Neurotherapeutics (2013) 10:307–319
DOI 10.1007/s13311-013-0176-7

REVIEW

Review of Clinical Trials for Mitochondrial Disorders: 1997–2012

Douglas S. Kerr

Published online: 30 January 2013

Abstract Over the last 15 years, some 16 open and controlled clinical trials for potential treatments of mitochondrial diseases have been reported or are in progress, and are summarized and reviewed herein. These include trials of administering dichloroacetate (an activator of pyruvate dehydrogenase complex), arginine or citrulline (precursors of nitric oxide), coenzyme Q_{10} (CoQ_{10}; part of the electron transport chain and an antioxidant), idebenone (a synthetic analogue of CoQ_{10}), EPI-743 (a novel oral potent 2-electron redox cycling agent), creatine (a precursor of phosphocreatine), combined administration (of creatine, α-lipoate, and CoQ_{10}), and exercise training (to increase muscle mitochondria). These trials have included patients with various mitochondrial disorders, a selected subcategory of mitochondrial disorders, or specific mitochondrial disorders (Leber hereditary optic neuropathy or mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). The trial designs have varied from open-label/uncontrolled, open-label/controlled, or double-blind/placebo-controlled/crossover. Primary outcomes have ranged from single, clinically-relevant scores to multiple measures. Eight of these trials have been well-controlled, completed trials. Of these only 1 (treatment with creatine) showed a significant change in primary outcomes, but this was not reproduced in 2 subsequent trials with creatine with different patients. One trial (idebenone treatment of Leber hereditary optic neuropathy) did not show significant improvement in the primary outcome, but there was significant improvement in a subgroup of patients. Despite the paucity of benefits found so far, well-controlled clinical trials are essential building blocks in the continuing search for more effective treatment of mitochondrial disease, and current trials based on information gained from these prior experiences are in progress. Because of difficulties in recruiting sufficient mitochondrial disease patients and the relatively large expense of conducting such trials, advantageous strategies include crossover designs (where possible), multicenter collaboration, and the selection of very few, clinically relevant, primary outcomes.

Key Words Placebo-controlled · crossover design · primary outcomes · dichloroacetate · arginine · citrulline · coenzyme Q_{10} · idebenone · EPI-743 · creatine · α-lipoate · exercise

Introduction

Many potentially therapeutic agents have been used to treat mitochondrial disorders, but few of these disorders have any proven effective therapy. Putatively, therapeutic agents that have been used include vitamins, amino acids, naturally-occurring metabolic intermediates, a variety of antioxidants, oxygen, experimental and established drugs, and attempted gene transfer. Several of these have been subjected to controlled clinical trials, without definitive beneficial outcomes. These clinical trials are the primary subject of this review, including open-label trials, controlled double-blind randomized trials that have been completed, and trials that are currently in progress. At this time, it is essential to keep these somewhat disappointing outcomes in a positive perspective because the limitation is not generally in trial design, but a shortage of scientific knowledge about what might be a promising, effective therapeutic strategy. Each well-designed trial is a learning experience that may lead to

Electronic supplementary material The online version of this article (doi:10.1007/s13311-013-0176-7) contains supplementary material, which is available to authorized users.

D. S. Kerr (✉)
Center for Inherited Disorders of Energy Metabolism,
Case Western Reserve University,
University Hospitals Case Medical Center, 11100 Euclid Avenue,
Cleveland, OH 44106-6004, USA
e-mail: douglas.kerr@case.edu

more refined approaches in evaluating new therapeutic agents. Difficult to organize and fund as clinical trials may be for rare and heterogeneous mitochondrial disorders, there really is no alternative in the future to bring new potentially more effective and safe therapy to those who are affected by mitochondrial disorders. The same was true of cancer therapy, which has come a very long way in recent decades.

This review builds on several prior, thorough reviews of clinical trials for mitochondrial disorders from different perspectives, which should be referred to for additional details and for other reported treatments that have not yet been evaluated through a formal clinical trial and therefore are not included here [1–5].

Dichloroacetate

Dichloroacetate (DCA), a structural analogue of pyruvate, is classified as an investigational drug. Its action in mitochondrial metabolism is to inhibit pyruvate dehydrogenase kinase, preventing inhibitory phosphorylation of pyruvate dehydrogenase, thereby keeping the pyruvate dehydrogenase complex (PDC) in its activated state. This action could maintain oxidative metabolism of carbohydrate despite physiological state or genetic deficiency of PDC and lower lactate, pyruvate, and alanine in more distal defects of mitochondrial electron transport or oxidative phosphorylation. For these reasons, DCA was used in humans as putative therapy prior to clinical trials, with apparently favorable results [6].

The first reported clinical trial of DCA in patients with mitochondrial disorders was conducted at University California at San Diego (UCSD) Medical Center [7]. This was an open-label trial because the investigators felt that it would be unethical or impractical to withhold such promising treatment from patients with mitochondrial disorders. The design of the study was that patients affected by mitochondrial disorders initially received 40–50 mg/kg/d of DCA. This dose with subsequently reduced to 25 mg/kg/d, as prolonged use of DCA inhibits its own catabolism, shown by associated kinetic studies. Thiamine was routinely added to DCA treatment because of prior evidence that this might ameliorate the risk of peripheral neuropathy. The primary outcome of this study was to lower cerebrospinal fluid (CSF) or blood lactate. Secondary outcomes included a neurological examination inventory and subjective assessments of the patient's status. The patients had a wide range of age, from 6 months to 53 years, and had variety of diagnoses based on decreased enzymatic activity of mitochondrial electron transport chain (ETC) enzyme activities or genetic mutations in mitochondrial DNA (mtDNA) or nuclear genes (see Table 1). Altogether, 37 patients were enrolled in this study and 22 completed 3–7 years. Although there was lowering of blood or CSF lactate in some patients, the results of this primary outcome after 12 months of treatment were not significant owing to large variations. Of the patients remaining in the study, there was no significant improvement of neurological function. However, 49 % reported improvement in their symptoms, 22 % reported worsening, and 29 % no change. Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) patients most frequently reported improvement (7 of 11). Nine patients died, presumably owing to complications of their underlying diseases. Importantly, 12 of 25 patients who had normal baseline nerve conduction showed decline within a year of treatment with DCA.

A simultaneous study of DCA in treatment of children and adolescents with mitochondrial disorders was conducted at the University of Florida [8]. This was a phase III, double-blind, placebo-controlled, randomized trial (Table 1). The design was to administer either DCA 25 mg/kg/d or placebo for 6 months, and then crossover to the alternative for another 6 months. The primary outcomes were a "Global Assessment of Treatment Efficacy" (GATE), including independent assessments by a research nurse, neurologist, and pediatrician, and a Quality of Life (QoL) questionnaire. Secondary outcomes included growth, postprandial blood lactate, and frequency of illnesses. Eligibility criteria was similar to the UCSD trial, including evidence of enzyme deficiency or a pathogenic mutation of 1 or more components of mitochondrial energy metabolism (ETC complexes or PDC deficiency), blood lactate >2.5 mM, and age from 6 months to 20 years. A total of 43 patients were enrolled, of whom 36 completed the 12-month crossover trial, 3 died, and 2 dropped out (Table 1). The primary outcome (GATE), compared between 6 and 12 months, was not significantly different for the DCA *vs* placebo groups or their diagnostic subgroups (the MELAS subgroup appeared to do a little better, but this was not a significant difference). Postprandial lactate, but not basal lactate, was significantly lower in the DCA group. The same observation was made that chronic use of DCA inhibits its own metabolism (prolonged half-life), which was attributed to inhibition of maleylacetoacetate isomerase. Half of the patients had evidence of impaired nerve conduction before receiving DCA, which did not change during the trial. This difference (lack of worsening of nerve conduction velocity due to DCA) from the UCSD trial may be related to the younger age of the subjects involved in the University of Florida trial [9].

