Review Article

Carbonic anhydrase inhibitors in the management of macular edema: A review of the literature

Marianne L. Shahsuvaryan [1]

[1] *Yerevan State Medical University, Republic of Armenia*

ABSTRACT

Background: Macular edema (ME) is a vision-threatening condition that commonly develops as a consequence of ocular diseases, including age-related macular degeneration, retinal vaso-occlusion of the central retinal vein and its branches, diabetic retinopathy, central serous chorioretinopathy, uveitis, retinitis pigmentosa, pseudophakia, ocular trauma, and drug toxicity. The treatment of ME remains challenging, although steroids and vascular endothelial growth factor inhibitors are available. Cost-effective therapy using a noninvasive administration route is required. This study aimed at reviewing the role of carbonic anhydrase inhibitors (CAIs) in the management of ME.

Methods: A literature search was conducted using PubMed/MEDLINE and Google Scholar for studies from January 2000 to March 2022. The following keywords were used in various combinations: "macular edema", "carbonic anhydrase", "carbonic anhydrase inhibitors", "acetazolamide", "dorzolamide", and "brinzolamide".

Results: Articles with high or medium clinical relevance were selected for this review. We found that multiple studies have demonstrated the relevance and efficacy rates of CAIs in the management of ME. Most published studies focused on acetazolamide and dorzolamide, with nearly all studies reporting therapeutic responses.

Conclusions: ME is the leading cause of vision loss and requires noninvasive and cost-effective pharmacotherapy. With progress in the understanding of ME, particularly the role of carbonic anhydrase as a key driver, CAIs are the focus of research. Further optimization of the choice of CAIs and retinal bioavailability, potentially with nanoparticle formulations, is required to enable the effective management of ME. Further research is warranted to address the therapeutic effects of CAIs in different formulations.

KEYWORDS

retina, macular edema, cystoid macular edema, VEGFs, vascular endothelial growth factors, steroids, carbonic anhydrase, carbonic anhydrase inhibitor, acetazolamide, dorzolamide, brinzolamide

INTRODUCTION

Macular edema (ME) is a leading vision-threatening condition that commonly develops as a complication of various eye diseases, including age-related macular degeneration, retinal vaso-occlusion, occlusion of the central retinal vein and its branches, diabetic retinopathy, central serous chorioretinopathy, uveitis, retinitis pigmentosa (RP), pseudophakia, ocular trauma, and drug toxicity [1-6].

ME manifests as swelling within or under the macula resulting from intercellular and intracellular fluid accumulation in the inner and outer plexiform retinal layers due to increased permeability [1-5]. The pathophysiology of ME involves a chain of inflammatory links in retinal microvascularity and the disintegration of tight junctions between cell walls. Various inflammatory mediators and cytokine growth factors are responsible for retinal swelling [2-5].

Correspondence: Marianne L. Shahsuvaryan, Professor of Ophthalmology, Yerevan State Medical University, Republic of Armenia. Email: mar_shah@hotmail.com
ORCID iD: https://orcid.org/0000-0003-3627-4137

How to cite this article: Shahsuvaryan ML. Carbonic anhydrase inhibitors in the management of macular edema: A review of the literature. Med Hypothesis Discov Innov Ophthalmol. 2022 Spring; 11(1): 34-41. https://doi.org/10.51329/mehdiophthal1443

Received: 11 March 2022; Accepted: 01 April 2022

ME may be an endpoint for conditions affecting the vessel wall, fluidics, and pumping actions in the neurosensory retina [2, 3]. It may manifest as diffuse ME due to generalized swelling of the macula or cystoid ME (CME) due to cyst formation in the petaloid pattern [2]. Advancements in ME therapy include intravitreal injections of antiangiogenics and intravitreal steroid implants [7]. However, the new modalities have disadvantages of side effects, unresponsiveness, the requirement of an unlimited number of injections, and low cost-effectiveness.

Therefore, this study aimed at reviewing the role of carbonic anhydrase inhibitors (CAIs) in the management of ME.

METHODS

We conducted a literature search on PubMed/MEDLINE and Google Scholar for studies conducted from January 2000 to March 2022. The following keywords were used in various combinations: "macular edema", "carbonic anhydrase", "carbonic anhydrase inhibitors", "acetazolamide", "dorzolamide", and "brinzolamide".

RESULTS

We found that studies have demonstrated the suitability and efficacy rates of CAIs in the management of ME. Most published studies have focused on acetazolamide and dorzolamide, with nearly all studies reporting therapeutic responses. Tables 1 [8-20] and 2 [10, 11, 15, 21-35] summarize studies on the efficacy of systemic and topical CAIs in ME, respectively.

Carbonic anhydrase (CA) is a prevalent enzyme in the body that acts as a mediator of inflammation. In addition to accumulation in the ciliary body epithelium, it is found in retinal cells, such as the retinal pigment epithelium (RPE), Muller cells, and red–green cones. Thus, it may be a potential therapeutic option [36-39]. The universal pathophysiology of CME is characterized by the suppression of K^+ channels in Muller cells [40]

Table 1. Summary of included studies on the efficacy of systemic carbonic anhydrase inhibitor acetazolamide in the management of macular edema

