Chapter 4
Carbonic Anhydrase Inhibitors in Ophthalmology: Glaucoma and Macular Oedema

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Abstract Carbonic anhydrase inhibitors (CAIs) are commonly used pharmacologic agents. A myriad of CAI classes and inhibition mechanisms has been identified over the past decade. The classical CAI is acetazolamide, which has been used for the systemic treatment of glaucoma since 1953. A topical CAI was introduced more than 40 years after the introduction of this systemic agent. The rationale for the development of topically active CAIs—dorzolamide and brinzolamide—was to eliminate the systemic side effects seen with the oral route, which currently makes them popular therapeutics that are used as ocular hypotensives in medical therapy of ocular hypertension and primary open-angle glaucoma. Carbonic anhydrase is one of the most ubiquitous enzyme systems in the body and also acts as an inflammatory mediator. It is found both in the ciliary body epithelium and in different retinal cells, thus revealing new intraocular targets and new roles for carbonic anhydrase inhibitors. Scientific understanding of glaucoma and of macular oedema accompanying several ocular diseases continues to develop, producing a consequent re-evaluation of the role of carbonic anhydrase in the pathogenesis of these conditions. This underscores the importance of accurate evaluation of the therapeutic potential of carbonic anhydrase inhibitors.

Keywords Carbonic anhydrase inhibitors · Acetazolamide · Dorzolamide · Brinzolamide · Glaucoma · Macular oedema

4.1 Introduction

The therapeutic carbonic anhydrase inhibitors (CAIs) employed hitherto are sulfonamide derivatives. A myriad of CAI classes and inhibition mechanisms has been identified over the past decade, mainly through structure-based drug design approaches (Supuran 2017).

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The main drug from this group is acetazolamide (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide; Diamox), developed by Roblin and Clapp in 1950 (Roblin and Clapp 1950).

Acetazolamide acts as a diuretic by inhibiting carbonic anhydrase. This results in metabolic acidosis due to increased renal elimination of Na^+/HCO^- and K^+ and decreased plasma bicarbonate respectively (Kaplan 2000).

4.2 Carbonic Anhydrase Inhibitors in Glaucoma

Glaucoma has been considered as a major cause of worldwide irreversible blindness (Nuzzi et al. 2018), affecting about 70 million people worldwide (Quigley and Broman 2006). Glaucoma is currently recognized to be a multifactorial, progressive neurodegenerative disorder. It is characterized by the death of retina ganglion cells and loss of their axons as well as optic nerve atrophy and loss of neurons in the lateral geniculate nucleus and the visual cortex (Kaushik et al. 2003; Nuzzi et al. 2018). The main risk factor for progression is an elevated intraocular pressure (IOP), which can cause damage to the optic nerve head and then to the visual field. Some clinical trials have shown that decreasing the IOP can be useful for slowing down glaucoma progression (Kass et al. 2002; Heijl et al. 2002; Leske et al. 2004), and IOP has been the only recognized modifiable risk factor until now (Jutley et al. 2017). Thus the mainstay of treatment has been aimed at the reduction of IOP with drugs.

4.2.1 Systemic Carbonic Anhydrase Inhibitors

4.2.1.1 Acetazolamide

The first study on the treatment of glaucoma with the CAI acetazolamide was initiated by Breinin and Görtz in 1953 and covered a four-month period of observation. The authors concluded that inhibition of carbonic anhydrase by acetazolamide was a new and useful means of lowering the IOP. Other researchers also observed that systemic inhibition of carbonic anhydrase by the administration of acetazolamide and related compounds results in a partial secretion of aqueous humor. These agents have proved most useful clinically in lowering IOP in glaucomatous eyes (Becker 1954, 1955a, b, Grant 1954, Breinin and Görtz 1954) by the ability to partially suppress the formation of aqueous humor. The physiology of aqueous humor formation with respect to ion transport is discussed by these authors, and it was shown that a key event is the catalytic formation of HCO_3^- from CO_2 and OH^-. The newly formed HCO_3^- is linked to Na^+ and fluid movement to produce aqueous humor. Researchers highlighted that inhibition of HCO_3^- production by sulfonamides reduces aqueous humor formation and lowers pressure both in healthy individuals and in patients with glaucoma.

In the early 1960s a sustained release formulation (Sustet) containing 500 mg of the active drug was marketed (Drance and Carr, 1961; Mestre et al. 1963). Several studies have confirmed the efficacy of regular tablets and a sustained release preparation in lowering IOP (Becker 1955a, b; Kupfer et al. 1955; de Carvalho et al. 1958; Drance and Carr 1961; Mestre et al. 1963; Garner et al. 1963; Garrison et al. 1967). However, with both formulations many side effects were encountered and these were thought to be dose-related (Lichter et al. 1978; Berson and Epstein 1980). In an effort to reduce these effects, smaller doses of acetazolamide were tried over short periods of time (Friedland et al. 1977; Foster et al. 1982). The effect on IOP, over 12- or 24-h dosage intervals, of the same doses of these two formulations (available in the UK) were also compared.

