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Advances in Mitochondrial Medicine

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This special issue of *Journal of Inborn Errors of Metabolism and Screening* provides an overview of the current state-of-the-art in several important areas of mitochondrial clinical medicine, including updates on clinical presentations, seizure management, use of anesthesia, and approaches to mitochondrial disease therapy. Individual reports herein focus on specific therapies that have been in use or in clinical trials for substantial periods, especially L-arginine and the quinone compounds coenzyme Q_{10}, idebenone, and EPI-743. However, there are a number of other potential therapies that are currently being evaluated in clinical trials, ranging from novel antioxidants to gene therapy. Indeed, as our understanding of the molecular basis of disease improves, treatments have been increasingly focused on specific aspects of mitochondrial disease pathogenesis, such as cardiolipin oxidation, nitric oxide production, and mitochondrial biogenesis signaling cascades (Table 1).

Historically, in order to choose a therapeutic regimen for a given patient, practitioners of mitochondrial medicine have often relied upon personal experience or small case series, typically involving the open-label use of a given compound or various compounds used in a combination "mitochondrial cocktail."[1] Anecdotal reports, common medical practice, or open-label studies are clearly insufficient to establish an evidence-based approach to care.[2] Despite the proliferation of potential new treatments of mitochondrial disease, results from nonrandomized and nonblinded studies using such compounds at best should be considered preliminary.[3] Nevertheless, open-label trials have the potential to provide useful initial clinical and safety data that may be helpful in developing more definitive studies.

Although randomized, controlled clinical trials in genetic mitochondrial disease have been the exception in the past, more recent studies have embraced rigorous trial design, and this trend will undoubtedly benefit patients in the long run (Table 1).[2,4–6] There are clearly challenges to developing rigorous trials for mitochondrial disorders, including the presence of molecular and clinical heterogeneity, relative lack of robust biomarkers, and current widespread, but inconsistent, use of various dietary supplements as a means of treatment. Nevertheless, as highlighted in a workshop convened by the National Institutes of Health Office of Dietary Supplements, well-designed clinical trials represent an important strategy for developing an evidence base for developing treatments of mitochondrial disease.[7]

Furthermore, the infrastructure to support clinical trials is improving as evidenced by efforts to establish mitochondrial disease registries and collaborations between multiple centers of excellence.[3] The North American Mitochondrial Disease Consortium (NAMDC),[8] mitoNET—German Network for Mitochondrial Disorders,[9] and the Mitochondria Research and Medicine Society[10] serve as examples of networks of specialist physicians and scientists devoted to improving the care of mitochondrial disease patients through high-quality research and multicenter investigations. Such networks have increasingly interacted with mitochondrial disease patient support groups in order to build connections between clinicians, basic scientists, and individuals and families affected by these conditions. Support groups will clearly play an increasingly important role related to clinical trial recruitment not only by serving as an interface between affected individuals and researchers but also by providing education about the importance of rigorous research and controlled studies to patients and families.

In addition to the relative proliferation of clinical trials for mitochondrial disorders, there has been an increase in efforts to standardize diagnostic and management approaches. For example, members of the Mitochondrial Medicine Society have recently published guidelines on the diagnosis and care of mitochondrial patients after having first surveyed specialist centers throughout North America on practice patterns.[11–14] Clinical guidelines have also been established by other expert centers, such as the Wellcome Trust Centre for Mitochondrial

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Table 1. Mitochondrial Disease Clinical Trials.

Investigational Agent	ClinicalTrials.gov Identifier	Condition(s)	Interventional Target(s)	Trial Design	Outcome
Coenzyme Q_{10}	NCT00432744	Mitochondrial disorders	ROS	RDBPC	Pending
Idebenone	NCT00747487	LHON	ROS	RDBPC	No change in visual acuity, Improved secondary end points
	NCT00887562	MELAS	ROS	RDBPC	Pending
EPI-743	NCT01642056	Neuromuscular disease with redox imbalance	ROS	RDBPC	Pending
	NCT01370447	Mitochondrial disorders	ROS	Open-label	Pending
	NCT01721733	Leigh syndrome	ROS	RDBPC	↓ rate of hospitalization and serious adverse events
	NCT01728064	Friedreich ataxia	ROS	RDBPC	Pending
KH176	NCT02544217	Mitochondrial disorders	ROS	RDBPC	Pending
L-Arginine	NCT01603446	MELAS	Nitric oxide	Open-label	↑ aerobic capacity and muscle metabolism
L-Argninine/ L-Citrulline	NCT01339494	MELAS	Nitric oxide	Open-label	↑ nitric oxide production, ↓ lactate (L-Citrulline)
Dichloroacetate	NCT02616484	Pyruvate dehydrogenase deficiency	PDC	RDBPC	Pending
MTP-131	NCT02367014	Mitochondrial myopathy	Cardiolipin	RDBPC	Pending
	NCT02693119	LHON	Cardiolipin	RDBPC	Pending
	NCT03098797	Barth syndrome	Cardiolipin	RDBPC	Pending
RTA 408	NCT02255422	Mitochondrial myopathy	Nrf2/NFκB	RDBPC	Pending
	NCT02255435	Friedreich ataxia	Nrf2/NFκB	RDBPC	Pending
RP103	NCT02023866	Mitochondrial disease	Glutathione	Open-label	Pending
Bezafibrate	NCT02398201	Mitochondrial myopathy	Mitochondrial biogenesis	Open-label	Pending
scAAV2-P1ND4	NCT02161380	LHON	ND4 gene therapy	Open-label	↑ visual acuity in 2 of 5 participants
GS010	NCT02652767	LHON	ND4 gene therapy	RDMSC	Pending
Allogenic HSCT	NCT02427178	MNGIE	Thymidine phosphorylase	Open-label	↑ thymidine phosphorylase in survivors (9 of 24 participants)

Abbreviations: LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MNGIE, mitochondrial neurogastrointestinal encephalopathy; NFκB, nuclear factor-κB; Nrf2, nuclear factor-erythroid 2-related factor 2; PDC, pyruvate dehydrogenase complex; RDBPC, randomized, double-blind, placebo-controlled; RDMSC, randomized, double-masked, sham-controlled; ROS, reactive oxygen species.

Research in Newcastle, United Kingdom,[15] and members of NAMDC are currently revising research diagnostic criteria for mitochondrial disorders. Another project, the Mitochondrial Disease Sequence Data Resource Consortium, has focused on the development of a central Internet portal to facilitate the compilation and analysis of mitochondrial and nuclear genomic sequence data related to patients with mitochondrial disease.[16] In short, multiple international efforts are underway to improve awareness, diagnosis, management, and translational research related to mitochondrial disorders. These efforts, in combination with continuously improving understanding of the basic underlying mechanisms of disease pathogenesis, offer optimism for the eventual development of effective treatments of mitochondrial disease.

Author's Note

GME reports (1) receiving funding for being an investigator in clinical trials related to EPI-743 (BioElectron Technology Corporation, previously known as Edison Pharmaceuticals, Inc) and RP-103 (Horizon Pharmaceuticals, Inc, Raptor Pharmaceuticals, Inc) and (2) has received unrestricted gift research funds from Edison Pharmaceuticals, Inc.

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