Author (Year of Publication)	Study design	Diagnosis	Therapeutic response
Lee and Gallemore (2021) [8]	Case report	SRF following macular hole repair	Persistence despite CAI administration and resolution by adding combined oral spironolactone and a topical NSAID.
Mackin et al. (2020) [9]	Case series	Idiopathic full-thickness macular hole with a diameter < 200 μm and CME	Hole closure with topical corticosteroids NSAIDs, and CAIs and oral CAIs.
Pepple et al. (2019) [10]	Case series	Uveitic or pseudophakic CME	Anatomical and visual improvement.
Bakthavatchalam et al. (2018) [11]	Systematic review	RP-CME	Effective.
Lam et al. (2018) [12]	Case report	Pseudophakic CME with a macular hole	Resolution.
Borruat et al. (2018) [13]	Case series	MME in optic neuropathy	Resolution with no change in visual function but recurrence after treatment cessation.
Pomykala et al. (2016) [14]	Case report	Recurrent RP-CSR	Resolution.
Liew et al. (2015) [15]	Cohort study	RP-CME	Improvement in OCT findings.
Chen et al. (2014) [16]	Case series	ME in macular telangiectasia type 2	Reduction in cystoid cavities and central macular thickness without change in visual acuity.
Apushkin et al.(2007) [17]	Case series	RP-CME	Initial objective improvement in CME but recurrence in three of six patients after extended use of acetazolamide for 2–3 months.
Chung et al. (2006) [18]	Case series	RP-CME	Improvement in OCT findings with variable recovery in BCVA.
Schilling et al. (2005) [19]	Prospective	Uveitis chronic CME	Effective and safe.
Pikkel et al. (2002) [20]	Non-randomized prospective comparative trial	CSR	Mean time of subjective visual improvement and clinical resolution shorter in CAI-treated than untreated eyes with a similar recurrence rate.

Abbreviations: SRF, subretinal fluid; CAI, carbonic anhydrase inhibitor; NSAID, non-steroidal anti-inflammatory drug; CME, cystoid macular edema; RP, retinitis pigmentosa; MME, microcystic macular edema; CSR, central serous retinopathy; OCT, optical coherence tomography; ME, macular edema; BCVA, best-corrected visual acuity.

Table 2. Summary of included studies on the efficacy of topical carbonic anhydrase inhibitors in the management of macular edema

Author (Year of Publication)	Study design	Diagnosis	Therapeutic response
Dorzolamide			
Shimokawa et al. (2022) [21]	Case series	RP-CME	Recurrence in 14 of 40 patients with a risk factor of a high baseline central subfield thickness.
Badawi et al. (2021) [22]	Prospective, non-randomized	Diabetic CME	Effective and safe.
Kokame et al. (2021) [23]	Case series	Macular hole	Resolution but recurrence in two of seven patients.
Liew et al. (2020) [24]	Prospective, interventional, non-randomized, controlled study	Chronic CSR	Rapid resolution in the treatment group but a similar change in BCVA at 3 months.
Pepple et al. (2019) [10]	Case series	Uveitic or pseudophakic ME	Anatomical and visual improvement.
Marques and Sousa (2019) [25]	Case report	Macular hole with multiple intraretinal cysts	Complete closure of the macular hole after 1 month with no significant change in VA due to the long-standing nature of the hole.
Kim et al. (2018) [26]	Case report	CME in hydroxychloroquine retinopathy	Case 1, resolution in both eyes with no recurrence and improvement in VA. Case 2, resolution in both eyes and improvement in VA at 5 months, with recurrence at 2 months after discontinuations and resolution with restarting the eye drop.
Dwivedi and Tiroumal (2018) [27]	Case report	Paclitaxel-related CME	Resolution in both eyes and improvement in BCVA.
Bakthavatchalam et al. (2018) [11]	Systematic review	RP-CME	Effective.
Lima-Gomez et al. (2015) [28]	Prospective, double blind, experimental, comparative study	DME after photocoagulation	Effective.
Lemos Reis et al. (2015) [29]	Randomized clinical trial	ME in RP and Usher syndrome	Improvement in BCVA.
Liew et al. (2015) [15]	Cohort study	RP-CME	Improvement in OCT findings.
Ikeda et al. (2013) [30]	Case series	RP-CME	Effective.
Ikeda et al. (2012) [31]	Case series	RP-CME	Effective.
Genead and Fishman (2010) [32]	Case series	CME in RP and Usher syndrome	Anatomical and visual improvement.
Fishman and Apushkin (2007) [33]	Case series	RP-CME	Sustained improvement in OCT findings in at least one eye of of eight patients,both eyes of four patients, with recurrence in both eyes of two patients, sustained improvement in one eye, and recurrent CME in the fellow eye of two patients. Clinically significant improvement in VA of at least one eye in three patients.
Grover et al. (2006) [34]	Prospective, non-randomized clinical trial	RP-CME	Effective but follow-up required because of the rebound phenomenon.
Brinzolamide			
Alkin et al. (2013) [35]	Retrospective cohort study	RP-CME	Improvement in OCT findings, with no significant change in BCVA.

Abbreviations: RP, retinitis pigmentosa; CME, cystoid macular edema; CSR, central serous retinopathy; BCVA, best-corrected visual acuity; ME, macular edema; VA, visual acuity; DME, diabetic macular edema; OCT, optical coherence tomography.

and increased synthesis of CA-1 and vascular endothelial growth factor, leading to inflow and outflow dysregulations in the macular zone at the Henle's fiber and inner nuclear layers, respectively [40]. In diabetes, retinal and subretinal fluid accumulation due to hypercapnia and elevated CAs relax tight cell junctions between the RPE and remnant retinal layers [41, 42].