In 1990 Joyce and Mills compared the effects of the same dose of the two formulations on IOP over 12- or 24-h dosage intervals. Twenty patients with primary open-angle glaucoma, uncontrolled on single topical therapy, completed a double-dummy crossover study to compare acetazolamide tablets with a sustained-release formulation (Sustet). The two preparations were equally effective. The authors stated that most patients in this study, who had primary open-angle glaucoma uncontrolled on single topical treatment, were adequately controlled on the addition of 500 mg (2×250 mg) of acetazolamide tablets or one Sustet (500 mg) at night. The severity of side effects was also reduced. Thus an evening dose of acetazolamide in conjunction with topical therapy may well have a beneficial effect on compliance in the treatment of open-angle glaucoma. Lichter et al. (1989) tested the effect on IOP of three commonly used oral CAI preparations in a controlled, randomized, comparative study also on patients with primary open-angle glaucoma. Preparations tested included acetazolamide tablets, acetazolamide Sequels, and methazolamide tablets. The authors concluded that maximal rapid reduction of intraocular pressure was obtained with a 500-mg dosage of acetazolamide.

Since several CA isozymes are widespread throughout the body, systemic CAIs possess undesired side effects such as numbness and tingling of extremities, metallic taste, depression, fatigue, malaise, weight loss, decreased libido, gastrointestinal irritation, metabolic acidosis, renal calculi and transient myopia (Mincione et al. 2007, 2008), Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, aplastic anemia, drug hypersensitivity, serum sickness, and nephritis.

4.2.2 Topical Carbonic Anhydrase Inhibitors

The general consensus, in order to avoid these undesirable side effects, was to search and develop topically effective CAIs free of such effects (Maren 1987; Mincione et al. 2011; Fabrizi et al. 2012). Four sulfonamides—acetazolamide, methazolamide, ethoxzolamide, and dichlorophenamide—have been used systemically. None of these works topically, since they do not reach the ciliary process in adequate concentrations. Consequently, subsequent research focused on the development of sulfonamides of different properties that cross the cornea in effective concentrations to inhibit

carbonic anhydrase (CA) in the ciliary process. The key to the problems was to search for a balance between water and lipid solubility, maintaining high activity against the enzyme. This has been achieved, and new structures described from different laboratories lower pressure in the rabbit nearly as well as systemic sulfonamides (Sugrue 1996; Pfeiffer 1997; Borras et al. 1999; Supuran et al. 1999; Menabuoni et al. 1999; Ilies et al. 2000; Renzi et al. 2000; Kobayashi and Naito 2000; Casini et al. 2001; Scozzafava et al. 2002; de Leval et al. 2004; Mincione et al. 2005).

The corneal permeabilities of these test compounds in vitro were found to be similar in rabbit and human, but access to the aqueous humor in vivo was less in human.

Topical CAIs took many years to develop. A topical version was first introduced more than 40 years after the introduction of the systemic agent. The rationale for the development of a topically active CAI was to eliminate the systemic side effects seen with oral acetazolamide use, such as drowsiness, confusion, allergic reactions, paresthesias, myelosuppression, renal calculi, loss of potassium, or hyperchloremic metabolic acidosis from extended use. Thus this class of drugs became the commonly used pharmacologic agents as ocular hypotensives in medical therapy for glaucoma, as a consequence of their ability to reduce aqueous humour production through decreased bicarbonate formation in ciliary body epithelium. In contrast to acetazolamide, the first topical CAI—dorzolamide—has a lipid-soluble nature and high affinity for carbonic anhydrase, which significantly increases the bioavailability of the drug (Kellner et al. 2004). The effects on intraocular pressure of the novel topical carbonic anhydrase inhibitor MK-927 were investigated for the first time in patients by Bron et al. (1989). Three drops of 2% MK-927 were administered in a two-center, double-masked, randomized, placebo-controlled, two-period crossover study to 25 patients with bilateral primary open-angle glaucoma or ocular hypertension, and it was shown that the peak mean percent change in intraocular pressure in eyes treated with MK-927 was −26.7% at six hours after the dose.

4.2.2.1 Dorzolamide

The multiple-dose, dose–response relationship, and duration of action of the novel, topical carbonic anhydrase inhibitor dorzolamide (previously known as MK-507) were investigated in a double-masked, randomized, placebo-controlled, parallel study in 73 patients with bilateral primary open-angle glaucoma or ocular hypertension (Lippa et al. 1991, 1992). Dorzolamide (0.7, 1.4%, or 2%) or placebo was administered every 12 h for five days and then every eight hours for seven days. Intraocular pressure was investigated with multiple 12-h diurnal curves. All concentrations of dorzolamide demonstrated substantial lowering of IOP throughout the day when given twice daily (9–21%) or three times daily (14–24%). Although a dose-dependent response was observed immediately following the first dose, there were no significant differences between concentrations or dose–response at either the twice or three times daily dosing regimen. Three times daily administration of 2% dorzolamide demonstrated a mean percent decrease in IOP of 18–22% throughout

the day (mean decrease, 4.5–6.1 mm Hg). Consequently the authors concluded that dorzolamide appeared to have substantial potential in the treatment of glaucoma and ocular hypertension.

Wilkerson et al. (1993) conducted a four-week, double-masked, randomized, placebo-controlled, parallel, three-center study, investigating the activity and local and systemic safety of dorzolamide hydrochloride in forty-eight patients with bilateral open-angle glaucoma or ocular hypertension and IOP greater than 22 mm Hg. Dorzolamide showed significant IOP lowering activity over four weeks. It was well tolerated and there were no clinically significant changes in ocular or systemic safety parameters.

