

Table 1: A summary to date of the pharmacological, nutritional and surgical interventional studies for RP-CMO

Authors	Year published	Study design	N (pts)	Intervention	Results	Comments	Level of evidence*
Carbonic Anhydrase Inhibitors							
Liew <i>et al</i>	2015	Retrospective cohort	81	125 eyes of 64 patients received topical dorzolamide, 32 eyes of 17 patients received oral acetazolamide 250mg BD or 500mg OD	CMT reduction greater in dorzolamide group than acetazolamide group VA improvement both groups		3B
Ginead <i>et al</i>	2010	Retrospective case series	32	Topical dorzolamide 2% TDS or BD for 6 - 58 months	CMT improvement more than VA improvement		4
Fishman <i>et al</i>	1994	Prospective, placebo-controlled, double-masked, crossover design	17	Methazolamide or placebo taken for 3 weeks Sub-group received additional 3/12 methazolamide treatment	Angiographic improvement more than VA improvement No change in VA with extended methazolamide treatment		3B
Grover <i>et al</i>	2006	Prospective, non-randomised	15	Topical dorzolamide TDS for at least 4 weeks BE	CMT improvement more than VA improvement	Recurrence in 4 patients	4

Fishman <i>et al</i>	1989	Prospective, masked, cross-over	12	Oral acetazolamide or placebo for 2 week periods	BCVA improved, CMT reduced. Improvement angiographically in almost 50%	500 mg/day acetazolamide more effective than 250 mg/day	3B
Ikeda <i>et al</i>	2013	Prospective	10	Topical dorzolamide 1% TDS BE for 18 months	CMT reduction with majority effect lasting 18 months. Macular sensitivity improvement No significant change in BCVA	Recurrence in 5 eyes between 12- 18 months	4
Ikeda <i>et al</i>	2012	Prospective	9	Topical dorzolamide 1% TDS BE for 6 months	CMT reduction greater than macular sensitivity improvement No difference in BCVA		4
Fishman <i>et al</i>	2007	Prospective cohort	8	Topical dorzolamide 2% TDS BE for 7 - 15 months	CMT improvement more than VA improvement	Patients previously included in study by Grover <i>et al</i> 2006 Two patients experienced rebound CMO	4
Orzalesi <i>et al</i>	1993	Prospective pilot	7	Oral acetazolamide for 2 weeks then reduced /	VA improvement	Effect independent of reduction	4

				maintained / increased according to response Follow-up between 3 weeks – 16 months		of CMO on FFA	
Apushkin <i>et al</i>	2007	Prospective cohort	6	500 mg oral acetazolamide	CMO improved at 3-5 weeks	Recurrence at 8-12 weeks	4
Grover <i>et al</i>	1997	Prospective, double-masked, crossover	5	Topical dorzolamide or placebo given for 4 weeks followed by crossover treatment for 4 weeks Oral acetazolamide then given for 2 weeks	VA no change using dorzolamide VA improvement using acetazolamide CMO and FFA improvement more marked using acetazolamide than dorzolamide	4 week flush-out period in between each phase	3B
Pacella <i>et al</i>	2014	Case reports	3	Topical dorzolamide BE	CMT improvement within 7 - 20 days No significant change in VA observed		4
Thobani & Fishman	2011	Retrospective case series	3	Only 2 patients with RP and CMO. Recurrence whilst taking 500mg oral	Improvement of macular oedema. VA not		4

				acetazolamide. Re-introduced to treatment after period of discontinuation	mentioned in RP patients.		
Fishman <i>et al</i>	1993	Prospective	3	Oral methazolamide 50mg BD	Slight improvement BCVA	Recurrence at 6-12 weeks	4
Chen <i>et al</i>	1990	Case study	1	Oral acetazolamide	BCVA improvement RE only Improvement of CMO BE		4
Steroids							
Wang <i>et al</i>	2003	Retrospective chart review	50	Only 2 of these patients were diagnosed with RP-CMO. Single bilateral intravitreal injection of triamcinolone given.	Improvement in CMT and VA.		4
Scorolli <i>et al</i>	2007	Prospective, nonrandomised, comparative trial	40	20 eyes received a unilateral single intravitreal injection of triamcinolone acetate, 20 eyes who declined were used as controls 1 year follow-up	No significant change in BCVA CMT reduction	IOP increased after the first day, at 1 month, and at 3 months in both groups but no significant increase afterwards	3B