CAIs move fluid from the retina into the choroid through the RPE by acidifying the subretinal space [36, 39]. The decongestant effect of CAIs is achieved by subretinal space acidification and accelerated fluid hydrodynamics through the RPE [43-45]. The inflammatory process causes vascular and RPE leakage, which manifests as CME. Systemic CAIs subside CME by increasing ion and fluid transports from the retina. Owing to their effect on bicarbonate-coupled ion transport and vessel dilatation, reduced serum K^+ levels could cause dehydration [40].

DISCUSSION

Systemic CAIs in ME

Systemic CAIs have been established as a treatment modality for ME, although systemic side effects have been widely reported [36-38]. Acetazolamide enables fluid pumping from the subretinal space to the choroids through the RPE [39]. It is effective in resolving pseudophakic CME and closing full-thickness macular hole [12]. In similar select cases with remnant subretinal fluid after topical combination therapy, including steroids, non-steroidal anti-inflammatory drugs (NSAIDs), and dorzolamide, acetazolamide was added to accentuate the effect. Holes closed with topical corticosteroids, NSAIDs, CAIs, and oral CAIs [9].

In the case of dome-shaped maculopathy and macular hole, which were surgically repaired, acetazolamide was administered postoperatively for 2 months to facilitate fluid resorption. However, subretinal fluid persisted despite CAI administration and was resolved by adding combined oral spironolactone and topical NSAIDs [8]. Acetazolamide resulted in anatomical and visual improvements in refractory pseudophakic and uveitis-related CME [10, 46].

A pilot study on the treatment of diabetes-related CME with acetazolamide had limitations in eligible patients and follow-up duration [47]. Improved fluorescein angiography and perimetric findings suggested the efficacy of acetazolamide, despite only slight vision improvement.

Pikkel et al. [20] reported the effect of acetazolamide on the course of central serous retinopathy (CSR) in a prospective non-randomized trial comparing 15 acetazolamide-treated and 7 untreated (control) CSR cases with a 24-month follow-up and found that acetazolamide treatment accelerated the speed of recovery. However, it did not affect the endpoint vision or recurrence rate of CSR [20]. In contrast, acetazolamide has been used in patients with optic neuropathy accompanied by microcystic ME [13]. Monitoring retinal layer thickness by optical coherence tomography (OCT) during treatment showed decreased thickness in all 14 eyes of the 11 patients, although visual acuity (VA) remained unchanged and ME recurred after treatment cessation.

Recurrent CSR associated with RP has been successfully treated with acetazolamide [14]. Positive anatomical outcomes, including reduced central macular thickness and macular cystic cavities, have been documented in macular telangiectasia, despite unchanged VA. Retinal thickness decreased in cases treated with acetazolamide, unlike those treated with methazolamide [16].

A recent multicenter prospective study comparing dexamethasone implants and oral acetazolamide in RP-related CME demonstrated a lower efficacy of CAIs, but the results required further assessment [48].

The long-term effect (mean follow-up of 3.1 years) of acetazolamide therapy in uveitis-related CME was evaluated in 33 eyes treated with acetazolamide monotherapy for quiet uveitis and 19 eyes treated with systemic anti-inflammatory therapy in addition for chronic uveitis [19]. Both groups showed significantly increased VA, with relatively better results in eyes with quiet uveitis [19]. Levin et al. found active uveitis at presentation with uveitic ME to be a good prognostic factor. Studies have shown a strong correlation between visual improvement and subsidence of the anterior chamber or vitreous cells and vitreous haze over time [49]. Ranibizumab is another potential treatment option for refractory ME in quiet uveitis, with a report of improved vision and central retinal thickness at 3 and 6 months without side effects [50].

Recent OCT studies on acetazolamide use in uveitic or pseudophakic CME demonstrated anatomical and visual benefits [10]. CME in RP causes vision loss in 10%–50% of patients [51-56]. Anti-CA antibodies and CME [57] were correlated in patients with RP with CME (hereafter referred to as "RP-CME"), confirming the efficacy of CAIs in RP-CME. The efficacy of acetazolamide in vision improvement has been inconsistent in some retinal dystrophies [58]. CME showed initial objective improvement in a case series of RP-CME. However, extended use of acetazolamide for 2–3 months caused a recurrence of CME in three of six patients [17].

A retrospective study [15] on systemic and topical CAIs in RP-CME documented positive OCT changes in 28% of the eyes of patients treated with acetazolamide compared to 40% of the eyes of patients treated with topical dorzolamide. Predictive factors for success in therapy were autosomal recessive RP and increased central macular thickness at presentation [15]. Acetazolamide (125 or 250 mg/day for 4–12 months) in patients with RP improved OCT-diagnosed CME, with variable recovery in best-corrected VA [18].

Topical CAIs in ME

The efficacy of topical monotherapy with CAIs has been reported in several conditions [59]. The effect of CAIs on retinal edema has been shown in RP with Usher syndrome [32]; choroideremia [60]; syndromic retinal dystrophies, such as Alström syndrome [61]; CME after cataract extraction [62]; and serous retinal detachment secondary to a dome-shaped macula [63].

The efficacy of several topical CAIs has been evaluated. A prospective, non-randomized clinical trial [34] involving 15 patients with RP-CME who received dorzolamide thrice daily for at least 4 weeks found dorzolamide to be effective. However, a rebound phenomenon was observed in some patients with long-term therapy, indicating the necessity of a careful follow-up. In a study limited by the small sample size and short follow-up duration, dorzolamide was effective in patients with RP [33].

