Efficacy and Prognostic Factors of Response to Carbonic Anhydrase Inhibitors in Management of Cystoid Macular Edema in Retinitis Pigmentosa

Gerald Liew,[1,2] Anthony T. Moore,[2,3] Andrew R. Webster,[2,3] and Michel Michaelides[2,3]

[1]Centre for Vision Research, Westmead Millennium Institute, University of Sydney, Sydney, Australia
[2]Moorfields Eye Hospital, London, United Kingdom
[3]University College London, Institute of Ophthalmology, London, United Kingdom

Correspondence: Michel Michaelides, University College London, Institute of Ophthalmology, Bath Street, London EC1V 9EL, UK; michel.michaelides@ucl.ac.uk.

Submitted: November 3, 2014
Accepted: February 3, 2015

Citation: 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;56:1531–1536. DOI:10.1167/iovs.14-15995

Purpose. To determine the efficacy and prognostic factors associated with carbonic anhydrase inhibitors (CAI) in the treatment of cystoid macular edema (CME) in retinitis pigmentosa (RP).

Methods. This was a cohort study of 81 subjects who were assessed before and after treatment. Spectral-domain optical coherence tomography (SD-OCT) was used to quantify CME. A reduction of at least 11% in central subfield (CSF) thickness was defined as objective evidence of response.

Results. In the 125 eyes that received topical dorzolamide, 40.0% demonstrated a response to treatment with a mean reduction in OCT CSF thickness of 105 μm (95% confidence interval [CI]: 82, 128). Mean starting visual acuity (VA) increased from 6/15 to 6/12 after a median time on treatment of 3.0 months. In patients prescribed oral acetazolamide, 28.1% of eyes (41.2% of patients) showed improvement in mean OCT CSF thickness of 115 μm (95% CI: 52, 177) over a median treatment interval of 4.0 months. Visual acuity improved from 6/15 to 6/12. Eyes that responded to topical dorzolamide were more likely to have autosomal recessive than autosomal dominant RP (44.6% vs. 23.3%, $P = 0.02$), and a higher mean baseline OCT CSF than eyes that did not respond ($P = 0.02$).

Conclusions. We report that 40.0% of eyes (53.1% of patients) showed an objective improvement in CME after treatment with topical dorzolamide and 28.1% of eyes (41.2% of patients) after treatment with oral acetazolamide. Autosomal recessive RP and greater initial central retinal thickness predicted response to treatment with topical dorzolamide.

Keywords: retinitis pigmentosa, acetazolamide, cystoid macular edema, dorzolamide

Retinitis pigmentosa (RP, OMIM #26800) is the most common group of inherited retinal disorders. It is genetically heterogeneous and is often classified according to the inheritance pattern, with autosomal dominant (AD), autosomal recessive (AD), and X-linked (XL) forms recognized. Over 100 genes/loci have been identified underlying RP.[1] Visual loss occurs from progressive degeneration of photoreceptors and the presence of complications such as cystoid macular edema (CME), epiretinal membrane, and cataract. The prevalence of CME in patients with RP is not known with certainty, but clinic-based surveys report a range of between 11% and 20% detected by fluorescein angiography and ophthalmoscopy,[2–5] and 38% to 49% on optical coherence tomography (OCT).[2,6,7] Specific forms of RP such as those associated with autosomal dominant rhodopsin (RHO) mutations may be associated with more severe and earlier onset of CME.[8]

A number of treatments have been reported to have some success in managing CME in RP.[2] However, there are no masked randomized clinical trial data available to guide management. Interventional case series suggest that topical and oral carbonic anhydrase inhibitors (CAI) such as dorzolamide and acetazolamide,[9,10] intravitreal triamcinolone,[11,12] intravitreal dexamethasone implants,[13,14] and intravitreal antivascular endothelial growth factor agents[15,16] may be of some benefit in treating CME.[2] In the largest case series to date, topical dorzolamide was effective in reducing CME in 67% of patients[17]; smaller cases series suggest a higher response rate of up to 81%.[18,19] Areas of uncertainty include the magnitude of effect, effect on visual acuity, and predictors of response. We therefore conducted a retrospective cohort study of 81 patients with RP and CME to determine the efficacy of treatment with topical dorzolamide and oral acetazolamide, and to assess predictors of response.

