be used with caution. If long-term, high-dose corticosteroids are required, the use of steroid-sparing agents with assistance of an internist should be considered.

Although the most common form of administration of systemic steroids is oral, there are published reports of small series using high-dose intravenous methylprednisolone for severe ocular inflammatory disease and for persistent pseudophakic CME with satisfactory results. Tehrani et al, in a noncomparative study, used deep intramuscular methylprednisolone in the treatment of uveitic CME. The authors supported that despite limited success, this form of treatment was associated with minimal ocular or systemic side effects, suggesting that it may have a role as an alternative to orally administered systemic corticosteroids in uveitis patients with unilateral CME because of the potential for increased patient compliance.

A promising treatment modality for patients poorly controlled or intolerant to repeated periocular corticosteroid injections, systemic corticosteroids, or steroid sparing immunosuppressive agents has recently been suggested with the introduction of intraocular steroid sustained drug delivery devices. It has been shown that these devices are nontoxic and produce constant intraocular drug levels for an extended period in human and experimental models. Jaffe et al, in a prospective, noncomparative case series of 7 eyes (5 patients) with severe uveitis, implanted non-biodegradable intraocular sustained drug delivery devices containing 2 mg and 15 mg fluocinolone acetonide. After an average of 10 months of follow-up, favorable effects were observed with improvement of intraocular inflammation and consequent marked reduction of anti-inflammatory medication, preservation or improvement of visual acuity, and reversal of CME. However, all eyes underwent cataract extraction at the time of device implantation or shortly thereafter, hence improvement in visual acuity cannot be directly related to the fluocinolone acetonide. Potential side effects of this treatment modality include rhegmatogenous retinal detachment, vitreous hemorrhage, device extrusion, endophthalmitis, increased intraocular pressure, and suture exposure. Large, randomized, controlled trials are currently underway in the USA, Europe, Asia, and Australia in order to evaluate more effectively their risks and benefits and their long-term follow-up.

The promising results following treatment of exudative age-related macular degeneration with intravitreal corticosteroids led clinicians to use the same therapeutic modality in patients with intractable CME attributable to chronic uveitis and more recently to diabetic or pseudophakic macular edema. Young et al, in a prospective, non-randomized pilot study of 6 patients with uveitic macular edema, reported clinical and angiographic resolution of CME in all patients following single intravitreal injection of 4 mg triamcinolone acetate, leading to a median improvement of visual acuity of 3 lines within 3 months of follow-up. However relapse of CME and reduction of visual acuity to pre-injection levels occurred in 4 cases by 12 months while the remaining two patients developed cataracts prohibiting accurate assessment of the macula. Other case series in subjects with longstanding inflammatory CME who failed to respond to conventional therapy showed with the aid of OCT that complete anatomic and, to a certain extent functional, recovery can be induced by intravitreal triamcinolone acetate.

Intravitreal injection of triamcinolone acetate has also been used alone or in combination with laser photocoagulation for treatment of diffuse diabetic macular edema. Martidis et al in a prospective, noncomparative, interventional case series reported improvement in visual acuity of 2.4 and 1.3 Snellen lines at the 3-month and 6-month follow-up reviews after intravitreal injections of 4 mg of triamcinolone acetate. Anatomical reduction of central macular thickness as measured by means of OCT was also achieved during the same intervals. More recently Jonas et al administered 25 mg of triamcinolone acetate as opposed to 4 mg that all previous studies had used for the treatment of diabetic macular edema. In a mean follow-up of just over 6 months, they reported significant improvement in visual acuity and reduction of fluorescein leakage when compared with pre-injection levels. However, the investigators pointed out that visual improvement showed a tendency to decline 5 months after the triamcinolone acetate injection. Although 36% of the cases developed intraocular pressure greater than 21mm Hg following injection of triamcinolone acetate, ocular hypertension was successfully controlled by topical antiglaucoma agents until triamcinolone acetate crystals had disappeared. Other potential complications that intravitreal steroid injection may entail is hastening of cataract formation and deposition of cortisone crystals on the macular region. However,
the latter can be avoided should patients be instructed to maintain an upright position for at least 2 hours following the injection.16,96,201

4. Immunomodulators

Steroid-sparing immunosuppressive drugs are frequently used as additional, second-line agents in patients with severe intraocular inflammation and consequently CME.78 Unfortunately, there does not appear to be any double-masked prospective controlled clinical trial involving the use of any of these agents in the treatment of CME secondary to uveitis.