The effect of topical dorzolamide on VA and CME verified by OCT was assessed in 32 patients with RP and Usher syndrome using a long-term follow-up [32]. Central foveal thickness reduced in most patients, and vision improved in one-third of the patients. Similarly, the prolonged use (> 1 year) of dorzolamide was effective in RP-CME, supporting its use as a first-line treatment [30, 31]. A systematic review [11] demonstrated the efficacy of oral (acetazolamide and methazolamide) and topical (dorzolamide and brinzolamide) CAIs in RP-CME, with priority to acetazolamide as the most potent agent, replaced by dorzolamide only in cases of systemic side effects due to oral therapy. Salvatore et al. [64] showed that CAIs are effective in retinal dystrophies, although not in all.

A meta-analysis concluded that CAIs significantly reduced central macular thickness in RP-CME, although the effect on VA was controversial and warranted multicenter prospective randomized controlled trials [65]. A retrospective study showed gradually decreased efficacy of 1.0% topical dorzolamide in RP-CME, highlighting increased baseline central subfield thickness as a poor prognostic factor for relapse of edema [21]. Dorzolamide improved best-corrected VA in patients with RP or Usher syndrome with OCT-diagnosed ME [29].

A double-blind comparative study was performed on dorzolamide use in patients with diabetes with focal ME who underwent photocoagulation. In eligible patients with diabetic ME and focal leakage, the pigment epithelium was unaltered, and the retina was overhydrated [28]. Three weeks after photocoagulation, the patients were randomly assigned to the study group treated with dorzolamide thrice daily for 3 weeks, and the control group treated with placebo. Dorzolamide was effective in reducing retinal thickness compared to placebo. The authors argued that microaneurysm closure by preliminary photocoagulation could facilitate fluid outflow into the choroid by topical CAIs [28]. Fluid is also excreted from neighboring capillaries with increased capacity owing to vasodilation after photocoagulation. This procedure contributes to the gene expression of angiotensin II receptor type 2 in the retina [66]. Venous dilation is caused by CAIs [67] and is more prominent with dorzolamide use than with acetazolamide [68].

A study on the impact of monotherapy with 2% topical dorzolamide thrice daily for 1 month on VA and central macular thickness in diabetic CME showed significant improvement in VA and decline in central macular thickness at 3 months [22]. The authors advocated the use of dorzolamide in diabetic CME, emphasizing its safety, efficacy, and affordability. However, this was the first study on monotherapy with dorzolamide for diabetic CME, and further large-scale randomized controlled trials are required.

A prospective non-randomized comparative trial involving 18 dorzolamide-treated (over 3 months) and 15 untreated (control) patients with CSR evaluated the effect of dorzolamide on the course of chronic CSR [24]. The results showed that dorzolamide treatment for CSR facilitated subjective and objective recovery without affecting visual functions. In another study, dorzolamide showed an anti-inflammatory effect on ME resorption in patients with epiretinal membrane who underwent simultaneous vitrectomy, phacoemulsification, and intraocular lens implantation [69]. The authors documented a substantial decrease in central macular thickness after dorzolamide use at 1 month and a mean aqueous flare at 2 weeks postoperatively. The anti-inflammatory effect of dorzolamide on proinflammatory cytokine interleukin-6 has been investigated [69, 70]. Hypothesizing that a macular hole results from the hydration of the retina in addition to the vitreous and internal limiting membrane tractional forces. Su et al. [71] treated patients with small (< 300 μm) full-thickness macular holes with topical dorzolamide-timolol for 1 month and demonstrated hole closure.

Dorzolamide efficacy in hydroxychloroquine retinopathy-related CME was assessed in two cases with well-documented therapeutic responses [26]. Similar results were obtained in the case of CME related to the chemotherapeutic drug paclitaxel, suggesting that topical dorzolamide may have therapeutic value for resorption of edema and recovery of vision [27].

A retrospective study [35] assessed whether or not the topical application of 1% brinzolamide in RP-CME could improve vision. The results showed no positive effects; however, central macular thickness decreased. Brinzolamide in combination with difluprednate 0.05% and nepafenac 0.1% was effective in CME cases related to Irvine-Gass syndrome, diabetic retinopathy, and branch retinal vein occlusion [62]. Dorzolamide or brinzolamide in combination with ketorolac and prednisolone acetate is effective in full-thickness macular hole management [9]. Another study [72] reported encouraging results, particularly in small holes with CME, consistent with studies by Marques and Sousa [25] and Kokame et al. [23].

The consensus is that CAIs are a promising and viable therapeutic option for ME. This review included only clinical studies on the management of ME using systemic and topical CAIs. The limitations of the included studies were the small sample size and unavailability of double-blind randomized multicenter studies. Further, the limitation of this review is that it is a narrative review. Considering the low permeability of CAIs through the retinal barrier [73], future pharmaceutical studies are required on increased drug retinal bioavailability through improved solubility and nanoparticles as nanocarriers [74], followed by randomized controlled studies on their efficacy and outcomes in ME.

CONCLUSIONS

ME commonly develops in several ocular diseases that require noninvasive, cost-effective pharmacotherapy. With progress in the understanding of ME, particularly the role of CA as a key driver, CAIs are the focus of research. To date, most published studies have focused on acetazolamide and dorzolamide, with nearly all studies reporting therapeutic responses. However, further optimization of the choice of CAIs and retinal bioavailability, potentially with nanoparticle formulations, is required to enable the effective management of ME.