Methods

Patients

This retrospective cohort study included 81 patients seen in the inherited retinal dystrophy clinics at Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom, from January 2012 to December 2012 inclusive. Patients were included in the study if they had CME secondary to RP and were started on either topical dorzolamide or oral acetazolamide therapy. Patients were excluded if they had CME secondary to other causes such as epiretinal membrane, vitreous traction, diabetes,

vascular occlusions or uveitis; if they did not have OCT scanning performed on at least two visits to monitor for CME changes; if they had cataract surgery in the preceding 2 years as this may contribute to postoperative CME; and if they had received any previous treatment for CME in the preceding year. The study was approved by the Human Research Ethics Committee of Moorfields Eye Hospital NHS Foundation Trust.

The diagnosis of RP was based on a history of nyctalopia and evidence of peripheral visual field constriction, characteristic fundus findings on ophthalmoscopic examination, presence of fundus autofluorescence abnormalities such as peripheral hypoautofluoresence and central perimacular hyperautofluorescent rings, and full field ERG testing suggestive of rod-cone dystrophy. Electroretinogram testing was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.[12–14] Pedigrees were constructed for all patients and RP was categorized as autosomal dominant (e.g., one affected parent or child, equal gender distribution), autosomal recessive (e.g., no affected parents, consanguinity) and X-linked RP (e.g., males only, no male-to-male transmission, mothers may have signs). A limited number of patients had a molecular diagnosis.

Snellen best-corrected visual acuities (BCVAs) at baseline and subsequent visits were documented and converted into logarithm of the minimal angle of resolution (logMAR) values for statistical analysis. The Spectralis HRA + OCT with viewing module version 5.1.2.0 (Heidelberg Engineering, Heidelberg, Germany) was used to acquire autofluorescence images as well as SD-OCT images. The protocol for SD-OCT included a dense horizontal linear scan centered on the fovea and the software interface (HEYEX version 1.6.2.0; Heidelberg Engineering) was used for registration of blood vessels to facilitate longitudinal analysis of changes in central retinal subfield (CSF) thickness. We defined response to therapy as reduction of 11% or greater in CSF thickness after initiation of therapy to be comparable with previous studies.[17,20] This magnitude of reduction has previously been reported as an objective outcome[17,20] and is considered to be a significant change that cannot be accounted for by intervisit variability in measurement.[20]

Statistical Analyses

We used statistical software (SAS version 9.2; SAS Institute, Cary, NC, USA) was used for analyses. Fishers' exact test was used for comparing categorical variables. Mean logMAR visual acuity and OCT CSF thickness were compared using the *t*-test with a two-tailed distribution. Other analyses were conducted using the nonparametric Kruskal-Wallis test. Results were considered significant if $P < 0.05$.

Results

This study examined 64 patients (125 eyes) who were treated with topical dorzolamide 2% and 17 patients (32 eyes) who were treated with oral acetazolamide 250 mg slow release twice a day or 500 mg once a day. Baseline characteristics of the patients are presented in Table 1. The mean age of patients started on dorzolamide was 45.4 (± 15.3) years while that of patients started on acetazolamide was 36.0 (±11.3) years. Females comprised 42.2% and 50.0% of patients started on dorzolamide and acetazolamide, respectively. Of patients receiving dorzolamide, 25.0% had autosomal dominant RP, 73.4% had autosomal recessive RP, and 1.6% had X-linked RP. Of those receiving acetazolamide, 50% had autosomal dominant RP and 50% had autosomal recessive RP.

In the 125 eyes that received topical dorzolamide, 40.0% demonstrated a response to treatment with a mean reduction in OCT CSF thickness of 105 μm (95% confidence interval [CI]: 82, 128; Table 2). Mean starting visual acuity increased from 6/15 to 6/12 after a median time on treatment of 3.0 months. At a patient level, 53.1% of patients showed an improvement in at least one eye (Table 2). In the 60.0% of eyes (46.9% of patients) that did not respond to treatment, OCT CSF was essentially unchanged and VA remained unchanged at 6/15 before and after treatment over a median of 3.0 months.

