

The successful management of Stargardt's Disease using topical diluted echothiophate iodide.

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ABSTRACT:

An off-label use of dilute echothiophate was used to treat a 27 year-old patient who was legally blind from Stargardt's disease. Visual acuity was restored to a functional level, and color vision was regained. With continuing therapy, the patient reads, navigates, and functions without the aid of tools or outside assistance. These improvements have been maintained through 26 months of ongoing treatment. Dilute echothiophate may offer an effective, non-surgical therapy for Stargardt's disease, where none previously existed.

Background and rationale for treatment

Stargardt's disease is a juvenile form of macular degeneration that affects 25,000 Americans. In Stargardt's the ABCA4 gene causes a toxic buildup of lipofuscin pigments throughout the RPE leading to the death of the adjacent photoreceptors¹. Symptoms typically manifest between ages 8 and 20 years. Visual acuity typically declines to 20/200, before leveling off.²

ECHO (echothiophate iodide) is a long-acting AChE inhibitor, which raises the level of acetylcholine in the iris, ciliary muscle and other parasympathetically innervated structures, causing miosis and the potentiation of accommodation. ECHO has been used for more than forty years as an effective treatment at a dose of 0.03% to 0.25% for chronic open-angle glaucoma and accommodative esotropia. Until now, there has been no report of benefit of ECHO for diseases of the posterior pole of the eye.

The traditional 0.125% dosage of ECHO has been associated with systemic cholinesterase increases⁴, ocular burning, lacrimation, brow ache and lens opacities. Corbel & Leser⁵ performed several longitudinal tests with lower-dose ECHO. Their findings indicate that dosages below 0.03%, administered daily, result in no systemic build-up, exhibit excellent local tolerance, with no lens modifications or cataractogenous effects. The work of both Harris⁶ and Axelsson⁷ confirm that any related side effects of daily, dilute ECHO are temporary and negligible.

The dosage used for treatment of this patient with Stargardt's disease is 0.015%, administered to each eye once every four days, immediately prior to sleep, minimizing runoff due to eye movement and blinking.

Our source for the eye drops is Wyeth-Ayerst, Philadelphia, PA. The product, Phospholine Iodide®, includes both ECHO and its buffered diluent.

Case History

The present case involves a 27-year-old female patient, diagnosed with Stargardt's disease at age 19. This individual presented with no familial history of blindness or retinal disease. She takes no medication other than birth control pills.

With the exception of a mild astigmatism, this patient was normally sighted through age 17, at which time she began noticing difficulty distinguishing between white board marker colors at high school. Her vision continued a mild decline until age 19, at which point she experienced an abrupt drop in both central vision and night vision. She consulted with several retinal specialists at university hospitals including Johns Hopkins Wilmer Eye Institute; each confirmed a diagnosis of Stargardt's disease.

Treatment Protocol

This patient presented to Nolan Eye and Laser Center in Farmington, CT at age 24. Her prior diagnosis of Stargardt's was verified via fluorescein angiography; her distant visual acuity was established using the Snellen test, near vision by the Rosenbaum test, and color vision by the Ishihara test. Pupillary constriction and corrective prescriptions were noted.

The patient's left eye was selected as the initial target eye. The patient was instructed in the proper self-administration of eye drops, then further instructed to self-administer just one drop of dilute (0.015%) ECHO to the target eye, immediately prior to receiving eight hours of uninterrupted sleep.

The following day, the patient returned for retesting of visual acuity. The patient was instructed to treat the other eye that evening, then to begin a regimen of treating alternating eyes every fourth night. Within the first month, this frequency was increased to every second evening. Each eye therefore received one drop of 0.015% ECHO every four days.

Follow-up fluorescein angiograms and acuity tests have been performed every three-to-six months.

Date	Distant Vision		Near Vision		Color Vision	
	OD	OS	OD	OS	OD	OS
01/29/97	CF/5/400	CF/5/400	J16 @ 12"	J16 @ 12"	"Markedly diminished"	
06/18/01	CF/5/400	CF/20/300	J5 @ 2"	J5 @ 2"	0%	10%
06/19/01	20/300⁺¹	20/300	J1 @ 12"	J1+ @ 12"	40%	100%
06/29/01	20/400	20/200 ⁺¹	J1 @ 12"	J1+ @ 12"	90%	90%
01/11/02	20/200	20/200 ⁺¹	J1- @ 12"	J1+ @ 12"	100%	100%
07/28/03	20/200 ⁺¹	20/200 ⁺¹	J1 @ 12"	J1+ @ 12"	100%	100%

Table 1: Visual acuity history of a Stargardt's patient. Initial treatment on the evening of 6/18/01.