ETHICAL DECLARATIONS

Ethical approval: No ethical approval was required.
Conflict of interest: None.

FUNDING

None.

ACKNOWLEDGEMENTS

None.

REFERENCES

1. Kleinman ME, Baffi JZ, Ambati J. The multifactorial nature of retinal vascular disease. Ophthalmologica. 2010;224 Suppl 1(Suppl 1):16-24. doi: 10.1159/000315152 pmid: 20714177
2. Johnson MW. Etiology and treatment of macular edema. Am J Ophthalmol. 2009;147(1):11-21.e1. doi: 10.1016/j.ajo.2008.07.024 pmid: 18789796
3. Daruich A, Matet A, Moulin A, Kowalczuk L, Nicolas M, Sellam A, et al. Mechanisms of macular edema: Beyond the surface. Prog Retin Eye Res. 2018;63:20-68. doi: 10.1016/j.preteyeres.2017.10.006 pmid: 29126927
4. Grzybowski A, Markeviciute A, Zemaitiene R. Treatment of Macular Edema in Vascular Retinal Diseases: A 2021 Update. J Clin Med. 2021;10(22):5300. doi: 10.3390/jcm10225300 pmid: 34830582
5. Tranos PG, Wickremasinghe SS, Stangos NT, Topouzis F, Tsinopoulos I, Pavesio CE. Macular edema. Surv Ophthalmol. 2004;49(5):470-90. doi:10.1016/j.survophthal.2004.06.002 pmid: 15325193
6. Yoshimura T, Sonoda KH, Sugahara M, Mochizuki Y, Enaida H, Oshima Y, et al. Comprehensive analysis of inflammatory immune mediators in vitreoretinal diseases. PLoS One. 2009;4(12):e8158. doi: 10.1371/journal.pone.0008158 pmid: 19997642
7. Wei Q, Chen R, Lou Q, Yu J. Intravitreal corticosteroid implant vs intravitreal ranibizumab for the treatment of macular edema: a meta-analysis of randomized controlled trials. Drug Des Devel Ther. 2019;13:301-307. doi: 10.2147/DDDT.S184520 pmid: 30666092
8. Lee S, Gallemore RP. Macular Hole Surgery in Dome-Shaped Maculopathy. Int Med Case Rep J. 2021;14:493-496. doi: 10.2147/IMCRJ.S282118 pmid: 34335059
9. Mackin A, Sokol J, Komati R, Schechet SA, Farooq A, Skondra D. Medical Treatment of Full-Thickness Macular Holes with Drop Regimen–The University of Chicago Experience. Investigative Ophthalmology & Visual Science. 2020;61(7):4379-. Link
10. Pepple KL, Nguyen MH, Pakzad-Vaezi K, Williamson K, Odell N, Lee C, et al. Response of inflammatory cystoid macular edema to treatment using oral

