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Case Report

Effectiveness of Ripasudil, a Rho-Associated Coiled/Coil-Containing Protein Kinase Inhibitor, in Improving Retinoschisis and Cystic-Like Foveal Cavities in Eyes with X-Linked Retinoschisis

Hitomi Suimon Masahiko Sugimoto Hisashi Matsubara Mineo Kondo

Department of Ophthalmology, Mie University Graduate School of Medicine, Tsu, Japan

Keywords

Cystic-like foveal cavities · Retinoschisis · Rho-associated coiled/coil-containing protein kinase inhibitor · Ripasudil hydrochloride hydrate · X-linked retinoschisis

Abstract

This is the first reported case of a successful resolution of cystic-like foveal cavities in eyes with X-linked juvenile retinoschisis (XLRS) treated with topical ripasudil hydrochloride hydrate, a Rho-associated coiled/coil-containing protein kinase (ROCK) inhibitor. A chart review was performed on 1 patient to collect all relevant clinical information and the optical coherence tomographic (OCT) images. A healthy 18-year-old young man presented with bilateral visual disturbances. The patient was diagnosed with XLRS from the spoke-wheel pattern around the macula, negative electroretinograms, and retinoschisis with cystic-like foveal cavities in the OCT images. Significant reductions of the retinoschisis and cystic-like cavities were observed after treatment with topical ripasudil. This is the first case of XLRS that had a resolution of cystic-like foveal cavities after topical ripasudil, a ROCK inhibitor. Since many XLRS patients have a worsening of their visual acuities due to the progressive nature of retinoschisis and cystic-like foveal cavities, topical ripasudil offers a potential treatment option.

KARGER

Masahiko Sugimoto
Department of Ophthalmology
Mie University Graduate School of Medicine
2-174 Edobashi, Tsu, Mie 514-8507 (Japan)
sugmochi@clin.medic.mie-u.ac.jp

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Introduction

X-linked juvenile retinoschisis (XLRS), first reported by Haas in 1898 [1], is a juvenile macular disorder that affects young men during their school age years. Spoke-like appearance around the macular and negative electroretinograms (ERGs) resulting from a greater reduction of the b-wave than the a-wave are characteristic findings in eyes with XLRS [2]. Recent advances in optical coherence tomographic (OCT) imaging have shown that there is also macular retinoschisis involved in all retinal layers for eyes with XLRS [3]. Almost all patients have foveal retinoschisis and have various degrees of visual depression depending on the extent of the morphological alterations [4]. Although there is no permanent treatment for XLRS, some reports have stated the usefulness of oral and topical carbonic anhydrase inhibitors (CAIs) for the cystic-like foveal cavities [5, 6]. Thus, there is a possibility on the usefulness of topical medications for the treatment of the cystic-like foveal cavities in eyes with XLRS.

Ripasudil hydrochloride hydrate (0.4% glanatec ophthalmic solution, Kowa Company, Ltd., Tokyo, Japan) is a Rho-associated coiled/coil-containing protein kinase (ROCK) inhibitor commercialized as a therapeutic agent for glaucoma. Since ROCK is expressed in the ciliary body and trabecular meshwork, topical application of ripasudil has been shown to reduce the intraocular pressure (IOP) [7, 8]. However, ROCK is also expressed in the retina and is associated with maintaining cellular conformation [9–11]. In fact, ripasudil has been shown to reduce the edema in eyes with diabetic macular edema [12].

We present our findings in a young man with retinoschisis and cystic-like foveal cavities associated with XLRS who was successfully treated with ripasudil.

Case Presentation

An 18-year-old healthy young man visited our hospital with bilateral visual disturbances which he reported he has had since elementary school. He had no other medical history. His visual acuity was 20/40 in both eyes, and his IOP was 11 mm Hg in the right eye and 8 mm Hg in the left eye. No apparent abnormal findings were observed in the anterior segment. Fundus examination showed a spoke-wheel pattern in the macular area, and OCT examinations revealed bilateral retinoschisis in the inner nuclear layer combined with cystic-like foveal cavities (Fig. 1a–f). The central foveal thickness (CFT) was 808 μm in the right eye (Fig. 1e) and 227 μm in the left eye (Fig. 1f). The full-field ERGs had a negative pattern, with the amplitude of the b-waves smaller than that of the a-waves (Fig. 1g).

His maternal grandfather had visual disturbances of unknown cause, and his elder brother had been diagnosed with XLRS in our clinic from clinical examinations. Since the visual acuity of his elder brother was 20/25 in the right eye and 20/28 in the left eye without any subjective symptoms, and OCT examinations revealed only bilateral retinoschisis without cystic-like foveal cavities, the elder brother refused any treatment and continued with follow-up.

