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Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention

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ABSTRACT

Hereditary retinal diseases are now the leading cause of blindness certification in the working age population (age 16–64 years) in England and Wales, of which retinitis pigmentosa (RP) is the most common disorder. RP may be complicated by cystoid macular oedema (CMO), causing a reduction of central vision. The underlying pathogenesis of RP-associated CMO (RP-CMO) remains uncertain, however, several mechanisms have been proposed, including: (1) breakdown of the blood-retinal barrier, (2) failure (or dysfunction) of the pumping mechanism in the retinal pigment epithelial, (3) Müller cell oedema and dysfunction, (4) antiretinal antibodies and (5) vitreous traction. There are limited data on efficacy of treatments for RP-CMO. Treatments attempted to date include oral and topical carbonic anhydrase inhibitors, oral, topical, intravitreal and periocular steroids, topical non-steroidal anti-inflammatory medications, photocoagulation, vitrectomy with internal limiting membrane peel, oral lutein and intravitreal antivascular endothelial growth factor injections. This review summarises the evidence supporting these treatment modalities. Successful management of RP-CMO should aim to improve both quality and quantity of vision in the short term and may also slow central vision loss over time.

INTRODUCTION

Cystoid macular oedema (CMO) may complicate retinitis pigmentosa (RP) and has been reported to occur in 10%–50% of patients.[1–4]

Hereditary retinal diseases are now the leading cause of blindness certification in the working age population (age 16–64 years) in England and Wales, of which RP is the most common disorder.[5] RP causes nyctalopia and progressive peripheral visual field loss, with particular disability experienced when disease progression results in central visual compromise. One important treatable cause of central vision loss is RP-associated CMO (RP-CMO).[6] Improved understanding of the underlying mechanisms and response to treatments of RP-CMO is required to facilitate better-targeted and more efficacious therapies. In this review, we will discuss the pathogenesis of RP-CMO and the multiple avenues of intervention that have been investigated or being considered.

PATHOGENESIS

No single aetiology has been definitively established to cause RP-CMO. While we describe several individually proposed mechanisms, it is plausible that RP-CMO may result from a combination of these.

Breakdown of the blood-retinal barrier

The blood-retinal barrier (BRB) exists to maintain homeostasis via the highly selective diffusion and active transport of molecules into and out of the retina, thus preventing extravascular accumulation of fluid within the retina.[7] This is achieved in two ways: (i) an outer barrier of apical tight junctions between retinal pigment epithelial (RPE) cells[8 9] and (ii) an inner barrier of tight junctions between vascular endothelial cells.[10] CMO can occur from BRB breakdown secondary to RPE and/or endothelial damage/dysfunction.

Studies have investigated whether one barrier is more affected than the other in order to better focus on potential therapies. Vinores et al[11] used immunolocalisation of endogenous albumin to highlight areas of extravasation in normal eyes compared with those with RP. In eyes with RP alone, albumin leakage was greatest from the inner barrier.[11] In RP-associated with other ocular complications (eg, aphakia, glaucoma), leakage varied between the inner and outer barriers. No correlation was found between severity of photoreceptor degeneration and albumin leakage,[11] suggesting that therapies for RP-CMO could be used regardless of underlying disease status.

The release of 'toxic products' from degenerating retina/RPE may cause RP-CMO by disrupting the BRB.[12] In keeping with CMO observed in other disorders, RP-CMO has been associated with release of vascular endothelial growth factor (VEGF), adenosine,[7] prostaglandins,[13] histamine,[14] insulin-like growth factor 1,[15] tumour necrosis factor α and interleukin-1α and interleukin-1β.[16]

Failure (or dysfunction) of the pumping mechanism in the RPE

An important function of the RPE is to pump fluid out from the subretinal space in order to maintain the negative hydrostatic pressure required for adhesion between RPE and photoreceptors.[17] Under normal conditions, Cl^- enters the RPE cell via Na^+/K^+ ATPase located on the apical membrane and exits via Cl^- channels on the basolateral membrane. It is this active transport that drives water through aquaporin channels from the subretinal space into the choriocapillaris. Failure (or dysfunction) of this pumping mechanism may occur in RP, thus resulting in CMO. The presence of CMO has been suggested to result in loss of polarised distribution of membrane-bound carbonic anhydrase (CA) IV in the RPE, further contributing to RP-CMO.[10]

Müller cell oedema and dysfunction

The Müller cell is essential for visual transduction and retinal homeostasis, including fluid dynamics.