acetazolamide. Retina. 2019;39(5):948-955. doi: 10.1097/IAE.0000000000002044 pmid: 29346240
11. Bakthavatchalam M, Lai FHP, Rong SS, Ng DS, Brelen ME. Treatment of cystoid macular edema secondary to retinitis pigmentosa: a systematic review. Surv Ophthalmol. 2018;63(3):329-339. doi: 10.1016/j.survophthal.2017.09.009 pmid: 28987613
12. Lam D, Srour M, Semoun O, Tilleul J, Souied EH. Resolution of a macular hole complicating a pseudophakic macular edema with nonsurgical treatment. Retin Cases Brief Rep. 2018;12(2):131-135. doi: 10.1097/ICB.0000000000000446 pmid: 27787409
13. Borruat FX, Dysli M, Voide N, Abegg M. Acetazolamide Reduces Retinal Inner Nuclear Layer Thickness in Microcystic Macular Edema Secondary to Optic Neuropathy. Eur Neurol. 2018;79(3-4):150-153. doi: 10.1159/000487665 pmid: 29514169
14. Pomykala M, Rubin P, Rubin JS. Recurrent central serous chorioretinopathy associated with retinitis pigmentosa treated with carbonic anhydrase inhibitors. Retin Cases Brief Rep. 2016;10(3):205-7. doi: 10.1097/ICB.0000000000000225 pmid: 26510001
15. Liew G, Moore AT, Webster AR, Michaelides M. Efficacy and prognostic factors of response to carbonic anhydrase inhibitors in management of cystoid macular edema in retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2015;56(3):1531-6. doi: 10.1167/iovs.14-15995 pmid: 25670491
16. Chen JJ, Sohn EH, Folk JC, Mahajan VB, Kay CN, Boldt HC, et al. Decreased macular thickness in nonproliferative macular telangiectasia type 2 with oral carbonic anhydrase inhibitors. Retina. 2014;34(7):1400-6. doi: 10.1097/IAE.0000000000000093 pmid: 24451922
17. Apushkin MA, Fishman GA, Grover S, Janowicz MJ. Rebound of cystoid macular edema with continued use of acetazolamide in patients with retinitis pigmentosa. Retina. 2007;27(8):1112-8. doi: 10.1097/IAE.0b013e31805f6b79 pmid: 18040255
18. Chung H, Hwang JU, Kim JG, Yoon YH. Optical coherence tomography in the diagnosis and monitoring of cystoid macular edema in patients with retinitis pigmentosa. Retina. 2006;26(8):922-7. doi: 10.1097/01.iae.0000250008.83779.23 pmid: 17031294
19. Schilling H, Heiligenhaus A, Laube T, Bornfeld N, Jurklies B. Long-term effect of acetazolamide treatment of patients with uveitic chronic cystoid macular edema is limited by persisting inflammation. Retina. 2005;25(2):182-8. doi: 10.1097/00006982-200502000-00011 pmid: 15689809
20. Pikkel J, Beiran I, Ophir A, Miller B. Acetazolamide for central serous retinopathy. Ophthalmology. 2002;109(9):1723-5. doi: 10.1016/s0161-6420(02)01157-0 pmid: 12208723
21. Shimokawa S, Murakami Y, Fujiwara K, Funatsu J, Nakatake S, Koyanagi Y, et al. Recurrence rate of cystoid macular edema with topical dorzolamide treatment and its risk factors in retinitis pigmentosa. Retina. 2022;42(1):168-173. doi: 10.1097/IAE.0000000000003286 pmid: 34393209
22. Badawi AE, Mokbel TH, Elhefney EM, Hagras SM, Abdelhameed AG. Efficacy of topical dorzolamide 2% in diabetic cystoid macular edema. Int J Ophthalmol. 2021;14(9):1413-1418. doi: 10.18240/ijo.2021.09.18 pmid: 34540619
23. Kokame GT, Johnson MW, Lim J, Flynn HW Jr, de Carlo TE, Yannuzzi NA, et al. Closure of Full-Thickness Macular Holes Associated with Macular Edema with Medical Therapy. Ophthalmologica. 2021. doi: 10.1159/000516018 pmid: 34182564
24. Liew G, Ho IV, Ong S, Gopinath B, Mitchell P. Efficacy of Topical Carbonic Anhydrase Inhibitors in Reducing Duration of Chronic Central Serous Chorioretinopathy. Transl Vis Sci Technol. 2020;9(13):6. doi: 10.1167/tvst.9.13.6 pmid: 33344050
25. Marques RE, Sousa DC. Macular Hole Closure with Topical Carbonic Anhydrase Inhibitor. Ophthalmol Retina. 2019;3(4):304. doi: 10.1016/j.oret.2019.01.002 pmid: 31014680
26. Kim DG, Yoon CK, Kim HW, Lee SJ. Effect of topical dorzolamide therapy on cystoid macular edema in hydroxychloroquine retinopathy. Can J Ophthalmol. 2018;53(3):e103-e107. doi: 10.1016/j.jcjo.2017.10.022 pmid: 29784170