Following these two trials of DCA in mixed populations of mitochondrial disorders and other case reports, it seemed that the benefit might be somewhat greater for MELAS patients. Therefore, a third trial was organized at Columbia University, which was specific for MELAS [10]. This also was a phase III double-blind, randomized, placebo-controlled trial (Table 1). The study design was to

Table 1 Summary of clinical trials for mitochondrial disorders

Agent	PI (location)	Status (report)[ref]	Type	Design	Primary outcome measures	Secondary outcome measures	Eligibility	Patients recruited/ completed (age, years)	Primary outcome results	Secondary outcome results	Adverse events
DCA	Barshop B (UCSD)	Completed (2004) [7]	Open-label	DCA 40–50, later 25 mg/ kg/d, plus thiamine	Blood, CSF lactate	Neurological scale, subjective	Enzymatic or genetic mito d.	37/22 (0.5–53)	No ↓ CSF lactate	Subjective: 49 % felt better; no Δ neurological examination	Neuropathy or ataxia in 11 %
DCA	Stacpoole P (University of Florida)	Completed (2006) [8]	Double-blind, placebo-controlled	DCA 25 mg/kg/d or placebo, crossover at 6 months, plus thiamine	Global (GATE), QoL	Growth, lactate	Enzymatic or genetic mito d.	43/36 (1–19)	No Δ GATE or QoL	↓ Postprandial lactate	50 % neuropa-thy at start, no Δ
DCA	Kaufman P and DeVivo D (Columbia University)	Terminated (2006) [10]	Double-blind, placebo-controlled	DCA 25 mg/kg/ d or placebo, crossover at 24 months× 12 months, plus thiamine	Global (GATE), ADL, neuropsychological examinations	MRS lactate, CSF and blood lactate, MRI, EMG	MELAS, *A3243G* mutation, and high CSF+MRS lactate	30/5×36 months, 19<36 months (16–44)	No Δ GATE	NS Δ MRS, CSF, or blood lactate post-24 months	NCV ↓68 % over 6 months in DCA rx group, terminated by DSMB
Arginine	Koga Y (Karume University, multicenter)	Completed (2005–7) [12–14]	Open-label	Acute Arg–HCl 500 mg/kg , chronic Arg 150–300 mg/kg/d	Neurological examination, number of admissions	Plasma AA, NO, cGMP	MELAS, >50 % muscle *A3423G* mutation	15/6–15 (8–30)	↓ Number and severity of stroke-like episodes	↑ Diameter brachial artery, ↑ plasma citrulline, NO, cGMP	?
Coenzyme Q_{10}	Tarnopolsky M (McMaster University)	Completed (2010) [25]	Double-blind, placebo-controlled	Ubiquinol (Qgel) 1200 mg/d or placebo×2 months, washout×2 months, crossover×2 months	Blood lactate postexercise, forearm handgrip strength, cycle ergometry	ADL, QoL, brain MRS, body composition, oxidative stress markers	Mito. d. with myopathy and/or mutation	30/30 (45–59)	No Δ lactate p handgrip, ↓ lactate p cycle after CoQ_{10}, no Δ forearm strength or exercise capacity	No Δ brain MRS, ADL, QoL, oxidative stress markers	None reported
Coenzyme Q_{10}	Stacpoole P (Univeristy of Florida, multicenter)	In progress (2012) [26]	Phase III, double-blind, controlled	Ubiquinol 10 mg/kg/d (max 400 mg/d) or placebo, crossover at 6 months, plus "cocktail"	GMFM II, QoL	Neurological exam, Child Inventory, plasma CoQ profile	Significant ETC deficiency or pathogenic mutation	Goal 50/28 (1–17)	(incomplete)	(incomplete)	None related to CoQ_{10}
Idebenone	Kaufmann P, Hirano M (Columbia University)	In progress [34]	Phase IIB, double-blind, controlled	A: Idebenone 900 mg/d; B: Idebenone 2400 mg/d; C: placebo	MRS lactate	Blood lactate, fatigue scale, QoL	MELAS, *A3243G* mutation, and ↑ CSF+ MRS lactate	Goal 21/? (8–65)	(incomplete)	(incomplete)	
Idebenone	Chinnery P, Klopstock T (Newcastle University, Ludwig-Maximilians University, University of Montreal)	Completed (2011) [39]	Randomized, placebo-controlled, blinded, multicenter	Parallel, Idebenone 900 mg/d or placebo (2:1), × 24 weeks	Best recovery VA (either eye)	Change best VA, change VA best eye, change VA both eyes, color contrast sensitivity	LHON<5 years due to 1 of 3 common mutations	85/78 (14–65)	No Δ best recovery overall, significant ↑recovery in discordant subgroup	No Δ overall, but ↑best VA and VA both eyes if discordant basal VA	None related to idebenone

Table 1 (continued)

Agent	PI (location)	Status (report)[ref]	Type	Design	Primary outcome measures	Secondary outcome measures	Eligibility	Patients recruited/ completed (age, years)	Primary outcome results	Secondary outcome results	Adverse events
EPI-743	Enns G and Miller G (Stanford University, MUSC, UCLA, CHOC, CHMCA Edison Pharmaceuticals)	In progress (2012) [41, 42]	Open-label, multicenter	Epi-743 100 mg/d×2 weeks, then 200 mg/d×2 weeks, then 300 mg/d×8 weeks (no other antioxidants), plus extension	NPMDS and Tc-99 m HMPAO SPECT imaging	PE, QoL, pharmaco-kinetics, standard safety monitoring	Genetically defined mito. d., need for hospice within 90 days	22+/21? (2–27)	11/14 showed clinical improvement and 10 improved (↓) NPMDS scores in 90 days	HMPAO SPECT scans correlated with clinical improvement	None related to EPI-743
EPI-743	Martinelli D and Miller G (Bambino Gesu Hosp Rome, Edison Pharmaceuticals)	Completed (2012) [43]	Open-label, phase IIA	Epi-743 300 mg/d×6 months (without other antioxidants), historical controls	NPMDS (sec I–III), GMFM, PedsQL (before and after)	MDCRS, pharmacokinetics	Genetically-defined Leigh syndrome and NPMDS score >15	10/9 (2–13)	↓ NPMDS, ↑GMFM and PedsQL scores (improved)	↑MDCRS scores (improved)	8 SAEs in 4 patients, none EPI-743 related
Creatine	Tarnopolsky M (McMaster University)	Completed (1997) [45]	Double-blind, counterbal-anced, placebo-controlled	Washout, creatine 10 g/d×2 weeks ->4 g/d×1 week, or placebo 3 week; pre- and postevaluations	Handgrip strength, basal and postexercise lactate	ADL, contraction strength, 2 minute walk, cycle ergometry	Mitochondrial cytopathy (6/7 with MELAS)	7/7 (25–64)	Significant ↑ forearm grip strength (19 %) and ↓ post-exercise lactate	No Δ ADL, contraction strength, 2 minute walk, exercise capacity	None
Creatine	Klopstock T (Ludwig-Maximilians University)	Completed (2000) [46]	Double-blind, placebo-controlled, crossover	Creatine 20 g/d or placebo×4 weeks, washout, reversed×4 weeks, evaluated pre-/post- both periods	Muscle strength tests (MRC scale), lactate pre-/postcycle exercise	ADL, motorability (Hammersmith), neurological symptoms, functions, ataxia	Mito myopathy (CPEO or MM)	16/16 (24–74)	No Δ strength or lactate	No Δ	None
Creatine	Kornblum C (University Bonn)	Completed (2005) [47]	Double-blind, placebo-controlled, crossover	Creatine 150 mg/kg/d or placebo×6 weeks, washout, reversed×6 weeks, evaluated pre-/post- both periods	Muscle ergometric exercise with ^{31}P-MRS PCr recovery	Clinical eval, tensiometric tests, other ^{31}P-MRS variables, ataxia	CPEO or KSS with mtDNA deletion	15/13 (8–55)	No Δ strength or ^{31}P-MRS	No Δ	None
Creatine, α-Lipoate+ CoQ_{10}	Tarnopolsky M (McMaster University)	Completed (2007) [48]	Double-blind, placebo-controlled, crossover	Creatine 6 g+α-lipoate acid 600 mg+CoQ_{10} 240 mg/d or placebo×5 weeks, washout, reversed×5 weeks	Muscle strength (handgrip, ankle dorsiflexion, knee extension)	Isometric fatigue test, pulmonary function, body comp., lactate	Mito. d.: (MELAS, CPEO, KSS, LHON, MNGIE, cytopathies)	17/16 (12–58)	No Δ strength?	No Δ fatigue, ↓lactate?, improved body comp.?, ↓urine 8-IsoP?	None reported
Exercise	Haller R (University of Texas, multicenter)	Completed (2001–3) [49–51, 54]	Open	1: Mito pts, exercise×14 weeks (pre- and postevaluations) 2: Baseline evaluation mito pts and controls	Physiological parameters during exercise (capacity)	Muscle ETC enzymes, % mutant DNA	mtDNA mutation and exercise intolerance	1: 10/10 (24–53) 2: 62	↑ Work capacity and phosphocreatine synthesis	↑ Mito enzymes NS Δ % mutant mtDNA	None reported

