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Efficacy of Carbonic Anhydrase Inhibitors on Cystoid Fluid Collections and Visual Acuity in Patients with X-Linked Retinoschisis

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Purpose: To date, there is no standard treatment regimen for carbonic anhydrase inhibitors (CAIs) in X-linked retinoschisis (XLRS) patients. This retrospective study aims to evaluate the efficacy of CAIs on visual acuity and cystoid fluid collections (CFC) in XRLS patients in Dutch and Belgian tertiary referral centers.

Design: Retrospective cohort study.

Participants: Forty-two patients with XLRS.

Methods: In total, 42 patients were enrolled. To be included, patients had to have previous treatment with an oral CAI (acetazolamide), a topical CAI (brinzolamide/dorzolamide), or a combination of an oral and a topical CAI for at least 4 consecutive weeks. We evaluated the effect of the CAI on best-corrected visual acuity (BCVA) and central foveal thickness (CFT) on OCT.

Main Outcome Measures: Central foveal thickness and BCVA.

Results: The median age at the baseline visit of the patients in this cohort study was 14.7 (range, 43.6) years, with a median (interquartile range [IQR]) follow-up period of 4.0 (2.2−5.2) years. During the follow-up period, 25 patients were treated once with an oral CAI (60%), 24 patients were treated once with a topical CAI (57%), and 11 patients were treated once with a combination of both topical and oral CAI (26%). We observed a significant reduction of CFT for oral CAI by 14.37 μm per 100 mg per day ($P < 0.001$; 95% confidence interval [CI], −19.62 to −9.10 μm) and for topical CAI by 7.52 μm per drop per day ($P = 0.017$; 95% CI, −13.67 to −1.32 μm). The visual acuity changed significantly while on treatment with oral CAI by −0.0059 logMAR per 100 mg ($P = 0.008$; 95% CI, −0.010 to −0.0013 logMAR). Seven patients (17%) had side effects leading to treatment discontinuation.

Conclusions: Our data indicate that treatment with (oral) CAI may be beneficial for short-term management of CFC in patients with XLRS. Despite a significant reduction in CFT, the change in visual acuity was modest and not of clinical significance. Nonetheless, the anatomic improvement of the central retina in these patients may be of value to create an optimal retinal condition for future potential treatment options such as gene therapy.

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X-linked retinoschisis (XLRS) is a relatively common inherited retinal degenerative disease that almost exclusively affects males.[1] With an estimated prevalence of 1 in 5000 to 30 000, XLRS is the most frequent macular dystrophy in young males.[2] This monogenic disease can be caused by 1 of the more than 200 known pathogenic variants in the *retinoschisin-1* (*RS1*) gene.[3] This gene encodes the extracellular retinoschisin protein, which is expressed and secreted by the photoreceptors and bipolar cells. Retinoschisin is vital for cell-to-cell adhesion and signal transduction between cells, and helps maintain the anatomic structure of the retina. Pathogenic variants of retinoschisin lead to loss of the integrity of the retina, causing the formation of cystoid cavities, especially in the macular area, with half of the patients also having peripheral retinoschisis.[1,4]

X-linked retinoschisis typically manifests itself in early childhood with mild-to-severe, bilateral, nonacute reduction of visual acuity with considerable variability in severity and disease progression.[1,5,6] The best-corrected visual acuity (BCVA) generally declines slowly and may remain relatively stable in the first decades of life. However, after the fourth to fifth decade of life, vision tends to deteriorate progressively due to the development of macular

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atrophy.[1,6–10] Moreover, XLRS patients have an increased risk for sight-threatening complications such as retinal detachment, vitreous hemorrhage, and neovascular glaucoma.[1,8,10,11] A characteristic finding of XRLS is the spoke-wheel pattern of foveal retinoschisis on ophthalmoscopy, along with an electronegative electroretinogram.[12]

