



Published in final edited form as:

Arch Ophthalmol. 2010 September ; 128(9): 1146–1150. doi:10.1001/archophthalmol.2010.172.

Efficacy for Sustained Use of Topical Dorzolamide Therapy for Cystic Macular Lesions in Patients with Retinitis Pigmentosa and Usher Syndrome

Mohamed A. Genead, MD and Gerald A. Fishman, MD

Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois, USA

Abstract

Objectives—To determine the efficacy for sustained use of topical therapy with dorzolamide hydrochloride 2% on visual acuity and cystic macular lesions in retinitis pigmentosa (RP) and Usher (USH) syndrome patients.

Design—Retrospective case series.

Setting—University hospital.

Patients—Sixty-four eyes of 32 patients with RP or USH syndrome who received treatment with topical dorzolamide formulation for a duration ranging from 6–58 months were enrolled.

Main Outcome Measures—Changes in visual acuity (**ETDRS**) and central foveal zone thickness on optical coherence tomography during follow-up for the duration of treatment.

Results—Among the study cohort, a positive response occurred in 20 of 32 patients (63%) in at least one eye and in 13 patients (41%) in both eyes. Four patients (20%) showed an initial response and a subsequent rebound of macular cysts. In 8 patients (25%) there was no response to treatment and the macular cysts worsened when compared with the pretreatment level. Ten patients (31%) had improvement in visual acuity by 7 letters in at least one eye at the most recent follow-up visit. Sixteen patients (67%) showed a reduction of >11% in the central foveal zone thickness in at least one eye when compared with the pretreatment level.

Conclusion—Treatment of cystoid macular edema with topical dorzolamide in patients with either RP or USH syndrome and followed by an OCT-guided strategy showed a decrease in central foveal zone thickness in the majority of cases. Visual acuity improved in almost 1/3 of the cases, suggesting a potential corresponding visual benefit.

Introduction

Retinitis pigmentosa (RP) is a genetically heterogeneous group of inherited retinal dystrophies caused by progressive loss of photoreceptors and characterized by night blindness, peripheral visual field loss, and retinal pigment deposits visible on fundus

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; 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.

The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

examination.¹ Usher (USH) syndrome is an autosomal recessive disorder characterized by the association of congenital sensorineural hearing loss and retinitis pigmentosa.²

Previous studies have demonstrated the presence of cystoid macular edema (CME) in RP and USH patients.^{3–7} The association between CME and antienolase and anticarbonic anhydrase antibodies in the serum of RP patients has been previously described.⁸ The successful use of either oral or a topical form of carbonic anhydrase inhibitor (CAI) for treatment of CME in RP patients has been previously reported.^{9–13}

Prior reports showed a recurrence of CME in patients with RP on treatment with the use of an oral CAI.^{14,15} While a previous study by Fishman and Apushkin has shown a beneficial effect from the use of a topical form of CAI in patients with RP,¹⁶ their study had a limited number of patients followed for a short period of time. Therefore, the aim of the present study was to determine the efficacy for sustained use of topical therapy with dorzolamide hydrochloride 2% on visual acuity (VA) and cystic macular lesions, as determined by OCT, in 32 patients with retinitis pigmentosa and Usher syndrome over a more extended period of time.

Patients and Methods

Patients

Sixty-four eyes of 32 patients with RP and USH syndrome were enrolled in the present study. The study was conducted in the Department of Ophthalmology at the University of Illinois at Chicago. It followed the tenets of the Declaration of Helsinki and was approved by an institutional review board at the University of Illinois at Chicago. An informed consent was obtained from all subjects. The study was conducted in accord with The American Health Insurance Portability and Accountability Act (HIPAA) regulations.

Inclusion criteria included patients with RP and USH syndrome who were treated with topical dorzolamide 2% from January 5, 2004, through November 25, 2009 (range, 6–58 months). All patients were 18 years of age or older, and had stable ocular fixation. Exclusion criteria consisted of pseudophakic and aphakic patients, posterior uveitis, diabetic retinopathy, optic neuropathies, past history of glaucoma, or any central media opacity sufficient to hinder an OCT examination. None of the patients had been treated with systemic or topical corticosteroids, thiazide diuretics, or non-steroidal anti-inflammatory drugs prior to or during the course of the study. One patient had used an oral form of CAI in the past before being enrolled in the present study.