Water enters the retina by two routes: directly from the blood, coupled with glucose uptake and/or as a by-product of aerobic metabolism; with the bidirectional movement of water osmotically coupled with the transport of osmolytes such as potassium.[18]

Potassium ions are released by activated retinal neurons. To prevent a build-up and potential excitotoxicity, potassium is passively taken up into Müller cells via inwardly rectifying channels (Kir2.1) with release of potassium occurring via Kir4.1 channels.[18] Kir channels consist of two transmembrane regions with cytosolic NH_2 and $COOH$ termini connected by a pore-forming loop. Molecules such as Mg^{2+} and polyamines are able to physically block this channel pore from allowing outward movement of K^+, while still able to accept inward movement of K^+[19] Under pathological conditions such as inflammation and oxidative stress, Kir4.1 channels redistribute, becoming more evenly spread throughout the Müller cell. However, Kir2.1 channels do not redistribute, resulting in intracellular potassium overload, increased osmotic pressure within the Müller cell, reduction in water efflux and ultimate Müller cell swelling.[18]

Makiyama et al used optical coherence tomography (OCT) to investigate the prevalence and spatial distribution of cystoid spaces (CS) in patients with RP. Seventy-four of 275 patients (27%) demonstrated RP-CMO in at least one eye. Inner nuclear layer (INL) CS were observed in 99% of eyes with CMO. The outer nuclear layer (ONL)/outer plexiform layer was involved in 28% and ganglion cell layer involved in 7%.[20] Müller cell bodies reside in the INL, which supports the hypothesis of Müller cell swelling and dysfunction. Interestingly, 79% of CS were located in areas of relatively well-preserved outer retina;[20] in keeping with the observation that CMO is seen more commonly in less advanced RP compared with late-stage RP.

Antiretinal antibodies
Serum levels of IgG, IgA and IgM have been investigated in 52 patients with RP compared with 40 controls. Higher levels of IgM were found in patients with RP compared with controls.[21] Spiro et al,[22] however, found no difference in IgM levels between 75 patients with RP and 51 controls. Spalton et al performed immunological studies on 17 patients with RP with central and/or peripheral vascular leakage observed on fluorescein angiogram (FA). Five out of 17 patients had raised IgM unrelated to degree of vascular leakage. All patients demonstrated positive immunofluorescence to rat photoreceptors at 1:5 dilution of serum, however, this could be attributed to cross-reactivity of smooth muscle antibodies with photoreceptor contractile organelles.[12]

Antiretinal antibodies have been prospectively studied in 30 patients with RP-CMO and 30 patients with RP without CMO. Antiretinal antibodies were found in 27 of 30 patients with RP-CMO compared with 4 of 30 patients with RP without CMO.[23] Nevertheless, the role of antiretinal antibodies in RP progression or RP-CMO remains unclear, with many unanswered questions including whether they are a secondary consequence of the degenerative process, the wide range of autoantibodies identified and the high prevalence in normal controls.[23 24]

Vitreous traction
It has been suggested that vitreous traction and epiretinal membrane contributes to RP-CMO by causing mechanical damage to Müller cells, an inflammatory reaction with subsequent capillary dilatation and leakage.[25 26] Schepens et al[26] and Takezawa et al[27] have reported cases of RP-CMO in the presence of vitreous traction.

DIAGNOSIS AND MONITORING OF RP-CMO
Prior to the advent of OCT, monitoring RP-CMO included slit-lamp biomicroscopy together with FA. OCT has since been shown to be more sensitive in detecting macular oedema compared with biomicroscopy in patients with diabetic retinopathy and RP-CMO.[28 29] OCT can detect CS in RP-CMO even when little, or no leakage is demonstrated on FA[29 30] and being non-invasive is ideal for monitoring RP-CMO. No studies have yet been performed using OCT-Angiography to investigate RP-CMO.

RP-CMO is not always associated with a reduction in visual acuity (VA).[31] Oishi et al[32] found no correlation between total macular thickness and VA. The integrity of the inner segment ellipsoid layer, however, has been shown to correlate well with VA and inform the likely prognosis.[31–33] Central vision loss in RP-CMO may be due to retinal thinning (from atrophy), thickening (from CMO) or a combination of both.[34] Anatomical but not functional improvement following treatment could be due to underlying retinal dysfunction/loss.