Table 1 (continued)

Agent	PI (location)	Status (report)[ref]	Type	Design	Primary outcome measures	Secondary outcome measures	Eligibility	Patients recruited/ completed (age, years)	Primary outcome results	Secondary outcome results	Adverse events
Exercise	Haller R (University of Texas, multicenter)	In progress [52]	Phase II, randomized, open	Exercise or not×6 months, crossover at 6 months; continue exercise× 12 months; basal, interval, postevaluations	Change total and % mutant mtDNA, exercise capacity and oxidative metabolism	MRI of heart and muscle, QoL	Mitochondrial myopathy with mutation or mtDNA deletion	Goal 50 (18–65)	(incomplete)	(incomplete)	

PI = principal investigator; DCA = dichloroacetate; UCSD = University of California San Diego; MUSC = Medical University S. Carolina; UCLA = University California Los Angeles; CHOC = Childrens Hospital Orange County; ACH = Akron Childrens Hospital; Arg–HCl = arginine–hydrogen chloride; CoQ_{10} = coenzyme Q10; mito. pts = mitochondrial patients; CSF = cerebrospinal fluid; GATE = Global Assessment of Treatment Efficacy; QoL = quality of life; ADL = activities of daily living; GMFM = Gross Motor Function Measure; MRS = magnetic resonance spectroscopy; VA = visual acuity; NPMDS = Newcastle Paediatric mitochondrial disease score; HMPAO SPECT = hexamethylpropyleneamin oxime–single proton emission comuted tomography; PedsQL = pediatric quality of life; MRC = Medical Research Council; PCr = phosphocreatine; mtDNA = mitochondrial DNA; MRI = magnetic resonance imaging; EMG = electromyography; AA = amino acids; NO = nitric oxide; cGMP = cyclic guanine monophosphate; PE = physical exam; MDCRS = Movement Disorder Childhood Rating Scale; ETC = electron transport chain; mito. d. = mitochondrial disease; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; LHON = Leber hereditary optic neuropathy; CPEO = chronic progressive external ophthalmoplegia; MM = mitochondrial myopathy; KSS = Kearns–Sayer syndrome; MNGIE = mitochondrial neurogastrointestinal encephalomyopathy; NS = not signficant; body comp. = body composition; NCV = nerve conduction velocity; rx group = treatment group; DSMB = Data Safety Monitoring Board; SAE = serious adverse event.

administer either DCA, 25 mg/kg/d, or placebo for 24 months, and then crossover to the alternative for 12 months. All subjects received thiamine, carnitine, coenzyme Q_{10} (CoQ_{10}), and α-lipoate throughout the study. The primary outcomes were the GATE, neuropsychological examinations, activities of daily living function (ADL), and health events. Secondary outcomes included lowering of brain lactate, determined by magnetic resonance spectroscopy (MRS), CSF and blood lactate, and changes of magnetic resonance imaging (MRI) and electromyography. Eligibility criteria were restricted to having the common A3243G mutation in the $tRNA^{leu}$ gene of mtDNA, a MELAS phenotype, CSF lactate ≥2.75 mM, and MRS brain lactate >5 IU (Table 1).

Thirty patients with MELAS were recruited into this trial, 15 men and 15 women aged 16–44 years, of whom 5 completed 36 months of the trial and 19 completed <36 months (3 died and 3 withdrew). This trial was terminated by the Data Safety and Monitoring Board because of evidence of excessive and frequently disabling peripheral neuropathy. Nerve conduction decreased in 68 % of the DCA-treated group within 6 months, and most patients (13/15) were taken off DCA [11]. There was no difference in GATE scores between the DCA and placebo groups at 3, 6, or 12 months, and no difference in MRS, CSF, or blood lactate in those who completed 24 months. To quote the authors, this experience "underscores the importance of randomized, controlled trials in evaluating the efficacy of new treatments for MELAS" [10].

Arginine

Another potentially promising treatment for MELAS, which has not yet been subjected to a randomized controlled clinical trial, is arginine. Arginine is the substrate of nitric oxide synthase, which produces nitric oxide (NO) and citrulline. NO stimulates guanosyl cyclase, which has a well-established role in vasodilation, and therefore arginine has been used for various clinical disorders in which vasoconstriction may play a significant role in pathophysiology. MELAS is associated with recurrent "metabolic strokes", attributed to possible vasoconstriction. This concept has been supported by a series of uncontrolled, open-label, chronic clinical trials of oral arginine administration, and also short-term controlled trials of acute administration of arginine–hydrogen chloride (HCl) during clinical exacerbations, originating from Karume University in collaboration with other medical centers in Japan [12–16]. Although arginine has been used widely for clinical purposes, including treatment of urea cycle disorders, it may be associated with adverse effects, particularly in the soluble arginine–HCl form, which is administered parenterally [17].

In the chronic open-label study, arginine (free base) was administered orally at 150–300 mg/kg/d (Table 1). The primary outcomes were frequency and severity of readmissions for stroke-like episodes compared with historical medical records from the same patients, and also arginine induced increase in the diameter of their brachial arteries. Recruitment criteria included ≥50 % heteroplasmy in muscle for the A3243G mutation associated with the MELAS phenotype.

Six or 15 patients, aged 8–30 years, were included in 1 or more various longitudinal studies. After 2 years of oral arginine, these patients showed significantly increased arginine–HCL stimulated dilation of their brachial arteries compared with similar studies at baseline [13]. They also had less severe and fewer admissions for stroke-like episodes [14].

In the short-term studies, acute intravenous administration of arginine–HCl (500 mg/d) in 5 % glucose was compared with just 5 % glucose. The response was followed with neuroimaging studies and measurements of NO, citrulline, and cyclic guanosine monophosphate in plasma. Fifteen to 22 patients were included in the various outcomes. The results of these studies showed improved clinical recovery and neuroimaging (statistical parametric mapping-single proton emission computed tomography, SPM-SPECT) in a few patients who received arginine–HCl, as well as significantly increased plasma NO, citrulline, and cyclic guanosine monophosphate [12]. Separate acute studies showed that MELAS patients had lower diameter brachial arteries compared with control patients at baseline, which improved after administration of intravenous arginine–HCl, but not to the full extent of controls [13]. Two follow-up open-label clinical trials of arginine have been conducted or are awaiting recruitment, for which the results are yet available [16, 18].