Ocular Examination

All subjects underwent a complete ocular examination, including assessment of visual acuity (VA) by using an early treatment diabetic retinopathy study (ETDRS) chart in most of the patients (28 patients) at their initial and most recent visits while a Snellen acuity chart was used in 4 patients at their initial visits. Slit-lamp biomicroscopic examinations, intraocular pressure (IOP) measurements with Goldmann applanation tonometry, and dilated fundus examinations using direct and indirect ophthalmoscopy were performed on all patients.

Optical Coherence Tomography (OCT) Techniques

All patients included in the study underwent OCT examinations at each visit to monitor any changes in their macular cysts using a time-domain system **with axial resolution of 10 μm** (TD-OCT) (Stratus OCT, version 4.0.1; Carl Zeiss Meditec Inc, Dublin, California) in 20 patients or a spectral-domain system (SD-OCT) **with axial resolution of 5 μm** (RTvue, with software version 3.5; Optovue Inc, Fremont, California) in 23 patients. The

examination protocols used for monitoring the macular cystic changes were as previously described.¹⁷

Data Analysis

To analyze the OCT findings qualitatively, the overall response or nonresponse to the topical dorzolamide formulation in all of the study patients was evaluated and graded as: improvement, improvement with a subsequent rebound, no improvement, and no improvement with worsening of the macular cysts. In addition, 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). Quantitative OCT evaluations were done by calculating the changes in the central foveal zone (CFZ) thickness (defined as the central area with a diameter of 1000 μm , centered on the foveola) to monitor the response to treatment. A change in the CFZ thickness from the pretreatment of $> 11\%$ (mean ± 2 SDs) was considered as a statistically significant inter-visit change as reported previously.¹⁸ Central foveal zone thickness data obtained by TD-OCT were compared with those reported by Chan et al.,¹⁹ (mean [SD] central foveal thickness is 212 [20] μm). The foveal zone thickness data obtained by SD-OCT were compared with normative data provided by the manufacturer which were not corrected for age and that were retrieved from 268 eyes of 134 normative control subjects (mean [SD] age of 44.1 [15.5] years, mean [SD] foveal thickness was 265.8 [23.9] μm).

Statistical Analysis

The main outcome measurements were visual acuity (VA) and CFZ thickness measured by OCT. In the 4 patients tested by Snellen acuity on their initial visits, their acuities were converted to logMAR for statistical analysis. An increase in VA was defined as a gain of greater than or equal to 7 letters based on a previous report.²⁰ The paired Student's *t*-test was used to compare the change in VA and OCT thickness from the pretreatment level. $P < 0.05$ was considered to be statistically significant.

Results

Of the 32 patients included in our study, 26 patients (81.2%) had RP, 3 patients (9.4%) had USH syndrome type II, and 3 patients (9.4%) had USH syndrome type I. Among the RP group of patients, our cohort was divided into 13 cases (50%) with autosomal dominant inheritance, 5 (19%) autosomal recessive, and 8 (31%) isolated cases. Among the study cohort, there were 18 females (56%) and 14 males (44%). Based on ethnicity, there were 27 white (84%), 4 African American (13%), and 1 Asian (3%) patients. Seven patients were genetically tested for disease causing mutations, in 4 patients (13%), the abnormal disease causing gene mutations were previously identified (Table 1, **online only**).

The mean (SD) age of the patients at their initial baseline visit was 38.2 (14.5) (median, 39; range, 19–67) years. The mean (SD) age at the most recent follow-up visit was 39.8 (14.6) (median, 40; range, 20–68) years. The average number of the visits was 5.8 (3.6) (median, 4; range, 3–14). The overall mean (SD) duration of follow-up was 19.0 (15.2) (median, 13; range, 6–58) months (Table 1, **online only**). Sixteen patients (50%) were followed-up for a duration more than 12 months.