Automated static perimetry may also be useful for monitoring RP-CMO given the documented correlation between changes in retinal thickness due to CMO and retinal sensitivity.[35–37]

INHERITANCE PATTERNS AND SPECIFIC ASSOCIATIONS
While pedigree structures may be informative, definitive conclusions on mode of inheritance can only be made with a molecular diagnosis.

In a retrospective cohort study, CMO was present in 133/581 (23%) Italian patients with RP. This appeared to be significantly associated with autosomal dominant (AD) inheritance.[2] In contrast, Liew et al[38] constructed pedigrees for patients with RP-CMO in a retrospective cohort and found 55/81 (68%) patients with autosomal recessive (AR) inheritance (4 of whom were molecularly proven).

A family with AD-RP associated with the p.P347L variant in rhodopsin (RHO) has been reported, where all four children had bilateral CMO, suggesting this RHO mutation may be associated with early onset CMO.[39]

RP-CMO has been associated with female gender[2] and does not appear to be age-related.[1]

AVENUES OF INTERVENTION
Despite RP being the most common inherited retinal degeneration in the working age population, it remains a rare condition with only a proportion of these patients developing CMO.[5] Therefore, it is challenging to set up clinical trials targeting RP-CMO, with most evidence to date comprising case reports/series and relatively small prospective/retrospective studies.

We conducted a PubMed search to include all reports/studies of interventional treatment for RP-CMO published between 1975 and 2016. The search strategy involved the terms 'RP', 'rod cone dystrophy', 'retinal dystrophy', 'inherited retinal dystrophy' and 'macular oedema'. We identified 203 publications, the abstracts of which were retrieved and reviewed. Inclusion criteria included prospective and retrospective reports/studies using a drug and/or procedure to treat RP-CMO. We also included patients with syndromic RP such as Usher syndrome and those with Coats-like exudation. We excluded patients with membrane-type frizzled-related protein (MFRP)-related nanophthalmos-retinitis pigmentosa-foveoschisis-optic disc drusen syndrome due to its complexity

and rarity. We identified 46 reports/studies that met our inclusion criteria and retrieved these articles.

The majority of published evidence was in the form of small cohort and case-control studies. These may be influenced by publication bias, as negative reports are less likely to be published. There are no large randomised control trials (RCTs) to date. We did not construct funnel plots or perform other statistical tests for publication bias due to the small number of studies and the highly heterogeneous populations and study designs.

Significant studies that describe interventions in detail or highlight important/interesting points are mentioned in the text. Online supplementary table S1 provides an overview of all studies that met our inclusion criteria.

Pharmacological

CA inhibitors: oral and topical

Inhibition of CA IV results in acidification of the subretinal space, increased chloride ion transport, with subsequent movement of water across the RPE into the choroid.[10]

Several studies have shown RP-CMO improvement following treatment with CA inhibitors (CAIs).[38 40–53] In the largest retrospective study to date involving 81 patients (157 eyes) with RP-CMO, objective improvement on OCT was observed in 53% of patients (40% of eyes) using topical dorzolamide and in 41% of patients (28% of eyes) using oral acetazolamide[38] (figure 1). VA improved from 6/15 to 6/12 in most patients. AR-RP and greater initial central macular thickness (CMT) predicted better response to treatment.

In another retrospective study, 33 eyes (51%) of 20 patients with RP-CMO using topical dorzolamide demonstrated CMT reduction of at least 11%.[46] While there are other reports in keeping with these findings,[42] some studies have documented improvement of anatomy or leakage on FA only, with little or no corresponding improvement in VA.[47–49]

In a prospective, crossover study, 9 out of 17 patients using oral methazolamide demonstrated angiographic improvement of CMO, however, VA improved in at least one eye, by at least 2 lines in only 3 patients.[43] Another prospective, masked, crossover study using oral acetazolamide versus placebo observed VA improvement of at least one line, in at least one eye in 10 out of 12 patients. Three of these patients initiated on placebo only demonstrated improvement once switched to acetazolamide.[44]

Location of CS in RP-CMO may influence response to treatment with CAIs. Acetazolamide cannot readily enter the neurosensory retina making it potentially less effective at reducing INL CS.[54] However, with good access to the RPE basolateral membrane,[41] acetazolamide may be more effective at reducing ONL CS.[55]

Rebound CMO has been observed after stopping CAIs.[42 47] Importantly, a restored response has been demonstrated after the re-introduction of CAI treatment following a period of discontinued usage (between 1 and 6 months) in three patients with rebound RP-CMO.[53]