Table 1. Baseline Characteristics of Patients in Study

	Dorzolamide 2% $n = 64$	Acetazolamide $n = 17$
Age, y (SD)	45.4 (15.3)	36.0 (11.3)
Female, *n* (%)	27 (42.2)	9 (52.9)
Retinitis pigmentosa, (%)		
Autosomal dominant, *n* (%)	16 (25.0)	9 (52.9)
RP1	3	1
PRPF31	2	2
RHO	3	
IMPDH1	1	
NRL	1	1
RP9		1
PRPF8		1
Unknown/not tested	6	3
Autosomal recessive, *n* (%)	47 (73.4)	8 (47.1)
USH2A	2	1
CRB1	1	
Unknown/not tested	44	7
X-linked	1 (1.6%)	0
Unknown/not tested	1	

Autosomal dominant, autosomal recessive, and X-linked were determined clinically, with molecular confirmation in some patients.

Oral acetazolamide treatment was prescribed to 17 patients (32 eyes); 28.1% of eyes (41.2% of patients) showed an improvement in mean OCT CSF thickness of 115 μm (95% CI: 52, 177) over a median treatment interval of 4.0 months (Table 2). Visual acuity improved over this period from 6/15 to 6/12. Among nonresponders, there was no appreciable change in mean OCT CSF thickness and VA remained the same at 6/12.

In Table 3, predictors of response to topical dorzolamide were examined. It was found that 44.6% of eyes with autosomal recessive RP showed a response, compared with 23.3% of eyes with autosomal dominant RP ($P = 0.02$). Both eyes with X-linked RP showed a response. Eyes that responded had a higher mean starting OCT CSF than eyes that did not respond ($P = 0.02$). Mean age at treatment and length of treatment did not predict response to dorzolamide. A similar relationship was observed with oral acetazolamide whereby more eyes with autosomal recessive RP (40.0%) than autosomal dominant RP (17.7%) responded to treatment, although this difference was not statistically significant (Table 3).

The Figure shows some examples of patients with autosomal recessive RP and CME who responded well to CAI therapy.

We performed sensitivity analyses where we defined response as a 20% change in OCT CSF thickness and found the same results. Autosomal recessive RP and greater initial OCT CSF thickness remained the only predictors of response to topical dorzolamide ($P = 0.01$ and $P < 0.001$, respectively).

We repeated analyses after excluding patients with follow up less than 2 months (one patient each at 1 and 1.5 months' follow-up) and found essentially the same results.

TABLE 2. Response of Participants to Dorzolamide or Acetazolamide

Intervention	Eyes, *n* (%)	Persons,* *n* (%)	Mean Reduction in OCT CSFT Thickness,* µm (95% CI)	Time on Treatment, mo median (range)	Mean Starting VA, logMAR (Snellen)	Mean Stopping VA, logMAR (Snellen)	*P* Value**
Dorzolamide 2% three times a day	*n* = 125	*n* = 64					
Response, *n* (%)	46 (40.0)	34 (53.1)	105 (82, 128)	3.0 (1.5–12.0)	0.40 (6/15)	0.35 (6/12)	
No response, *n* (%)	69 (60.0)	30 (46.9)	4 (−2, 9)	3.0 (2.0–16.0)	0.42 (6/15)	0.42 (6/15)	0.05
Acetazolamide 250 mg twice a day or 500 mg once a day	*n* = 32	*n* = 17					
Response, *n* (%)	9 (28.1)	7 (41.2)	115 (52, 177)	4.0 (2.0–12.0)	0.43 (6/15)	0.36 (6/12)	
No response, *n* (%)	23 (71.9)	10 (58.8)	6 (−2, 10)	4.0 (1.0–16.0)	0.30 (6/12)	0.26 (6/12)	0.52

Response was defined as a reduction in central subfield OCT thickness of 11%. CSFT, central subfield thickness.
* Response in at least one treated eye.
** For visual acuity, change between responders and nonresponders, calculated using *t*-test.