The mean logMAR VA at the initial baseline visit was 0.33 (0.21) (median, 0.30; range, 0–1.08), whereas the mean logMAR VA at the most recent follow-up visit was 0.28 (0.24) (median, 0.18; range, 0–1.30) ($p = 0.005$) (Table 2, **online only**).

On their most recent follow-up visit while receiving treatment with topical dorzolamide, 9 patients (28%) reported a subjective improvement in their central vision.

Among our 32 study patients, 13 eyes (20%) of 10 patients (31%) had improvement in their BCVA by 7 letters on an ETDRS chart in at least one eye at the most recent follow-up visit. Regarding the right eyes, 6 eyes (19%) had improvement in their BCVA by 7 letters on an ETDRS chart at the most recent follow-up visit. Thirteen eyes (41%) did not show significant improvement in their BCVA (0.02–0.10 logMAR). While 6 eyes (19%) did not have a change from the initial baseline (pretreatment) level, 7 eyes (21%) showed a decrease in their BCVA from 1 to 9 letters on an EDTRS chart (0.02–0.18 logMAR) when compared with their baseline level.

Regarding the left eyes, 7 eyes (21%) showed an improvement in their BCVA by 7 letters on an ETDRS chart at the most recent follow-up visit, whereas 13 eyes (41%) had gained < 7 letters at their most recent visit (0.02–0.12 logMAR). Five eyes (16%) did not have a change from the initial baseline level, while 7 eyes (21%) had a decrease in BCVA from 1 to 11 letters on an ETDRS chart (0.02–0.22 logMAR) when compared with their baseline level (Table 2, **online only**).

At the initial baseline visit, 20 patients (63%) had their macular cysts measured by the TD-OCT and 12 patients (37%) by SD-OCT, while at the most recent follow-up visit, 23 patients (72%) had their macular schisis measured by SD-OCT and 9 patients (28%) by TD-OCT.

Regarding the frequency of the administration of the topical dorzolamide hydrochloride 2%, all 32 study patients were prescribed the topical drops at a frequency of three times a day in both eyes. In 4 patients (13%), the frequency was decreased to twice a day after a mean period of 11.3 (10.2) (median, 8) months in both eyes owing to continued improvement in the thickness of their macular cysts.

Based on qualitative analysis, our cohort showed that 33 eyes (51%) of 20 patients (63%) had an improvement of their macular cystic changes to treatment in at least one eye and in 13 patients (41%) in both eyes. Among those patients who responded positively to topical dorzolamide 2%, an initial favorable response to treatment was noticed after a mean (SD) period of 1.6 (0.7) (range, 1–3) months. At their most recent follow-up visits of those who responded, 13 eyes (39.4%) of 8 patients showed a marked improvement in the size and extent of their macular cysts (Figure 1), 10 eyes (30.3%) of 10 patients showed a moderate improvement, and 10 eyes (30.3%) of 8 patients showed a mild improvement as determined qualitatively (Table 3, **online only**).

Among the 33 eyes that showed a degree of response to treatment over the follow-up period, 12 eyes (36%) of 8 patients (40%) showed a sustained improvement from treatment over a mean period of 39.5 (15.8) months. Among these 12 eyes, 4 eyes (33%) of 2 patients (25%) showed a sustained improvement on twice a day regimen. Seven eyes (21%) of 4 patients (20%) showed an initial response to treatment and a subsequent rebound of their CME on OCT testing over a mean period of 8.8 (5.7) (median, 9.5) months owing to a decrease in the frequency of treatment administration from 3 times a day to twice a day (Figure 2).

Our data showed that 19 eyes (30%) of 13 patients (41%) did not show any response to treatment while the macular cysts did not worsen when compared with the pretreatment level and 12 eyes (19%) of 8 patients (25%) which showed no response to treatment and the macular cysts worsened when compared with the pretreatment level. The degree of worsening was mild in 10 eyes (83%) of 8 patients (Figure 3) and moderate in 2 eyes (17%) of 2 patients by using the qualitative method of analysis.