Dorzolamide was approved by the FDA in 1994 for the treatment of elevated intraocular pressure in primary open-angle glaucoma and ocular hypertension. Strahlman and associates (1995) reported a 1-year study of the safety profile and efficacy of a topical CAI, dorzolamide hydrochloride (Trusopt), as either primary or supplemental therapy in addition to 0.5% timolol maleate or 0.5% betaxolol hydrochlorid for primary open-angle glaucoma and ocular hypertension. This was the first topical CAI to show sufficient efficacy for clinical use and that appeared to nearly match the pressure-lowering of oral CAIs without having their systemic side effects. Having advanced to Food and Drug Administration phase three trials, it was approved and marketed (Palmberg 1995).

Similar research, to assess the safety and intraocular pressure (IOP)-lowering activity of 2% dorzolamide compared to 0.5% timolol and 0.5% betaxolol eyedrops, was conducted by Simpson et al. (1996) as a parallel, masked, randomized one-year clinical trial evaluating 16 patients with open-angle glaucoma or ocular hypertension. This was a subset of a multicentre study which enrolled 523 subjects. The authors observed that dozolamide 2% given thrice daily was well tolerated and safe, with a clinically significant effect on IOP comparable to betaxolol 0.5% twice daily, but not as great as timolol 0.5% twice daily. The data of Gillies and Brooks (1996) were in agreement with this. In a comparative study comparing the efficacy of topical dorzolamide with that of systemic acetazolamide in lowering ocular pressure dorzolamide (1% eye drops) proved to be as effective as acetazolamide tablets in reducing the IOP curve (Centofanti et al. 1997).

In the eye, carbonic anhydrase is expressed in the ciliary processes of the ciliary body, in the corneal endothelial cells, and in the pigment epithelium. In the corneal endothelium CAII plays a role in the pumping mechanism, which helps to maintain the relatively dehydrated state of the corneal stroma. Inhibition of this mechanism may lead to the development of corneal decompensation and oedema, with secondary impaired vision.

To check long-term corneal tolerability of dorzolamide hydrochloride (Trusopt, Merck and Co Inc, White-house Station, NJ), timolol maleate, and betaxolol hydrochloride, measuring corneal endothelial cell density and corneal thickness in patients with normal corneas at baseline, Lass et al. (1998) initiated a 1-year multicenter study in 298 patients with ocular hypertension or open-angle glaucoma. At the end of the study it was noted that dorzolamide was equivalent to timolol and betaxolol in terms of the change in central endothelial cell density and thickness after

one year of therapy and exhibited good long-term corneal tolerability. Another study conducted to evaluate the impact of dorzolamide on corneal thickness, endothelial cell count, and corneal sensibility after 90 days use, confirmed that dorzolamide, applied topically three times a day as a monotherapy or in combination with timolol or pilocarpine, was not associated with clinically meaningful changes in the cornea (Kaminski et al. 1998).

In contrast to the presented findings in two published case reports, corneal decompensation has been described in patients with keratopathy after treatment with dorzolamide (Adamson 1999; Konowal et al. 1999).

The latest findings on the matter, presented by Inoue et al. (2003), reconfirm the safety of the topical use of 1% dorzolamide during three months, without negative impact on corneal endothelial morphology.

The most frequently reported adverse side effects of dorzolamide are burning, stinging, discomfort, and bitter taste following administration of the solution (Lippa et al. 1992; Wilkerson et al. 1993; Strahlman et al. 1995). Ocular allergy and superficial punctuate keratitis occur in 10–15% of patients. Other side effects include conjunctivitis, eyelid inflammation, and irritation. Blurred vision, dryness, tearing, and photophobia have been reported in 1–5% of patients.

Balfour and Wilde (1997) evaluated dorzolamide hydrochloride, the first topical, highly water-soluble CAI to become available for clinical use as a 2% eyedrop for the management of glaucoma and ocular hypertension. They reported that, when administered three times daily, it was effective in lowering IOP. The mean IOP was reduced by approximately 4–6 mm Hg at peak (two hours post-dose) and 3–4.5 mm Hg at trough (eight hours post-dose). Dorzolamide has additive ocular hypotensive effects when used in conjunction with topical beta-adrenergic antagonists and was as effective as pilocarpine (2%), administered four times daily, as adjunctive therapy in patients receiving timolol. Dorzolamide does not appear to produce the acid–base or electrolyte disturbances and severe systemic adverse events associated with oral CAIs, and unlike beta-adrenergic antagonists, it is not contraindicated in patients with asthma, reactive airways disease, or heart disease. Furthermore, as CAIs do not cause miosis, they may cause less interference with vision than pilocarpine or epinephrine (adrenaline). The most common adverse effects associated with dorzolamide are bitter taste and transient local burning or stinging. The authors concluded that dorzolamide has potential as an alternative therapy option in patients with glaucoma or ocular hypertension who are intolerant of, or unable to receive, ophthalmic beta-adrenergic antagonists, and as adjunctive therapy in patients already receiving these agents.