Although we recommended genetic testing for the *RS1* gene in our patient, he and his family declined any genetic testing. Since there were no abnormalities in the retina, such as high myopia and inflammatory changes except the spoke-like appearance, and because of the typical XLRS findings such as spoke-wheel pattern around the macula, negative ERGs, bilateral retinoschisis, and a positive family history, we diagnosed the patient as having XLRS.

Since the longitudinal course of retinoschisis and cystic-like foveal cavities are progressive and can lead to severe visual disturbances, [4] and no other established treatment had been approved for XLRS, we began treating the patient with topical ripasudil twice a day in both eyes after discussing the advantages and disadvantages of the treatment. The patient signed an informed consent form for the treatment. The dosage of topical ripasudil was selected to be twice a day as indicated for the treatment of glaucoma patients.

Four months after starting the ripasudil treatment, a reduction of the cystic-like foveal cavities was observed in both eyes. The CFT decreased from 808 to 201 μm, a reduction of 75.1% from the baseline CFT in the right eye (Fig. 2a) and from 227 to 130 μm, a reduction of 42.7% from the baseline CFT in the left eye (Fig. 2b). His subjective symptoms were improved, but his visual acuity was still 20/50 OD and 20/30 OS. His IOP was 11 mm Hg OD and 8 mm Hg OS.

However, the patient discontinued for all follow-up examinations and 6 months later, 10 months after beginning ripasudil, he visited our clinic due to a recurrence of the visual disturbances. The compliance to the use of ripasudil during this 6 months was poor. His visual acuity was 20/50 in the right eye and 20/25 in the left eye with a recurrence of the cystic-like foveal cavities (Figs. 2c, d). The topical ripasudil was restarted, and 20 months later, there was a resolution of not only the cystic-like foveal cavities but also of the retinoschisis. The CFT had decreased to 97 μm, a reduction of 88.0% from the baseline CFT in the right eye (Fig. 2e) and to 130 μm, a reduction of 57.3% from the baseline CFT in the left eye (Fig. 2f). His visual acuity improved to 20/40 in the right eye and 20/25 in the left eye.

At present, this patient is continuing with ripasudil to prevent a progression of the retinoschisis and cystic-like foveal cavities.

Discussion and Conclusions

Several gene mutations have been reported to cause XLRS [13], including the *RS1* gene mutation [14]. Retinoschisin has been shown to be secreted from photoreceptors and bipolar cells [15], and it has been identified in all neuroretinal layers. It plays an important role in cellular adhesions related to maintaining retinal conformation and fluid transport across the retina and retinal pigment epithelium (RPE) [16]. *RS1* gene mutations cause a misfolding and disfunction of retinoschisin which results in the retinoschisis [14]. Although previous studies reported about the effectiveness of CAIs on the cystic-like foveal cavities in eyes with XLRS, the pathophysiological mechanism for the retinoschisis is still undetermined. There is a possibility that the extracellular pH gradients caused by CAIs may result in increasing the fluid transport in the subretinal space across the RPE which is manifested as an improvement in the retinoschisis [6, 17]. This is not a direct effect of CAIs on the retinoschisin.

Apushkin et al. [5] also reported that the CFT reduction by >19.6% was considered as a significant change for patients with XLRS. Cousa and Kapusta [18] reported that dorzolamide (a topical CAI agent) treatments in XLRS cases resulted in a 50% CFT reduction at 2 months after starting the treatment. In our case, the CFT reduction was 88.0% for the right eye and 57.3% for left eye at 20 months after starting the treatment with ripasudil. Although the follow-up period was different, both dorzolamide and ripasudil could reduce the CFT remarkably, and ripasudil seemed to work better with respect to the structural recovery after a longer observation period.

On the other hand, a ROCK inhibitor was reported to modify the conformation of the cytoskeleton and enhance the endocrine activity of retinoschisin [19]. Since retinoschisin also

plays an important role in cell-cell adhesion between the photoreceptors and bipolar cells [20, 21], its disfunction can induce hyperpermeability of the retina. These backgrounds may relate to the onset of the retinoschisis and the cystic-like foveal cavities which can lead to visual disturbances. The reduction of retinoschisis and cystic-like foveal cavities by ripasudil is through the pathways different from those of CAIs. Since the discontinuation of ripasudil led to a recurrence of the cystic-like foveal cavities in our case, we conclude that the ROCK inhibition is also useful for treating the cystic-like foveal cavities in eyes with XLRS.

The longitudinal course of retinoschisis and cystic-like foveal cavities could cause primary Mueller cell defects resulting in severe visual disturbances. In our case, a marked resolution of both retinoschisis and cystic-like foveal cavities was obtained, but these changes did not result in an improvement of the visual acuity. This was demonstrated by a lack of a significant correlation between the visual acuity and the foveal thickness or cystic area [3].