Based on quantitative analysis, at their most recent follow-up visits, our patient cohort showed that 42 eyes (66%) of 24 patients (75%) had a degree of improvement in their cystic macular lesions thickness to treatment on OCT testing in at least one eye while 18 patients (56%) showed a positive response with improvement of their macular thickness to treatment in both eyes.

The overall mean (SD) CFZ thickness at the initial baseline visit was 356.0 (98.8) μm , while it was 326.1 (92.0) μm at the most recent follow-up visit ($p=0.0004$). When we used the criterion of a change in the CFZ thickness from pretreatment of $> 11\%$ (mean ± 2 SDs) as a statistically significant inter-visit change as previously reported,¹⁸ twenty five eyes (60%) of 16 patients (67%) showed more than an 11% decrease in the CFZ thickness from the initial baseline level in at least one eye and 9 patients (38%) in both eyes (Table 3, **online only**).

Comment

The purpose of this study was to evaluate the functional and anatomic effects of topical dorzolamide therapy 2% on cystic macular lesions for patients with retinitis pigmentosa and Usher syndrome over a more extended period of time. All treatment decisions were based on OCT imaging.

In our current series, based on qualitative assessment, we demonstrated that 33 eyes (51%) of 20 patients had a positive response to treatment with topical dorzolamide formulation, which was evident by an improvement of the cystic macular lesions on OCT. Our findings agree with previous reports that showed similar efficacy of topical dorzolamide hydrochloride therapy in the resolution of cystoid macular edema (CME) on OCT testing in patients with RP.^{16,18}

In our current study, among those 33 eyes that showed a favorable response to treatment, 12 eyes showed sustained improvement in their macular cysts over a mean (SD) period of 39.5 (15.8) months, which was a longer duration of follow-up compared to a previous report on 8 patients that showed the same sustained efficacy of topical dorzolamide [mean (SD) 11.6 (2.4) months].¹⁶

Among our cohort of patients, 9 (28%) reported a subjective improvement in their central vision after initiating the use of the topical therapy for at least 3 months. Thirteen eyes (20%) of 10 patients (31%) showed a significant improvement in their BCVA by 7 letters on an ETDRS chart in at least one eye at the most recent follow-up visit during a mean (SD) period of 23.5 (16.2) months.

In general, the changes in VA did not correlate well with the changes of cystic macular lesions on OCT. This finding was similar to previous studies that reported a poor correlation between the change in VA and decrease in retinal thickness on OCT.^{16,18,21} Also in our current series, some patients did not respond to topical dorzolamide. We found that in 12 eyes (19%) of 8 patients, their macular cystic lesions worsened when compared with the pretreatment level, as noted on both their results on clinical fundus and OCT examinations.

Currently, we know of no way to predict which patients will fail therapy. An explanation for this finding may be related to different genetic mutations causing different mechanisms of protein dysfunction in such disorders. 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.²²⁻²⁴ It would be beneficial to conduct a future study that correlates the different genetic mutations in such patients with a response to topical dorzolamide formulation.

Our study also showed that 7 out of 33 eyes (21%) showed a rebound in macular cysts when the CFZ thickness and extent of the cysts on OCT returned to at least baseline levels over a mean (SD) period of 8.8 (5.7) (median, 9.5) months. Our current study showed less of a rebound rate with the use of topical dorzolamide over an extended period of time when compared to previous reports on a fewer number of patients followed for a shorter period of time which showed a higher rate of rebound for CME in patients treated with a CAI.^{14,15,16,18}

Limitations of our study include its retrospective nature and that the normative data for macular thickness provided by the manufacturer for the SD-OCT system was not corrected for age. In addition, some patients were initially followed up with TD-OCT and subsequently underwent SD-OCT. Longitudinal change in CFZ thickness could not be calculated precisely because of the difference in the measurements between the two systems. However, previous reports,^{25,26} showed that differences between TD and SD OCTs are minimal and not likely to be clinically relevant.

