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

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Objective: To determine the efficacy of sustained topical therapy with dorzolamide hydrochloride, 2%, on visual acuity and cystic macular lesions in patients with retinitis pigmentosa and Usher syndrome.

Methods: In a retrospective case series at a university hospital, 64 eyes of 32 patients with retinitis pigmentosa or Usher syndrome receiving treatment with the topical dorzolamide formulation for 6 to 58 months were enrolled. Changes in visual acuity on the Early Treatment Diabetic Retinopathy Study chart and central foveal zone thickness on optical coherence tomography were measured during follow-up for the duration of treatment.

Results: Among the study cohort, 20 of 32 patients (63%) showed a positive response to treatment in at least 1 eye and 13 patients (41%) showed a positive response 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 or more letters in at least 1 eye at the most recent follow-up visit. Sixteen patients (67%) showed a reduction of more than 11% in the central foveal zone thickness in at least 1 eye when compared with the pretreatment level.

Conclusions: Patients with either retinitis pigmentosa or Usher syndrome who received treatment of cystoid macular edema with topical dorzolamide followed by an optical coherence tomography–guided strategy showed a decrease in central foveal zone thickness in most cases. Visual acuity improved in almost one-third of the cases, suggesting a potential corresponding visual benefit.

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R E T I N I T I S  P I G M E N T O S A  (R P)  I S  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 examination. Usher syndrome is an autosomal recessive disorder characterized by the association of congenital sensorineural hearing loss and RP.

Previous studies have demonstrated the presence of cystoid macular edema (CME) in patients with RP and Usher syndrome. The association between CME and antienolase and anticarbonic anhydrase antibodies in the serum of patients with RP has been previously described. The successful use of either an oral or topical carbonic anhydrase inhibitor (CAI) for treatment of CME in patients with RP has been previously reported. Prior reports showed a recurrence of CME in patients with RP on treatment with an oral CAI. While a previous study by Fishman and Apushkin showed a beneficial effect from a topical CAI in patients with RP, their study had a limited number of patients and short follow-up. Therefore, the aim of the present study was to determine the efficacy of sustained topical therapy with dorzolamide hydrochloride, 2%, on visual acuity (VA) and cystic macular lesions as determined by optical coherence tomography (OCT) in 32 patients with RP and Usher syndrome over a more extended period.

METHODS

PATIENTS

Sixty-four eyes of 32 patients with RP and Usher syndrome were enrolled in our study. The study was conducted in the Department of Ophthalmology and Visual Sciences, 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. Informed consent was obtained from all subjects. The study was con-
ducted in accordance with Health Insurance Portability and Accountability Act regulations.

Inclusion criteria included patients with RP and Usher syndrome who were treated with topical dorzolamide, 2%, from January 5, 2004, through November 25, 2009 (range, 6-58 months). All patients were aged 18 years or older and had stable ocular fixation. Exclusion criteria consisted of pseudophakia and aphakia, posterior uveitis, diabetic retinopathy, optic neuropathies, history of glaucoma, or any central media opacity sufficient to hinder an OCT examination. No patients were treated with systemic or topical corticosteroids, thiazide diuretics, or nonsteroidal 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 our study.

Ocular Examination

All subjects underwent a complete ocular examination, including assessment of VA with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart in most of the patients (28 patients) at their initial and most recent visits or with a Snellen VA chart in 4 patients at their initial visits. Slitlamp biomicroscopic examinations, intraocular pressure measurements with Goldmann applanation tonometry, and dilated fundus examinations using direct and indirect ophthalmoscopy were performed on all patients.

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 (TD) system with axial resolution of 10 µm (Stratus OCT, with software version 4.0.1; Carl Zeiss Meditec Inc, Dublin, California) in 20 patients or a spectral-domain (SD) system 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, or 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), or 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 greater than 11% in the CFZ thickness from the pretreatment level (mean ± 2 SDs) was considered a statistically significant intervisit change as reported previously.16 Central foveal zone thickness data obtained by TD-OCT were compared with those reported by Chan et al19 (mean [SD] CFZ thickness, 212 [20] µm). The CFZ thickness data obtained by SD-OCT were compared with normative data provided by the manufacturer, which were not corrected for age and were retrieved from 268 eyes of 134 normative control subjects (mean [SD] age, 44.1 [11.5] years; mean [SD] CFZ thickness, 265.8 [23.9] µm).

Statistical Analysis

The main outcome measurements were VA and CFZ thickness measured by OCT. In the 4 patients tested by Snellen VA on their initial visits, their VAs were converted to logMAR for statistical analysis. An increase in VA was defined as a gain of 7 or more letters based on a previous report.20 The paired t test was used to compare the change in VA and OCT thickness from the pretreatment level. P < .05 was considered statistically significant.