Giusti <i>et al</i>	2002	Pilot	10	Treated for 1 year with oral deflazacort	Near VA, FFA and perimetry improved significantly Distance VA varied only slightly		4
Ozdemir <i>et al</i>	2005	Prospective small series	5	IVTA given Follow up 6-8 months	CMT improvement No improvement VA seen	Refractory to oral acetazolamide Recurrence in 3 patients between 3 – 6 months	4
Srouf <i>et al</i>	2013	Prospective	3	Intravitreal dexamethasone implant (Ozurdex) Follow-up for 6 months	CMT and VA improvement	Refractory to oral acetazolamide, sub-tenon triamcinolone, topical NSAID Recurrence at 3 months in 2 patients requiring re-treatment	4
Schaal <i>et al</i>	2016	Case study	1	Right eye received a sub-tenon injection of triamcinolone A 2 nd sub-tenon injection was performed in the right eye 8	VA and CMT improvement 2-weeks post 1 st injection Mild rebound CMO at 8 months following 1 st injection	Refractory to oral acetazolamide 500mg OD for 2 years and topical 2% dorzolamide TDS together with topical	4

				months following the 1 st injection		0.09% bromfenac OD for 1 year IOP increase at 4 months controlled with 0.5% timolol BD	
Ahn et al	2014	Case study	1	0.7mg intravitreal Ozurdex	BCVA improved OCT central thickness improved	Refractory to oral acetazolamide and intravitreal bevacizumab	4
Patil L & Lotery A.J	2014	Case study	1	Treated with 0.7mg of intravitreal injection of dexamethasone implant (Ozurdex)	VA and CMT improvement, maintained after 10 months Exudation at the disc and the inferior retina resolved.	Patient from De Salvo 2011 study. RE RP-CMO and Coats'-like exudative RD. Refractory to oral acetazolamide, topical dorzolamide, orbital floor injection of depo-medrone and CMO recurrence following initial success	4

						with cryotherapy.	
Alhassan, M & Quintyn, J.C	2013	Case study	1	Single unilateral intravitreal dexamethasone implant (Ozurdex)	Bilateral BCVA improvement and CMT reduction at 1 month	Refractory to oral acetazolamide 500mg OD and topical brinzolamide BD	4
Barge <i>et al</i>	2013	Case study	1	Bilateral intravitreal injections of triamcinolone (IVTA) before sub-tenon depot of triamcinolone	BCVA improved CMT reduced IOP raised BE	Refractory to oral acetazolamide and topical ketoralac Recurrence at 2-5 months post-IVTA	4
Buchaim <i>et al</i>	2013	Case study	1	Bilateral intravitreal dexamethasone implant (Ozurdex)	BCVA improved No CMO at 4 months	Previously received 19 IVTAs RE and 13 IVTAs LE but with decreasing therapeutic effect	4
Saati <i>et al</i>	2013	Case study	1	Bilateral intravitreal dexamethasone implant (Ozurdex)	CMO resolution at 1/52 VA improvement	Refractory to topical dorzolamide Recurrence BE between 2-3 months	4
Urban <i>et al</i>	2009	Case study	1	4 x unilateral intravitreal triamcinolone	FT reduction within 3 months	Intolerant to oral acetazolamide	4

				repeated every 4 months	BCVA improvement Endophthalmitis following 4th IVT diagnosed day of RTA Traumatic inferior RD, migration of triamcinolone into sub-retinal space. Scleral buckling and vitrectomy performed Resolution of CMO observed, however, BCVA remained at 20/100.	Previous autologous plasmin enzyme–assisted vitrectomy without ILM peel	
Kim <i>et al</i>	2006	Case study	1	2 x Intravitreal triamcinolone (4mg/0.1ml) RE cataract surgery at 3 months post-1 st IVTA	1 st IVTAs resolution of CMO by 1/12. No significant change in VA 2nd IVTAs resolution of CMO by 2 weeks	Refractory to oral acetazolamide 500mg for 1 year and sub-tenon triamcinolone 40mg Recurrence in BE at 11 months post 1 st IVTA.	4
Minella <i>et al</i>	2006	Case study	1	IVTA	CMT reduced		4

				Follow-up for 6 months	No significant change FERG amplitude/phase VA showed a significant tendency to improve		
Sallum <i>et al</i>	2003	Case study	1	Bilateral IVTAs	CMO resolution between 30 - 40 days VA improvement LE only	Refractory to oral acetazolamide Recurrence at 6 months	4
Saraiva <i>et al</i>	2003	Case study	1	Bilateral IVTAs	CMO reduction VA improvement LE only	Refractory to oral acetazolamide Recurrence at 6 months	4
Non-steroidal anti-inflammatory together with steroid or CAI							
Lemos-Reis <i>et al</i>	2015	Prospective, randomized and interventional	18	15 eyes received topical ketorolac and 13 eyes received topical dorzolamide for 12 months	No significant change in CMT in either group Improvement BCVA both groups at 6/12 but reduced in dorzolamide group at 1 year		3B
Park <i>et al</i>	2013	Case study	1	Topical prednisolone and ketorolac 3 months	VA improvement and resolution of CMO at 3 months	Treatment re-introduced at 6 months due to recurrence of CMO	4

