Efficacy for Sustained Use of Topical Dorzolamide for Treatment of Cystic Macular Lesions in Patients with X-Linked Retinoschisis (XLRS)

Mohamed A. Genead, MD; Gerald A. Fishman, MD; Saloni Walia, MD

Institute affiliation: Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois, USA.

Correspondence to: Gerald A. Fishman, MD

Department of Ophthalmology and Visual Sciences (MC 648), Room 3.85, Eye and Ear Infirmary, 1855 W Taylor Street, Chicago, Illinois 60612-7234.

Tel: +1- 312-996-8939; Fax: +1-312-996-1950; email: gerafish@uic.edu

Address for requests of reprints:

Department of Ophthalmology and Visual Sciences (MC 648), Room 3.85,

Eye and Ear Infirmary, 1855 W Taylor Street, Chicago, Illinois 60612-7234.

Tel: +1- 312-996-8939; Fax: +1-312-996-1950

None of the authors have any proprietary interest in this work.

Total word count for text: 3975

Word count for references: 600

Total word count: 3375

Abstract

Objectives: To determine the efficacy for sustained use of topical 2% dorzolamide on visual acuity (VA) and macular cystic-appearing lesions in XLRS patients.

Design: Retrospective analysis.

Setting: University hospital tertiary care referral.

Patients: Twenty nine eyes of 15 patients with XLRS on treatment with topical 2% dorzolamide for a duration ranged from 4-41 months were enrolled.

Main Outcome Measures: Changes in VA, cystic macular lesions, and central foveal zone (CFZ) thickness on optical coherence tomography over a treatment duration follow-up (FU) period.

Results: Among the 15 patients with XLRS, 20 eyes (68.9%) of 11 patients showed a positive response to treatment. Five of the 20 eyes (25.0%) in 3 of these 11 patients showed an initial response and a subsequent rebound of macular cysts. In 4 eyes (13.8%) of 3 patients, there was no response to treatment but the macular cysts did not worsen when compared to a baseline level. In five additional eyes (17.3%) of 4 patients, there was also no response to treatment and the macular cysts worsened when compared to a baseline level. Sixteen eyes (55.2%) of 12 patients had improvement in VA by ≥7 letters in at least one eye at the most recent FU visit. Seventeen eyes (58.6%) of 10 patients showed a reduction in the CFZ thickness in at least one eye when compared to the pretreatment level.

Conclusion: In our cohort of XLRS patients, we observed that such patients have the potential to experience a beneficial effect from sustained treatment of 2% dorzolamide.

Introduction

X-linked juvenile retinoschisis (XLRS) is a relatively rare hereditary retinal disease with an estimated prevalence of between 1 in 15,000 and 1 in 30,000,[1] caused by mutations in the *RS1* gene on Xp22,[2] which leads to splitting of the neural retina and reduced visual acuity in affected males. It is the most common cause of juvenile-onset macular degeneration in males. The patients typically have a cystic-like stellate maculopathy or foveal schisis.[2-5] Affected individuals have a reduction in central vision which typically is observed between 5 and 10 years of age.[3,5] Visual impairment is usually mild and generally stable until the fourth or fifth decade of life when progressive visual deterioration often occurs. However, less commonly, XLRS patients may present in early infancy with a squint, nystagmus, and bilateral, highly elevated bullous retinoschisis often with hemorrhage within the schisis cavity or into the vitreous.[5-6] Other findings that may occur, generally in later stages of XLRS, include vitreous hemorrhage, chorioretinal atrophy, and retinal detachment.[6] While not always present, a distinctive feature of this disease is a selective or predominant b-wave amplitude reduction shown by full-field electroretinography (ERG).[7] Retinal morphological changes in XLRS patients evaluated by high speed, high resolution Fourier domain (FD-OCT) show the presence of foveal schisis involving the outer and the inner plexiform layers as well as disruption and irregularity of photoreceptor outer and inner segment layers.[8]

Carbonic anhydrase inhibitors (CAI) have been used clinically for several years to lower intraocular pressure.[9] Recently, their use has been shown to be effective for the improvement of cystoid macular edema (CME) in patients with several retinal diseases such as retinitis pigmentosa,[10-12] uveitis,[13] and when found in conjunction with epiretinal macular membranes.[14] Topical and oral forms of CAI have also been demonstrated to cause an improvement in the macular cystic-like cavities in some cases of XLRS, as documented by OCT, and an improvement in visual acuity (VA).[15-17]

While prior studies have shown a beneficial effect from the use of a topical form of CAI in patients with XLRS,[15,17] these studies had a limited number of patients followed for a short period of time. Therefore, the aim of the current study was to determine the efficacy for sustained use of topical 2% dorzolamide on VA and foveal cystic-appearing lesions, as determined by OCT, in patients with XLRS.