To date, no curative medical therapy is available for XLRS. However, for the management of cystoid fluid collections (CFC) in these patients, both topical and oral carbonic anhydrase inhibitors (CAIs) have been used.[8,9,13–16] These CAIs are thought to reduce CFC by increasing fluid transport across the retinal pigment epithelium (RPE) after binding to the membrane-bound type IV carbonic anhydrase receptors in the retinal pigment epithelial (RPE) cells.[14,17–19] However, in clinical practice, no standard treatment regimen is available for CAI for XLRS patients. This is due to a lack of longitudinal follow-up data and relatively small cohort sizes available to date. In this retrospective study, we investigated current clinical practice of CAI usage in XLRS in Dutch and Belgian centers, and evaluated the effect of CAI on CFC and visual function in a comparatively large cohort of XLRS patients.

Methods

Study Population

This retrospective study included medical records of 42 XLRS patients treated with oral acetazolamide, and/or topical brinzolamide or dorzolamide for $\geq$ 4 consecutive weeks between 2010 and 2022. Eligible patients also had to be molecularly diagnosed with a pathogenic variant in the *RS1* gene or be related to a first-degree family member with such a variant. Patients without a genetically confirmed diagnosis were also included when all the following clinical findings were present: an X-linked disease inheritance pattern; decreased visual acuity; and typical central retinoschisis on spectral-domain OCT (SD-OCT) and/or a spoke-wheel pattern in the macula on fundoscopic examination. Exclusion criteria were as follows: the presence of macular atrophy or any loss of visual function due to factors other than XLRS (such as ocular trauma or glaucoma), which might have affected the outcome measures.

Clinical Data Collection

Data of Dutch patients were obtained from the medical records in the Delleman Archive, a database for hereditary eye diseases of the Amsterdam University Medical Centers, and various centers within the RD5000 consortium, a Dutch cooperative nationwide register for patients with inherited retinal dystrophies.[20] In addition, patients were included from the Ophthalmic Genetics Unit at the Department of Ophthalmology & Center for Medical Genetics Ghent, Belgium. This retrospective study was approved by the Medical Ethics Committee of the Erasmus Medical Center and Ghent University Hospital. It adhered to the tenets of the Declaration of Helsinki, and we obtained written informed consent from the patients or their legal guardians. The University Hospital Ghent waived the need for informed consent for the Belgian patients because of the use of anonymized data. Inclusion in this study required records of clinical visits with OCTs obtained before the start of and after a minimum of 4 weeks of CAI therapy. We defined the baseline visit as the last recent visit before the start of a cycle of the CAI. The patients underwent ophthalmological examination and (multimodal) imaging at the baseline visit, and during follow-up. Clinical characteristics of interest were age at diagnosis, best-corrected visual acuity (BCVA), and central foveal thickness (CFT) on SD-OCT. The mean CFT was calculated at the inner 1000-μm diameter circle of the ETDRS grid using the retinal thickness analysis protocol provided by the instrumental software. In addition, one of the authors (J.H.) also measured the CFT manually on the horizontal OCT scan at the foveal center. We obtained OCT scans with 1 of these 3 different OCT scanners: Heidelberg Spectralis HRA+OCT (Heidelberg Engineering Inc), Canon OCT-HS100 (Canon Inc), or Topcon 3D OCT 2000 (Topcon Corp), depending on the participating center.

Statistical Analysis

Statistical analyses were all performed using SPSS statistics (version 25.0; IBM Corp); except for the linear mixed-effects models, we used R software version 4.0.3 (R Foundation for Statistical Computing). Linear mixed-effects models were used to evaluate the effects of CAI therapy on the CFT and the BCVA. These models account for the correlations of the observations between the 2 eyes within 1 patient. Therefore, we included both eyes in the analyses except for patients with an amblyopic eye, for whom we excluded the amblyopic eye. The linear mixed-effects models were adjusted for age at the baseline visit and included a main effect of time to capture the natural progression of this disease. This adaption to the natural course of XLRS was necessary, as the CFC fluctuates over time and could even coalesce and collapse after a long period without treatment.[21–24] The BCVA was measured using Snellen charts and converted into logarithm of the minimal angle of resolution (logMAR) values for statistical analyses. A decrease of $\geq$ 0.14 logMAR was considered clinically relevant, as this corresponds to an improvement by $\geq$ 7 letters on the ETDRS chart.[14,22,25] Best-corrected visual acuity measurements during a period of vitreous hemorrhages (VHs) were excluded from the analyses for 1 patient, as this could have distorted the visual outcomes, although it is considered a complication of the disease. The analyses included all the other BCVA measurements of that patient who experienced VH.