Although these studies have indicated promising beneficial results for MELAS patients, they have not yet been followed with a well-controlled, randomized clinical trial. Recent evidence has shown, counterintuitively, that administration of citrulline results in greater production of NO than arginine in MELAS patients, presumably because of an advantage of *in vivo* synthesis of arginine (from citrulline) as a substrate for NOS within endothelial arterial cells [19, 20]. This observation should provide sufficient background for a controlled comparative effectiveness trial of both arginine and citrulline in long-term treatment of MELAS.

CoQ_{10} and Idebenone

These two antioxidants have much in common, but differ in that CoQ_{10} is the natural intermediate in the ETC and idebeone is a synthetic compound that is more water soluble and may penetrate the blood–brain barrier more efficiently. The redox state of both compounds can alternate between the quinone (oxidized) and quinol (reduced) forms, and both can accept and donate electrons from ETC complex I to complex II. CoQ_{10} is readily available without prescription and is very widely recommended and administered in many formulations to individuals with various mitochondrial and other disorders (also for the general public), but has infrequently been evaluated in controlled clinical trials specifically for primary mitochondrial disorders. It seems intuitively obvious or mandatory to treat defects of CoQ_{10} biosynthesis by supplementation with CoQ_{10}, although the beneficial results of such treatment are quite variable and appear to depend on how early this intervention may occur and other variables not yet identified [21, 22]. The rationale for administering antioxidants, in general, rests heavily on the role of scavenging reactive oxygen species (ROS) in the pathogenesis of mitochondrial disorders [23]. A more specific proposed rationale is the possibility of bypassing deficiency of ETC complex III, as was reported many years ago with vitamin K_3 (menadione) and ascorbic acid [24], but the possible advantage of substitution of CoQ_{10} for menadione in this situation has not been reported. The rationales for efficacy of CoQ_{10} in various forms of ETC complex and oxidative phosphorylation deficiencies include all of the above.

A trial of CoQ_{10} in adults with mitochondrial disorders was competed at McMaster University [25]. This was a randomized, double-blind, placebo-controlled study to determine the effects on exercise tolerance and capacity (Table 1). The study design was to administer CoQ_{10} (Tishcon Qgel®, ubiquinol) at 1200 mg/d or placebo for 60 days, and then patients were crossed over (after a washout period of 2 months) to the alternative regimen for another 60 days. The primary outcome measures were blood lactate before and after exercise, forearm hand grip strength, and cycle ergometry capacity testing. Secondary outcome measures were ADL and QoL questionnaires, MRS of brain metabolites, body composition, and urinary markers of oxidative damage. Recruitment criteria were adults with a mitochondrial disorder and a defined mutation.

Thirty patients, aged 45–59 years, were recruited, of whom 15 had MELAS and 11 had chronic external ophthalmoplegia (CPEO). Blood lactate 3 minutes post-handgrip exercise was not different following CoQ_{10} or placebo, but was significantly decreased post 1 min cycle exercise following CoQ_{10} for 60 days. Maximal isometric forearm strength or cardiorespiratory function after cycle ergometry (for 15 patients who completed this testing) was not significantly different between the two treatments. Blood lactate after handgrip exercising increased equally following the 2 treatments (n=30), but increased significantly less after 15 minutes of cycling exercise (n=15), as did oxygen consumption, after receiving CoQ_{10}. Resting blood or brain lactate was not significantly

different in the 2 treatment phases, nor were body composition, measures of ADL or QoL, other brain metabolites, or urinary markers of oxidative stress. Plasma CoQ_{10} increased 5-fold on this dose, to 5.5 μg/ml.

A phase III, placebo-controlled, double-blind, randomized, multicentered trial of CoQ_{10} in children and adolescents with mitochondrial disorders has been in progress for the past few years, based at the University of Florida, which is not yet completed [26]. Design of this study is to administer ubiquinol (LiQnol®) 10 mg/kg d (up to 400 mg) or placebo for 6 months, followed by crossover to the alternative agent for another 6 months (Table 1). All patients receive a "cocktail" of thiamine, riboflavin, ascorbic acid, and carnitine throughout. The primary outcome measures are the validated Gross Motor Function Measure-88 (GMFM-88), which was selected to be applicable across the age range and spectrum of disability that occur in mitochondrial disorders, and a QoL questionnaire. Secondary outcome measures are a standard neurological examination, Child Development Inventory, and plasma CoQ_{10} levels. Eligibility criteria for patients include a well-characterized deficiency of one or more ETC complexes with evidence of sample integrity, or a pathogenic mutation affecting ETC or oxidative phosphorylation, and associated phenotypic features of a mitochondrial disorder [26].

The goal for recruitment was 50 patients. As of the interim report, 107 patients had undergone consent and review of their medical records, of which 42 were considered eligible, and 37 were randomized. Nine patients have dropped out and 28 have completed the trial. Plasma total CoQ_{10} in 17 of the patients who completed the trial averaged 5.4 μg/ml, which is favorable compared with the adults in the McMaster University study receiving 1200 mg/d of ubiquinol, or the highest levels obtained in adults with Parkinson's disease (PD) receiving 2400 mg/d of generic CoQ_{10}, or children with Down syndrome receiving a similar dose of ubiquinol to that used in this trial [27, 28].

The much larger and successive trials of CoQ_{10} in adults with PD, which also is associated with evidence of mitochondrial dysfunction, are instructive models for trials of CoQ_{10} in less common mitochondrial disorders [29–31]. Although these trials have not shown dramatic effects in improved outcome, they serve as excellent models of collaborative multicenter work—they are well-controlled, with agreed upon primary outcomes, and each trial has built on the incremental experience of prior trials [3].

Idebenone

As discussed earlier, idebenone is similar to CoQ_{10} in its ability to function within the ETC and to be a scavenger for ROS, and may be better transported into the brain. This has led to trials of idebenone in Friedreich ataxia (FA), MELAS, and Leber hereditary optic neuropathy (LHON) [32–34].

Friedreich ataxia (FA) is due to mutations in the *FXN* gene, which encodes frataxin, an iron carrier protein and donor for iron–sulfur cluster biosynthesis, critical for components of the mitochondrial ETC. Deficiency of frataxin results in intramitochondrial iron accumulation and progressive neurological degeneration, cardiomyopathy, and diabetes. Over the last 13 years there have been 13 clinical trials of idebenone in FA, using progressively larger does and emerging to phase III trials, indicating that higher doses of idebenone are well tolerated and may stabilize neurological function in young patients with FA [35–37]. Again, these successive trials are instructive for smaller trials in less common mitochondrial disorders in that they involve multicenter collaboration, carefully controlled trial design, agreed upon primary outcomes, and build upon the experience of previous trials [3].

An ongoing trial of idebenone in MELAS is being conducted at Columbia University. This is a phase IIa (dose-finding), double-blind, randomized, placebo-controlled study [38]. The study design randomizes patients to 1 of 3 groups: group A receives idebenone 900 mg/d for 1 month, group B receives idebenone at 2250 mg/d, and group C receives a placebo (Table 1). Lowering of cerebral lactate determined by MRS is the primary outcome. Venous lactate, fatigability, and QoL are secondary outcome measures. The eligibility of patients is similar to the DCA trial, including the A3243G mutation, MELAS phenotype, and MRS lactate >5 IU, and aged 8–65 years. The target is to recruit 7 patients into each group (Table 1).