Patients and Methods

Participants

This was an observational retrospective case series study. All patients 18 years of age or older with XLRS who were treated with topical 2% dorzolamide during the period of September 2005 through March 2009 (range: 4-41 months), in the Department of Ophthalmology at the University of Illinois at Chicago were enrolled in the study. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and was approved by an institutional review board at the University of Illinois at Chicago.

Twenty nine eyes of 15 patients with XLRS were included, and informed consent was obtained on all participants. Inclusion criteria included patients with juvenile XLRS and stable ocular fixation with no clinically significant media opacities. Exclusion criteria were patients with a refractive error greater than ± 6 diopter (D) sphere, uveitis, optic neuropathy, presence of nystagmus, or any other retinal diseases affecting the macula other than retinoschisis, past history of glaucoma and or increased intraocular pressure of ≥ 21 mmHg, prior history of intraocular surgery, and poor OCT image quality.

All subjects underwent a complete ocular examination, including best-corrected visual acuity (BCVA) using an early treatment diabetic retinopathy study (ETDRS) chart (The Lighthouse, Long Island City, NY). On the basis of previous studies,[15,18] the authors determined that an increase of ≥7 letters on an ETDRS chart would be considered a significant change in visual acuity. Slit-lamp biomicroscopic examination and intraocular pressure (IOP) measurements with Goldmann applanation tonometry were performed on all patients. Dilated fundus examination was performed using both direct and indirect ophthalmoscopy as well as stereoscopic biomicroscopy with a

noncontact +78 D lens. None of the subjects included in the study had been treated with either systemic or topical corticosteroids, thiazide diuretics, or nonsteroidal anti-inflammatory drugs. Also, none of the patients had taken an oral or topical form of CAI prior to its use in this study.

OCT Examination Protocols

All subjects included in the study underwent OCT examinations at each visit to monitor the changes in their macular cysts by using either a time domain (TD-OCT) system (The Stratus OCT, with software versions 4.0.1, Carl Zeiss Meditec Inc, Dublin, California, USA) or a spectral domain (SD-OCT) system (Optovue technology, RTvue version 3.5; Optovue Inc, Fremont, California, USA).

The examination protocols used for monitoring the macular cystic changes were as follows; in the TD-OCT, we used the macular thickness scan protocol which consisted of 6-mm radial scans acquired sequentially at 30° polar intervals, passing through the center of the fovea and the total time taken for their acquisition was 11.76 seconds. Each radial scan consisted of 512 A-scans. The MM5 and Radial Lines protocols were used for SD-OCT, where the radial scan consisted of twelve 6-mm radial scans at 15° polar intervals passing through the center of the fovea. All 12 scans were acquired simultaneously, and the total time taken for their acquisition was 0.27 seconds. Each radial line consisted of 1024 A-scans. The MM5 scan protocol consisted of a raster protocol of 5 x 5 mm centered at the fovea, with a total acquisition time of 0.78 seconds.

Data analysis

- ***Qualitative analysis***

The overall response and nonreponse to treatment in all the study patients was evaluated separately in a qualitative manner by the authors (M.A.G. and G.A.F.) and were graded as: improvement,

improvement with a subsequent rebound, no improvement, and no improvement with worsening of the macular cysts. Additionally, we assessed the degree of the response to treatment which was graded as: no response, improvement (mild, moderate, or marked), and worsening (mild, moderate, or marked). Moreover, the foveal cyst sizes based on OCT examinations on initial and most recent visits were qualitatively graded as (0), no cyst; (1), small size cysts; (2), moderate size cysts; (3), large size cysts.