Oral CAIs have more side effects than topical CAIs ranging from fatigue, loss of appetite and limb paraesthesia to the development of kidney stones, aplastic anaemia and electrolyte disturbance including hypokalaemia with potential associated cardiac arrhythmia.[55]

Steroids: oral, periocular and intravitreal

Steroids reduce the synthesis and release of pro-inflammatory cytokines, including: prostaglandins, leukotrienes, VEGF and
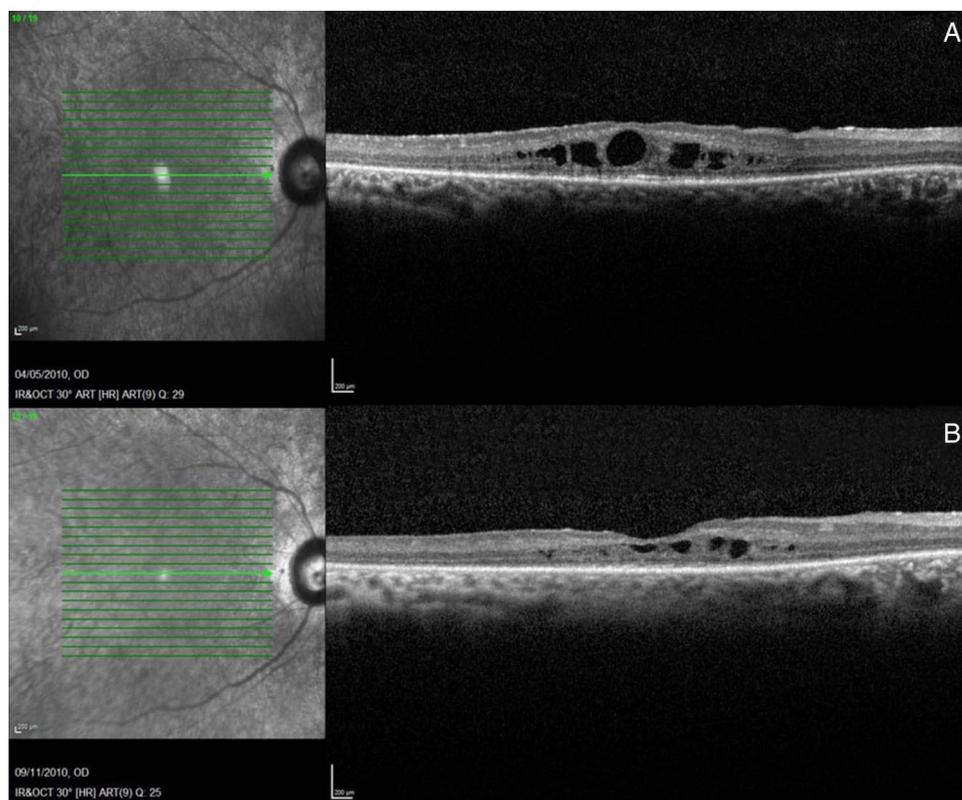

Figure 1 Spectral domain optical coherence tomography of a man aged 30 years with autosomal recessive retinitis pigmentosa and cystoid macular oedema. (A) Before treatment was initiated (visual acuity (VA) 6/18). (B) Following 6 months usage of topical carbonic anhydrase inhibitors (VA 6/12).

intercellular adhesion molecule 1.[56–59] This, together with suppression of inflammatory cell proliferation and migration contributes to improved BRB function and reduction of CMO. Steroids have been observed to improve VA and/or CMT in RP-CMO.[4 6 60–74]

A 1-year pilot study using oral deflazacort in 10 patients with RP-CMO reported significant improvements in near VA, retinal sensitivity and angiographic findings.[64] No ocular or systemic side effects were recorded.