DISCUSSION

Cystoid macular edema is one of the few treatable causes of visual loss in RP. In this retrospective cohort study of 125 eyes in 64 patients treated with topical dorzolamide, we report that 40% of eyes (53% of patients) showed an objective improvement in CME after a median of 3 months of treatment (range, 1.5–12.0 months). This reduction in CME was associated with a modest improvement in mean VA from 6/15 to 6/12. A further 32 eyes in 17 patients were treated with oral acetazolamide and 28% of eyes (41% of patients) showed an improvement after a median of 4 months of treatment (range, 2.0–12.0 months). Mean VA in responders improved from 6/15 to 6/12 but this difference was not statistically significant. Mean visual acuity in nonresponders to topical dorzolamide or oral acetazolamide remained unchanged after treatment.

Our findings suggest a somewhat lower efficacy for topical dorzolamide than reported by other investigators (Table 4). Genead et al.[17] in a retrospective case series of 64 eyes from 32 patients with Usher syndrome or RP reported that 60% of eyes (67% of patients) showed an improvement in CME using the same objective OCT criteria as in our study. Grover et al.[20] in a nonrandomized clinical trial of 15 patients, reported improvement in CME according to similar criteria in 87% of patients. Ikeda et al.[18] studied 16 eyes of 9 patients and reported that 81% of eyes had a reduction in retinal thickness, although in this study any absolute reduction was taken to signify a response. Possible reasons for the lower response rate in our study include the nonrandom allocation of patients and use of objective OCT criteria to define response, as compared to previous studies, some of which used more subjective angiographic evidence of response. Differences in age range and duration of follow-up, and different degrees of initial severity of CME among the different studies may also explain some of the differences in response rates reported. In our study, nonresponders were continued on treatment for a median of 3.0 months (range, 2.0–16.0 months) and longer treatment duration may have resulted in a higher percentage of responders. Some studies have reported treatment for 1 month is sufficient to determine if treatment should be discontinued.[20]

In the current study, a higher proportion of eyes responded to topical dorzolamide (40%) than to oral acetazolamide (28%). These proportions are not directly comparable as the patients were not assigned randomly to each treatment. There are few head to head studies comparing acetazolamide to dorzolamide. Grover et al.[21] reported results from a prospective, double masked, cross-over study of five patients that all (100%) showed angiographic improvement with oral acetazolamide, compared with two (40%) who improved with topical dorzolamide. Again differences in patient age, initial severity of CME and methods of assessing CME may underlie differences reported in our cohort compared to other cohorts.

We examined prognostic factors for response to treatment and found that autosomal recessive RP and greater initial central retinal thickness predicted a favorable response to topical dorzolamide. To our knowledge, no predictors of response have previously been reported in the literature. Although autosomal recessive and autosomal dominant RP are genetically heterogeneous disorders, they have in general distinct clinical presentations with earlier onset and greater severity in autosomal recessive RP.[22] Further, the most common cause of autosomal dominant RP is mutations in rhodopsin (RHO), which accounts for approximately 30% of cases,[23] and may in some cases be associated with more severe and earlier onset of CME.[8] It is possible that response to therapy may be similarly different. The observation that patients with greater initial central retinal thickness have a

Table 3. Predictors of Response to CAI

	Topical Dorzolamide			Oral Acetazolamide		
	Response Eyes $n = 46$, n (%)	No Response Eyes $n = 69$, n (%)	P Value*	Response Eyes $n = 9$, n (%)	No Response Eyes $n = 23$, n (%)	P Value*
Retinitis pigmentosa						
AD	7 (23.3)	23 (76.7)		3 (17.7)	14 (82.4)	
AR	37 (44.6)	46 (55.4)		6 (40.0)	9 (60.0)	
XL	2 (100.0)	0 (0.0)	0.02	0	0	0.24
Median age at treatment, y (range)	46 (12–68)	49 (20–76)	0.13	39 (20–50)	35 (13–58)	0.30
Mean starting OCT CSFT thickness, μm (95% CI)	413 (381, 446)	363 (335, 391)	0.02	452 (371, 532)	394 (352, 437)	0.16
Median length of treatment, mo (range)	3.0 (1.5–12.0)	3.0 (2.0–16.0)	0.89	4.0 (2.0–12.0)	4.0 (1.0–16.0)	0.92