27. Dwivedi R, Tiroumal S. Possible efficacy of topical dorzolamide in the treatment of paclitaxel-related cystoid macular edema. Retin Cases Brief Rep. 2018;12(1):75-79. doi: 10.1097/ICB.0000000000000433 pmid: 27749791
28. Lima-Gómez V, Bermúdez-Zapata DA, Blanco-Hernández DM. Eficacia de la dorzolamida para reducir el grosor retiniano después de fotocoagulación en el edema macular diabético [Efficacy of dorzolamide in reducing retinal thickness after photocoagulation in diabetic macular oedema]. Cir Cir. 2015;83(1):3-8. Spanish. doi: 10.1016/j.circir.2014.08.001 pmid: 25982601
29. Lemos Reis RF, Moreira-Gonçalves N, Estrela Silva SE, Brandão EM, Falcão-Reis FM. Comparison of topical dorzolamide and ketorolac treatment for cystoid macular edema in retinitis pigmentosa and Usher's syndrome. Ophthalmologica. 2015;233(1):43-50. doi: 10.1159/000368052 pmid: 25428176
30. Ikeda Y, Yoshida N, Notomi S, Murakami Y, Hisatomi T, Enaida H, et al. Therapeutic effect of prolonged treatment with topical dorzolamide for cystoid macular oedema in patients with retinitis pigmentosa. Br J Ophthalmol. 2013;97(9):1187-91. doi: 10.1136/bjophthalmol-2012-303005 pmid: 23782868
31. Ikeda Y, Hisatomi T, Yoshida N, Notomi S, Murakami Y, Enaida H, et al. The clinical efficacy of a topical dorzolamide in the management of cystoid macular edema in patients with retinitis pigmentosa. Graefes Arch Clin Exp Ophthalmol. 2012;250(6):809-14. doi: 10.1007/s00417-011-1904-5 pmid: 22215259
32. Genead MA, Fishman GA. Efficacy of sustained topical dorzolamide therapy for cystic macular lesions in patients with retinitis pigmentosa and usher syndrome. Arch Ophthalmol. 2010;128(9):1146-50. doi: 10.1001/archophthalmol.2010.172 pmid: 20837798
33. Fishman GA, Apushkin MA. Continued use of dorzolamide for the treatment of cystoid macular oedema in patients with retinitis pigmentosa. Br J Ophthalmol. 2007;91(6):743-5. doi: 10.1136/bjo.2006.107466 pmid: 17215269
34. Grover S, Apushkin MA, Fishman GA. Topical dorzolamide for the treatment of cystoid macular edema in patients with retinitis pigmentosa. Am J Ophthalmol. 2006;141(5):850-8. doi: 10.1016/j.ajo.2005.12.030 pmid: 16546110
35. Alkin Z, Özkaya A, Karataş G, Yazici AT, Demirok A. Brinzolamide therapy in cystoid macular edema secondary to retinitis pigmentosa. Retina-Vitreus. 2013; 21:82-86. Link
36. Mishra CB, Tiwari M, Supuran CT. Progress in the development of human carbonic anhydrase inhibitors and their pharmacological applications: Where are we today? Med Res Rev. 2020;40(6):2485-2565. doi: 10.1002/med.21713 pmid: 32691504
37. Kumar S, Rulhania S, Jaswal S, Monga V. Recent advances in the medicinal chemistry of carbonic anhydrase inhibitors. Eur J Med Chem. 2021;209:112923. doi: 10.1016/j.ejmech.2020.112923 pmid: 33121862
38. Supuran CT. Emerging role of carbonic anhydrase inhibitors. Clin Sci (Lond). 2021;135(10):1233-1249. doi: 10.1042/CS20210040 pmid: 34013961
39. Supuran CT. Multitargeting approaches involving carbonic anhydrase inhibitors: hybrid drugs against a variety of disorders. J Enzyme Inhib Med Chem. 2021;36(1):1702-1714. doi: 10.1080/14756366.2021.1945049 pmid: 34325588
40. Bringmann A, Reichenbach A, Wiedemann P. Pathomechanisms of cystoid macular edema. Ophthalmic Res. 2004;36(5):241-9. doi: 10.1159/000081203 pmid: 15583429
41. Adijanto J, Banzon T, Jalickee S, Wang NS, Miller SS. CO2-induced ion and fluid transport in human retinal pigment epithelium. J Gen Physiol. 2009;133(6):603-22. doi: 10.1085/jgp.200810169 pmid: 19468075
42. Gao BB, Clermont A, Rook S, Fonda SJ, Srinivasan VJ, Wojtkowski M, et al. Extracellular carbonic anhydrase mediates hemorrhagic retinal and cerebral vascular permeability through prekallikrein activation. Nat Med. 2007;13(2):181-8. doi: 10.1038/nm1534 pmid: 17259996