Five patients with RP-CMO underwent unilateral intravitreal injection of 4 mg (0.1 mL) of triamcinolone acetonide (IVTA). CMT improved from 418 μm (range, 376–626 μm) at baseline to 224 μm (range, 214–326 μm) at 1 month, 275 μm (range, 215–584 μm) at 3 months and 312 μm (range, 239–521 μm) at 6 months. VA improved in two patients by 1 month but was not maintained. CMO recurrence occurred in two patients between 3 and 6 months.[4]

In comparison, a prospective, non-randomised trial compared 20 eyes of 20 patients with RP-CMO treated with IVTA with 20 eyes of 20 patients with RP-CMO who declined treatment. All treated patients showed anatomical improvement, greatest at 3 months postinjection. No statistical improvement in VA was observed. At day 1 post-IVTA, 10 eyes (50%) had a raised intraocular pressure (IOP) (>21 mm Hg) including 2 patients (10%) measuring between 30 and 35 mm Hg. All IOPs returned to baseline within 6 months.[6]

A case report of bilateral RP-CMO refractory to IVTA reported CMO reduction and VA improvement following bilateral sub-Tenon injections of triamcinolone.[62] CMO recurred in one eye at 3 months.

Intravitreal dexamethasone implant (Ozurdex, Allergan, Irvine, California, USA) has also been used in three patients with RP-CMO refractory to oral CAIs and/or sub-Tenon triamcinolone and/or topical non-steroidal anti-inflammatory (NSAID). Two patients required retreatment at 3 months due to recurrence.[72] Another case report demonstrated similar outcomes with initial improvement of CMO and VA, but recurrence at 2–3 months.[68]

The use of regular steroids in RP-CMO is significantly limited by their side-effect profile. Ozurdex appears to have a lower incidence of cataract and raised IOP compared with IVTA in treatment of retinal vein occlusion-CMO,[75 76] however, the incidence in RP-CMO is unknown.

Combination of topical NSAID together with topical steroid or topical CAI

A case report using topical steroid (prednisolone acetate 1%) together with topical NSAID (ketorolac trometamol 0.5%) in a woman aged 85 years with unilateral RP-CMO demonstrated CMO resolution and VA improvement at 3 months. CMO recurrence on cessation required retreatment to good effect.[77]

A recent prospective study of 18 patients randomised 15 eyes to topical ketorolac and 13 eyes to topical dorzolamide for 12 months. No significant change in CMT was observed in either group. VA improved in both groups at 6 months, however, this improvement was lost in the dorzolamide group at 12 months.[78]

Intravitreal anti-VEGF
The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor.[79] In addition to promoting angiogenesis, VEGF-A reduces endothelial barrier function and increases permeability of choroidal vessels, both of which cause CMO.[79]

Salom et al identified markedly lower levels of VEGF-A in the aqueous humour of 16 eyes of 16 patients with RP (94.9±99.8 (mean±SD) pg/mL) compared with the same number of controls (336.5±116.8 pg/mL). Relative hyperoxia of the inner retina due to photoreceptor cell death may reduce VEGF production from retinal cells such as pericytes, endothelial cells, glial cells, Müller cells and ganglion cells.[80]

While no studies have assessed vitreous levels of VEGF in patients with RP or RP-CMO, anatomical and/or functional improvement of RP-CMO has been observed following intravitreal anti-VEGF medication.[81–86] Anti-VEGF agents are routinely used to treat CMO and neovascularisation (NV) in multiple retinal diseases. NV is rare in RP; Triolo et al[87] reported choroidal NV in 3 of 176 eyes (2%) with RP. Indeed, intravitreal bevacizumab (Avastin, Genentech/Roche, South San Francisco, California, USA) has been observed to improve RP-choroidal NV.[88 89] While VEGF may contribute to RP-CMO formation, anti-VEGF medication remains under active study as a treatment modality.

Pegaptanib
A case report using a single intravitreal injection of 0.3 mg pegaptanib (Macugen, Eyetech Pharmaceuticals and Pfizer, New York, New York, USA) together with oral acetazolamide in a man aged 33 years with RP-CMO demonstrated improvement of CMT and VA, which was maintained at 4 months.[81]

Bevacizumab
Bevacizumab has been used off-label to treat RP-CMO with varying results. Melo et al observed neither anatomical nor functional improvement in two eyes of two patients following treatment with a single injection of intravitreal 1.25 mg bevacizumab: case 1 maintained VA of 20/200 both prebevacizumab and postbevacizumab injection with no further improvement following IVTA. Case 2 had a baseline VA of 20/100, which worsened at 1 month postbevacizumab to 20/200. Due to worsening cataract, the patient subsequently underwent phacoemulsification plus IVTA and VA at 3 months postoperation improved to 20/25.[90] In contrast, Yuzbasioglu et al performed an average of 3.3 (range, 1–8) injections of 1.25 mg bevacizumab over 10.3 (range, 6–14) months in 13 eyes of 7 patients and observed a reduction of CMT from 370.15 μm (range, 245–603 μm) at baseline to 142.53 μm (range, 124–168 μm). Pretreatment and post-treatment VA ranged from 5/400–20/100 to 20/200–20/63, respectively.[82]