In conclusion, the present study demonstrates that treatment of CME in patients with RP and USH syndrome with topical 2% dorzolamide hydrochloride can reduce central foveal thickness on OCT testing in a notable percentage of cases. Visual acuity may also improve in some cases.

Acknowledgments

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. Marmor MF, Aguirre G, Arden GB, et al. Retinitis pigmentosa: A symposium on terminology and methods of examination. *Ophthalmology*. 1983; 90:126–131. [PubMed: 6856249]
2. Rosenberg T, Haim M, Hauch AM, Parving A. The prevalence of Usher syndrome and other retinal dystrophy-hearing impairment associations. *Clin Genet*. 1997; 51:314–321. [PubMed: 9212179]
3. Walia S, Fishman GA, Hajali M. Prevalence of cystic macular lesions in patients with Usher II syndrome. *Eye*. 2009; 23:1206–1209. [PubMed: 18425067]
4. Hajali M, Fishman GA. The prevalence of cystoid macular edema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. *Eye*. 2009; 23:915–919. [PubMed: 18425064]
5. Fetkenhour CL, Chromokos E, Weinstein J, Shoch D. Cystoid macular edema in retinitis pigmentosa. *Trans Am Acad Ophthalmol Otol*. 1977; 83:515–521.
6. Fishman GA, Fishman M, Maggiano JM. Macular lesions associated with retinitis pigmentosa. *Arch Ophthalmol*. 1977; 95:798–803. [PubMed: 860943]
7. Ffytche TJ. Cystoid maculopathy in retinitis pigmentosa. *Trans Ophthalmol Soc UK*. 1972; 92:265–283. [PubMed: 4541521]
8. Wolfensberger TJ, Aptsiauri N, Godley B, et al. Antiretinale Antikörper assoziiert mit zystoidem Makulaödem. *Klin Monatsbl Augenheilkd*. 2000; 216:283–285. [PubMed: 10863693]
9. Fishman GA, Gilbert LD, Anderson RJ, et al. Effect of methazolamide on chronic macular edema in patients with retinitis pigmentosa. *Ophthalmology*. 1994; 101:687–693. [PubMed: 8152764]
10. Wolfensberger TJ. The role of carbonic anhydrase inhibitors in the management of macular edema. *Doc Ophthalmol*. 1999; 97:387–397. [PubMed: 10896355]
11. Cox SN, Hay E, Bird AC. Treatment of chronic macular edema with acetazolamide. *Arch Ophthalmol*. 1988; 106:1190–1195. [PubMed: 3415543]

12. 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. [PubMed: 2803090]
13. 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. [PubMed: 9196934]
14. 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; 27:1112–1128. [PubMed: 18040255]
15. Fishman GA, Glenn AM, Gilbert LD. Rebound of macular edema with continued use of methazolamide in patients with retinitis pigmentosa. *Arch Ophthalmol*. 1993; 111:1640–1646. [PubMed: 8155034]
16. Fishman GA, Apushkin MA. Continued use of dorzolamide for the treatment of cystoid macular edema in patients with retinitis pigmentosa. *Br J Ophthalmol*. 2007; 91:743–745. [PubMed: 17215269]
17. Genead MA, Fishman GA, Walia S. Efficacy of sustained topical dorzolamide therapy for cystic macular lesions in patients with X-linked retinoschisis. *Arch Ophthalmol*. 2009 (In press).
18. 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. [PubMed: 16546110]
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. [PubMed: 16476888]
20. Grover S, Fishman GA, Gilbert LD, Anderson RJ. Reproducibility of visual acuity measurements in patients with retinitis pigmentosa. *Retina*. 1997; 17:33–37. [PubMed: 9051840]
21. Greenstein VC, Holopigian K, Siderides E, Seiple W, Carr RE. The effects of acetazolamide on visual function in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1993; 34:269–273. [PubMed: 8425835]
22. 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. [PubMed: 7409984]
23. Tsuboi S, Pederson JE. Experimental retinal detachment. X. Effect of acetazolamide on vitreous fluorescein disappearance. *Arch Ophthalmol*. 1985; 103:1557–1558. [PubMed: 4051858]
24. 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. [PubMed: 3492349]
25. London NJS, Fung AE. Evaluating the nerve and macular thickness measurements of the Optovue RTVue, Zeiss Stratus, and Cirrus OCTs [e-abstract 4241]. *Invest Ophthalmol Vis Sci*. 2008; 49:A334.
26. Fullerton JM, Kim JE, Xiang Q, Szabo A. Comparison of spectral domain OCT and time domain OCT for measurements of retinal thickness [e-abstract 1073]. *Invest Ophthalmol Vis Sci*. 2009; 50:D1017.