- ***Quantitative analysis***

Changes in the central foveal zone (CFZ) thickness, which was defined as the central 1,000 μm centered on the foveola, were used to monitor the response to treatment. A change in the CFZ thickness from the baseline level (pretreatment) of > 17.1% (mean ± 2 SDs) was used as a statistically significant inter-visit change as reported previously.[15]

Macular thickness data obtained by TD-OCT were compared to those reported by Chan et al.,[19] (mean foveal thickness is 212 ± 20 μm "mean thickness in the central 1,000 μm diameter area")

The macular thickness data obtained by SD-OCT were compared with normative data provided to us by the company that was not corrected for age and optic disc size and which were retrieved from 268 eyes of 134 normative control subjects (mean age of 44.1 ± 15.5 years) (mean foveal thickness was 265.8 ± 23.9 μm). The paired Student's *t*-test was used to statistically analyze mean CFZ thickness and logMAR VAs. *P* values < 0.05 were considered statistically significant.

Results

We analyzed data on 29 eyes; 14 right eyes (48.3%) and 15 left eyes (51.7%), from 15 patients with XLRS. In 1 patient (6.7%), only one eye was included due to the presence of rotatory nystagmus. There were 12 Caucasian (80.0%), and 3 Hispanic (20.0%) patients enrolled in the study. In 8 patients (53.3%), the abnormal disease causing gene mutations were previously identified **(Table 1)**.

The mean age of the patients at their initial baseline visit was 31.9 years with a SD of ± 10.47 (median: 32, range: 18-53 years). The mean age at the most recent follow-up (FU) visit was 33.7 years with a SD of ± 10.45 (median: 32, range: 19-54). The average number of the visits was 6.8 ± 3.61 (median: 5, range: 3-14 visits) **(Table 1)**. The overall mean follow-up period was 16.5 ± 13.8 months (median: 8, range: 4-41 months). Three patients (20.0%) were followed less than 6 months with a mean of 4.3 months and a SD of ± 0.47, 5 patients (33.3%) from 6-12 months with a mean of 6.6 months and a SD of ± 0.80, and 7 patients (46.7%) were followed for more than 12 months with a mean of 28.7 months and a SD of ± 10.0 **(Table 2)**.

The mean logMAR visual acuity (VA) at the initial baseline visit in the right eyes was 0.60 with a SD of ± 0.17 (median: 0.57, range: 0.40-1.00), while the mean logMAR VA at the most recent FU visit was 0.53 with a SD of ± 0.22 (median: 0.53, range: 0.22-1.00) *(p=0.016)*. In the left eyes, the initial mean logMAR VA was 0.60 with a SD of ± 0.26 (median: 0.54, range: 0.30-1.20), while the mean logMAR VA at the most recent FU visit was 0.52 with a SD of ± 0.26 (median: 0.48, range: 0.16-1.00) *(p= 0.014)* **(Table 3)**.

On their most recent FU visit while receiving treatment with topical 2% dorzolamide, 6 patients (40.0%) reported a subjective improvement in their central vision.

Among our 15 study patients, 16 eyes (55.2%) of 12 patients (80.0%) had improvement in their BCVA by ≥7 letters on an ETDRS chart in at least one eye at the most recent FU visit. Regarding the right eyes, 8 patients (57.1%) had improvement in their BCVA by ≥7 letters on an ETDRS chart at the most recent FU visit. Six patients (42.9%) did not show significant improvement in their BCVA. Among these 6 patients, 1 patient did not change from the initial baseline (pretreatment) level, while 5 patients showed a minimal decrease in their BCVA between 1-4 letters on an EDTRS chart (0.02-0.08 logMAR) when compared to their baseline level. Regarding the left eyes, 8 patients (53.3%) showed an improvement in their BCVA by ≥7 letters on an ETDRS chart at the most recent FU visit, while 7 patients (46.7%) had gained < 7 letters at their most recent visit. Among these 7 patients, 1 patient did not change from the initial baseline level, while 2 additional patients had gained only either 1 or 4 letters on an ETDRS chart (0.02 or 0.08 logMAR). Four other patients had a minimal decrease in their BCVA between 1-5 letters on an ETDRS chart (0.02-0.10 logMAR) when compared to their baseline level.

All the 15 study patients showed initial evidence of macular cysts diagnosed by means of direct ophthalmoscopy, biomicroscopy, and OCT. At their most recent visit, 13 patients (86.7%) still showed evidence of macular cysts, although the size of the cystic cavities was less in most patients (N=11) and 2 patients showed that the size of their macular cysts was unchanged.