Results

The median (IQR) age at baseline of the study population was 14.7 (10.2–21.7) years. We evaluated the data from 77 eyes of 42 patients after excluding 7 eyes due to phthisis, amblyopia, and lacking follow-up scans. The patients in this study had a median (IQR) follow-up time of 4.0 (2.2–5.2) years, with a median (IQR) of 6 (5.0–12.0) visits (Table 1). Because there is no gold standard in the dosing and administration of CAIs for XLRS, the included patients received different dosing regimens and treatment strategies based on their physician's preference, the effect on the CFC, and potential adverse events at follow-up. During follow-up, 25 patients (60%) had used oral CAI at least once as CAI monotherapy, and 24 patients (57%) had used topical CAI at least once as CAI monotherapy. Eleven patients (26%) used a combination therapy of topical and oral CAI at least once. Moreover, 15 patients (36%) had multiple on-and-off cycles of CAI treatment during their follow-up period. Twenty-one of the 31 patients (68%) who used topical CAI during follow-up used a dosage of 2 to 3 times a day, whereas 10 of 31 patients (32%) used a dosage of 4 to

Table 1. Baseline Clinical Characteristics of XLRS Patients

Characteristics	Data XLRS Patients (n = 42)
Age at baseline (yrs)	
Mean ± SD	17.8 ± 10.6
Median (IQR)	14.7 (10.2–21.7)
Range	43.6
Age at last examination (yrs)	
Mean ± SD	21.9 ± 10.3
Median (IQR)	18.7 (15.9–26.8)
Range	43.1
Number of visits	
Mean ± SD	7.9 ± 4.7
Median (IQR)	6.0 (5.0–12.0)
Range	23.0
Follow-up time (yrs)	
Mean ± SD	4.2 ± 2.9
Median (IQR)	4.0 (2.2–5.2)
Range	12.6

IQR = interquartile range; SD = standard deviation; XLRS = X-linked retinoschisis.

8 times a day. All 29 patients treated with oral CAI had a dosage varying from 125 mg once every 2 days to 250 mg 3 times a day. The most common dosage of acetazolamide was 2 times 250 mg a day, which was used in 14 of 29 patients (48%). Seven of 29 (24%) patients used a dosage of 125 mg acetazolamide twice a day. There was no clear evidence of a synergistic interaction between topical and oral CAI on the change of the CFT ($P = 0.86$; 95% CI, −1.95 to +2.33 μm) or on the change in BCVA ($P = 0.37$; 95% CI, −0.00094 to +0.0026 logMAR).