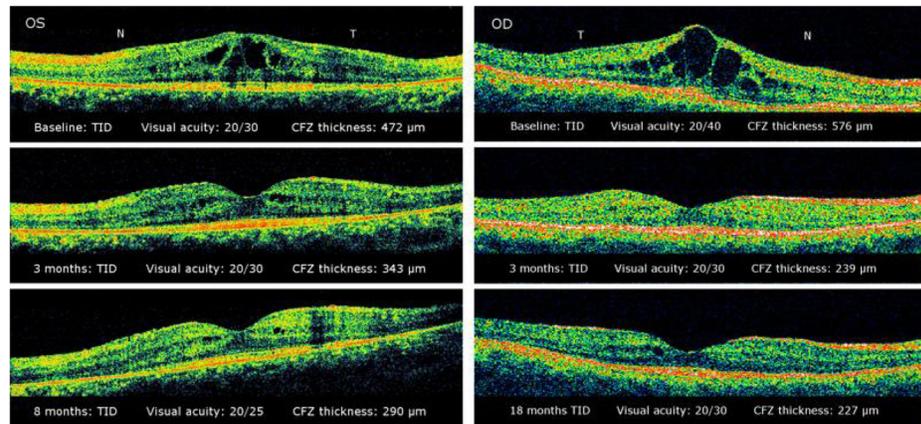


Figure 1. Horizontal OCT scans in 2 patients [1 patient with USH syndrome type-I (left column) and 1 with RP (right column)] on treatment with topical dorzolamide hydrochloride 2%. Both patients demonstrated marked improvement of their cystic macular lesions on spectral-domain OCT (left column) and time-domain OCT (right column).