Idebenone also has been evaluated in a controlled, international collaborative treatment trial of LHON [39]. LHON is associated with mutations in mtDNA affecting complex I of the ETC, is the most common mitochondrial disorder causing progressive blindness, and is most prevalent in young adult males. This was the first adequately powered, multicenter, randomized, placebo-controlled trial for this disorder, which followed earlier uncontrolled reports that idebenone resulted in improvement of vision in LHON. The trial design was parallel random assignment of patients to either idebenone 900 mg/d or placebo (randomization ratio 2:1) for 24 weeks, with comparison of visual acuity (VA) and other eye findings before and after intervention (Table 1). The primary outcome measure was the best recovery of VA (in either eye). Secondary outcomes included the change in best VA (either eye), change in VA in the best eye at baseline, and change in VA for both eyes. Color-contrast sensitivity and optic nerve fiber layer thickness were also measured in most patients. Eligibility was for patients aged between 14 and 64 years with LHON associated with 1 of the 3 most common mtDNA mutations, and a history of vision loss for less than 5 years.

A total of 85 patients (73 men, 12 women) were recruited in 3 medical centers (Newcastle-upon-Tyne, Munich, and

Montreal), of whom 55 were assigned to receive idebenone and 30 to receive placebo. The characteristics of both groups were very similar. Seven patients discontinued treatment and there were no adverse events related to whether they were taking idebenone or placebo. There were no significant differences in improvement of the primary or secondary outcome measures for the whole group. However, there were significant differences in the both the primary outcome and VA of both eyes for those patients with discordant VA at baseline (n=30), indicating a beneficial effect of idebenone in this subgroup. Discordant VA in LHON has been thought to be related to early stages of the disease, although that was not confirmed by history in this subgroup. Color-contrast for blue–yellow also improved significantly in those receiving idebenone, but not red–green, indicating a benefit for the larger stratified nerve fibers. Based on this finding, a follow-up phase III clinical trial has been proposed [40].

EPI-743

EPI-743 is a designed para-benzoquinone analog, differing structurally from CoQ_{10} and idebenone by having bis-methyl groups substituting for bis-methoxy groups on the quinone ring and a shorter side chain of 3 isoprene units (*vs* 10 in CoQ_{10}) linked via a hydroxybutyl group [41]. This structural modification increases the antioxidant protective effect of EPI-743 for cells in culture more than 1000-fold compared with CoQ_{10} and idebenone. To evaluate EPI-743 as a therapeutic agent for mitochondrial disorders, a open-label, expanded access, multicenter trial with patients approaching end-of-life care was initiated at Stanford University and 4 other medical centers [41]. The trial design was to start with 100 mg/day (not weight based), escalating to 200 mg/d after 2 weeks, then 300 mg/d for the duration of the protocol, lasting a total of 12 weeks, followed by a long-term extension (Table 1). Other antioxidant therapies were discontinued. Primary outcome measures were the Newcastle Paediatric Mitochondrial Disease Scale (NPMDS) and brain hexamethylpropyleneamine oxime-single proton emission computed tomogragphy (HMPAO SPECT) technicium-99m radionucleotide imaging. HMPAO was selected because of its ability to serve as a redox sensor. Secondary measures included physical examination, QoL assessment, pharmacokinetics, and standard chemistry and hematological parameters. Inclusion criteria were a genetically-defined mitochondrial disease and at risk for need of end-of-life hospice care within 90 days.

Initial experience with 14 patients, aged 2–27 years, with various mitochondrial diseases, was that 12 survived the duration of the protocol, of whom 11 showed clinical improvement and 10 had somewhat improved NPMDS scores. HMPAO SPECT brain scans correlated with clinical improvement. No adverse events were observed that were considered related to drug treatment. In a follow-up report of this same protocol, including 22 patients, there was a significant correlation of the changes of technicium-99m-HMPAQ-SPECT cerebellar uptake and the clinical response evaluated by the Newcastle Mitochondrial Disease Scale (adult or pediatric) before and after 3 months of treatment with EPI-743 [42].

Another clinical trial of EPI-743 for children with genetically-defined Leigh syndrome was conducted in Rome [43]. This also was an open-label trial. EPI-743 was administered at a dose of 300 mg/d (not weight based) for 6 months, with discontinuation of other antioxidants (Table 1). Primary outcome measures were changes in the NPMDS score (section I–III), GMFM, and PedsQL Neuromuscular Module. Secondary outcome measures were the Movement Disorder-Childhood Rating Scale and pharmacokinetic studies. Patient eligibility included children with genetically-defined Leigh syndrome, a NPMDS score greater than 15, and MRI confirmation of necrotizing encephalopathy.

Ten children, aged 2–13 years, were recruited, of whom 9 continued treatment for 6 months. The primary outcomes showed significant decreases (improvement) in the NPMDS (sections I–IV) scores, increases (improvement) in GMFM, PedsQL Neuromuscular Module, and Movement Disorder-Childhood Rating Scale scores, with all 9 patients who remained on treatment showing at least slight improvement. The 1 patient who discontinued treatment showed initial improvement and then decline in most measures after discontinuing treatment. Eight serious adverse events occurred in 4 patients, considered unrelated to drug treatment. Comparison of these outcomes with a literature review of 180 children with Leigh syndrome associated with the similar mutations of this EPI-743-treated trial cohort showed a better outcome than frequent rapidly degenerative outcomes and early childhood death in the historical group, although these EPI-743 treated cases may have been more stable before treatment [44]. As a result of these 2 initial open trials of EPI-743, a randomized, placebo-controlled trial in genetically-proven Leigh syndrome is in progress [42, 43].

Creatine (Alone or in Combination with Antioxidants)

Provision of supplemental creatine was one of the first interventions tried for mitochondrial disorders, and was the first to be evaluated in a controlled clinical trial [45]. The rationale for providing supplemental creatine arose from prior observations that muscle creatine phosphate (PCr) may be decreased in various clinical situations, that adenosine triphosphate generated from glycolysis may be transferred to PCr for limited energy storage in muscle, and increasing PCr could be beneficial in promoting anaerobic metabolism, as well as high-intensity aerobic exercise

tolerance. While creatine is normally synthesized in the liver, normal dietary intake of creatine is significant and supplemental creatine has been found to be well tolerated and employed to increase exercise capacity in normal volunteers, and was reported to be beneficial in a patient with MELAS.

This first trial was conducted at McMaster University and was a double-blind, placebo-controlled, randomized, crossover, "counter-balanced" trial (Table 1). This started with a 5-week washout period, followed by administration of a "loading" dose of creatine (monohydrate), 10 g/d for 2 weeks, followed by dose reduction to 4 g/d for 1 week, or administration of a placebo for a total of 3 weeks (presumably, the order of the 2 phases of this crossover trial from creatine to placebo or vice versa was randomized, but this is not explicitly stated). The main outcome measures were change in ischemic handgrip strength with a dynamometer, and changes in basal and post-cycle exercise blood lactate. Additional outcome measures included a subjective ADL questionnaire, a 2-minute walk test, nonischemic testing of strength of other muscles, cycle ergometry, and body composition by dual-energy X-ray absorptiometry scanning. Seven patients were recruited, aged 25–64 years, 6 of whom had MELAS and 1 had mitochondrial myopathy, and all of whom had elevated resting blood lactate (>2.7 mM). All patients completed both trials and most of the pre-post tests.

It was found that there was a statistically significant 19 % increase of ischemic, isometric handgrip strength after intake of supplemental creatine for 3 weeks. There were no differences in basal/resting pre-exercise blood lactate, but there was a significant increase (11 %) of post-exercise blood lactate for both ischemic handgrip testing and aerobic cycle ergometry after creatine *vs* placebo, presumably reflecting increased capacity for anaerobic metabolism. None of the other measures showed significant differences between the creatine and placebo groups, and no adverse events were reported (see Table 1).