However, the need still exists to increase the duration of action of dorzolamide. In an effort to reach this goal Kouchak et al. (2018) prepared a dorzolamide-loaded nanoliposome and tested it in a randomized comparative study with marketed dorzolamide solution in 20 patients with primary open-angle glaucoma or ocular hypertension. A statistically significantly higher hypotensive effect was demonstrated in the dorzolamide-loaded eye drop group. The authors have argued that the long-lasting efficacy of the dorzolamide-loaded nanoliposome eye drops may be attributed to

their highly enhanced permeability through the cornea due to small particle size and similarity between phospholipid bilayer of liposomes and the biological membrane.

4.2.2.2 Brinzolamide

Brinzolamide is a highly specific, non-competitive, reversible, and effective inhibitor of carbonic anhydrase II (CA II) (DeSantis 2000). It was launched more recently and was approved by the FDA in 1998 for the treatment of elevated intraocular pressure in primary open-angle glaucoma and ocular hypertension.

The commercially available preparation of brinzolamide is Azopt® (Alcon Laboratories, Inc, Ft. Worth, Texas, USA) (Cvetkvic and Perry 2003, Iester I2008a, b). To achieve pharmacological effect, the near total inhibition of CA is required (Maren 1967; Kaur et al 2002). Brinzolamide is cleared from the aqueous humor and cornea with half-lives of approximately three and five hours, respectively. Therefore, the cornea acts as a reservoir, providing sustained release of the drug to the ciliary processes of the ciliary body long after topical dosing (Maren 1967; Kaur et al. 2002).

The efficacy of brinzolamide in different concentrations 0.3–3% twice daily has been evaluated in several randomized, double-blind, multicenter, comparative clinical trials (March and Ochsner, 2000; Sall 2000; Shin 2000; Silver 1998, 2000; Michaud and Friren 2001). A dose–response study, comparing brinzolamide in concentrations of 0.3%, 1%, 2%, and 3%, demonstrated mean IOP reductions of 3 mmHg (11.3%), 4.4 mmHg (16.1%), 4.3 mmHg (16.1%), and 4.2 mmHg (15.4%), respectively. When diurnal IOP was measured, 1% or 3% brinzolamide reduced IOP significantly better than 0.3% brinzolamide (Silver 2000). These observations suggested that the optimal therapeutic concentration for IOP reduction was 1%. Its recommended dosing frequency is three times daily in the US and twice daily in the EU and Japan. However, three phase III trials have reported that brinzolamide 1% *b.i.d.* and *t.i.d*. produced statistically significant IOP reductions from baseline and that both treatments were clinically equivalent to one another (Silver 1998; March and Ochsner 2000; Shin 2000).

In a randomized, double-blind clinical trial, 372 glaucomatous and ocular hypertension (OH) patients received brinzolamide 1% or timolol 0.5%. After 18 months of treatment, no significant change was found in corneal thickness and corneal endothelium cell density (March and Ochsner 2000). However, in this study only subjects with healthy corneas were included. Some concerns remained in patients with compromised corneas. Zhau and Chen (2005) have reported two cases of corneal decompensation after 15 months and two years of brinzolamide therapy. Corneal oedema reversed with discontinuation of the treatment; however, the reason was difficult to assess, and neither patient was re-challenged after recovery. No change in central corneal thickness was found (Wang et al. 2004).

Several clinical trials (Zeyen and Caprioli 1993; Silver 1998; Sall 2000; Shin 2000; Wang et al. 2004; Zhao and Chen 2005; Menon and Vernon 2006) have evaluated the safety of brinzolamide 1% ophthalmic suspension. The most common ocular

adverse events were blurred vision (3–8%), ocular discomfort (1.8–5.9%), and eye pain (0.7–4.0%). Other ocular adverse events occurring at an incidence of less than 3% included hyperemia, pruritus, tearing, discharge, blepharitis, keratitis, foreign body sensation, dry eye, conjunctivitis, and lid margin crusting.

The most common systemic adverse event was taste perversion, which occurred in 3.0–7.8% of patients (Silver 1998; Sall 2000; Shin 2000). There were no clinically significant changes from baseline in heart rate and blood pressure, and in laboratory values for hematology, blood chemistry, or urinalysis variables. In addition, mean total carbonic anhydrase activity in red blood cells was reduced by only 51–55%. However, one case of systemic metabolic acidosis has been described by Menon and Vernon (2006).

Detailed pharmacokinetics of topically-administered brinzolamide were evaluated by DeSantis (2000) and March and Ochsner (2000). Systemic absorption of brinzolamide has been demonstrated in the tissues of healthy volunteers (DeSantis 2000). Brinzolamide, administered topically, enters the blood circulation and binds preferentially to CA in the erythrocytes, leaving the concentration of free brinzolamide in plasma below the quantification level. In the red cells, less than 1% of CA-II activity is required to maintain physiological function (March and Ochsner 2000). Thus, in the erythrocytes the concentration of CAIs was insufficient to produce complete saturation of CA. In the kidney, the concentration of free brinzolamide is not sufficient to inhibit in the proximal convoluted tubules and luminal CA. Furthermore, the low affinity of brinzolamide for the other CA isoforms, and the low blood concentration, may explain the low incidence of systemic adverse effects after topical administration (March and Ochsner 2000).