At the initial baseline visit, 3 patients (20.0%) had their macular schisis measured by the SD-OCT and 12 patients (80.0%) by TD-OCT, while at the most recent FU visit, 8 patients (53.3%) had their macular schisis measured by the SD-OCT and 7 patients (46.7%) by TD-OCT.

Regarding the frequency of the administration of the topical 2% dorzolamide, all the study patients were prescribed the topical drops at a frequency of three times per day (TID) in both eyes, in 5 patients (33.3%) the frequency was decreased to two times per day (BID) after a mean period of 7.6

months with a SD of ± 1.52 (median: 7 months) in both eyes due to continued improvement in the thickness of their macular cysts.

Among our XLRS cohort, at their most recent FU visit, 20 eyes (68.9%) of 11 patients (73.3%) showed an improvement on OCT testing in the degree of macular cystic changes to treatment, 9 patients (60.0%) showed a positive response to treatment in both eyes, while 2 patients (13.3%) showed a positive response to treatment in one eye. Five eyes (25.0%) of 3 patients (27.3%) showed an initial response to treatment and a subsequent worsening of their CME based on OCT evaluation over a mean period of 10.6 months with a SD of ± 7.24 (median: 6.0 months) due to either a decrease in the frequency of treatment administration from TID to a BID dose (N=3 eyes) or due to poor patient compliance (N=2 eyes) **(Figure 1)**. On following-up of these 5 eyes, 3 eyes (60.0%) eventually showed a positive response to treatment, after the dose was increased again from BID to TID, while only 2 eyes (40.0%) continued to show no response to continued treatment on a TID dose, partially due to poor patient compliance.

Our data showed that in 4 eyes (13.8%) of 3 patients (20.0%) did not show any response to treatment while the macular cysts did not worsen when compared to the pretreatment level, and 5 eyes (17.3%) of 4 patients (26.7%) which showed no response to treatment and the macular cysts worsened when compared to the pretreatment level and the degree of worsening was moderate by using the qualitative method of evaluation **(Figure 2)**.

Among those patients who responded positively to 2% dorzolamide, an initial favorable response to treatment was noticed after a mean period of 1.9 months with a SD of 1.22 (median: 1.6 months). At their most recent FU visits of those who responded, 14 eyes (70.0%) of 9 patients showed a marked improvement in the size and extent of their macular cysts as determined qualitatively and a mean of 46.4% percent reduction in measured retinal CFZ thickness (median: 45.8%, range: 19.5-67.5)

(Figure 3), 2 eyes (10.0%) of 1 patient showed a moderate improvement, and 4 eyes (20.0%) of 3 patients showed a mild improvement determined qualitatively **(Table 4)**.

Among the 20 eyes that showed a degree of response to treatment over the FU period, 15 eyes (75.0%) showed a sustained improvement from treatment throughout the entire FU period (mean 16.5 ± 13.8 months). Among these 15 eyes, 8 eyes (53.3%) showed a sustained improvement on a BID dose.

The overall mean of the CFZ thickness (μm) at the initial baseline visit was 391.9 μm ± 115.24, while it was 296.4 μm ± 133.97 at the most recent FU visit *(p=0.008)*. Using the criterion of a change in the CFZ thickness from pretreatment of > 17.1% (mean ±2 SDs) as a statistically significant inter-visit change as previously reported,[15] seventeen eyes (58.6%) of 10 patients (66.7%) showed more than a 17.1% decrease in the CFZ thickness from the initial baseline (pretreatment) level in at least one eye **(Table 5)**.

Comment

Topical and oral forms of a CAI have been demonstrated to cause a reduction in the macular cystic-like lesions in some cases of XLRS, as documented by OCT, and an improvement in VA.[15-17] Our study also demonstrates that the changes in VA and OCT apparent macular cystic changes did not correlate with the clinically-evident fundus cystic-appearing macular changes. Often clinically-evident improvement in the cystic macular lesions was less apparent than improvement on OCT measurements and modest improvement of only 1 line in visual acuity was observed even with appreciable improvement in cystic changes on OCT. We also noted that individual patients did not reach their full potential to respond to treatment until after a period of up to 5 months. Previous reports had shown that the macular cystic-like lesions in XLRS may spontaneously resolve which is followed by the development of an atrophic lesion in the macula.[5-6] Hence, it is likely important to treat the macular cysts present in XLRS patients to possibly reduce the occurrence of later-onset atrophic macular lesions.[17]