* Fishers' exact test was used for comparing categorical variables (AD, AR, XL cases). Mean starting OCT CSFT was compared using *t*-test. Other analyses were conducted using the nonparametric Kruskal-Wallis test.

better response to dorzolamide (mean starting CSF of 413 μm in responders compared to 363 μm in nonresponders) is consistent with the response to therapy in other conditions where CME occurs, for example in retinal vein occlusions and diabetic macular edema.[24]

The mechanism by which CAIs reduce CME remains unclear.[2] Some authors have theorized there is an imbalance in the distribution of RPE membrane bound carbonic anhydrase isozyme IV in CME, with greater density in the basolateral than apical domains.[9,25,26] Carbonic anhydrase

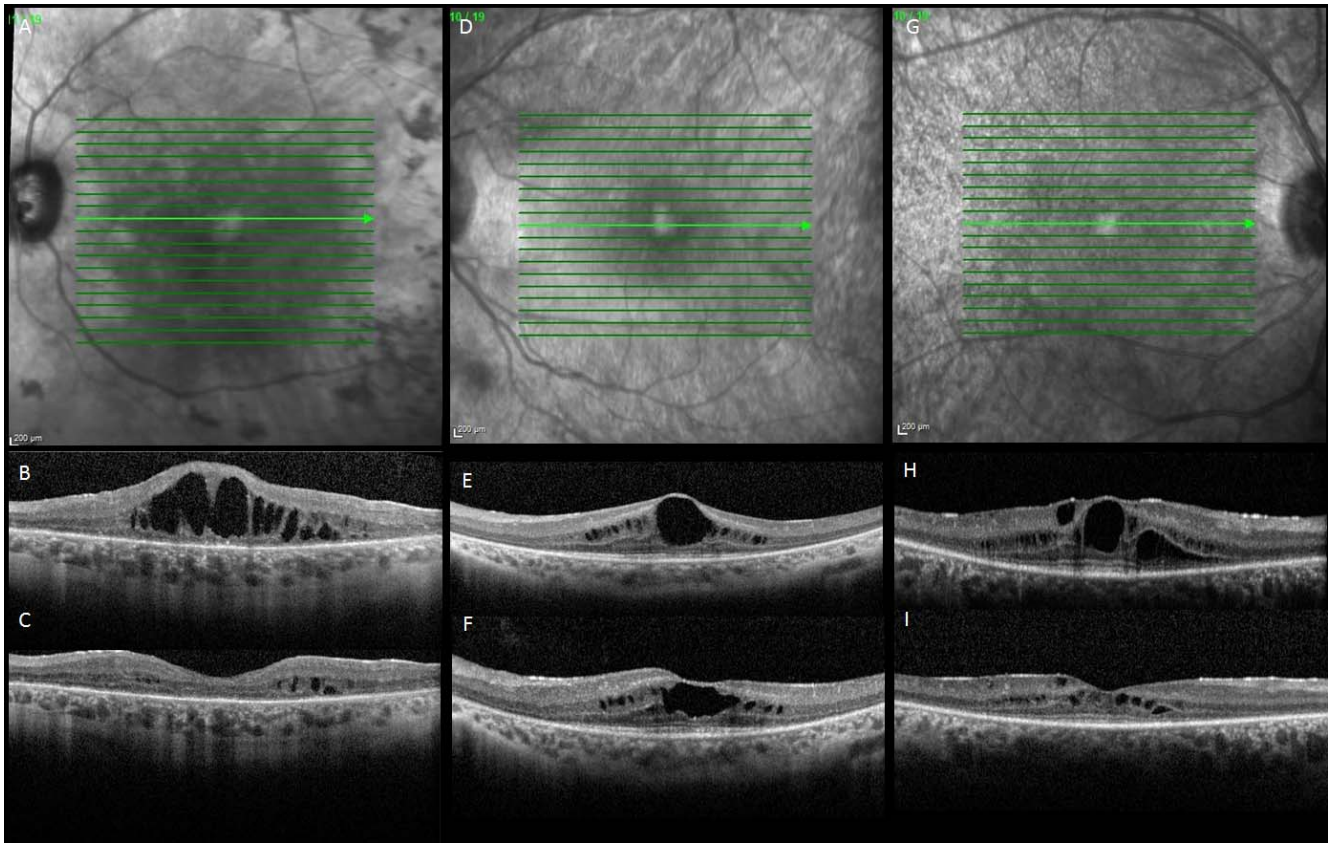

Figure. Spectral-domain OCT of three patients with CME showing response to carbonic anhydrase inhibitors. (**A**) Near-infrared images of left eye of 62-year-old female patient with autosomal recessive retinitis pigmentosa (*USH2A*-associated), visual acuity 1/60 prior to treatment. (**B**) Spectral-domain OCT image showing central CME. (**C**) Same patient after 9 months of treatment with topical dorzolamide three times a day showing marked improvement in cystoid macular edema but without any improvement in visual acuity. (**D**) Near-infrared image of Left eye of 20-year-old female patient with autosomal recessive retinitis pigmentosa and a clinical diagnosis of Ushers syndrome type 1. Visual acuity prior to treatment was 6/18. (**E**) Spectral-domain OCT image showing central CME. (**F**) Same patient after 4 months of treatment with topical dorzolamide three times a day showing improvement in cystoid macular edema. Visual acuity improved to 6/12. (**G**) Near-infrared image of Right eye of 38-year-old female with autosomal recessive retinitis pigmentosa with vision of 6/36 prior to treatment. (**H**) Spectral-domain OCT image showing central CME. (**I**) Same eye of patient after 7 months of treatment with 250 mg slow release oral acetazolamide twice a day and improved vision to 6/18.