In a meta-analysis of randomized clinical trials, Van der Valk et al. (2005) estimated the IOP reduction achieved by the most frequently prescribed glaucoma drugs and a placebo: they found that the highest reduction of IOP achieved by brinzolamide was 17%.

Wang et al. (2004) conducted a small, prospective, double-masked study, comparing brinzolamide 1% *b.i.d.* with timolol 0.5% *b.i.d*., in 50 patients with open-angle glaucoma. After six weeks of treatment, IOP dropped 4.8 mm Hg (17%) in brinzolamide-treated eyes and 5.7 mm Hg (19.7%) in timolol-treated eyes.

A multicenter, double-masked, prospective, parallel-group study was conducted to compare brinzolamide (1.0%), administered two and three times a day, dorzolamide (2.0%) three times a day, and timolol (0.5%) twice a day in 572 patients with primary open-angle glaucoma or ocular hypertension (Silver 1998). Brinzolamide (1.0%) produced clinically relevant intraocular pressure reductions in substantial numbers of patients, with efficacy equaling that of dorzolamide (2.0%), and produced less ocular discomfort (burning and stinging) on application.

Clinical studies comparing the two drugs as adjuncts as well as monotherapy have shown them to have comparable efficacy, with brinzolamide having a more favorable adverse event profile (Silver 1998; Silver 2000; Sall 2000; March and Ochsner 2000; Barnebey and Kwok 2000; Michaud and Friren 2001; Stewart et al. 2004; Tsukamoto et al. 2005; Mundorf et al. 2008; Manni et al. 2009; Martínez and Sánchez-Salorio 2009; Rossi et al. 2011).

The latest similar research to assess the safety and intraocular pressure (IOP)-lowering activity of 1% brinzolamide compared to 2% dorzolamide eyedrops was initiated by Yadav et al. (2014). In a prospective, randomized study, 100 eyes (50 subjects) received dorzolamide 2% three times daily or brinzolamide 1% twice daily for three months. The authors observed that both brinzolamide (1.0%) and dorzolamide (2%) produced clinically relevant and statistically significant IOP reductions and were statistically equivalent when compared. They also noted that brinzolamide produced significantly less ocular discomfort (burning and stinging) both immediately on application and on chronic use.

4.2.3 Carbonic Anhydrase Inhibitors in Ocular Perfusion

Although elevated IOP is the principal risk factor, deterioration of ocular perfusion by the vascular system accelerates progression of glaucomatous optic nerve atrophy (Siesky et al. 2009).

CAIs may improve blood perfusion in the human eye. It has been shown that acetazolamide leads to a dilation of retinal vessels and increases blood flow in the optic nerve head (Haustein et al. 2013). Similarly, topical application of dorzolamide leads to a significant increase of flow velocities of the retrobulbar vessels as measured by color Doppler imaging (Huber-van der Velden et al. 2012).

Few studies have reported the effect of brinzolamide on ocular blood flow. Moreover, the results of these studies have been contradictory, possibly due to the different study designs and measurement methodologies employed. Barnes et al. (2000) found that brinzolamide significantly increased optic nerve head blood flow in Dutch rabbits. However, Martinez and Sanchez-Salorio (2009) noted that, after five years of treatment, brinzolamide did not augment retrobulbar blood flow when added to timolol in glaucoma patients.

Dong et al. (2016) demonstrated that dorzolamide directly induced relaxation of isolated rabbit ciliary arteries. In a later study (Dong et al. 2018), compared the effects of brinzolamide, dorzolamide, and acetazolamide ex vivo and found that acetazolamide could not induce vasodilation, and dorzolamide-induced vascular relaxation was smaller than that induced by brinzolamide. It has been shown that brinzolamide decreases IOP and increases ocular blood flow. The direct vasodilatory effect of brizolamide is mediated by suppression of Ca^{2+} release from intracellular calcium stores.

The mechanism by which IOP-lowering medications increase ocular blood flow in glaucoma remains unclear. Currently it is difficult to determine if the CAI-induced increase in ocular perfusion is secondary to IOP reduction or if it is a primary effect on the ocular vasculature.

Future directions

A new generation of multifunctional compounds has been synthesized, and their functional properties were investigated (Zubrienė et al. 2017; Taslimi et al. 2018; Türker et al. 2018; Sarı et al. 2017; Zakšauskas et al. 2018).

A novel class of fluoro-substituted tris-chalcones derivatives (5a-5i) was synthesized from phloroglucinol and corresponding benzaldehyde (Burmaoglu et al. 2019). The compounds' inhibitory activities were tested against human carbonic anhydrase I and II isoenzymes (hCA I and hCA II), acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and α-glycosidase (α-Gly). These results strongly supported the promising nature of the tris-chalcone scaffold as a selective carbonic anhydrase, acetylcholinesterase, butyrylcholinesterase, and α-glycosidase inhibitor. Overall, due to these derivatives' inhibitory potential on the tested enzymes, as was stated by the authors, "they are promising drug candidates for the treatment of diseases like glaucoma".

In the preclinical study of Chiaramonte et al. (2018), two compounds, evaluated in rabbit models of glaucoma, significantly reduced intraocular pressure, making them interesting candidates for further studies.

These data suggest the advisability of focusing future endeavours on increasing drug delivery and bioavailability by the use of novel formulations, bioadhesive polymers, and micro- and nano-systems (Nagai 2016; Andrés-Guerrero et al. 2017).