Our study demonstrated that 20 eyes (68.9%) of 11 patients had a positive response to treatment with topical 2% dorzolamide, which was evident by an improvement of the macular cystic-like lesions on OCT testing. Our finding agrees with previous reports by Apushkin et al.,[15] and Ghajarnia et al.,[16] which described similar positive effects on the macular cystic lesions using a CAI. Also, 6 patients (40.0%) in our group of XLRS patients noticed subjective improvement in their central vision described as images becoming more distinctly brighter after the use of the treatment for at least 2-3 months. Significant improvement in BCVA was noted in 8 patients (57.1%) in their right eyes, while in 8 patients (53.3%) their left eyes demonstrated a gain in VA $\geq$7 letters on an ETDRS chart at the most recent FU visit over a mean period of 18.1 months with a SD of $\pm$15.22.

In our study, 5 eyes (17.3%) of 4 patients showed no response to treatment and the macular cysts worsened as noted by both clinical fundus and OCT exams. An explanation for this finding is not clearly apparent. It may be related to different genetic mutations causing different mechanisms of retinoschisin protein dysfunction. It may also depend on the residual function of the retinal pigment epithelial cells in individual patients as a CAI has been shown to affect the pumping mechanism in these cells.[20-23] It would be reasonable to conduct a future study which correlates the genotype in XLRS patients with a response to treatment with 2% dorzolamide.

One of the interesting findings in our study was that among 20 eyes that showed a favorable response to treatment, 15 eyes showed sustained improvement in their macular cysts through the entire FU period, while 5 eyes showed a rebound in macular cysts when the CFZ thickness and extent of the cysts on OCT returned to at least baseline levels. On following-up of these 5 eyes, 3 eyes again showed a notable improvement with continued treatment after the dosage was increased from BID to TID. These findings suggest the necessity to monitor XLRS patients on dorzolamide for a potential rebound of their macular cysts or a lack of response while on treatment.

One limitation of the study was that the normative data for macular thickness provided by the manufacturer for the Optovue system was not corrected for age. Also, some patients were followed up partially on TD-OCT and subsequently scanned with a SD-OCT. Longitudinal change in CFZ thickness could not be properly made due to the difference in the measurements between the two systems. However, a previous report by London et al.,[24] showed that the differences between the Stratus and Optovue OCTs are minimal and not likely to be clinically relevant. Similar findings were also noticed in a recent report by Fullerton et al.,[25] who stated that the macular thickness measurements obtained by TD-OCT were consistently lower but highly correlated with SD-OCT. The highest correlation was observed in the central 1 mm foveal region.

From our experience, we suggest the following guidelines for using 2% dorzolamide eye drops in XLRS patients with cystic-like cavities. Obtain a baseline ocular examination including VA and OCT and begin dorzolamide 2% at a TID dose in both eyes and then follow-up after 2 months with both clinical and OCT examinations. If there is improvement in the CFZ thickness on OCT, continue to use the eye drops TID for another 2 months. Then if after 4 months, the CFZ thickness on OCT shows sustained improvement, the dose can be decreased to BID. The patient should be followed again in 2 months to look for a sustained response or a rebound. If the CFZ thickness on OCT shows a rebound of the macular schisis, increase the dosage back to TID. If after six months, there is still a favorable response on BID/TID dose, continue to use the eye drop on BID/TID dose. However, if either no response is noted or a rebound is noted after six months of treatment on a TID dosage, discontinue using the eye drops. These suggested guidelines may be expanded or modified as more experience is accrued on a larger number of patients with an even longer follow-up period.

Additional suggestions include the recommendation to continue the use of topical dorzolamide even when there is no notable initial response since some cases of XLRS patients may not show a clinically significant response to treatment until after a period of treatment for up to 5 months. It is vital to ascertain whether patients are compliant in using their medications and are instilling the drops properly.

While not all patients will respond to dorzolamide, our study determined that patients with XLRS can sustain a beneficial effect from sustained treatment with a topical form of CAI such as 2% dorzolamide.

Acknowledgements

Supported by funds from the Foundation Fighting Blindness, Owings Mills, Maryland; Grant Healthcare Foundation, Lake Forest, Illinois; NIH core grant EYO1792; and an unrestricted departmental grant from Research to Prevent Blindness.