Investigative Ophthalmology & Visual Science

Table 4. Table of Studies With 5 Patients or More That Examined CAI in Treatment of CME in RP

Treatment	Authors	Year	Patients, *n*	Responders, %	CME Definition
Oral acetazolamide	Cox et al.[9]	1988	6	66%	Fluorescein angiography
	Fishman et al.[10]	1989	12	50%	Fluorescein angiography
	Grover et al.[21]	1997	5	100%	Fluorescein angiography
	Apushkin et al.[30]	2007	6	100%	OCT
Oral methazolamide	Fishman et al.[31]	1994	17	53%	Fluorescein angiography
	Shahidi et al.[32]	1994	6	83%	Fluorescein angiography and retinal thickness analyzer
Topical dorzolamide	Grover et al.[21]	1997	5	40%	Fluorescein angiography
	Grover et al.[20]	2006	15	87%	OCT
	Fishman et al.[33]	2007	8	100%	OCT
	Genead et al.[17]	2010	32	63–67%	OCT
	Ikeda et al.[18]	2011	9	>81%	OCT

inhibitors have a greater inhibitory effect on basolateral than apical isozymes, leading to a more normal distribution of carbonic anhydrase activity and polarity of RPE cells and subsequent fluid egress from the retina into the choroid.[26] This view is supported by a study showing reduced fluorescein leakage from the RPE in CME following application of azetazolamide.[9] Other studies have observed that carbonic anhydrase inhibitors reduce fluorescein leakage primarily from the perifoveal capillaries,[10] suggesting a direct effect on the retinal vasculature may be responsible for the improvement in CME. This view is supported by work demonstrating that carbonic anhydrase inhibitors directly improve retinal blood flow and oxygenation,[27–29] potentially restoring the normal mechanisms by which CME is resolved.