In conclusion, our results showed that topical ripasudil in a patient with XLRS was successful in resolving the retinoschisis and cystic-like foveal cavities. However, this was only one case, and longitudinal observations on many patients with XLRS are needed to confirm our findings.

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Statement of Ethics

The procedures were approved by the Ethics Committee of Mie University Hospital (Tsu, Mie, Japan, No. 89–101). The patient gave written permission for clinical details and images in this study. This report does not contain any personal information that could lead to the identification of the patient.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

H.S., H.M. and M.S. cared the patient, worked up, treated, and collected data. M.S. and M.K. analyzed the ophthalmological findings and gave critical suggestions. All authors agree to be accountable for all aspects of work. All authors approve the final version of the manuscript for publication.

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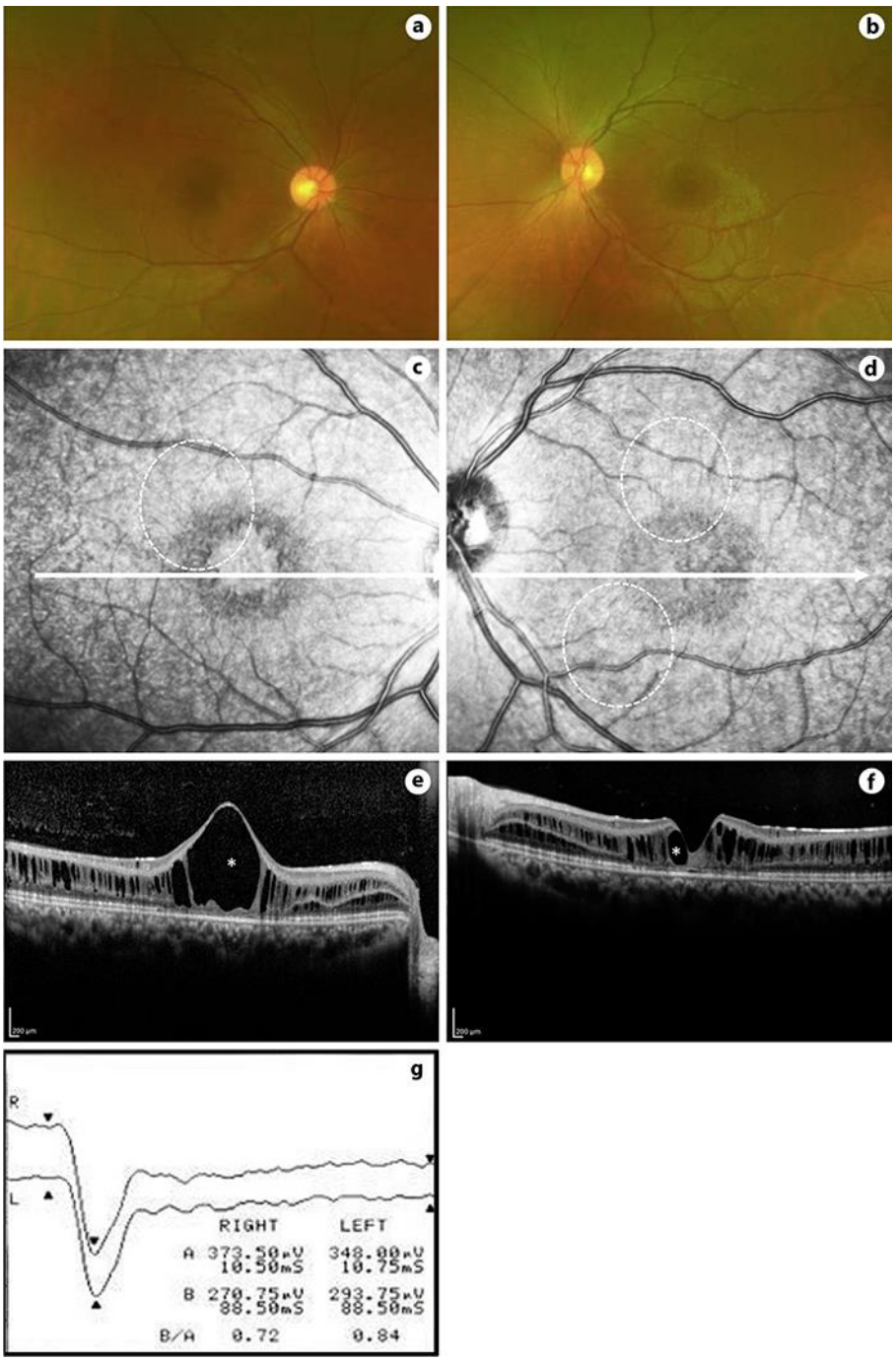

Fig. 1. Results of ophthalmic examinations at the initial visit. Although the color fundus images show no abnormalities in the right eye (**a**) and left eye (**b**), spoke-wheel patterns (circle) can be seen around the macular area in the red-free fundus image for the right eye (**c**) and left eye (**d**). OCT images show retinoschisis in the inner nuclear layer combined with cystic-like foveal cavities in the right eye (**e**) and left eye (**f**). ERGs have a negative-type ERG pattern (**g**). Arrow: OCT-scanned line shown in **e** and **f**. Circle: spoke-like appearance around the macula. Asterisk: cystic-like foveal cavities.

