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Development of a novel observer reported outcome tool as the primary efficacy outcome measure for a rare disease randomized controlled trial

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ABSTRACT

We developed an Observer-Reported Outcome (ObsRO) survey instrument to be applied in a multicenter, placebo-controlled, crossover randomized controlled trial of dichloroacetate in children with pyruvate dehydrogenase complex deficiency. The instrument quantifies a subject's at-home level of functionality, as reported by a parent/caregiver, who were instrumental in providing the clinical descriptors and domains that formed the instrument's content. Feasibility testing of the ObsRO tool showed it to be easy to use and comprehensive in capturing the major clinical functional limitations of affected children and requires less than 5 min for a parent/caregiver to complete daily.

1. Introduction

No therapy for any primary mitochondrial disease has been approved by the Food and Drug Administration (FDA). Among the reasons contributing to this stark deficiency are a historical aversion by both practitioners and patients to participate in controlled clinical trials; an over-reliance on unproven nutritional supplements; heterogeneity in the clinical presentation and course of disease, even among cohorts expressing an identical molecular genetic etiology; and lack of validated biochemical biomarkers or clinical assessment tools applicable as primary outcome measures for randomized controlled trials (RCTs) of investigational therapies (Stacpoole, 2011a, 2012; Robinson et al., 1987; Imbard et al., 2011; Patel et al., 2012; DeBrosse et al., 2012). Given these challenges, and the inherent logistical difficulties in conducting multicenter RCTs in rare disorders, it is not surprising that no drug has advanced to filing in the United States of a New Drug Application for treating a mitochondrial disease.

Pyruvate dehydrogenase complex deficiency (PDCD) is due to any of several loss-of-function mutations in the nuclear-encoded genes that give rise to PDC, a mitochondrial matrix enzyme mega-complex that is essential to cellular bioenergetics (Fig. 1). PDC irreversibly decarboxylates pyruvate to acetyl coenzyme A (acetyl CoA) and thus provides a requisite metabolic bridge between cytoplasmic glycolysis and mitochondrial oxidative phosphorylation. A functional PDC is also required for the oxidative removal of lactate. Consequently, PDCD is considered the most common cause of congenital lactic acidosis during the neonatal period. Patients who survive early life typically exhibit progressive neurological and neuromuscular degeneration and early death due to end organ failure and/or to over-whelming metabolic acidosis (Robinson et al., 1987; Imbard et al., 2011; Patel et al., 2012; DeBrosse et al., 2012).

Dichloroacetate (DCA) is an investigational drug having Orphan Product designation for the treatment of congenital lactic acidosis (James and Stacpoole, 2016; James et al., 2017). The drug inhibits pyruvate dehydrogenase kinase (PDK) isoforms that inhibit PDC by reversible phosphorylation of the E1 alpha (E1α) subunit of PDC. Repeated DCA administration also decreases turnover of the complex. Oral DCA is rapidly absorbed, readily crosses the blood-brain and lowers blood lactate concentrations within minutes of its administration. The drug is biotransformed by glutathione transferase zeta 1 (GSTZ1) to glyoxylate, which is inactive towards PDK. Haplotype variations in *GSTZ1* influence the kinetics and biotransformation of DCA,

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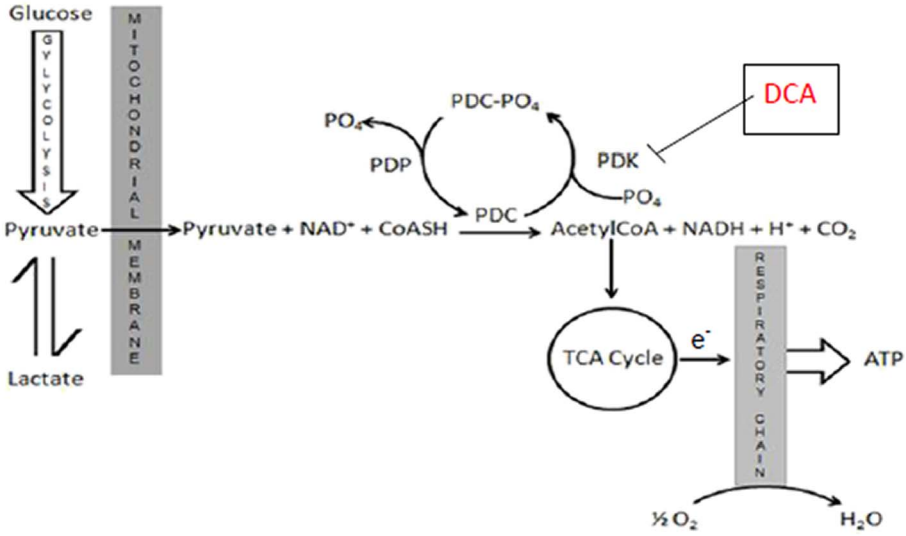

Fig. 1. Role of PDC in cellular energy metabolism and site of action of DCA. PDP, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; TCA, tricarboxylic acid; e^-, electrons; DCA, dichloroacetate.

