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Initial experience in the treatment of inherited mitochondrial disease with EPI-743

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ABSTRACT

Inherited mitochondrial respiratory chain disorders are progressive, life-threatening conditions for which there are limited supportive treatment options and no approved drugs. Because of this unmet medical need, as well as the implication of mitochondrial dysfunction as a contributor to more common age-related and neurodegenerative disorders, mitochondrial diseases represent an important therapeutic target. Thirteen children and one adult with genetically-confirmed mitochondrial disease (polymerase γ deficiency, $n=4$; Leigh syndrome, $n=4$; MELAS, $n=3$; mtDNA deletion syndrome, $n=2$; Friedreich ataxia, $n=1$) at risk for progressing to end-of-life care within 90 days were treated with EPI-743, a novel *para*-benzoquinone therapeutic, in a subject controlled, open-label study. Serial measures of safety and efficacy were obtained that included biochemical, neurological, quality-of-life, and brain redox assessments using technetium-99m-hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) radionuclide imaging. Twelve patients treated with EPI-743 have survived; one polymerase γ deficiency patient died after developing pneumonia and one patient with Surf-1 deficiency died after completion of the protocol. Of the 12 survivors, 11 demonstrated clinical improvement, with 3 showing partial relapse, and 10 of the survivors also had an improvement in quality-of-life scores at the end of the 13-week emergency treatment protocol. HMPAO SPECT scans correlated with clinical response; increased regional and whole brain HMPAO uptake was noted in the clinical responders and the one subject who did not respond clinically had decreased regional and whole brain HMPAO uptake. EPI-743 has modified disease progression in >90% of patients in this open-label study as assessed by clinical, quality-of-life, and non-invasive brain imaging parameters. Data obtained herein suggest that EPI-743 may represent a new drug for the treatment of inherited mitochondrial respiratory chain disorders. Prospective controlled trials will be undertaken to substantiate these initial promising observations. Furthermore, HMPAO SPECT imaging may be a valuable tool for the detection of central nervous system redox defects and for monitoring response to treatments directed at modulating abnormal redox.

1. Introduction

Inherited mitochondrial diseases are a family of disorders that share a common element in defective cellular energy metabolism [1]. While an estimated 1 in 5000 individuals are affected by mitochondrial disease caused by mitochondrial DNA (mtDNA) abnormalities, many children with signs and symptoms of mitochondrial disease lack a definitive genetic diagnosis and an increasing number of conditions that affect mitochondrial respiratory chain function have been related to nuclear DNA (nDNA) mutations, so the true prevalence of these

Abbreviations: ARE, antioxidant response element; BSO, L-buthionine-(S,R)-sulfoximine; FRDA, Friedreich ataxia; HMPAO, technetium-99m-hexamethylpropyleneamine oxime; KSS, Kearns–Sayre syndrome; LHON, Leber hereditary optic neuropathy; LS, Leigh syndrome; MELAS, Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; NMDAS, Newcastle Mitochondrial Disease Adult Scale; NPMDS, Newcastle Paediatric Mitochondrial Disease Scale; POLG, Polymerase gamma-1 deficiency; SPECT, single-photon emission computed tomography.

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disorders may be significantly higher [2,3]. There are no approved drug treatments for inherited mitochondrial disease [4], and these conditions are associated with substantial morbidity and mortality.

In addition to impaired ATP synthesis, inherited mitochondrial disorders manifest a variety of biochemical redox disturbances [5]. Alterations in cellular redox state have been implicated in the pathogenesis of these diseases through several mechanisms, including increased oxidative stress, depletion of cellular antioxidant defense systems, such as glutathione, and acceleration of programmed cell death [6,7]. Therefore, it is understandable that the predominant strategy employed to treat mitochondrial disease has focused on the use of antioxidants to target the oxidative stress axis of these conditions [8]. While a variety of antioxidants and cofactors have been studied, coenzyme Q_{10} (CoQ_{10}) has received the most detailed examination [4,9–13]. Results from over 50 clinical trials of CoQ_{10} suggest a marginal but real treatment effect [4]. To improve upon the bioavailability of CoQ_{10}, a truncated side-chain analog—idebenone—was developed over a decade ago and has been repurposed to treat inherited mitochondrial disease. There have been reports of idebenone improving some clinical parameters in MELAS and LHON patients [14–16]. Modest improvement in cardiac or neurological function following the use of idebenone in Friedreich ataxia patients has also been described, although recent double-blind trials have not noted statistically significant clinical effects [17,18].