4.3 Carbonic Anhydrase Inhibitors in Macular Oedema

Macular oedema (MO) is a swelling within or under a specific area of the retina, known as the macula, caused by extravasation of fluid and plasma components from blood vessels and/or derangements in cellular ion flux leading to the accumulation of intracellular and intercellular fluid in the outer plexiform and inner retinal layers (Kleinman et al. 2010).

The pathophysiology of macular oedema encompasses a cascade of inflammatory events in retinal microvessels and the decay of tight junctions in cell walls. Several decades of basic science research have revealed a growing and complex array of cytokine growth factors and proinflammatory mediators that are capable of initiating the cellular changes that result in accumulation of fluid within the retina. MO commonly develops secondary to vascular insufficiency in disease states such as diabetic retinopathy (DR), branch and/or central retinal vein occlusion, ocular ischemic syndrome, radiation retinopathy, pseudophakia, age-related macular degeneration, uveitis, retinitis pigmentosa, ocular trauma or drug toxicity (Kleinman et al. 2010).

Thus, MO may be considered as the final common pathway of many intraocular and systemic insults and the anatomic result of numerous pathologic processes that alter the blood flow, vascular integrity, and fluidic balance in the neurosensory retina (Tranos et al. 2004). 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 oedema (CMO).

CA is one of the most ubiquitous enzyme systems in the body and also acts as an inflammatory mediator. In addition to the ciliary body epithelium, it is also found in the red-green cones, within the Mueller cells of the retina, and in the retinal pigment epithelium (RPE), thus suggesting new intraocular targets. CA inhibitors have been shown to have direct effects both on retinal and RPE cell function by inducing an acidification of the subretinal space, a decrease of the standing potential, and an increase in retinal adhesiveness. It is thought that acidification of the subretinal space is ultimately responsible for the increase of fluid resorption from the retina through the RPE into the choroid (Marmer 1990; Wolfensberger 1999).

CA plays a role in the biochemical reaction cascades in the universal pathomechanisms of CMO, where prostaglandins accelerate vascular permeability causing leakage, and upregulate generation of vascular endothelial growth factor (VEGF) and carbonic anhydrase-1 (CA-1) expression and downregulation of K^+ channels in Müller cells, resulted to increasing the inflow and reducing the outflow of ions and fluid from the inner nuclear layer and Henle fiber layer in the macular region (Bringmann et al. 2004).

The pigment epithelium of the retina withdraws the fluid through a Na^+/K^+ ATPase located in the basolateral membrane, the activity of which is facilitated when the concentration of H_2CO_3 in the sub-retinal space increases. High levels of CO_2 in the sub-retinal space reduce adhesion among the pigment epithelium and the neurosensory retina, and allows for the accumulation of intra-retinal and sub-retinal fluid (Adijanto et al. 2009); this condition is more common when there are high concentrations of CAs, as in the case of diabetes (Gao et al. 2007).

The anti-oedematic effect of CAI is achieved by increasing the fluid hydrodynamics through the RPE and pump function due to acidification of the sub-retinal space, thus controlling and adjusting the extracellular pH gradients produced by the metabolic activity of cells (Cox et al. 1988; Gallemore et al. 1997; Wolfensberger 1999). At the same time suppression of the inflammatory process underlying the vascular and RPE leakage occurs, causing CMO as was demonstrated by Bringmann et al. (2004).

Recently, synergistic effects between CAIs and some non-steroidal anti-inflammatory drugs (NSAIDs) for the management of CMO were highlighted by Supuran (2016a; b), who argued previously reported positive results of CMO resorption, confirmed by fluorescein angiography and optical coherence tomography (OCT), in a case series treated topically by simultaneous use of a CAI, an NSAID and a steroid (Asahi et al. 2015).

Piozzi et al. (2017) hypothesized that "the efficacy of topical NSAIDs and systemic CAI association indicates that the imbalance in the distribution of RPE membrane-bound CA could play a major role in CMO pathogenesis of gyrate atrophy of the choroid and retina", a rare chorio-retinal dystrophy.

4.3.1 Systemic Carbonic Anhydrase Inhibitors

Systemic CAIs have been used since 1988 to treat the MO caused by several diseases (Cox et al.1988), although their use was restricted due to associated systemic adverse events.

It has been reported that the response to treatment with CAIs is better in MO caused by pigment epithelium alterations than that presented in vascular diseases, such as diabetic retinopathy (DR) or venous occlusions (Wolfensberger 1999).

Acetazolamide facilitates the transport of water across the RPE from the subretinal space to the choroids (Fung 1995). One case report suggests a direct correlation of resolution of pseudophakic CMO with acetazolamide therapy (Tripathi et al. 1991).

A study conducted by Cox et al. (1988) demonstrated that 16 of 41 patients responded to acetazolamide treatment with partial or complete resolution of oedema and improved vision. These patients had MO secondary to a host of other conditions, including the Irvine-Gass syndrome.

Hayreh (1998) found that sustained release acetazolamide (Diamox Sequels, 500 mg twice daily) was effective in reducing MO and improving visual acuity in some patients with non-ischemic central retinal vein occlusion and MO. If a patient did not respond within two weeks, the therapy was discontinued because there was little chance of further improvement. In contrast to this, a normal clinical starting dose of acetazolamide is 500 mg/day by Wolfensberger (1999), which should be continued for at least one month to see an effect.