References

1. De La Chapelle A, Alitalo T, Forsius H. X-linked juvenile retinoschisis. In:Wright A, Jay B, editors. Molecular genetics of inherited eye disorders. Switzerland: Harwood Academic; 1994. P.339-357.
2. Yassur Y, Nissenkorn I, Ben-Sira I, Kaffe S, Goodman RM. Autosomal dominant inheritance of retinoschisis. *Am J Ophthalmol*. 1982; 94:338-343.
3. Forsius H, Krause U, Helve J, et al. Visual acuity in 183 cases of X-chromosomal retinoschisis. *Can J Ophthalmol*.1973; 8:385-393.
4. Kellner U, Brummer S, Foerster MH, Wessing A. X-linked congenital retinoschisis. *Graefe's Arch Ophthalmol*. 1990; 228:432-437.
5. George ND, Yates JR, Moore AT. X linked retinoschisis. *Br J Ophthalmol*. 1995; 79:697-702.
6. George ND, Yates JR, Moore AT. Clinical features in affected males with X-linked retinoschisis. *Arch Ophthalmol*. 1996; 114:274-280.
7. Renner AB, Kellner U, Fiebig B, Cropp E, Foerster MH, Weber BH. ERG variability in X-linked congenital retinoschisis patients with mutations in the RS1 gene and the diagnostic importance of fundus autofluorescence and OCT. *Doc Ophthalmol*. 2008; 116:97-109.
8. Gerth C, Zawadzki RJ, Werner JS, Héon E. Retinal morphological changes of patients with X-linked retinoschisis evaluated by Fourier-domain optical coherence tomography. *Arch Ophthalmol*. 2008; 126:807-811.
9. Becker B. Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor. *Am J Ophthalmol*. 1954; 37:13-15.
10. Cox SN, Hay E, Bird AC. Treatment of chronic macular edema with acetazolamide. *Arch Ophthalmol*. 1988; 106:1190-1195.

11. 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.
12. 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.
13. Farber MD, Lam S, Tessler HH, Jennings TJ, Cross A, Rusin MM. Reduction of macular oedema by acetazolamide in patients with chronic iridocyclitis: a randomized prospective crossover study. *Br J Ophthalmol*. 1994; 78:4-7.
14. Marmor MF. Hypothesis concerning carbonic anhydrase treatment of cystoid macular edema: example with epiretinal membrane. *Arch Ophthalmol.* 1990; 108:1524-1525.
15. Apushkin MA, Fishman GA. Use of dorzolamide for patients with X-linked retinoschisis. *Retina* 2006; 26:741-745.
16. Ghajarnia M, Gorin MB. Acetazolamide in the treatment of X-linked retinoschisis maculopathy. *Arch Ophthalmol*. 2007; 125:571-573.
17. Walia S, Fishman GA, Molday RS, Dyka FM, Kumar NM, Ehlinger MA, et al. Relation of response to treatment with dorzolamide in X-linked retinoschisis to the mechanism of functional loss in retinoschisin. *Am J Ophthalmol*. 2009; 147:111-115.
18. Grover S, Fishman GA, Gilbert LD, Anderson RJ. Reproducibility of visual acuity measurements in patients with retinitis pigmentosa. *Retina* 1997; 17:33-37.
19. Chan A, Duker JS, Ko TH, Fujimoto JG, Schuman JS. Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. *Arch Ophthalmol*. 2006; 124:193-198.

20. Marmor MF, Maack T. Enhancement of retinal adhesion and subretinal fluid resorption by acetazolamide. *Invest Ophthalmol Vis Sci* 1982; 23:121-124.
21. Marmor MF, Abdul-Rahim AS, Cohen DS. The effect of metabolic inhibitors on retinal adhesion and subretinal fluid resorption. *Invest Ophthalmol Vis Sci* 1980; 19:893-903.
22. Tsuboi S, Pederson JE. Experimental retinal detachment. X. Effect of acetazolamide on vitreous fluorescein disappearance. *Arch Ophthalmol*. 1985; 103:1557-1558.
23. Kawasaki K, Mukoh S, Yonemura D, Fujii S, Segawa Y. Acetazolamide-induced changes of the membrane potentials of the retinal pigment epithelial cell. *Doc Ophthalmol*. 1986; 63: 375-381.
24. N. J. S. London and A. E. Fung Evaluating the Nerve and Macular Thickness Measurements of the Optovue RTVue, Zeiss Stratus, and Cirrus OCTs. *Invest Ophthalmol Vis Sci*. 2008; 49: E-Abstract 4241.
25. Fullerton JM, Kim JE, Xiang Q, Szabo A. Comparison of Spectral Domain OCT and Time Domain OCT for Measurements of Retinal Thickness. *Invest. Ophthalmol. Vis. Sci.* 2009; 50: E-Abstract 1073.