Intravitreal anti-vascular endothelial growth factor							
Artunay <i>et al</i>	2009	Prospective cohort	30	15 eyes received intravitreal ranibizumab, 15 eyes remained off treatment	CMT improved but no change in BCVA at 6 months	Refractory to oral acetazolamide	3B
Yuzbasioglu <i>et al</i>	2009	Prospective	7	Intravitreal bevacizumab	CMT and VA improvement		4
Melo <i>et al</i>	2007	Case reports	2	Single unilateral intravitreal bevacizumab 1st patient received IVTA at 3/12 post IVT 2nd patient underwent cataract surgery/IVTA at 1 month post IVT	Unchanged CMT, VA same or worse following IVT 1st patient CMT improved following IVTA 2nd patient: VA reduced due to lens opacity. VA and CMT improvement documented at 3 months post-cataract surgery	Previously received 2 or 3 IVTAs with transient VA improvement	4
Strong <i>et al</i>	2016	Case report	1	Bilateral intravitreal injections of Eylea	CMT improvement	Refractory to topical dorzolamide. Minimal response previously to intravitreal ranibizumab.	4

Moustafa <i>et al</i>	2015	Case study	1	Single unilateral intravitreal injection of aflibercept	VA and CMT improvement No significant multifocal ERG changes	Improvements maintained at 6 months	4
Shah <i>et al</i>	2010	Case study	1	3 x Intravitreal unilateral injections of ranibizumab	CMT reduction BCVA improvement after 3 rd IVT	Unable to tolerate PO acetazolamide Refractory to topical dorzolamide Recurrence at 3 months after 3 rd IVT	4
Querques <i>et al</i>	2009	Case study	1	Single unilateral intravitreal injection of pegaptanib sodium 0.3mg given whilst PO acetazolamide continued	VA and CMT improvement No recurrence of CMO seen at 4 months post-IVT	Refractory to oral acetazolamide	4
Oral lutein							
Adackapara <i>et al</i>	2008	Prospective	39	Patients already enrolled in phase I/II clinical trial with double-masked, placebo-lutein, crossover design	No significant effect on CMT in patients with, or without CMO	19 / 39 patients had RP-CMO, 20 /39 patients had RP without CMO	3B
Laser							

Newson <i>et al</i>	1987	Prospective pilot	16	Unilateral grid photocoagulation performed Follow-up between 4 - 21 months	Decreased dye accumulation on FFA VA better in treated compared to untreated eyes		4
Vitrectomy							
Garcia-Arumi <i>et al</i>	2003	Prospective non-comparative case series	8	Pars plana vitrectomy with ILM peel	VA and CMT improvement	Refractory to oral acetazolamide 250mg BD for 1 month	4
Other							
Siqueira <i>et al</i>	2013	Case report within phase 2 study	1	Unilateral intravitreal autologous BM-derived hematopoietic stem cell transplantation	CMO resolution and VA/macular sensitivity improvement	Refractory to oral acetazolamide and topical dorzolamide	4
De Salvo <i>et al</i>	2011	Case study	1	Cryotherapy applied to infero-temporal quadrant of RE retina	Slight increase BCVA with mild residual CMO at 6 months	Coats'-like exudative RD. Refractory to oral acetazolamide , topical dorzolamide and orbital floor injection depomedrone	4

*Oxford Centre for evidence-based medicine – Levels of evidence (March 2009)

Abbreviations

BCVA: best corrected visual acuity

BM: bone marrow

CMO: cystoid macular oedema

CMT: central macular thickness

ERG: electroretinogram

FERG: focal electroretinogram

FFA: fundus fluorescein angiogram

FT: foveal thickness

ILM: internal limiting membrane

IOL: intra-ocular lens

IOP: intra-ocular pressure

IVT: intravitreal treatment

IVTA: intravitreal triamcinolone

NSAID: non-steroidal anti-inflammatory

OCT: optical coherence tomography

OD/BD/TDS: once per day/twice per day/three times per day

Pts: patients

RD: retinal detachment

RE/LE/BE: right eye/left eye/both eyes

RTA: road traffic accident

VA: visual acuity