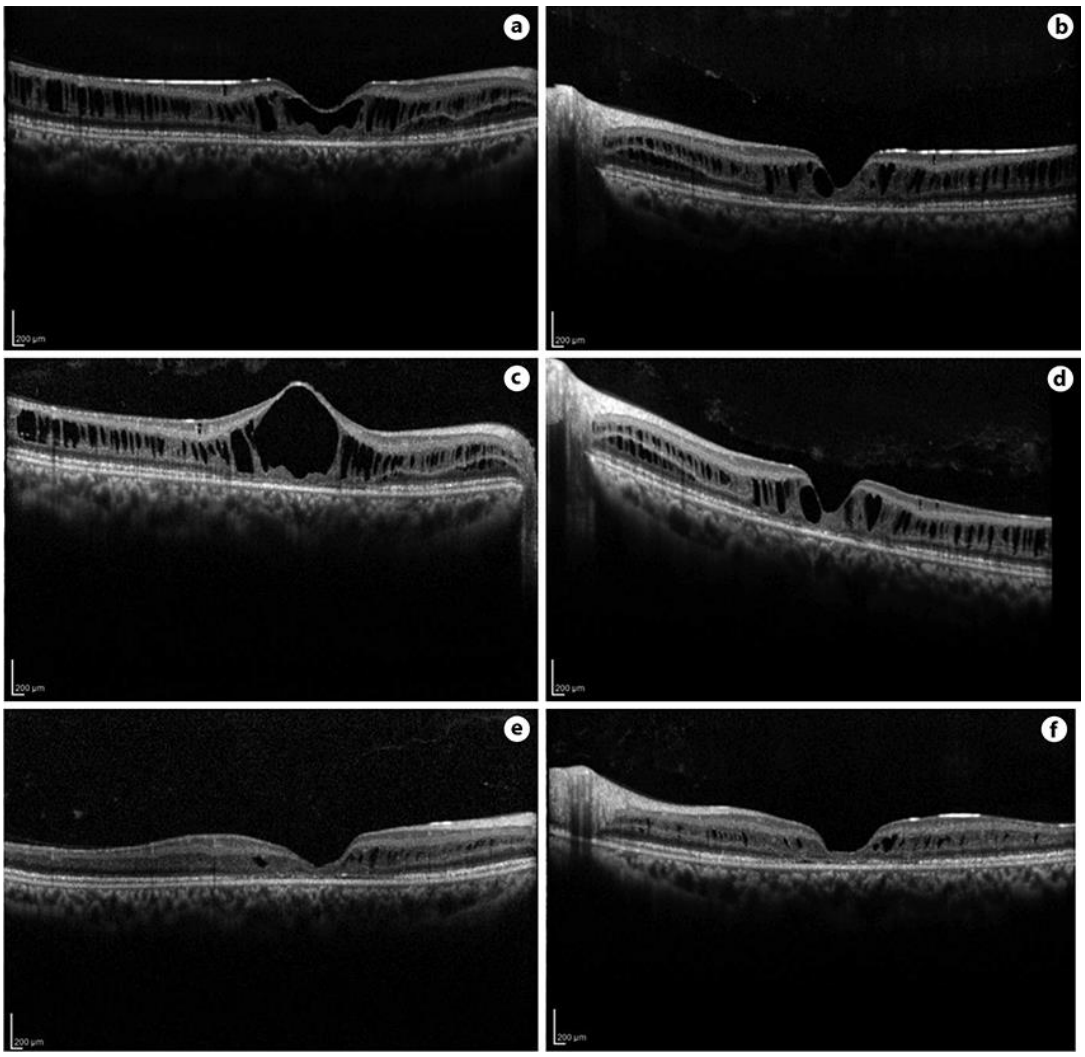

Fig. 2. OCT images during the follow-up period. OCT images for the right eye (**a**, **c**, **e**) and for the left eye (**b**, **d**, **e**) are shown. Four months after beginning the topical ripasudil treatment, a reduction of the cystic-like foveal cavities was observed (**a**, **b**). Six months after discontinuing ripasudil, there was a recurrence of the cystic-like foveal cavities (**c**, **d**). Twenty months after the re-starting of topical ripasudil treatment, there was a resolution of the retinoschisis and cystic-like foveal cavities (**e**, **f**).