Figure Legends

Figure 1. Demonstrates an example of rebound in macular cysts on Stratus OCT testing in a patient with XLRS on treatment with topical 2% dorzolamide. Also demonstrated is an improvement after 36 months of treatment.

Figure 2. Demonstrates an example of moderate worsening of macular cysts on Stratus OCT testing in a patient with XLRS on treatment with topical 2% dorzolamide.

Figure 3. Demonstrates an example of marked improvement of macular cysts on Stratus (a) and Optovue (b) OCTs in two patients with XLRS on treatment with topical 2% dorzolamide.

Table 1. Demographics and Genetic mutations of the study cohort

Patient No.	Race	Age at initial visit (yrs.)*	Age at most recent visit (yrs.)*	No. of visits	*RS1* genetic mutation
1	Caucasian	32	32	3	Try96Arg exon 4 hemizygous
2	Caucasian	47	47	6	
3	Caucasian	18	20	8	Deletion of Splicing acceptor site IVS4 del ttCtcgg
4	Caucasian	36	39	12	Gly70Ser exon 4 hemizygous
5	Caucasian	21	24	10	Arg141His exon 5 hemizygous
6	Caucasian	38	39	3	
7	Caucasian	42	45	5	
8	Hispanic	35	38	9	Gly70Ser exon 4 hemizygous
9	Hispanic	23	23	4	
10	Caucasian	36	39	14	Trp96Arg exon 4 hemizygous
11	Caucasian	18	19	5	
12	Caucasian	53	54	3	
13	Caucasian	27	27	4	
14	Caucasian	24	27	11	20bp insertion exon 4 Codon 74 hemizygous
15	Hispanic	29	32	5	Gly70Ser exon 4 hemizygous

***** *yrs.=years*

Table 2. Follow-up period in the study cohort

Follow up period (mo.)*	No. of patients	%	Mean Follow up period ± SD
<6	3	20.0	4.3 ± 0.47
6-12	5	33.3	6.6 ± 0.80
>12	7	46.7	28.7 ± 10.0

**mo. = months*

Table 3. Visual acuity (VA) changes over follow-up periods (mo.)

No.	Initial VA LogMAR OD	Most recent VA LogMAR OD	Initial VA Snellen OD	Most recent VA Snellen OD	LogMAR difference OD*	Initial VA LogMAR OS	Most recent VA LogMAR OS	Initial VA Snellen OS	Most recent VA Snellen OS	LogMAR difference OS*	Follow-up (mo.)***
1	0.80	0.84	20/200	20/200	0.04	0.88	0.86	20/200	20/200	-0.02	4
2	0.70	0.56	20/100-1	20/70-1	-0.14	0.48	0.50	20/60+3	20/60+2	0.02	8
3	_**	_**	_**	_**	_**	1.20	0.90	20/200	20/60-1	-0.30	21
4	0.74	0.60	20/100-1	20/80-1	-0.14	0.80	0.64	20/100	20/80	-0.14	36
5	0.58	0.60	20/70	20/80	0.02	0.62	0.48	20/80-1	20/60	-0.14	35
6	0.70	0.50	20/100-1	20/60+2	-0.20	0.60	0.70	20/80-1	20/100	0.10	5
7	0.40	0.22	20/50-1	20/30-2	-0.18	0.44	0.28	20/50	20/30+1	-0.16	6
8	0.46	0.50	20/50	20/60	0.04	0.54	0.40	20/70	20/50-2	-0.14	19
9	0.54	0.58	20/70	20/70-2	0.04	0.56	0.42	20/70-1	20/50	-0.14	4
10	0.44	0.28	20/50-2	20/40	-0.16	0.30	0.16	20/40+2	20/30+1	-0.14	41
11	0.48	0.32	20/60	20/40-1	-0.16	0.48	0.20	20/60-1	20/30-1	-0.28	13
12	1.00	1.00	20/200	20/200	0.00	1.00	1.00	20/200	20/200	0.00	6
13	0.56	0.38	20/70-2	20/40	-0.18	0.40	0.48	20/50	20/60	0.08	7
14	0.44	0.30	20/50-1	20/40+1	-0.14	0.32	0.24	20/40+1	20/30-2	-0.08	36
15	0.62	0.70	20/80-1	20/100+1	0.08	0.44	0.48	20/60+2	20/60	0.04	6