Based on results obtained with CoQ_{10} and idebenone, we set out to design and test a *para*-benzoquinone analog with improved pharmacologic properties and therapeutic efficacy. Design considerations were implemented for EPI-743 to avoid the potential of mitochondrial respiratory chain inhibition or uncoupling as previously demonstrated with idebenone [19]. Our strategy centered on the synthesis of a rational series of *para*-benzoquinone analogs that systematically differed in redox potential of the quinone ring and the structure of the lipid sidechain. The result of this optimization effort is EPI-743 (Fig. 1) [20]. EPI-743 is approximately one thousand- to ten thousand-fold more potent than CoQ_{10} or idebenone in protecting cells subjected to oxidative stress in patient fibroblast assays modeling the effects of mitochondrial disease. The biological activity of EPI-743 depends upon the intrinsic properties of the *para*-benzoquinone moiety to undergo a reversible two electron cycling reaction, as is demonstrated by the inactivity of a redox-silent version (bis-pivoyl adduct) of EPI-743 in cell assay systems [20].

Because of EPI-743's favorable efficacy and safety profile, and in light of the predictable mortality associated with end-stage mitochondrial disease and absence of approved therapies, the United States Food and Drug Administration granted approval to use EPI-743 to treat patients with genetically confirmed mitochondrial respiratory chain disease who were considered to be within 90 days of end-of-life care. To augment clinical evaluation of EPI-743, we employed technetium-99m-hexamethylpropyleneamine oxime (HMPAO) single-photon emission computed tomography (SPECT) radionuclide imaging, an *in vivo* technique that has the potential to detect alterations in brain redox state [21]. While this property has not been fully appreciated or understood, the ability of HMPAO to serve as a redox sensor suggested that HMPAO SPECT has possible utility in the study of the redox imbalance that is central to mitochondrial disease pathogenesis. Herein we report the clinical data obtained in this open-label expanded access investigational new drug (IND) protocol in the first fourteen subjects treated with EPI-743 at our collaborating institutions.

2. Materials and methods

2.1. Participants

This protocol was reviewed by the Stanford University, Medical University of South Carolina, University of California, Los Angeles, CHOC Children's Hospital, and Akron Children's Hospital Institutional Review Boards. Participants were enrolled only after screening to ensure inclusion criteria, and no exclusion criteria, were met. Signed informed consent was obtained from the parents of each subject. Each of the fourteen participants (Table 1) met the two central criteria for enrollment: 1) diagnosed with a genetically defined inherited mitochondrial disease and 2) at risk for need for end-of-life (hospice) care within 90 days. Participants were asked to discontinue the use of CoQ_{10} and other antioxidant supplements for the duration of the treatment protocol. Although the clinical course of a given patient with mitochondrial disease cannot be predicted with certainly, investigators enrolled subjects who had significant morbidity secondary to their underlying condition and who were demonstrating relatively rapid progression of disease. After informed consent, cultured fibroblasts were obtained from two patients (Patients 2 and 3), for assessing response to EPI-743 *ex vivo* (Fig. 2), and performing antioxidant response element (ARE) expression analyses (Table 2).

2.2. Procedures

A baseline physical examination, standard chemistry and hematology panels, functional and quality-of-life assessment (modules I–IV, Newcastle Paediatric Mitochondrial Disease Scale [NPMDS] or Newcastle Mitochondrial Disease Adult Scale [NMDAS]) [22,23] were obtained for all patients. Serial HMPAO SPECT brain scans [21,24] were performed in 12 patients. Therapy was initiated at an EPI-743 test dose of 50 mg twice per day via mouth or gastrostomy tube for 14 days. Because no drug-related adverse clinical or

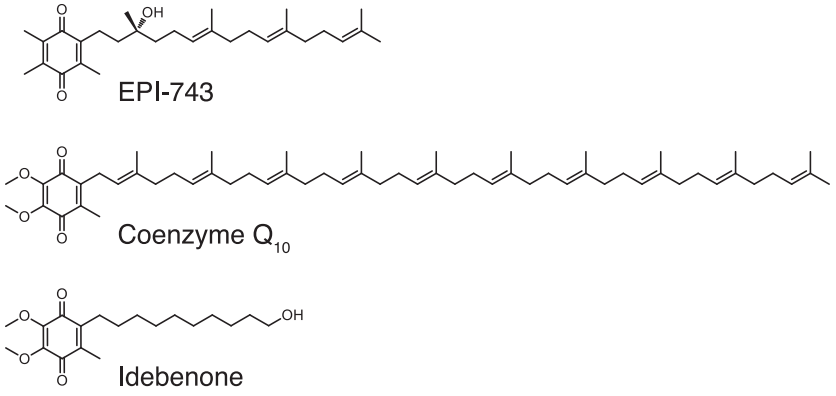

Fig. 1. Chemical structures of EPI-743, coenzyme Q_{10} and idebenone. EPI-743 is an orally bioavailable molecule that readily crosses the blood–brain barrier with a preclinical no-observable-adverse-effect level of 100 mg/kg. In addition to a truncated isoprene tail, EPI-743 possesses an important change in the quinone ring substitution pattern. In comparison to the *bis*-methoxy groups of coenzyme Q_{10} and idebenone series, EPI-743 possesses a *bis*-methyl substitution pattern that undergoes oxidation-reduction at a redox potential offset by −75 mV in comparison to coenzyme Q_{10} and idebenone [20].