Cyclosporin is a fungal metabolite with immunosuppressive activity. It reversibly inhibits the response of T-lymphocytes (especially T-helper cells) to antigenic stimulation. Nussenblatt et al compared the efficacy of cyclosporine A to prednisolone in the treatment of 56 patients with endogenous uveitis. He reported resolution of macular edema in 7 of 15 patients of the cyclosporine-treated group, and in 10 of 16 patients of the prednisolone-treated group.145 Several studies have evaluated the effect of intravitreal sustained-release cyclosporine in the treatment of experimental uveitis. The cyclosporine A devices were well tolerated with no long-term complications, suggesting that it may be useful in the treatment of patients with severe chronic uveitis and CME, who are intolerant to currently available therapies.46,92,93,154 Other immunosuppressive drugs used in treatment of uveitic CME include azathioprine, mycophenolate mofetil, tacrolimus (FK506), methotrexate, and anti-CD4+ monoclonal antibodies.60,117 However, existing literature dealing with the use of these agents in the treatment of uveitis does not address the specific issue of CME even though visual acuity is used as an endpoint in most of the trials and it is likely that CME was the main reason for poor vision.

Despite the potential therapeutic role of immunomodulators in the treatment of uveitic CME, it has been suggested that immunosuppressives are ineffective in the presence of macular ischemia on fluorescein angiography. In these patients the rationale for treatment should be revised and immunomodulators should be prescribed with caution.22

5. Hyperbaric Oxygen

Hyperbaric oxygen has been reported to improve visual function in patients with chronic macular edema associated predominantly with retinal vein occlusions. Branch retinal vein occlusion has been found to have more favorable prognosis as opposed to central retinal vein occlusion.138,139 Oxygen may also be beneficial in aphakic/pseudophakic macular edema or chronic CME attributable to uveitis.179 The dose given was 2.2 atm (222.92 kPa) oxygen for 1.5 hours twice a day for 7 days followed by 2 hours daily for 14 days. Improvements in vision have also been reported with the transcorneal delivery of oxygen in a group of patients with chronic aphakia.21

The mechanism, which results in reduction of leakage is probably associated with the vasoconstrictive effect of oxygen. This decreases the venous pressure and allows the reformation of junctional complexes between endothelial cells. The intraretinal edema clears and the integrity of the BRB is restored. Oxygen may mainly affect the retinal cells in the marginal zone of the ischemic retina or the macular region. The therapeutic effect is stable and leads to a significant improvement in visual acuity.157,158 The severity of macular ischemia has been found to be a more significant determinant for the visual prognosis following treatment than the degree of macular edema.138

Although the literature suggests that hyperbaric oxygen may be a potentially valuable adjuvant in patients with sight-threatening macular edema, the existing evidence is mainly based on small series with short follow-up. The absence of randomized controlled trials and the limited information regarding the long-term visual prognosis of these cases prohibits its use routinely in the clinical practice.