*****_LogMAR difference is the difference in VA in LogMAR between most recent and initial visits_

** Not treated eye due to presence of nystagmus; *** mo. = months;

Table 4. Demonstrates the overall qualitative response to treatment in our study cohort as judged by the authors

Patient No.	FU (mo.)	Cyst sizes on initial and most recent FU period*		Degree of response to treatment	
		Right eye	Left eye	Right eye	Left eye
1	4	3→3	2→2	Moderate worsening	No improvement
2	8	3→1→0	3→1→0	Moderate improvement	Moderate improvement
3**	21	_	2→1→2→3	_	Moderate worsening
4	36	3→0→2→2→1	3→1→2→3→1	Marked improvement (rebound when on BID then improved again)	Marked improvement (rebound when on BID then improved again)
5	35	3→2→2→2→2→3	3→1→1→2→2→1	No improvement	Marked improvement
6	5	2→0→0→0	3→1→2→2	Marked improvement	Marked improvement
7	6	3→1→2→1	3→1→2→2	Marked improvement	Mild improvement
8	19	3→3→2→2→0→0	2→2→2→1→1→0	Marked improvement	Mild improvement
9	4	2→3→3→3	2→3→3→3	Moderate worsening	Moderate worsening
10	41	2→1→1	2→1→0	Marked improvement	Marked improvement
11	13	3→1→1	3→1→0	Marked improvement	Marked improvement
12	6	3→3	3→2	Moderate worsening	Marked improvement
13	7	3→2→2→2	3→2→1→1	Mild improvement	Mild improvement
14	36	3→3→0→0	3→3→0→0	Marked improvement	Marked improvement
15	6	2→3→2	2→3→2	No improvement	No improvement

**** 0**, no cysts; **1**, small size cysts; **2**, moderate size cysts; **3**, large size cysts*

*** Not treated eye due to presence of nystagmus*

Table 5. Demonstrates the CFZ thickness at the initial baseline visit (pretreatment) and the most recent visit (post treatment), and percent (%) changes in CFZ thickness from the baseline

Patient No.	Visit No. /FU (mo.)	CFZ thickness (µm) at the initial baseline visit*		CFZ thickness (µm) at the most recent visit*		% change in CFZ thickness over the follow-up period***	
		Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye
1	2/4	355 SD	318 SD	564 SD	303 SD	+58.9	-4.7
2	6/8	507 TD	412 TD	175 TD	168 TD	-65.5	-59.2
3**	8/21	_	272 TD	_	435 TD	_	+59.9
4	12/36	416 TD	395 TD	293 SD	214 SD	-29.6	-45.8
5	10/35	525 TD	551 TD	569 SD	179 SD	+8.4	-67.5
6	3/5	305 SD	344 SD	214 SD	289 SD	-29.8	-16.0
7	5/6	387 TD	348 TD	198 TD	280 TD	-48.8	-19.5
8	9/19	323 TD	218 TD	138 TD	136 TD	-57.3	-37.6
9	4/4	316 TD	311 TD	537 TD	511 TD	+69.9	+64.3
10	14/41	315 TD	262 TD	195 SD	193 SD	-38.1	-26.3
11	4/6	449 TD	547 TD	244 SD	189 SD	-45.7	-65.5
12	3/6	416 TD	451 TD	468 TD	274 TD	+12.5	-39.2
13	4/7	457 SD	439 SD	452 SD	400 SD	-1.09	-8.9
14	11/36	664 TD	606 TD	223 SD	228 SD	-66.4	-62.4
15	5/6	225 TD	231 TD	292 TD	235 TD	+29.8	+1.7

**** CFZ was defined as the central 1.000 µm centered on the fovea; TD= time-domain OCT, SD= spectral-domain OCT***

***** Not treated eye; *** level of significance of CFZ thickness changes is >17.1%; positive and negative values of the percent differences represent a direction of change: -, a decrease in CFZ thickness; +, an increase in CFZ thickness.***