distinguishing "slow" from "fast" drug metabolizers. Fast metabolizers possess at least one wild type (EGT) *GSTZ1* allele, while slow metabolizers lack this allele (James and Stacpoole, 2016; James et al., 2017). This genetic distinction has been exploited in a phase 1 trial of DCA in adults with recurrent malignant brain tumors to mitigate or prevent drug-induced reversible peripheral neuropathy (Dunbar et al., 2014), which is the only known dose-limiting toxicity associated with chronic DCA administration (reviewed in Stacpoole, 2011b) and is also incorporated into the PDCD trial (see below). Anecdotal reports and a RCT indicate chronic, oral DCA administration is generally well tolerated and safe in children with primary mitochondrial diseases, including PDCD, and is effective in causing sustained reductions in blood and cerebrospinal lactate (Berendzen et al., 2006; Stacpoole et al., 2006). Open label studies in PDCD patients also suggest DCA may improve clinical functionality within 24 h of initiating treatment and, may also increase survival (Stacpoole et al., 2008, and personal observ.). Therefore, in 2013, we began to plan a multicenter phase 3 trial of DCA (IND028625) in PDCD (NCT02616484) as the first such RCT of any therapy for this disease. Here we report on the process of developing a unique Observer-Reported Outcome survey of at-home patient functionality. The use of such a tool has been endorsed by the FDA as the primary efficacy outcome measure for the trial.

1.1. Development of survey tool

Initial discussions with the Division of Gastroenterology and Inborn Errors Products (GIEP), FDA, made clear that surrogate metabolic markers, such as blood lactate, could not be used as primary efficacy outcome measures and that, instead, we should apply an outcome measure that would identify changes in how patients in the proposed treatment arms felt and functioned. This posed an interesting challenge. Although prior clinical data suggested that DCA may mitigate, or at least stabilize, some of the common clinical signs of PDCD and improve functionality, there are no validated tools to evaluate how young children with PDCD feel or function before or after a therapeutic intervention. The Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) is a validated clinician-observer reported outcome tool in which the content was derived from expert clinical opinions rather than from parents/caregivers (Phoenix et al., 2006). It has been applied to an open label study of a synthetic coenzyme Q_{10} analog for treating patients with Leigh syndrome (Martinelli et al., 2012), a neurodegenerative complication of many mitochondrial disease patients, including some with PDCD (Robinson et al., 1987; Imbard et al., 2011; Patel et al., 2012; DeBrosse et al., 2012). The scale is quite time-consuming and, although completed by the clinician, it relies heavily on recall of the parent/caregiver. Comparisons are made between a patient's development and functional abilities to those expected from a child of that age. Due to the necessity of this baseline knowledge, the NPMDS was deemed usable only by pediatricians, preferably with experience in mitochondrial diseases. The NPMDS is also dependent on up to four-week recalls by the parent/caregiver to evaluate "current function." This limitation was identified by a National Institute for Neurological Diseases and Stroke -sponsored committee charged with evaluating current biobehavioral tools for the purpose of developing appropriate Common Data Elements for both future mitochondrial disease clinical trials and primary clinical care (http://www.commondataelements.NINDS.NIH.gov/MITO.aspx#lab = DataStandards, n.d.). In addition, GIEP informed us that it does not evaluate drugs for approval based on QOL assessments and discourages tools that rely on patient or observer recall, because of the likelihood of inaccurate reporting. The Karnofsky/Lansky scale (Lansky et al., 1987) is a validated clinician-observer instrument for measuring at-home functionality in children with cancer and other certain other life-threatening diseases. It should be applicable to children with PDCD, although it has never been applied in studies of pediatric primary mitochondrial diseases. The GIEP recommend that the Karnofsky/Lansky scale could be used as a secondary (exploratory) endpoint in our trial. Thus, we and the FDA recognized there was a need for a robust clinical outcome assessment measure able to capture and quantify functional signs in young children with PDCD over time, especially during the course of an interventional trial.

Accordingly, following multiple discussions with GIEP, and cognizant of published federal regulatory guidelines regarding the development and application of such outcome measures (FDA Guidance for Industry, 2009; Papadopoulos et al., n.d.; McLeod et al., 2011), we sought to generate an Observer-Reported Outcome (ObsRO) tool for this trial. Given the youth and cognitive disabilities of most, if not all, children to be entered into our study, we decided that a Patient-Reported Outcome Measure would be impracticable. Furthermore, because the study design (described below) limited the number of patient visits to participating clinical sites, a Clinician-Reported Outcome Measure would, by itself, be insufficient in monitoring progress during the trial.

The evaluation of the ObsRO assessment began with a questionnaire sent in April 2013, to parents of 25 PDCD children, asking what signs they observed when their child became ill, presumably associated with metabolic decompensation. Patients were asked to record the frequency of each sign, its relative severity on a Likert scale (i.e., the degree of "worry", from least to most worrisome) and the sign they observed first when their child became sick. The parents were members of an