B. SURGICAL

1. Laser Photocoagulation

Photocoagulation is a therapeutic technique using a strong light source to coagulate tissue. Several theories attempted to explain the beneficial effect of laser photocoagulation to macular edema. Laser lesions in experimental animals show a temporary breakdown of the BRB and a subsequent repair, as the retinal pigment epithelium cells adjacent to the burns proliferate and slide to replace the necrotic cells. The new retinal pigment epithelium cells produce tight junctions within several weeks, which restores the integrity of the retinal pigment epithelium barrier.2 An alternative hypothesis states that the grid laser by destroying photoreceptors reduces the oxygen consumption of the outer retina and allows oxygen to diffuse from the choroid to the inner retina, where it raises the oxygen tension and relieves hypoxia.141,174 This increased oxygen tension causes retinal arteriolar constriction and increased resistance in the arterioles, leading to reduced hydrostatic pressure in the capillaries and venules.141,174 The decreased hydrostatic pressure causes vessel constriction according to Laplace’s law, vessel shortening,112 and less flux of fluid from vessel to tissue as is postulated in Starling’s law.18,175
Diabetic macular edema and macular edema following branch retinal vein occlusion may improve following focal or grid laser photocoagulation. Laser treatment is not indicated for predominantly ischemic maculopathy. Most authors agree that the prognosis is best with localized leakage with or without circinate rings of hard exudates.\(^3\)–\(^7\) Should PRP be also needed, this should be carried out after or in conjunction with macular treatment, because post-PRP inflammation and altered retinal blood flow may result in deterioration of macular edema.\(^3\)–\(^6\),\(^12\)\(^9\)

The Early Treatment for Diabetic Retinopathy Study (ETDRS) provided the indications for laser treatment of diabetic macular edema. Clinically significant macular edema (edema that has reduced or is threatening to reduce vision) as defined by the ETDRS is one or more of the following:\(^7\)

- Retinal thickening at or within 500 μm of the foveal avascular zone
- Hard exudates at or within 500 μm of the center of the foveal avascular zone, if associated with thickening of the adjacent retina
- Retinal thickening >1,500 μm within 1,500 μm of the center of the foveal avascular zone

Focal laser treatment aims to close or obliterate the microaneurysms producing focal areas of leakage.\(^4\)–\(^7\) Grid photocoagulation may reduce leakage attributable to permeability abnormalities within dilated macular capillaries, with a positive effect on visual acuity and fluorescein leakage in diffuse diabetic macular edema, radiation retinopathy, and macular edema due to branch retinal vein occlusion (Fig. 9).\(^9\)

Grid laser photocoagulation has also been proposed for the treatment of uveitic macular edema. Schulten et al reported that 5 patients with chronic, refractory CME exhibited anatomic reduction of the edema but no significant increase in visual acuity, findings similar to those obtained with grid laser photocoagulation after central retinal vein occlusion (CRVO).\(^2\),\(^17\)\(^8\)

Side effects such as scotomas, corresponding to the laser burns, have been frequently noticed by the patients following photocoagulation. These scotomas generally fade over a period of several weeks. Symptoms are more likely to occur if laser burns are placed too close to each other.

Recently the MicroPulse 810 nm diode laser has been introduced for the treatment of macular edema secondary to either branch retinal vein occlusion (BRVO) or diabetic maculopathy. With shorter than conventional laser exposure times (<1msec), thermal injury may be limited to the retinal pigment epithelium, sparing the overlying photoreceptors.\(^14\),\(^14\)\(^2\),\(^17\)\(^1\) Moorman et al used a MicroPulse diode laser in a modified grid pattern for the treatment of diffuse macular edema secondary to diabetes or BRVO. They reported resolution of macular edema in 57% of the cases at 6 months, suggesting that Micropulse technique compares favorably with argon laser in the resolution of macular edema, although resolution may be slightly prolonged.\(^14\)\(^2\) Although the first results from the use of MicroPulse diode laser appear to be encouraging, the exact parameters of this new development have not been established yet and concerns have been expressed for its reproducibility when subthreshold energies are used.\(^16\)\(^0\),\(^17\)\(^1\)

2. Vitrectomy

a. Inflammatory CME

There have been sporadic reports on the outcome of pars plana vitrectomy (PPV) in inflammatory CME, unresponsive to medical therapy.\(^45\),\(^7\)\(^9\),\(^10\)\(^3\),\(^19\)\(^3\) Dugel et al,\(^45\) in an uncontrolled study, investigated the efficacy of PPV in 11 eyes of nine patients with intraocular inflammation-related CME that was unresponsive to corticosteroids. Seven eyes (64%) improved four or more lines of Snellen visual acuity within 4 weeks whereas 2 eyes (18%) remained unchanged and 2 eyes (18%) worsened. Cystoid macular edema improvement was confirmed both by clinical examination and by fluorescein angiography in 9 eyes (82%) and by clinical examination alone in 2 eyes (18%). Other retrospective, non comparative studies have also suggested that PPV may be associated with a beneficial effect in CME attributable to intermediate uveitis or sarcoidosis.\(^10\)\(^3\),\(^19\)\(^3\) Despite the general impression that duration and severity of uveitis play a role in the visual outcome following vitrectomy, recent studies suggest that the above factors are not