Results

Of the 32 patients included in our study, 26 (81%) had RP, 3 (9%) had Usher syndrome type II, and 3 (9%) had Usher syndrome type I. Among the group with RP, our cohort was divided into 13 cases (50%) with autosomal dominant inheritance, 5 (19%) with autosomal recessive inheritance, and 8 (31%) that were isolated. Among the study cohort, there were 18 women (56%) and 14 men (44%). Based on ethnicity, there were 27 white patients (84%), 4 African American patients (13%), and 1 Asian patient (3%). Seven patients were genetically tested for disease-causing mutations; in 4 patients (13%), the abnormal disease-causing gene mutations were previously identified (eTable 1, http://www.archophthalmol.com).

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

The mean (SD) logMAR VA at the initial baseline visit was 0.33 (0.21) (median, 0.30; range, 0.00-1.08), whereas the mean (SD) logMAR VA at the most recent follow-up visit was 0.28 (0.24) (median, 0.18; range, 0.00-1.30) (P = .005) (eTable 2).

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 best-corrected (BC) VA by 7 or more letters on an ETDRS chart in at least 1 eye at the most recent follow-up visit. Regarding the right eyes, 6 eyes (19%) had improvement in their BCVA by 7 or more 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 level, 7 eyes (21%) showed a decrease in their BCVA from 1 to 9 letters on an ETDRS 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 or more letters on an ETDRS chart at the most recent follow-up visit, whereas 13 eyes (41%) had gained fewer than 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 (eTable 2).

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

Regarding the frequency of the administration of topical dorzolamide, 2%, all 32 study patients were prescribed the topical eyedrops at a frequency of 3 times a day in both eyes. In 4 patients (13%), the frequency was decreased to twice a day after a mean (SD) period of 11.3 (10.2) months (median, 8 months) in both eyes owing to continued improvement in the thickness of their macular cysts.

Based on qualitative analysis, an improvement of the macular cystic changes in response to treatment was apparent in 33 eyes (51%) of 20 patients (63%) in at least 1 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) months (range, 1-3 months). At the most recent follow-up visits of those who responded, 13 eyes (39%) of 8 patients showed a marked improvement in the size and extent of their macular cysts (Figure 1), 10 eyes (30%) of 10 patients showed a moderate improvement, and 10 eyes (30%) of 8 patients showed a mild improvement as determined qualitatively (eTable 3).

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 (SD) period of 39.5 (15.8) months. Among these 12 eyes, 4 eyes (33%) of 2 patients (25%) showed a sustained improvement on a 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 (SD) period of 8.8 (5.7) months (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; 12 eyes (19%) of 8 patients (25%) showed no response to treatment while 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 when analyzed by the qualitative method.

Based on quantitative analysis, OCT testing at the most recent follow-up visits showed that 42 eyes (66%) of 24 patients (75%) had a degree of improvement in cystic macular lesion thickness in at least 1 eye in response to treatment, while 18 patients (56%) showed a positive response to treatment with improvement of their macular thickness in both eyes.

The overall mean (SD) CFZ thickness was 356.0 (98.8) µm at the initial baseline visit and 326.1 (92.0) µm at the most recent follow-up visit (P < .001). When we used the criterion of a change greater than 11% in the CFZ thickness from the pretreatment level (mean ± 2 SDs) as a statistically significant intervisit change as previously reported,18 25 eyes (60%) of 16 patients (67%) showed more than an 11% decrease in the CFZ thickness from the initial baseline level in at least 1 eye and 9 patients (38%) showed this in both eyes (eTable 3).

![Figure 3](http://archopht.jamanetwork.com/pdfaccess.ashx?url=/data/journals/ophth/22439/)

**Figure 3.** Horizontal time-domain optical coherence tomographic scans of a patient with retinitis pigmentosa. The scans demonstrate an example of mild worsening of macular cysts while the patient received treatment with topical dorzolamide hydrochloride, 2%. OS indicates left eye; N, nasal; T, temporal; TID, 3 times a day; and CFZ, central foveal zone.

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

In our current series, based on qualitative assessment, we demonstrated that 33 eyes (51%) of 20 patients had a positive response to treatment with the 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 therapy in the resolution of 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 showed sustained improvement in their macular cysts over a mean (SD) period of 39.5 (15.8) months. This was a longer follow-up compared with a previous report of 8 patients who showed the same sustained efficacy of topical dorzolamide (mean [SD] follow-up, 11.6 [2.4] months).16

Among our cohort, 9 patients (28%) reported a subjective improvement in their central vision after receiving the topical therapy for at least 3 months. Thirteen eyes (20%) of 10 patients (31%) showed a significant improvement in their BCVA by 7 or more letters on an ETDRS chart in at least 1 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 a 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, the macular cystic lesions worsened when compared with the pretreatment level as noted on results of both clinical fundus and OCT examinations.

Currenttly, we know of no way to predict which patients will have failed 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 the topical dorzolamide formulation.

Seven 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) months (median, 9.5 months). Our study showed less of a rebound rate with the use of topical dorzolamide over an extended period when compared with previous reports of fewer patients followed up for a shorter period that showed a higher rate of rebound for CME in patients treated with a CAI.16-18

Limitations of our study include its retrospective nature and the fact that the normative data for macular thickness provided by the manufacturer for the SD-OCT system were 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 2 systems. However, previous reports22-26 showed that differences between TD-OCT and SD-OCT are minimal and not likely to be clinically relevant.

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