Effects of CAI on Retinal Parameters on OCT

The manually measured CFT on OCT had a Spearman's rank correlation of 0.98 for the right eyes (n = 37) and 0.97 for the left eyes (n = 40) with the automated CFT calculation. The median (IQR) CFT at baseline was 514.0 (418.5–635.5, n = 37) μm for right eyes and 490.5 (367.8–630.8, n = 40) μm for left eyes. Patients using oral acetazolamide had a significant reduction of their CFT by 14.37 μm per 100 mg a day ($P < 0.001$; 95% CI, −19.62 to −9.10 μm). Topical CAI also had a significant mean reduction of 7.52 μm per drop a day ($P = 0.017$; 95% CI, −13.67 to −1.32 μm). Interestingly, untreated patients also had a significant reduction of their CFT over time per year by 10.93 ($P = 0.015$; 95% CI, −19.62 to −2.63) μm without any treatment. The median (IQR) CFT at the last available visit for the included patients was 414.0 (232.5–571.5, n = 37) μm for right eyes and 347.0 (167.3–526.8, n = 40) μm for left eyes. There was an asymmetrical effect of CAI on the CFT in 1 patient with the topical CAI monotherapy and 1 patient with the combination treatment. Although both left eyes of these patients had residual but reduced CFT, their right eyes still had no significant reduction of CFT. Twelve patients who used topical CAI monotherapy (50%) and 5 using oral CAI monotherapy (20%) showed no reduction of the CFT on OCT while on medication. Complete resolution of CFC occurred in 6 eyes from 5 of 25 patients (20%) who used oral acetazolamide monotherapy. One patient had complete resolution in both eyes, but this patient had no follow-up scans after complete resolution. The 4 other patients (16%) had complete resolution only in 1 eye. Two of these 4 patients had a recurrence of their CFC after 3.7 months and 9.9 months, respectively, while they had the same dosage. Of the 2 remaining patients, 1 had CFC recurrence after 6.3 months after treatment discontinuation, and the other had recurrence after 3.4 months after lowering the dosage from 3 to 2 times 125 mg acetazolamide a day. Complete resolution in both eyes also occurred in both eyes of 1 of 24 patients (4%) using topical CAI monotherapy and lasted 41 months, but the CFC reappeared in the right eye after stopping topical therapy. Fourteen eyes from 9 of 42 patients (21%) using CAI showed reduction until residual CFC on OCT while on CAI therapy. Of these patients, 2 patients (4 eyes) used oral CAI monotherapy, 4 patients (4 eyes) received topical CAI monotherapy, and 3 patients (6 eyes) received combination treatment (Fig 1; Fig S2, available at www.ophthalmologyretina.org).

During follow-up, the dosage administered to the patient varied based on the effect on the CFC and adverse events. Of the patients with minimal fluctuations in their dosage, the CFC reduction remained stable in 6 patients (25%) using topical CAI, in 10 patients (40%) using oral CAI, and in 4 patients (36%) using a combination of topical and oral CAI.

Effects of CAI on Best-Corrected Visual Acuity

The median (IQR) BCVA at baseline was 0.40 (0.22–0.52, n = 33) logMAR for the right eyes and 0.40 (0.30–0.49, n = 37) logMAR for the left eyes. The visual acuity improved significantly in the patients using daily oral CAI by −0.0059 logMAR per 100 mg ($P = 0.008$; 95% CI, −0.010 to −0.0013), equivalent to 0.30 ETDRS letters. The improvement in patients using daily topical CAI was −0.0048 logMAR per droplet ($P = 0.06$; 95% CI, −0.0098 to +0.00019), which is equivalent to 0.24 ETDRS letters. The median (IQR) BCVA at the last available visit was 0.40 (0.22–0.52, n = 36) logMAR for the right eye and 0.30 (0.22–0.52, n = 39) logMAR for the left eye. A clinically relevant improvement in BCVA (i.e., decrease of 0.14 logMAR equivalent to 7 ETDRS letters) was achieved in 7/77 eyes (9%) of 5 of 42 (12%) patients who had CFT reduction. Of these patients, 1 patient (2 eyes included) had oral CAI monotherapy, 2 patients (3 eyes included) had topical CAI monotherapy, and 2 patients (4 eyes included) received combination treatment. This BCVA improvement was achieved only in the right eye of the patients using oral CAI monotherapy, and lasted 6.0 months while on treatment without an increase of the CFC. The 2 patients using combination treatment had a 0.14 logMAR BCVA improvement in both eyes. This improvement lasted for 3.4 months in 1 patient, after which the CFC recurred despite treatment. The BCVA improvement in the other patient with the combination treatment lasted 12.7 months and disappeared when the patients stopped using the drops while continuing oral acetazolamide. Best-corrected visual acuity improvement in 1 patient using topical CAI monotherapy lasted for 33.3 months and disappeared after cessation of the drops.