Fig. 9. Argon grid laser photocoagulation for the treatment of diffuse diabetic macular edema.
significant prognostic determinants. The role of internal limiting membrane removal during PPV remains unclear. Wiekens et al in a retrospective, uncontrolled study of 42 eyes who underwent PPV for uveitic CME unresponsive to medical treatment, performed internal limiting membrane peel without use of indocyanine green or tripan blue in 15 (35.7%) cases. They reported no difference in the clinical outcome with or without internal limiting membrane peel. However, the authors stated that removal of internal limiting membrane from the diffusely edematous macula was very difficult and sometimes could only be accomplished with fragmentation of internal limiting membrane in multiple small pieces.

Generally, although there is some evidence that PPV may be a useful alternative in the management of refractory inflammatory CME and in selected cases, it should be considered earlier in the course of the disease, visual improvement may be the result of increased media clarity rather than due to induced changes to pre-existing CME. In addition, there seems to be no convincing data that vitrectomy reduces the number of recurrences in uveitic patients, even though some authors suggest that this may occur.

b. Diabetic Macular Edema

It has been postulated that intractable diabetic macular edema unresponsive to laser treatment may be due to posterior hyaloid traction and not traditional mechanisms. Vitreous surgery may improve perifoveal microcirculation in the eyes of diabetic patients with CME and resolve the macular edema improving the visual acuity. Following Lewis et al’s report of the beneficial effect of PPV in patients with diabetic macular traction and edema associated with posterior hyaloid thickening, several clinical studies have confirmed the initial observation.

OCT has been proposed to be particularly useful in the detection of shallow, subclinical, macular detachment in eyes with diabetic macular edema associated with posterior hyaloid traction. It has been suggested that vitrectomy should be considered when shallow macular detachments can be demonstrated by OCT. Furthermore, clinical recovery with resolution of macular edema and improvement of visual acuity following PPV has been reported, even when there was no evidence of macular traction on ophthalmoscopy. Based on the available published data, 38–100% of the patients who underwent vitrectomy for diabetic macular edema showed improvement in visual acuity. However, there are significant confounding parameters, including small sample size, short duration of macular edema, retrospective and non-randomized studies, and visual acuity not measured by masked observers using a specific protocol.

In a recent non-randomized, controlled clinical trial, 7 patients with bilateral diabetic macular edema underwent PPV in one eye while the fellow eye was left untreated. After a mean follow-up of 5 months, visual acuity levels in eyes that underwent vitrectomy improved by more than two lines in 4 (57%) cases and remained the same in 3 (43%) eyes. In the control (untreated) group visual acuity improved more than two lines in 1 (14%) eye, remained the same in 3 (43%) eyes, and decreased in 3 (43%) eyes. In addition, macular thickness measured by OCT was significantly reduced in all eyes of the vitrectomy group. The authors suggested that PPV facilitates significant absorption of diabetic macular edema. However, the fact that anatomical reduction of retinal thickening is not always accompanied by improvement of visual function may indicate that postoperative visual outcome is compromised by preoperative irreversible damage of photoreceptors.

c. Aphakic/Pseudophakic CME

The Vitrectomy-Aphakic-Cystoid Macular Edema Study, a prospective, multicenter study of patients with chronic aphakic CME, showed significant improvement in visual acuity following vitrectomy. In eyes with vitreous loss at the time of cataract surgery and subsequent development of vitreous adhesions to anterior segment structures, lysis of vitreous strands to the cataract wound with the aid of Nd:YAG laser may reduce vitreous traction leading to resolution of CME. Should this fail or the vitreous is too extensive, vitrectomy may be considered. Vitrectomy should remove any vitreous from the anterior chamber. Harbour et al in a more recent, retrospective, non-comparative study of 24 eyes with chronic, unresponsive to medical treatment, pseudophakic CME, performed vitrectomy with removal of vitreous adhesions to anterior segment structures. Visual acuity improved in all patients with 71% of subjects experiencing postoperative visual improvement of three or more lines. The authors reported that postoperative visual outcome was not associated with the duration of CME or the preoperative levels of visual acuity.