Efficacy of acetazolamide in CMO secondary to diabetes was analyzed by Giusti et al. (2001) in a pilot study, limitations of which were the small number of patients and the short follow-up. However, despite these factors the authors stated that acetazolamide could be effective in reducing fluorescein-angiographic findings and improving perimetric data in diabetes patients with MO, though visual acuity (VA) improved only slightly.

To investigate the impact of acetazolamide on the course of central serous retinopathy (CSR), Pikkel et al. (2002) initiated a prospective, nonrandomized, comparative trial including 15 acetazolamide-treated and seven untreated (control) CSR patients with long-term follow-up of at least 24 months. It was shown that acetazolamide treatment for CSR shortened the time for subjective and objective clinical resolution, but had no effect on either final VA or recurrence rate of the disease.

Pomykala et al. (2016) presented a case of recurring CSR associated with retinitis pigmentosa (RP) successfully treated with oral acetazolamide maintained on alternating and then biweekly doses of the drug.

Acetazolamide also reduced central macular thickness and macular cystic cavities in macular teleangiectasia without, however, improvement of visual acuity (VA) (Chen et al. 2014).

Several authors have described a positive effect of acetazolamide on the resolution of MO from various etiologies. These include uveitis and postoperative inflammation after cataract extraction (Farber et al. 1994), RP (Fishman and Gilbert 1989)

and serpiginous choroiditis (Chen et al. 1990), and in conjunction with epiretinal membrane (Marmer Marmor, 1990).

Schilling et al. (2005) assessed the long-term effect (mean follow-up 3.1 years) of acetazolamide treatment on fifty-two eyes of 45 patients with CMO in the course of intermediate or posterior chronic uveitis. Two subgroups were identified: group 1, quiescence of uveitis with acetazolamide as the single therapeutic agent (33 eyes); and group 2, chronically active uveitis requiring additional systemic anti-inflammatory drugs. In both groups, VA improvement was statistically significant. This treatment was more effective in patients with quiescence of uveitis than in those with chronically active uveitis, leading to the conclusion that low-dose acetazolamide can be a useful therapeutic option for chronic CMO in uveitis, but in active swelling it does not improve vision, which is why its use has decreased (Karim et al. 2013; Shoughy and Kozak, 2014).

Earlier randomised prospective studies (Farber et al. 1994) demonstrated that patients aged less than 55-years, with chronic iridocyclitis-related MO, were more like to respond to 500 mg acetazolamide twice daily comparing to older patients.

CMO is a well-confirmed cause of visual loss in patients with RP, with a prevalence ranging from 10 to 50%. (Adackapara et al. 2008; Hajali et al. 2008; Hajali and Fishman, 2009; Testa et al. 2014; Liew et al. 2018). The study of RP patients with CMO revealed a correlation between anti-carbonic anhydrase antibodies and CMO (Wolfensberger et al. 2000), suggesting that the use of CA inhibitors may be effective in treating this condition.

The efficacy of oral acetazolamide versus placebo, evaluated in a prospective, masked, crossover study, documented VA increase of at least one line, in at least one eye in 10 out of 12 patients with RP (Fishman et al. 1989). Three of these patients, initiated on placebo only, demonstrated improvement once switched to acetazolamide. In other prospective crossover studies (Fishman et al. 1994), nine out of 17 patients, using oral methazolamide, demonstrated angiographic improvement of CMO. However, vision improved in at least one eye, by at least two lines in only three patients. Acetazolamide cannot readily enter the neurosensory retina (Goren et al. 1961) thus explaining its low efficacy. Earlier reports showed a recurrence of CMO in patients with RP by oral CAI (Fishman et al. 1993; Apushkin et al. 2007). In retrospective studies initiated by Liew et al. (2015) involving 81 patients (157 eyes) with RP-CMO, objective improvement on OCT was observed in 28% of eyes of patients using oral acetazolamide and in 40% of eyes of patients using topical dorzolamide. VA improved from 6/15 to 6/12 in most patients. It was shown that autosomal recessive RP and greater initial central macular thickness (CMT) predicted better response to treatment.

4.3.2 Topical Carbonic Anhydrase Inhibitors

CAI drops alone have been known to be effective for treatment of MO in several ocular conditions (Wolfensberger 1999). They have been shown to reduce oedema in

patients with choroideremia (Genead et al. 2012) and more recently were included in a treatment regimen for Vogt–Koyanagi–Harada disease (Onishi et al. 2015). They have been recommended for syndromic retinal dystrophies such as Alström syndrome (Larrañaga-Fragoso et al. 2016), and also for CMO after cataract extraction (Asahi et al. 2015).

4.3.2.1 Dorzolamide

Dorzolamide is an effective ocular hypotensive agent (Harris et al. 1996).

The proposed mechanism of action for dorzolamide is the inhibition of CAs of the RPE, which favors the activity of Na/K^+ ATPase and increases the transport of fluid toward the choroid.