Despite this evidence for a significant benefit of creatine supplementation, 2 other subsequent clinical trials did not show a significant beneficial effect, albeit with patients who had somewhat different types of mitochondrial disorders. The second trial, conducted at Ludwig-Maximilians University was also a double blind, placebo-controlled, crossover trial [46]. Patients were randomized to receive creatine, 20 g/d (a higher dose), or placebo for 4 weeks, then, after a 4-week washout interval, received the other alternative for another 4 weeks (Table 1). The primary outcome measures were similar—changes in muscle strength testing Medical Research Council (MRC, scale) and blood lactate before and after cycle exercising. Secondary outcome measures were an ADL scale, motor ability (Hammersmith scale), neuromuscular symptoms, function time test, and ataxia score. Patient eligibility was a mitochondrial myopathy and/or mtDNA deletion. Of 16 recruited patients, 13 had CPEO and 3 had mitochondrial myopathy, all had ragged red fibers on muscle biopsy (indicative of mitochondrial proliferation) and 5 had mtDNA analysis, confirming large deletions typical of these disorders.

All 16 patients, aged 24–74 years, completed the study over 3 months. There were no significant differences in muscle strength, post-exercise blood lactate, or other measures after taking creatine or placebo for 4 weeks. The authors comment that although there were no significant subjective or objective differences in the muscle functions tested, which were relevant to the patients' daily activities, they could not exclude a possible benefit for creatine in high-intensity exercise.

The third study, conducted at the University of Bonn, was, again, a double-blind, placebo-controlled, randomized crossover trial type [47]. The design was to randomize the patient to initially receive either creatine, 150 mg/kg d (= 7.5 g/d for 70 kg) or placebo for 6 weeks, followed by a 4-week washout, before crossing over to the alternative of creatine or placebo for 6 weeks (Table 1). The primary outcome measures were standardized calf muscle aerobic and ischemic exercise testing, and concordant ^{31}P MRS determination of the intramuscular PCr/adenosine diphosphate ratio. Secondary outcomes included clinical evaluation, tensiometric tests, and routine laboratory tests. These values were also compared with healthy control volunteers. Fifteen patients, aged 8–56 years, were recruited with confirmed mitochondrial disease by muscle biopsy and proven mtDNA deletions; of these, 13 had CPEO and 2 had Kearns–Sayre syndrome.

Thirteen of the 15 patients completed this protocol. There were no significant differences after creatine and placebo administration of muscle strength (including hand grip strength) or PCr recovery after aerobic or ischemic exercise. Somewhat surprisingly, muscle PCr content (determined by ^{31}P MRS) was not increased in these patients after creatine administration, although plasma creatine was much increased; this is in contrast to prior findings in normal controls. There also were no significant differences in any secondary outcome measures. No adverse effects of creatine were observed.

Following this trial, another clinical trial was performed at McMaster University to evaluate the possible beneficial effects of combined therapy for mitochondrial disorders with creatine, CoQ_{10}, and lipoic acid [48]. Again, this was a double-blind, placebo-controlled, randomized crossover trial. The design was to randomly assign patients initially to first receive either combined treatment [creatine 6 g, α-lipoic acid 600 mg, and CoQ_{10} (Qgel) 240 mg] daily or placebo for 2 months, then a washout period of 5 weeks, and finally crossover to the alternative of placebo or combined therapy for another 2 months (Table 1). The primary outcome

measures were muscle strength (handgrip, ankle dorsiflexion, and knee extension) measured by a force transducer. Additional measures included a 1-minute isometric handgrip and ankle dorsiflexion fatigue test, pulmonary function testing, determination of body composition, and measurements of blood lactate, plasma CoQ_{10} and creatine, and urinary markers of oxidative stress. Seventeen patients, aged 12–58 years with definite or probable mitochondrial disease were recruited; diagnoses included MELAS (3), CPEO (3), Kearns–Sayre syndrome (1), LHON (2), mitochondrial neurogastrointestinal encephalomyopathy (1) and "cytopathy" (3 with mtDNA point mutations and 3 without known mutations).

One patient did not complete the study and was not included in data analysis. There were no significant differences in peak handgrip or ankle dorsiflexion muscle strength or fatigue tests from before to after combined therapy. However, ankle dorsiflexion decreased slightly (7 %), but significantly, from before to after placebo, although the final values after combined therapy and after placebo were very similar (within 1 %). There was a moderate, but significant, reduction of blood lactate from before to after combined therapy, but not from before to after placebo, although, again, lactate was not significantly lower in the overall groups after combined therapy compared with after placebo. Lower urinary 8-isoprostanes/creatinine ratios were observed following combined therapy (which includes creatine, the precursor or creatinine). Urinary creatine/creatinine and plasma CoQ_{10} increased in the combined treatment group, as expected (data not shown). Body composition improved (increased weight and fat-free mass) significantly only in the MELAS subgroup (3/16 patients), but not overall. Other secondary parameters did not change significantly. Although it was concluded that combined therapy resulted in significant improvement, the caveats mentioned leave a question as to whether this was really significant.

Exercise Training

Sustained exercise is associated with mitochondrial proliferation, as occurs in many mitochondrial disorders, presumably in both cases as an adaptive response to the need for greater oxidative energy metabolism. It seems intuitive that some degree of sustained, controlled exercise would therefore be beneficial to patients with mitochondrial disorders, who frequently suffer from exercise intolerance. The specific questions that come up in those disorders associated with heteroplasmic mtDNA mutations is whether exercise preferentially promotes proliferation of normal mitochondria, or, if not, whether proliferation of both normal mitochondria and abnormal mitochondria is beneficial. The former could increase adenosine triphosphate production, whereas the latter could increase production of ROS. These questions have not yet been totally resolved, but have and are being addressed in ongoing clinical trials.

A series of such collaborative trials have been conducted at the University of Texas, Southwest Medical Center [49–51]. These initial trials were open label and sequential, recruiting patients with mtDNA mutations, and, starting with baseline evaluation, bicycle exercise for 14 weeks and final re-evaluation. This showed improvement in work capacity and phosphocreatine replenishment, but not cardiac output. The activity of several mitochondrial enzymes increased, and the percentage of mutant mtDNA increased slightly (9 %). Follow-up collaborative studies confirmed the physiological benefits and safety of exercise in subjects with mtDNA mutations, and showed that total mtDNA content increases without significantly altering the ratio of mutant/normal mtDNA.

These observations led to a larger phase II, randomized, "open-label", crossover trial which has not yet been reported [52]. The design of this trial was that group 1 has exercise training for 6 months, then no exercise training for another 6 months. Group 2 had no exercise training for 6 months, followed by exercise training for 6 months (Table 1). Both groups had evaluations, including exercise testing and a muscle needle biopsy, at baseline, after 6 months, and after 12 months. Continued exercise was encouraged for another year with final testing at the end of the second year. Primary outcomes were changes in muscle total mtDNA, % mutant/normal mtDNA, and physiological assessments of exercise-stimulated oxidative metabolism. Secondary outcome measures included MRI of the heart and skeletal muscle, and a QoL questionnaire. Eligibility criteria for patients included being18–65 years old with mitochondrial myopathy due to a point mutation or deletion of mtDNA.

Summary and Conclusions

It should be clear from the series of clinical trials summarized here that anecdotal case reports or common medical practice of specific therapies for mitochondrial disorders are insufficient for evidence-based medicine. When subjected to controlled trials, formerly advocated therapies have not usually been proven to be effective and/or may have unacceptable side effects. This is borne out particularly by experience with DCA, creatine, and CoQ_{10}. Over the 15 years of reviewed controlled clinical trials for treatment of primary mitochondrial disorders, no particular therapeutic agent or combination or agents has been proven definitively to be both substantially beneficial and safe. There have been open-label trials that have indicated positive trends and should lead to additional future trials. Examples of this

anticipation of benefit include open-label trials of arginine (or probably citrulline) for MELAS, EPI-743 for general mitochondrial disorders, exercise in disorders due to mtDNA mutations, and the controlled trial of idebenone for LHON. Follow-up trials for most of these trials are already in progress or planned.