Ranibizumab
Artunay et al enrolled 30 eyes of 30 patients with RP-CMO into a prospective, controlled interventional study of 0.5 mg intravitreal ranibizumab (Lucentis; Genentech). Thirteen eyes (87%) in the treatment group demonstrated a significant reduction of CMO at 6 months. No statistically significant difference in VA was seen between the groups.[83]

Aflibercept
Improvement of CMT and VA following a single unilateral intravitreal injection of aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, New York, USA and Bayer Healthcare Pharmaceuticals, Berlin, Germany) in a patient aged 52 years with RP-CMO was observed and maintained at 6 months.[84] We have observed similar responses[85] and have commenced a prospective study to determine safety and efficacy of intravitreal aflibercept in RP-CMO (ClinicalTrials.gov identifier NCT02661711). Aflibercept may be superior to other

anti-VEGF medications due to its intermediate size (115 kDa) and higher binding affinity.

Nutritional
Oral lutein
Lutein and zeaxanthin are carotenoid pigments that contribute to the formation of macular pigment, which is thought to be protective against oxidative damage.[91] A 48-week study tested the effect of oral lutein on CMT in 39 patients with RP. Lutein was found to have no statistically significant effect on CMT in patients with RP with or without CMO.[3]

Oral iodine
While oral iodine has not been trialled specifically for RP-CMO, higher urinary iodine concentration has been observed to be significantly associated with reduced CMT in non-smoking adults with RP-CMO.[92]

Surgical
Laser
In 1987, grid laser photocoagulation was undertaken in one eye of 16 patients with bilateral RP-CMO. Six treated eyes gained one or more lines of vision, while none of the untreated eyes did. Seven untreated eyes lost one or more lines of vision, while none of the treated eyes did. Thirteen of 16 eyes showed decreased fluorescein leakage after treatment.[93] Laser may remove hypoxic degenerating retina, thus reducing VEGF production.[94]

Vitrectomy
In 2003, vitrectomy combined with inner limiting membrane peel was carried out on 12 eyes of 8 patients with RP-CMO refractory to treatment with acetazolamide. The presence or absence of preoperative vitreomacular traction was not confirmed. Mean CMT improved from 478 μm (range, 380–570 μm) preoperatively to 260 μm (range, 177–424 μm) at 6 months. Mean VA improved from 20/115 (range, 20/60–20/400) preoperatively to 20/45 (range, 20/30–20/100) at 6 months.[25]

Conclusions and future directions
RP-CMO commonly complicates RP, however, its exact underlying pathogenesis remains uncertain. Proposed mechanisms that are most likely to be involved include breakdown of the BRB and/or RPE pump mechanism failure and/or Müller cell oedema and dysfunction. When CS are present they are most commonly located in the INL, suggesting that inner BRB dysfunction may have a greater role than the outer BRB, in development of RP-CMO. A better understanding of these mechanisms will facilitate better targeted and likely more efficacious and durable therapies.

Setting up clinical trials for RP-CMO, however, remains a challenge due to its low prevalence, the highly variable course of disease progression, significant genetic and allelic heterogeneity and very slow progression to visual loss. With the majority of studies producing levels of evidence between 3 and 4 and no large RCTs, we remain in a position where there are no studies yet providing high-level evidence for RP-CMO treatments. In the absence of RCTs, the effect of known and unknown confounders cannot be excluded. The majority of studies did not have a control group (level 4 evidence) inherently limiting the validity of findings, as these may be a result of natural history rather than the intervention. Many studies were retrospective which may be affected by recall bias. This review has highlighted the lack of high-quality evidence for RP-CMO treatments. While concrete conclusions cannot be drawn, the evidence currently available suggests that topical CAIs may be used as a first-line approach. Consideration should be given to the possibility of side effects and potential for rebound CMO. Oral CAIs may be a second-line agent, but there is the risk of more side effects.

As there are currently no treatments for the underlying retinal degeneration in RP and given the potentially reversible nature of RP-CMO, there is a real need to better understand disease mechanisms and undertake prospective clinical trials of therapeutic agents to provide the evidence base to improve treatment of RP-CMO. Successful management of CMO should aim to both improve quality and quantity of vision in the short term and slow the rate of vision loss over time.

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