The impact of topical CA inhibition has been analyzed in multiple studies. The efficacy of topical dorzolamide was evaluated in a prospective, nonrandomized clinical trial (Grover et al. 2006) involving 15 patients who received dorzolamide three times daily, for at least four weeks in both eyes. At the end of the study the researchers highlighted the potential efficacy of topical dorzolamide for treating CMO in patients with RP, but at the same time documented that some patients have shown a "rebound phenomenon" with continued use of the medication.

While Fishman and Apushkin (2007) demonstrated a beneficial effect of dorzolamide in patients with RP, their study followed a limited number of patients for a short period of time. Over a more extended period of time, Genead and Fishman (2010) studied the effect of sustained topical therapy with dorzolamide hydrochloride (2%) on visual acuity and cystic macular lesions verified by OCT, in 32 patients with RP and Usher syndrome. The authors observed that treatment of CMO in these patients, with topical dorzolamide, reduced central foveal thickness in a notable percentage of cases with improvement of VA in some. Similar results were obtained by Ikeda et al. (2012, 2013) in more recent studies. The authors concluded that prolonged use (more than one year) of topical dorzolamide was effective in treating CMO in RP patients, and proposed this as first-line treatment.

As was stated by Salvatore et al. (2013) CA inhibitors have proven to be potentially efficacious, although not in all cases.

Bakthavatchalam et al. (2017) systematically reviewed various treatments advocated for RP-related CMO and concluded that oral CAIs (acetazolamide and methazolamide) and topical CAIs (dorzolamide and brinzolamide) are effective first-line treatments. The authors postulated that oral acetazolamide had the strongest clinical basis for treatment and was superior to topical dorzolamide, which should be reserved as an alternative for cases revealing intolerance to the adverse effects of oral acetazolamide.

The latest meta-analysis conducted by Huang et al. (2017) showed that treatment with CA inhibitors of CMO in RP patients significantly reduced central macular thickness, but the effects on visual acuity were contradictory across studies. It was concluded that multicenter prospective randomized controlled trials were required to evaluate a clinical efficacy of CAI in RP patients.

The efficacy of dorzolamide was evaluated in a comparative, prospective, longitudinal, double-blind study in 69 eyes of patients with diabetes and focal MO, who underwent photocoagulation (Gómeza et al. 2015). Diabetic MO with focal leakage did not affect the pigment epithelium and the amount of fluid leaking toward the retina exceeded the capacity of the latter to withdraw it (Gómeza et al. 2015).

Treated eyes were randomly assigned three weeks after the procedure to receive dorzolamide (group 1) or placebo (group 2), three times daily for three weeks. The researchers highlighted that dorzolamide applied for three weeks was more effective than a placebo in reducing retinal thickness after focal photocoagulation in diabetic MO, and argued that, by closing microaneurysms with photocoagulation, topical CAIs may increase the transport of fluid toward the choroid, which does not occur when they are administered as the sole treatment. After photocoagulation, fluid is also withdrawn through competent adjacent capillaries, the capacity of which increases through vasodilation. The procedure promotes this effect by increasing gene expression of angiotensin II receptor type 2 in the retina (Wilson et al. 2003). CAIs also induce retinal venous vasodilation (Haustein et al. 2013), which is higher with the administration of dorzolamide than with the administration of acetazolamide (Torring et al. 2009).

The anti-inflammatory effect of dorzolamide in MO resorption, in patients who have undergone vitrectomy combined with phacoemulsification and intraocular lens implantation for epiretinal membrane, was documented by Suzuki et al. (2013). They demonstrated that topical dorzolamide significantly reduced mean central macular thickness at one month, and mean aqueous flare at two weeks, after surgery for epiretinal membranes. It was previously reported that dorzolamide suppresses production of the proinflammatory cytokine interleukin-6, which is a major participant in the inflammatory process (Kawai et al. 2010).

Effect of dorzolamide on CMO in hydroxychloroquine retinopathy was evaluated in two cases by Kim et al. (2018). The authors observed good therapeutic response.

Another case report on the use of dorzolamide in CMO secondary to paclitaxel, a chemotherapeutic drug, was presented by Dwivedi and Tiroumal (2018). The authors proposed topical dorzolamide as an early treatment option, helping to avoid possible irreversible pigmentary change at the macula, and accelerate CMO resorption and vision recovery.

4.3.2.2 Brinzolamide

Alkin et al. (2013) have evaluated the effect of brinzolamide on RP-related CMO in a retrospective study of six patients (eight eyes) with RP. Despite a positive anatomical change manifested by a decrease of central macular thickness, an increase of VA was not achieved.

A synergistic efficacy of brinzolamide in a therapeutic cocktail containing also difluprednate 0.05% and nepafenac 0.1% was shown by Asahi et al. (2015) in three cases of Irvine-Gass syndrome, and single cases of diabetic CMO and branch retinal vein occlusion, respectively.

Zur (June 2018) initiated a Clinical Trial «**Brinzolamide for the Treatment of Chronic Central Serous Chorioretinopathy»** (https://ichgcp.net/clinical-trials-registry/NCT03542006) to examine the efficacy of topical brinzolamide given twice daily for three months to patients aged 18–60 years with chronic CSR, affecting the fovea, and non-resolving after four months of follow-up. This is an open-label study based in Argentina and Israel.

In summary, currently available findings are insufficient to conclude that CA inhibition alone has the potential to be a big game changer in the management of MO.

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