Results

The pre-treatment examination determined the patient's vision to be counting fingers 5/400 in each eye with a corresponding near vision acuity of Jaeger five at two inches. Her gaze was eccentric with particular difficulty in near vision focus. Color vision was contrast-only in her right eye and 10% in her left.

The morning following initial ECHO administration, the patient reported a moderate dimming of vision in the target eye (OS) upon waking. She experienced little subjective change in vision until nearly an hour after waking, at which time she noticed that she could see colors in the hotel room not discernable the day before. Upon looking out the window, she saw traffic passing 200 yards away and could call out the colors of individual cars as they passed.

Examination 24 hours after initial treatment revealed characteristic pupillary constriction. The patient's distance acuity had improved from CF 5/400 to 20/300 in both eyes. Near vision improved remarkably to Jaeger one at 12 inches bilaterally. Color vision improved from 0% to 40% in the treated eye and from 10% to 100% in the untreated eye.

Subjective complaints during the first several weeks of therapy included lid twitching and transient dimming and blurring of vision on the morning following administration. Mild vision-related headaches were also reported, but did not discourage the patient from continuing treatment. These side effects were transient and limited to the first two months. Pupillary constriction remains on the day following administration, however this is reported by the patient to be a beneficial side effect; the pinhole vision is a boost to visual clarity. None of the complaints of ocular burning, lacrimation, brow-ache and lens opacities associated with the traditional 0.25% protocol of ECHO treatment have been reported by this patient.

Within the first month of therapy, the patient's color vision improved to 100% in both eyes and her near and distant acuity reached its current plateau of 20/200⁺¹ distance and Jaeger 1 near, where it has been maintained for more than 24 months. She now wears glasses for distance only (-1.25D).

The patient went without ECHO therapy for only one two-week period during the past two years, after forgetting her medication when packing for a honeymoon. After five days without ECHO, her vision

dropped back to legal blindness. However, her vision improved and stabilized upon the resumption of ECHO.

Discussion

In this patient's case, dilute ECHO has provided an effective, non-surgical therapy where none previously existed. This Stargardt's patient was legally blind, as validated by several leading institutes. She was unable to navigate her surroundings without the assistance of a cane or guide dog. She could not read or write a grocery list, keep a job or watch television. Her vision gains have restored her independence and returned her to the workforce.

Across more than two years of successful therapy, we have observed no local or systemic side effects, no development of tolerance and no decline in drug efficacy. Indeed, ongoing angiograms show markedly less retinal damage than predicted from literature review and experience.

The mechanism of action of ECHO in this patient with Stargardt's disease is not yet known. Our hypothesis is that dilute ECHO makes ACh more available to diseased neuroreceptor populations across the retina. Increased ACh levels may amplify the synaptic potential of the surviving photoreceptors and ganglion cells, making it possible for these reduced populations to achieve threshold and resume the propagation of visual information to the brain. This effect would parallel previously described mechanisms of drug action in other neurological diseases, such as Parkinsonism, Alzheimer's Disease and Clinical Depression.

These therapeutic benefits may have remained hidden as the result of two key factors; first, the ECHO dosage must be below 0.030% -- higher dosages have not been noted to have similar effects. Second, due to this low dosage, the medication must be administered immediately prior to 6-8 hours of uninterrupted sleep in order to guarantee scleral absorption.

Stargardt's Disease is one of a number of degenerative retinal diseases, including retinitis pigmentosa and age-related macular degeneration, which may respond to this therapy. If this were the case, this therapy may hold the potential to lessen the disability from a number of blinding retinal diseases."

References

¹ Understanding the etiology of Stargardt's disease. Glazer LC, Dryja TP. *Ophthalmol Clin North Amer* 2002 Mar; 151(1):93-100

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³ The gene for Stargardt disease, ABCA4, is a major retinal gene: a mini-review. Koenekoop RK. *Ophthalmic Genetics*. 2003 Jun; 24(2):75-80.

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