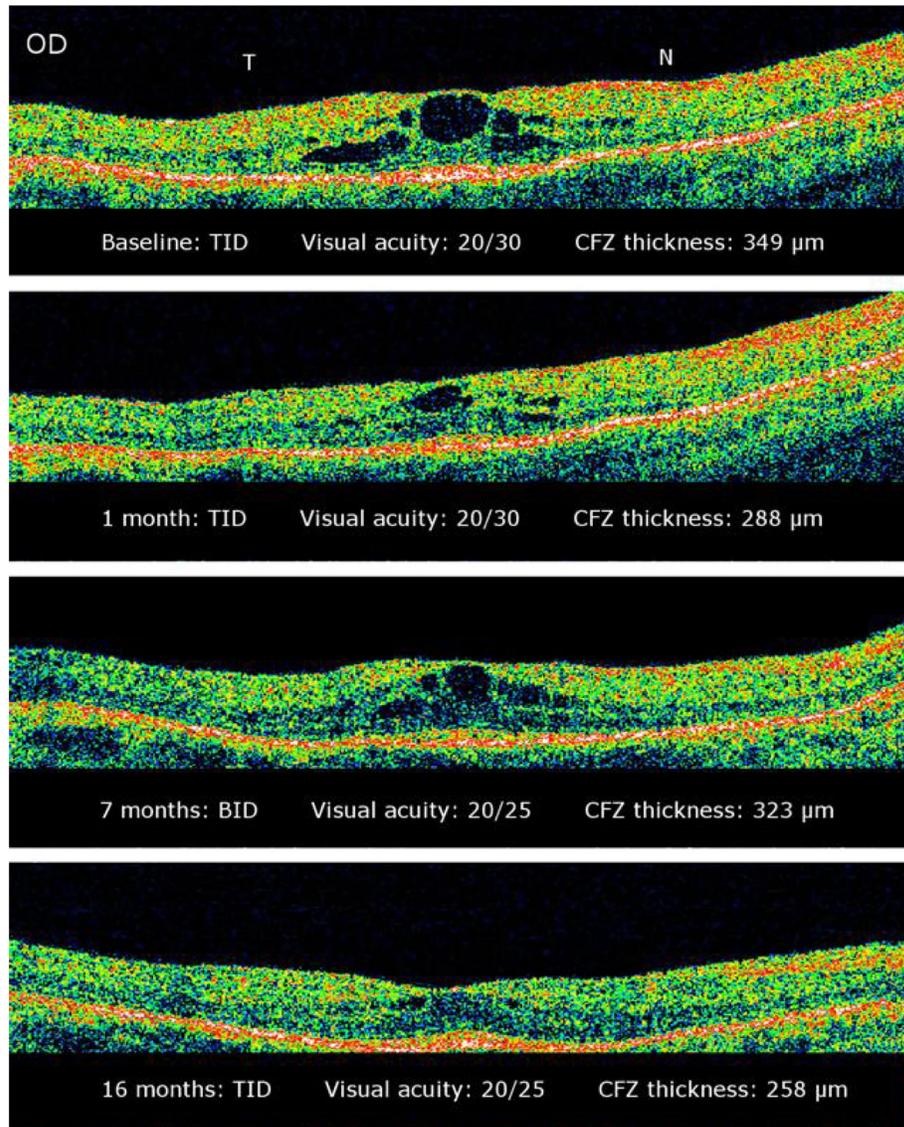


Figure 2. Horizontal time-domain OCT scans of a patient with RP. The sequence of scans demonstrate an example of an initial improvement of macular cysts and subsequent rebound after decreasing the dose of topical dorzolamide hydrochloride 2% from three times a day to twice a day followed subsequently by an improvement of the macular cysts after an increase in the dose of topical dorzolamide back to three times a day.

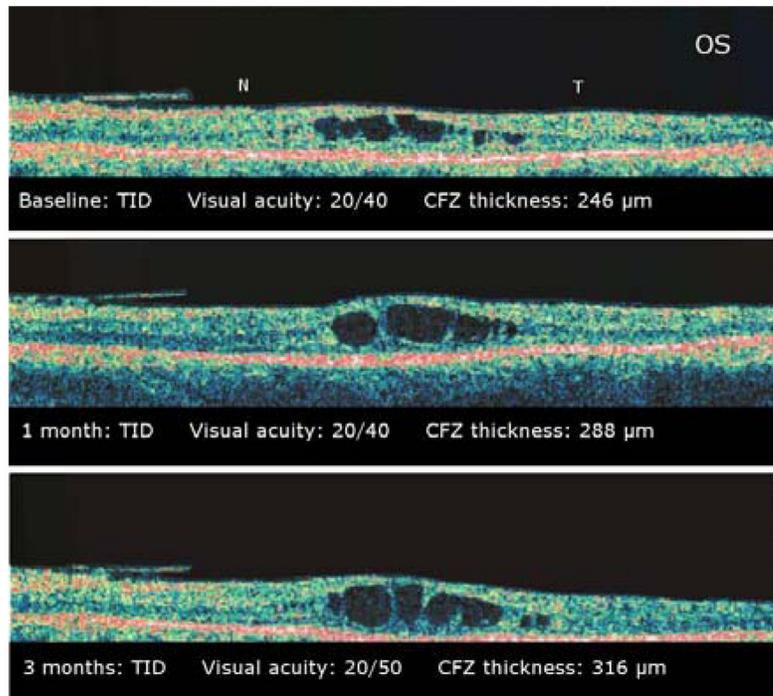


Figure 3. Horizontal time-domain OCT scans of a patient with RP. The scans demonstrate an example of mild worsening of macular cysts while on treatment with topical dorzolamide hydrochloride 2%.