The rationale for these various potential candidate therapies have included activation or enhancement of the impaired primary metabolic pathway of energy metabolism (DCA and exercise), enhancing relevant secondary metabolic pathways (increasing NO by supplementation with arginine or citrulline in MELAS), or antioxidant prevention of the damaging effects of ROS secondary to defects of mitochondrial electron transport (CoQ_{10}, idebenone, EPI-743). None of these interventions was expected to "cure", reverse, or bypass the primary mitochondrial metabolic defect, such as replacement of CoQ_{10} in defects of CoQ_{10} biosynthesis, supplementation of carnitine in carnitine transporter deficiency, dietary changes (low/high fat) in disorders of fatty acid or glucose oxidation), or cardiac transplantation of primary mitochondrial cardiomyopathy. These examples are less likely to be subjects of clinical trials as they seem intuitively necessary, do not require regulatory approval, are presumed to be effective, and therefore would be difficult to recruit a control group. However, a clinical trial of bone marrow transplantation for treatment of mitochondrial neurogastrointestinal encephalomyopathy is now in preparation [38]. The future of gene transfer therapy for mitochondrial disorders seems attractive, but will require further preclinical research before implementation in clinical trials, and will, most likely, be preceded by clinical trials for other genetic disorders.

Nevertheless, experience gained through these clinical trials for treatment of mitochondrial disorders provides a valuable background for more effective potential future treatments, including gene transfer. This collective experience has been instructive in characterizing the challenges of conducting trials in a population of relatively rare mitochondrial disorders with considerable genetic and phenotypic variation, even within disorders due to the same genetic defect. Most disorders due to mutations of mtDNA are associated with well known, widely variable phenotypes due to unpredictable heteroplasmy, as are X-lined gene disorders, such as mutations of *PDHA1* (pyruvate dehydrogenase, E1-alpha subunit) in females due to Lyonization or even in males for unexplained reasons [53]. Individuals with LHON may have discordant effects on both their eyes, which may be a favorable factor in predicting response to idebenone. Because of understandably relatively small numbers of recruitable patients, many of these trials have included subjects with defined mutations of different genes and phenotypic disorders. Finally, mitochondrial disorders are frequently characterized by variable clinical courses with waxing and waning of their clinical status.

For all of these reasons, it is evident that a double-blind, crossover design with random assignment to the order of interventions has a great advantage, in that each patient serves as their own control, limiting the number of patients required for statistical significance and diminishing the effects of heterogeneity in the starting population. The outcomes should be compared at the end of both interventions, not comparison of the difference from before and after each of the interventions, to avoid unknown prior effects or unrelated variations in the course of the disease. With a diverse patient group there is always a temptation to employ post hoc subgroup analyses; these may be helpful in planning follow-up trials, but should not be considered clinically significant as outcomes (as was found in successive trials of DCA in MELAS subjects). Of course, crossover designs preclude selection of primary outcomes that may take a long time to emerge, such as mental development or deterioration of visual acuity or neuromuscular function.

A second point is that careful selection of 1 or 2 clinically relevant, objectively measured, primary outcomes is critical. The most important conclusion of the trial depends on the primary outcomes, and including multiple primary outcomes increases the likelihood of finding irrelevant statistically "significant" outcomes. Selection of primary outcomes may be best achieved by using a standardized, widely agreed upon, clinical scale, or composite score, as was used in some of these reviewed trials, and with the larger trials of PD and FA [5]. Less clinically relevant or subjectively evaluated, biomarkers, compliance and safety measures can be included as secondary outcomes, but the "significance" of differences in these additional measures also may occur by chance and not be clinically relevant, as illustrated by this review.

Finally, there are general advantages and frequent necessity in organizing multicenter collaborative clinical trials to increase the number of patients, to be able to recruit subjects with less variable eligibility criteria, to reach consensus among colleagues of clinically significant primary outcomes, and to take advantage of special resources that different institutions may offer for analyses, design, and data analysis. The best examples of these advantages come from the trials referred to above in PD, FA, and LHON. Collaborative trials certainly increase the cost of the trial, but that may be offset, in the view of the funding agency or supporting company, by the greater probability that the trial will succeed and be relevant. Such collaborative trials also are more likely to be facilitated and attract support of disease-based organizations and professional groups, such as the United Mitochondrial Disease Foundation (www.umdf.org), the North American Mitochondrial Disease Consortium (www.rarediseasesnetwork.epi.usf.edu/namdc/), and EUmtiocombat (www.eumitocombat.org/).

Clearly, continuation of well-controlled clinical trials is necessary to define effectiveness of current potential therapies