Adverse Events

Two patients using topical CAI reported side effects. One patient had a burning sensation in the treated eyes, and the other had painful eye movements. Thirteen of 29 patients (45%) using oral CAI experienced adverse events. The most common were paresthesia (54%), fatigue (31%), and headache (23%). Other reported

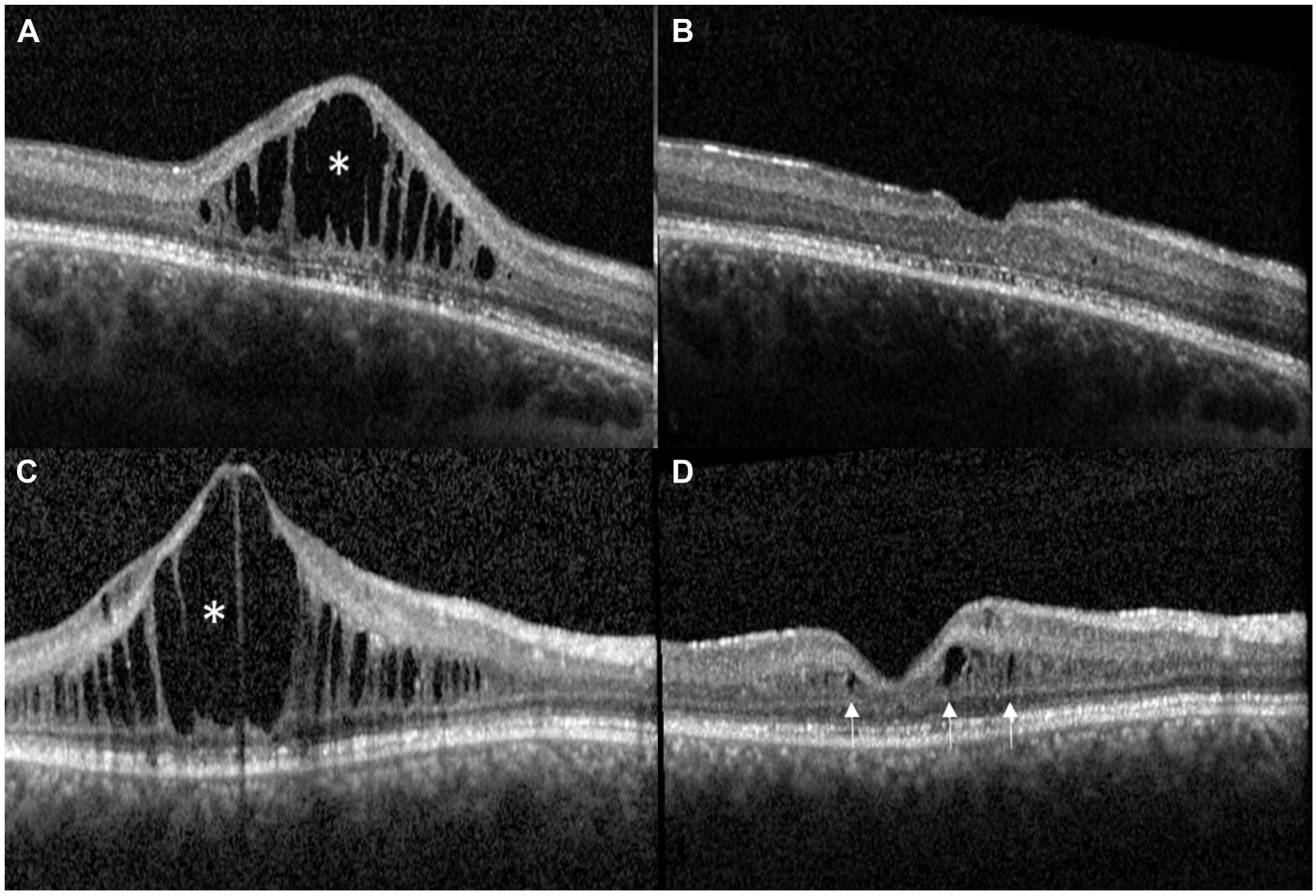

Figure 1. Spectral-domain–OCT images through the fovea of the right eye of 2 X-linked retinoschisis (XLRS) patients treated with carbonic anhydrase inhibitors. **A,** Spectral-domain–OCT image of the macula of the right eye of a 17-year-old XLRS patient at baseline with large cystoid fluid collections (CFC), and (**B**) after 2 months of oral acetazolamide 250 mg twice a day resulting in complete resolution of the CFC. Best-corrected visual acuity (logarithm of the minimum angle of resolution) improved from 0.80 to 0.70. **C**, Spectral-domain–OCT image of the macula of the right eye of an 18-year-old XLRS patient at baseline with large CFC, and **(D)** after 2.5 months using topical brinzolamide 3 times a day, showing only small residual CFC (marked by arrows). Best-corrected visual acuity did not improve in this patient.

side effects were dizziness (15%), nausea (15%), dysgeusia (15%), and blurred vision (8%). Six patients (21%) using oral CAI and 1 patient (3%) using topical CAI discontinued their treatment due to these adverse events.

Discussion

This study investigated the effect of CAI on CFT (based on SD-OCT) and visual function in a cohort of XRLS patients. Both oral acetazolamide and topical CAI had a statistically significant impact on CFT and achieved a complete resolution of CFC in a minority of the treated patients. These changes appeared to be transient, as reported previously by Ambrosio et al.[15] Oral acetazolamide had a higher impact on CFT than topical CAI, as other studies reported this finding.[26,27] The lesser therapeutic effect of topical CAI is presumably due to the lower bioavailability in the retina and RPE compared with systemic administration.[28–30] Interestingly, as seen in other studies, we saw a markedly heterogeneous treatment response to oral and topical CAI between patients, and even between different eyes in 2 patients.