Strengths of this study include the largest cohort reported to date and objective measurement of CME on SD-OCT. Limitations of the study include the retrospective, observational design without a randomized control group, which renders our estimates of efficacy less reliable than those from a randomized controlled trial. To our knowledge, no such trial exists nor are any planned. Differences in the response rates from our study and others published in the literature may be related to different patient mix (e.g., age, initial severity of CME, methods of assessing CME) in the various studies. Another limitation is that the majority of patients did not have a molecular diagnosis. Such information would be important to determine if response to carbonic anhydrase inhibitors is dependent on genotype. Finally, there were only two eyes from the same patient with X-linked RP in this study, and both eyes showed an improvement in CME with topical dorzolamide. These numbers are too small to draw meaningful conclusions and further research regarding the efficacy of dorzolamide in this group of patients is needed. Future research should focus on the need for a multicentered randomized controlled trial to address these issues, and to clarify if mutation type plays a role in determining response to CAI. Rebound CME may occur, usually within 3 months of treatment,[20] and additional monitoring with longer follow up would be useful to detect this. This was not an aim of the current study and we are not able to report on rates of rebound CME.

In conclusion, we report that 40% of eyes (53% of patients) showed an objective improvement in CME after a median of 3 months of treatment with topical dorzolamide. Visual acuity in these patients improved modestly from 6/15 to 6/12. In patients treated with oral acetazolamide, 28% of eyes (41% of patients) showed an improvement in CME after a median of 4 months of treatment. In patients treated with topical dorzolamide, those with autosomal recessive RP and with greater initial central retinal thickness were more likely to respond to treatment.

Acknowledgments

Supported by grants from the Eye Foundation, Royal Australian New Zealand College of Ophthalmologists, National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital National Health Service Foundation Trust and UCL Institute of Ophthalmology, Fight For Sight (UK) and FFS Mercer Fund, Moorfields Eye Hospital Special Trustees, Macular Disease Society, the Foundation Fighting Blindness (USA), Retinitis Pigmentosa Fighting Blindness; and an FFB Career Development Award (MM). The authors alone are responsible for the content and writing of the paper.

Disclosure: **G. Liew**, None; **A.T. Moore**, None; **A.R. Webster**, None; **M. Michaelides**, None

References

1. Retinal Information Network. https://sph.uth.edu/RetNet/. Accessed October 10, 2014.
2. Salvatore S, Fishman GA, Genead MA. Treatment of cystic macular lesions in hereditary retinal dystrophies. *Surv Ophthalmol*. 2013;58:560–584.
3. Fishman GA, Maggiano JM, Fishman M. Foveal lesions seen in retinitis pigmentosa. *Arch Ophthalmol*. 1977;95:1993–1996.
4. Fishman GA, Fishman M, Maggiano J. Macular lesions associated with retinitis pigmentosa. *Arch Ophthalmol*. 1977;95:798–803.
5. Pruett RC. Retinitis pigmentosa: clinical observations and correlations. *Trans Am Ophthalmol Soc*. 1983;81:693–735.
6. 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;28:103–110.
7. 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;23:915–919.
8. Kim C, Chung H, Yu HG. Association of p.P347L in the rhodopsin gene with early-onset cystoid macular edema in patients with retinitis pigmentosa. *Ophthalmic Genet*. 2012; 33:96–99.
9. Cox SN, Hay E, Bird AC. Treatment of chronic macular edema with acetazolamide. *Arch Ophthalmol*. 1988;106:1190–1195.
10. Fishman GA, Gilbert LD, Fiscella RG, Kimura AE, Jampol LM. Acetazolamide for treatment of chronic macular edema in retinitis pigmentosa. *Arch Ophthalmol*. 1989;107:1445–1452.
11. Ozdemir H, Karacorlu M, Karacorlu S. Intravitreal triamcinolone acetonide for treatment of cystoid macular oedema in patients with retinitis pigmentosa. *Acta Ophthalmol Scand*. 2005;83:248–251.