43. Wolfensberger TJ, Chiang RK, Takeuchi A, Marmor MF. Inhibition of membrane-bound carbonic anhydrase enhances subretinal fluid absorption and retinal adhesiveness. Graefes Arch Clin Exp Ophthalmol. 2000;238(1):76-80. doi: 10.1007/s004170050013 pmid: 10664057
44. Wolfensberger TJ, Gregor ZJ. Macular edema--rationale for therapy. Dev Ophthalmol. 2010;47:49-58. doi: 10.1159/000320073 pmid: 20703043
45. Wolfensberger TJ. Macular Edema - Rationale for Therapy. Dev Ophthalmol. 2017;58:74-86. doi: 10.1159/000455275 pmid: 28351053
46. Wielders LHP, Schouten JSAG, Nuijts RMMA. Prevention of macular edema after cataract surgery. Curr Opin Ophthalmol. 2018;29(1):48-53. doi: 10.1097/ICU.0000000000000436 pmid: 28914687
47. Giusti C, Forte R, Vingolo EM, Gargiulo P. Is acetazolamide effective in the treatment of diabetic macular edema? A pilot study. Int Ophthalmol. 2001;24(2):79-88. doi: 10.1023/a:1016354517304 pmid: 12201348
48. Veritti D, Sarao V, De Nadai K, Chizzolini M, Parmeggiani F, Perissin L, et al. Dexamethasone Implant Produces Better Outcomes than Oral Acetazolamide in Patients with Cystoid Macular Edema Secondary to Retinitis Pigmentosa. J Ocul Pharmacol Ther. 2020;36(3):190-197. doi: 10.1089/jop.2018.0153 pmid: 31886707
49. Levin MH, Pistilli M, Daniel E, Gangaputra SS, Nussenblatt RB, Rosenbaum JT, et al; Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study. Incidence of visual improvement in uveitis cases with visual impairment caused by macular edema. Ophthalmology. 2014;121(2):588-95.e1. doi: 10.1016/j.ophtha.2013.09.023 pmid: 24332536
50. Acharya NR, Hong KC, Lee SM. Ranibizumab for refractory uveitis-related macular edema. Am J Ophthalmol. 2009;148(2):303-309.e2. doi: 10.1016/j.ajo.2009.03.028 pmid: 19427988
51. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. Br J Ophthalmol. 2017;101(1):31-37. doi: 10.1136/bjophthalmol-2016-309376 pmid: 27913439
52. Adackapara CA, Sunness JS, Dibernardo CW, Melia BM, Dagnelie G. Prevalence of cystoid macular edema and stability in oct retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. Retina. 2008;28(1):103-10. doi: 10.1097/IAE.0b013e31809862aa pmid: 18185146
53. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. Br J Ophthalmol. 2008;92(8):1065-8. doi: 10.1136/bjo.2008.138560 pmid: 18653601
54. Hajali M, Fishman GA. The prevalence of cystoid macular oedema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. Eye (Lond). 2009;23(4):915-9. doi: 10.1038/eye.2008.110 pmid: 18425064
55. Testa F, Rossi S, Colucci R, Gallo B, Di Iorio V, della Corte M, et al. Macular abnormalities in Italian patients with retinitis pigmentosa. Br J Ophthalmol. 2014;98(7):946-50. doi: 10.1136/bjophthalmol-2013-304082 pmid: 24532797
56. Liew G, Strong S, Bradley P, Severn P, Moore AT, Webster AR, et al. Prevalence of cystoid macular oedema, epiretinal membrane and cataract in retinitis pigmentosa. Br J Ophthalmol. 2019;103(8):1163-1166. doi: 10.1136/bjophthalmol-2018-311964 pmid: 30291136
57. Chatzistergiou V, Papasavvas I, Escher P, Durig J, Vaudaux J, Pournaras JA, et al. Optical Coherence Tomography Analysis of Cystoid Macular Edema in Retinal Dystrophy Treated with Oral Acetazolamide: Two Cases. Klin Monbl Augenheilkd. 2020;237(4):484-486. English. doi: 10.1055/a-1068-2762 pmid: 32092772
58. Lingao MD, Ganesh A, Karthikeyan AS, Al Zuhaibi S, Al-Hosni A, Al Khayat A, et al. Macular cystoid spaces in patients with retinal dystrophy. Ophthalmic Genet. 2016;37(4):377-383. doi: 10.3109/13816810.2015.1101775 pmid: 26894784
59. Supuran CT. Agents for the prevention and treatment of age-related macular degeneration and macular edema: a literature and patent review. Expert Opin Ther Pat. 2019;29(10):761-767. doi: 10.1080/13543776.2019.1671353 pmid: 31540558
60. Genead MA, McAnany JJ, Fishman GA. Topical dorzolamide for treatment of cystoid macular edema in patients with choroideremia. Retina. 2012;32(4):826-33. doi: 10.1097/IAE.0b013e3182215ae9 pmid: 21886018
61. Larrañaga-Fragoso P, Pastora N, Bravo-Ljubetic L, Peralta J, Abelairas-Gómez J. Topical carbonic anhydrase inhibitors in macular edema associated with Alström syndrome. Ophthalmic Genet. 2016;37(4):427-429. doi: 10.3109/13816810.2015.1094493 pmid: 26894450
62. Asahi MG, Bobarnac Dogaru GL, Onishi SM, Gallemore RP. Strong topical steroid, NSAID, and carbonic anhydrase inhibitor cocktail for treatment of cystoid macular edema. Int Med Case Rep J. 2015;8:305-12. doi: 10.2147/IMCRJ.S92794 pmid: 26664246
63. Chen NN, Chen CL, Lai CH. Resolution of Unilateral Dome-Shaped Macula With Serous Detachment After Treatment of Topical Carbonic Anhydrase Inhibitors. Ophthalmic Surg Lasers Imaging Retina. 2019;50(8):e218-e221. doi: 10.3928/23258160-20190806-16 pmid: 31415708
64. Salvatore S, Fishman GA, Genead MA. Treatment of cystic macular lesions in hereditary retinal dystrophies. Surv Ophthalmol. 2013;58(6):560-84. doi: 10.1016/j.survophthal.2012.11.006 pmid: 24160730
65. Huang Q, Chen R, Lin X, Xiang Z. Efficacy of carbonic anhydrase inhibitors in management of cystoid macular edema in retinitis pigmentosa: A meta-analysis. PLoS One. 2017;12(10):e0186180. doi: 10.1371/journal.pone.0186180 pmid: 29023491
66. Wilson AS, Hobbs BG, Shen WY, Speed TP, Schmidt U, Begley CG, et al. Argon laser photocoagulation-induced modification of gene expression in the retina. Invest Ophthalmol Vis Sci. 2003;44(4):1426-34. doi: 10.1167/iovs.02-0622 pmid: 12657576
67. Haustein M, Spoerl E, Boehm AG. The effect of acetazolamide on different ocular vascular beds. Graefes Arch Clin Exp Ophthalmol. 2013;251(5):1389-98. doi: 10.1007/s00417-012-2242-y pmid: 23275036
68. Torring MS, Holmgaard K, Hessellund A, Aalkjaer C, Bek T. The vasodilating effect of acetazolamide and dorzolamide involves mechanisms other than carbonic anhydrase inhibition. Invest Ophthalmol Vis Sci. 2009;50(1):345-51. doi: 10.1167/iovs.08-2435 pmid: 18757514
69. Suzuki T, Hayakawa K, Nakagawa Y, Onouchi H, Ogata M, Kawai K. Topical dorzolamide for macular edema in the early phase after vitrectomy and epiretinal membrane removal. Clin Ophthalmol. 2013;7:549-53. doi: 10.2147/OPTH.S42188 pmid: 23620653
70. Kawai K, Ohashi H, Suzuki T, Kitagaki H, Fujisawa S. [Effect of anti-glaucoma drugs on inflammatory cytokine production by human and murine peripheral blood mononuclear cells]. Nippon Ganka Gakkai Zasshi. 2010;114(8):669-77. Japanese. pmid: 20803986
71. Su D, Obeid A, Hsu J. Topical Aqueous Suppression and Closure of Idiopathic Full-Thickness Macular Holes. Ophthalmic Surg Lasers Imaging Retina. 2019;50(2):e38-e43. doi: 10.3928/23258160-20190129-17 pmid: 30768228
72. Niffenegger JH, Fong DS, Wong KL, Modjtahedi BS. Treatment of Secondary Full-Thickness Macular Holes with Topical Therapy. Ophthalmol Retina. 2020;4(7):695-699. doi: 10.1016/j.oret.2020.01.014 pmid: 32284268
73. Loftsson T. Topical drug delivery to the retina: obstacles and routes to success. Expert Opin Drug Deliv. 2022;19(1):9-21. doi: 10.1080/17425247.2022.2017878 pmid: 34890514
74. Jansook P, Hnin HM, Loftsson T, Stefánsson E. Cyclodextrin-based formulation of carbonic anhydrase inhibitors for ocular delivery - A review. Int J Pharm. 2021;606:120955. doi: 10.1016/j.ijpharm.2021.120955 pmid: 34332063