[13,16,31] The variability of the response of CFC to CAI in our study suggests that the efficacy of CAI might be related to other factors, such as variation in carbonic anhydrase receptor sensitivity, the disease stage, and the condition of the RPE.[16,22,32] Namely, the mechanism of action of CAI on CFC in the macula is presumably through the inhibition of membrane-bound type IV carbonic anhydrase receptors in the RPE cells.[19] We saw no clear sign of synergistic interaction between topical and oral CAI. However, these analyses were complicated by the relatively few patients receiving combination treatments and variability in administrated dosages. The treatment allocation was not random but based on the physician's preference, adverse events, and prior effects on the CFC of the used treatment strategy before inclusion into this study.

In this study, oral and topical CAI significantly improved the visual acuity even after adjustment for age at baseline

and progression over time. Our results are in line with previously reported effects of oral CAI on visual acuity.[14,15,31,33] However, the median change of 0.03 logMAR in BCVA in patients using 500 mg acetazolamide a day in our study was very modest (approximately 1 ETDRS letter), and although statistically significant, this limited improvement in BCVA does not seem clinically relevant in the overall patient group. Only 5 patients had a clinically relevant BCVA improvement of $\geq$ 0.14 logMAR (approximately 7 ETDRS letters) during CAI treatment, but this improvement waned during treatment (in 2 patients) or after cessation of treatment (in 2 patients). Similarly, in a group of 14 XLRS patients, Ambrosio et al[15] found that the effect of both oral and topical CAI on the visual acuity decreased after 6 months and even disappeared after 2 years despite the continuation of treatment. A complete resolution of CFC in the patients in our study was not associated with a clinically relevant improvement in the BCVA, as reported by other studies.[13,25,31]

Side effects were more common with oral CAI than topical CAI, and due to these side effects oral CAI had to be discontinued in 21% of patients. The most common side effects in these patients were paresthesia and fatigue. These adverse events were seen with an acetazolamide dosage of $\geq$ 2 times 125 mg a day. It is relevant to take these side effects into account, as they might affect the therapeutic adherence of patients.