d. Branch Retinal Vein Occlusion

Osterloh et al first described PPV with adventitial sheathotomy for the treatment of macular edema associated with BRVO. Subsequent studies demonstrated that surgical lysis of the common adventitial sheath surrounding the crossing site of the affected branch retinal vein and artery can improve visual
acuity after this procedure. Shah et al reported substantial visual improvement after surgical sheathotomy in four of five patients with a follow-up of up to 7 years. Although arteriovenous adventitial sheathotomy may be beneficial in these patients, the lack of randomized controlled studies make it impossible to determine whether the visual improvement exceeds that obtained with no therapy.

C. FUTURE TREATMENTS

Breakdown of the capillary BRB, causing macular edema, appears to be dependent on a number of active processes that may be open to pharmacological manipulation. In diabetes mellitus, hyperglycemia has been found to result in increased levels of dialglycerol, which in turn activates the protein kinase C (PKC) pathway. The latter functions as signal for growth factors, especially the vascular endothelial growth factor (VEGF), which plays a dominant role in retinal vascular leakage and formation of macular edema. Experimental studies have clearly shown that blockage of VEGF action by inhibiting PKCβ may prevent the above process. Recently investigators have largely concentrated on LY333531, which is a highly selective inhibitor for the PKCβ isoform that has very little affect on other enzymes, minimizing the risk of systemic side effects resulting from its use. A randomized, double-masked, placebo-controlled study in diabetic patients of less than 10 years duration and no or mild retinopathy has reported normalization of retinal blood flow in patients treated with LY333531 as opposed to placebo-treated subjects.

Phase I studies of LY333531 have shown that the compound is well tolerated at therapeutic doses having minimal interference with normal metabolism. Two phase II/III studies evaluating the ability of LY333531 to slow or reverse the progression of macular edema have been completed and the reports are to be published soon. In summary, oral pharmacological therapies involving PKCβ-isoproduct-selective inhibitors may prove efficacious for the treatment of VEGF-associated ocular disorders such as diabetic retinopathy.

Other studies investigating the use of intravitreal anti-VEGF proteins for diabetic macular edema are also underway. The safety and efficacious dose of EYE001, an anti-VEGF pegylated aptamer for the treatment of clinically significant macular edema is being studied in a phase II randomized, double-blind, controlled trial. The macular edema trial is currently investigating the therapeutic effect of steroid ocular implants (Posurdex; Allergan, Irvine, CA) for persistent macular edema associated with diabetic retinopathy, retinal vascular occlusive disease, cataract surgery, and uveitis. The micro-sized biodegradable implants provide sustained delivery of dexamethasone directly to the targeted disease site. Preliminary findings from this trial demonstrate that Posurdex is highly effective in improving vision in patients with persistent macular edema. Ninety days following implantation, patients experienced a statistically significant improvement in visual acuity of two lines or more when compared to untreated controls, which was accompanied by decreases in both retinal thickness and fluorescein leakage (unpublished data). Phase 3 clinical trials for Posurdex are planned to initiate during the fourth quarter of 2004.

Method of Literature Search

In this review, we identified pertinent articles on macular edema from a combination of sources including electronic database searches and manual searches through the literature. A computerized search of the PubMed database (National Library of Medicine) was performed up to January 2003. The term *macular edema* was used for a broad and sensitive search. Subsequently all the abstracts were carefully scanned and were divided into subcategories covering topics including pathogenesis, etiology, clinical manifestations, investigations and treatment of macular edema. Non-English articles were included when deemed necessary. Copies of the entire articles were obtained. Reference lists of identified sources were used to glean more articles on the same topic. Additional books cited from these references were also used.

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