for mitochondrial disorders and future, hopefully more effective, interventions. Experience gained from previous clinical trials and collaboration within the professional community and family-based organizations should further this goal.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Horvath R, Gorman G, Chinnery PF. How can we treat mitochondrial encephalomyopathies? Approaches to therapy. Neurotherapeutics 2008;5:558-568.
2. DiMauro S, Rustin P. A critical approach to the therapy of mitochondrial respiratory chain and oxidative phosphorylation diseases. Biochim Biophys Acta 2009;1792:1159-1167.
3. Kerr DS. Treatment of mitochondrial electron transport chain disorders: a review of clinical trials over the past decade. Mol Genet Metab 2010;99:246-55.
4. Stacpoole PW. Why are there no proven therapies for genetic mitochondrial diseases? Mitochondrion 2011;11:679-685.
5. Pfeffer G, Majamaa K, Turnbull DM, Thorburn D, Chinnery PF. Treatment for mitochondrial disorders. Cochrane Database Syst Rev 2012;4:CD004426.
6. Stacpoole PW, Barnes CL, Hurbanis MD, Cannon SL, Kerr DS. Treatment of congenital lactic acidosis with dichloroacetate: A review. Arch Dis Child 1997;77:535-541.
7. Barshop BA, Naviaux RK, McGowan KA, Levine F, Nyhan WL, Loupis-Geller A, et al. Chronic treatment of mitochondrial disease patients with dichloroacetate. Mol Genet Metab 2004;83:138-149.
8. Stacpoole PW, Kerr DS, Barnes C, Bunch ST, Carney PR, Fennell EM, et al. Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. Pediatrics 2006;117:1519-531.
9. Stacpoole PW. The dichloroacetate dilemma: environmental hazard versus therapeutic goldmine–both or neither? Environ Health Perspect 2011;119:155-158.
10. Kaufmann P, Engelstad K, Wei Y, Jhung S, Sano MC, Shungu DC, et al. Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. Neurology 2006;66:324-330.
11. Kaufmann P, Pascual JM, Anziska Y, Gooch CL, Engelstad K, Jhung S, et al. Nerve conduction abnormalities in patients with MELAS and the A3243G mutation. Arch Neurol 2006;63:746-748.
12. Koga Y, Akita Y, Nishioka J, Yatsuga S, Povalko N, Tanabe Y, et al. L-arginine improves the symptoms of strokelike episodes in MELAS. Neurology 2005;64:710-712.
13. Koga Y, Akita Y, Junko N, Yatsuga S, Povalko N, Fukiyama R, et al. Endothelial dysfunction in MELAS improved by L-arginine supplementation. Neurology 2006;66:1766-1769.
14. Koga Y, Akita Y, Nishioka J, Yatsuga S, Povalko N, Katayama K, et al. MELAS and L-arginine therapy. Mitochondrion 2007;7:133-139.
15. Koga Y, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T. MELAS and L-arginine therapy: pathophysiology of stroke-like episodes. Ann N Y Acad Sci 2010;1201:104-110.
16. Koga Y, Abe T, Taniwaki T, Nataliya P. MELAS and L-arginine therapy – therapeutic timing and long term effects. Mitochondrion 2012;12;551.
17. Coman D, Yaplito-Lee J, Boneh A. New indications and controversies in arginine therapy. Clin Nutr 2008;27:489-496.
18. Tein I. L-Arginine therapy on endothelium-dependent vasodilation & mitochondrial metabolism in MELAS syndrome. ClinicalTrials.gov: NCT01603446. 2012.
19. El-Hattab AW, Hsu JW, Emrick LT, Wong LJ, Craigen WJ, Jahoor F, et al. Restoration of impaired nitric oxide production in MELAS syndrome with citrulline and arginine supplementation. Mol Genet Metab 2012;105:607-614.
20. El-Hattab AW, Emrick LT, Craigen WJ, Scaglia F. Citrulline and arginine utility in treating nitric oxide deficiency in mitochondrial disorders. Mol Genet Metab 2012;107:247-252.
21. Quinzii CM, Lopez LC, Naini A, DiMauro S, Hirano M. Human CoQ10 deficiencies. Biofactors 2008;32:113-118.
22. Hirano M, Garone C, Quinzii CM. CoQ10 deficiencies and MNGIE: two treatable mitochondrial disorders. Biochim Biophys Acta 2012;1820:625-631.
23. Shults CW, Haas R. Clinical trials of coenzyme Q10 in neurological disorders. Biofactors 2005;25:117-126.
24. Eleff S, Kennaway NG, Buist NR, Darley-Usmar VM, Capaldi RA, Bank WJ, et al. 31P NMR study of improvement in oxidative phosphorylation by vitamins K3 and C in a patient with a defect in electron transport at complex III in skeletal muscle. Proc Natl Acad Sci U S A 1984;81:3529-3533.
25. Glover EI, Martin J, Maher A, Thornhill RE, Moran GR, Tarnopolsky MA. A randomized trial of coenzyme Q10 in mitochondrial disorders. Muscle Nerve 2010;42:739-748.
26. Stacpoole PW, deGrauw TJ, Feigenbaum AS, Hoppel C, Kerr DS, McCandless SE, et al. Design and implementation of the first randomized controlled trial of coenzyme Q10 in children with primary mitochondrial diseases. Mitochondrion 2012;12:623-629.
27. Shults CW, Flint BM, Song D, Fontaine D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. Exp Neurol 2004;188:491-494.
28. Miles MV, Patterson BJ, Schapiro MB, Hickey FJ, Chalfonte-Evans M, Horn PS, et al. Coenzyme Q10 absorption and tolerance in children with Down syndrome: a dose-ranging trial. Pediatr Neurol 2006;35:30-37.
29. NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. Neurology 2007;68:20-28.
30. Storch A, Jost WH, Vieregge P, Spiegel J, Greulich W, Durner J, et al. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q10 in Parkinson disease. Arch Neurol 2007;64:938-944.
31. Beal MF, Oakes D, Shoulson I. Effects of coenzme Q10 (CoQ) in Parkinson disease; ClinicalTrials.gov: NCT007407140. 2009.
32. Di Prospero NA, Baker A, Jeffries N, Fischbeck KH. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. Lancet Neurol 2007;6:878-886.
33. Perlman S, Lynch D. Study of the efficacy, safety, and tolerability of idebenone in the treatment of Friedreich's ataxia; ClinicalTrials.gov: NCT00537680. 2009.
34. Kaufmann P, Hirano M. Study of idebenone in the treatment of mitochondrial encephalopathy lactic acidosis & stroke-like episodes (MELAS); ClinicalTrials.gov, NCT00887562. 2009.
35. Meier T, Buyse G. Idebenone: an emerging therapy for Friedreich ataxia. J Neurol 2009;256(Suppl. 1):25-30.
36. Lynch DR, Perlman SL, Meier T. A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. Arch Neurol 2010;67:941-947.
37. Meier T, Perlman SL, Rummey C, Coppard NJ, Lynch DR. Assessment of neurological efficacy of idebenone in pediatric patients with Friedreich's ataxia: data from a 6-month controlled study followed by a 12-month open-label extension study. J Neurol 2012;259:284-291.
38. Hirano M. Study of idebenone in the treatment of mitochondrial encephalopathy lactic acidosis & stroke-like episodes (MELAS); clinicaltrials.gov, NCT00887562. 2012.

39. Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain 2011;134:2677-2686.
40. Santhera Pharmaceuticals. Study with idebenone in patients with chronic vision loss due to Leber's hereditary optic neuropathy (LHON); ClinicalTrials.gov, NCT01495715. 2012.
41. Enns GM, Kinsman SL, Perlman SL, Spicer KM, Abdenur JE, Cohen BH, et al. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. Mol Genet Metab 2012;105:91-102.
42. Blankenberg FG, Kinsman SL, Cohen BH, Goris ML, Spicer KM, Perlman SL, et al. Brain uptake of Tc99m-HMPAO correlates with clinical response to the novel redox modulating agent EPI-743 in patients with mitochondrial disease. Mol Genet Metab 2012;107:690-699.
43. Martinelli D, Catteruccia M, Piemonte F, Pastore A, Tozzi G, Dionisi-Vici C, et al. EPI-743 reverses the progression of the pediatric mitochondrial disease-Genetically defined Leigh Syndrome. Mol Genet Metab 2012;107:383-388.
44. Finsterer J. Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol 2008;39:223-235.
45. Tarnopolsky MA, Roy BD, MacDonald JR. A randomized, controlled trial of creatine monohydrate in patients with mitochondrial cytopathies. Muscle Nerve 1997;20:1502-1509.
46. Klopstock T, Querner V, Schmidt F, Gekeler F, Walter M, Hartard M, et al. A placebo-controlled crossover trial of creatine in mitochondrial diseases. Neurology 2000;55:1748-1751.
47. Kornblum C, Schroder R, Muller K, Vorgerd M, Eggers J, Bogdanow M, et al. Creatine has no beneficial effect on skeletal muscle energy metabolism in patients with single mitochondrial DNA deletions: a placebo-controlled, double-blind 31P-MRS crossover study. Eur J Neurol 2005;12:300-309.
48. Rodriguez MC, MacDonald JR, Mahoney DJ, Parise G, Beal MF, Tarnopolsky MA. Beneficial effects of creatine, CoQ10, and lipoic acid in mitochondrial disorders. Muscle Nerve 2007;35:235-242.
49. Taivassalo T, Shoubridge EA, Chen J, Kennaway NG, DiMauro S, Arnold DL, et al. Aerobic conditioning in patients with mitochondrial myopathies: physiological, biochemical, and genetic effects. Ann Neurol 2001;50:133-141.
50. Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. Brain 2003;126:413-423.
51. Taivassalo T, Gardner JL, Taylor RW, Schaefer AM, Newman J, Barron MJ, et al. Endurance training and detraining in mitochondrial myopathies due to single large-scale mtDNA deletions. Brain 2006;129:3391-3401.
52. Haller RG. The effects of exercise vs. inactivity on people with mitochondrial muscle diseases; ClinicalTrials.gov; NCT00457314. 2012.
53. DeBrosse S, Okajima K, Zhang S, Nakouzi G, Schmotzer C, Lusk-Kopp M, et al. Spectrum of neurological and survival outcomes in pyruvate dehydrogenase complex (PDC) deficiency: Lack of correlation with genotype. Mol Genet Metab 2012;107:394-402.
54. Murphy JL, Blakely EL, Schaefer AM, He L, Wyrick P, Haller RG, et al. Resistance training in patients with single, large-scale deletions of mitochondrial DNA. Brain 2008;131:2832-2840.