Thus far, 2 independent phase I/IIa clinical trials are ongoing to evaluate the safety and efficacy of intravitreal AAV-*RS1* gene augmentation therapy.[34,35] A study by Cukras et al[34] used an AAV8-*RS1* vector in 12 XLRS patients, and published the safety and efficacy results from 9 patients. In that study, the CFC fluctuated with a very slight variability, pretreatment and posttreatment, in 3 patients from the low-dose group. The CFC in the other 6 patients from the mid-dose and high-dose groups showed more variable fluctuation (i.e., reduction/expansion) on OCT. However, the BCVA did not improve in all patients after intravitreal gene therapy despite the change in the amount of CFC on OCT.[34] The other trial by Pennesi et al[35] also showed no overall reduction of cyst cavity volume or improvement in BCVA in the study eyes compared with the fellow eyes in all 27 participants after AAV2-*RS1* gene therapy. Only 1 patient (4%) who received high-dose treatment had a significant decrease of CFC in the study eye but did not have visual improvement. Hence, future studies may look into the potential of subretinal injection of gene therapy in XLRS. The delivery of subretinal viral vectors may be most efficient in the transduction of the transgene to the retina and is the preferred route of choice.[36,37] However, in XLRS, the presence of significant CFC in the macula may complicate subretinal injection, and increase the risk of surgery-related adverse events such as the formation of a macular hole. Also, the presence of CFC may preclude the apposition of retinal layers when retinoschisin protein is expressed after successful gene transfer to the retina. Therefore, the short-term use of acetazolamide could also be useful in upcoming treatments such as gene therapy in an attempt to achieve a decrease or resolution in CFC and a more normal macular structure before such treatment to increase therapy efficacy. In addition, an absence of CFC may also reduce the risk of damage to the retina caused by the subretinal injection.

Our study was limited by its retrospective design and the associated variation in dosage and duration of CAI therapy. The follow-up interval varied between subjects, which restricts an optimal comparison of the different regimens of CAI treatment over time. Another important limitation is the absence of a control group of untreated or placebo-treated XLRS patients. The CFT in untreated XLRS patients may also fluctuate over time as part of the natural course of the disease, and the treatment effect of the CAI could therefore be overestimated.[23] In line with previous studies, we have shown that XLRS patients have a tendency for a gradual decrease of CFC in the natural history of the disease regardless of treatment, and XLRS commonly evolves toward a picture of macular atrophy after the fourth to fifth decade of life.[7,8,17] Long-term CFC reduction in XLRS in these patients by acetazolamide may also play a role in preserving the residual macular structure and decreasing the risk of retinal atrophy and vision loss in the long term. However, it is possible that evident fluctuations in CFC, whether or not caused by treatment variability, may be detrimental to macular structure and function. Therefore, a prospective natural history study with an age-matched control group and risk-benefit analysis on the long-term treatment effect of acetazolamide on visual function (including microperimetry) and CFC in XLRS in relation to the side effects would be highly informative. Information regarding the retinal sensitivity on microperimetry could be valuable for monitoring macular function and give us more detailed information about the beneficial effect of CAI on visual function because retinal sensitivity on microperimetry appears to be one of the most sensitive parameters to measure a functional change in disease that affects the macula as shown in several other studies.[38–41]

So far, studies assessing the efficacy of CAI in the treatment of macular cysts in XLRS are limited to a few case series or small-cohort studies. The current large-cohort study has shown relatively limited efficacy of oral CAI therapy on CFT and reduction of CFC in XLRS patients, and a limited effect on BCVA. The use of CAI may be useful in creating the optimal condition of the macula before upcoming definitive therapeutic options such as gene therapy.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. This retrospective study was approved by the medical ethics committee of the Erasmus Medical Center and Ghent University Hospital. It adhered to the tenets of the Declaration of Helsinki, and we obtained written informed consent from the patients or their legal guardians. The University Hospital Ghent waived the need for informed consent for the Belgian patients because of the use of anonymized data.

No animal subjects were used in this study.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CAI** = carbonic anhydrase inhibitor; **CFC** = cystoid fluid collections; **CFT** = central foveal thickness; **CI** = confidence interval; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **RPE** = retinal pigment epithelium; ***RS1*** = *retinoschisin-1*; **SD-OCT** = spectral-domain OCT; **XLRS** = X-linked retinoschisis.

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