12. Scorolli L, Morara M, Meduri A, et al. Treatment of cystoid macular edema in retinitis pigmentosa with intravitreal triamcinolone. *Arch Ophthalmol*. 2007;125:759–764.
13. Srour M, Querques G, Leveziel N, et al. Intravitreal dexamethasone implant (Ozurdex) for macular edema secondary to retinitis pigmentosa. *Graefes Arch Clin Exp Ophthalmol*. 2013;251:1501–1506.
14. Ahn SJ, Kim KE, Woo SJ, Park KH. The effect of an intravitreal dexamethasone implant for cystoid macular edema in retinitis pigmentosa: a case report and literature review. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45:160–164.
15. Artunay O, Yuzbasioglu E, Rasier R, Sengul A, Bahcecioglu H. Intravitreal ranibizumab in the treatment of cystoid macular edema associated with retinitis pigmentosa. *J Ocul Pharmacol Ther*. 2009;25:545–550.
16. Yuzbasioglu E, Artunay O, Rasier R, Sengul A, Bahcecioglu H. Intravitreal bevacizumab (Avastin) injection in retinitis pigmentosa. *Curr Eye Res*. 2009;34:231–237.
17. 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;128:1146–1150.
18. Ikeda Y, Hisatomi T, Yoshida N, 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;250:809–814.
19. Ikeda Y, Yoshida N, Notomi S, et al. Therapeutic effect of prolonged treatment with topical dorzolamide for cystoid macular oedema in patients with retinitis pigmentosa. *Br J Ophthalmol*. 2013;97:1187–1191.
20. Grover S, Apushkin MA, Fishman GA. Topical dorzolamide for the treatment of cystoid macular edema in patients with retinitis pigmentosa. *Am J Ophthalmol*. 2006;141:850–858.
21. Grover S, Fishman GA, Fiscella RG, Adelman AE. Efficacy of dorzolamide hydrochloride in the management of chronic cystoid macular edema in patients with retinitis pigmentosa. *Retina*. 1997;17:222–231.
22. Fahim AT, Daiger SP, Weleber RG. Retinitis pigmentosa overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*. Seattle: University of Washington; 1993.
23. Inglehearn CF, Keen TJ, Bashir R, et al. A completed screen for mutations of the rhodopsin gene in a panel of patients with autosomal dominant retinitis pigmentosa. *Hum Mol Genet*. 1992;1:41–45.
24. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118:615–625.
25. Vinores SA, Derevjanik NL, Ozaki H, Okamoto N, Campochiaro PA. Cellular mechanisms of blood-retinal barrier dysfunction in macular edema. *Doc Ophthalmol*. 1999;97:217–228.
26. Wolfensberger TJ, Dmitriev AV, Govardovskii VI. Inhibition of membrane-bound carbonic anhydrase decreases subretinal pH and volume. *Doc Ophthalmol*. 1999;97:261–271.
27. Pedersen DB, Koch JP, la Cour M, et al. Carbonic anhydrase inhibition increases retinal oxygen tension and dilates retinal vessels. *Graefes Arch Clin Exp Ophthalmol*. 2005;243:163–168.
28. Reber F, Gersch U, Funk RW. Blockers of carbonic anhydrase can cause increase of retinal capillary diameter, decrease of extracellular and increase of intracellular pH in rat retinal organ culture. *Graefes Arch Clin Exp Ophthalmol*. 2003;241:140–148.
29. Siesky B, Harris A, Brizendine E, et al. Literature review and meta-analysis of topical carbonic anhydrase inhibitors and ocular blood flow. *Surv Ophthalmol*. 2009;54:33–46.
30. 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;27:1112–1118.
31. Fishman GA, Gilbert LD, Anderson RJ, Marmor MF, Weleber RG, Viana MA. Effect of methazolamide on chronic macular edema in patients with retinitis pigmentosa. *Ophthalmology*. 1994;101:687–693.
32. Shahidi M, Fishman G, Ogura Y, Ambroz K, Zeimer R. Foveal thickening in retinitis pigmentosa patients with cystoid macular edema. *Retina*. 1994;14:243–247.
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;91:743–745.

Investigative Ophthalmology & Visual Science