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Review article

Clinical trials in mitochondrial disorders, an update

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ABSTRACT

Mitochondrial disorders comprise a molecular and clinically diverse group of diseases that are associated with mitochondrial dysfunction leading to multi-organ disease. With recent advances in molecular technologies, the understanding of the pathomechanisms of a growing list of mitochondrial disorders has been greatly expanded. However, the therapeutic approaches for mitochondrial disorders have lagged behind with treatment options limited mainly to symptom specific therapies and supportive measures. There is an increasing number of clinical trials in mitochondrial disorders aiming for more specific and effective therapies. This review will cover different treatment modalities currently used in mitochondrial disorders, focusing on recent and ongoing clinical trials.

1. Introduction

Primary mitochondrial disorders represent an expanding group of clinically heterogeneous diseases that are associated with mitochondrial dysfunction due to underlying mutations in mitochondrial DNA (mtDNA) or nuclear encoded mitochondrial genes. mtDNA codes for 13 subunits of the oxidative phosphorylation (OXPHOS) complexes, 22 transfer RNAs (tRNA), and 2 ribosomal RNAs (rRNA). Therefore, mutations in mtDNA affect OXPHOS complexes production or mitochondrial translational machinery. The majority of mitochondrial proteins are encoded by nuclear genes, including most of the subunits of OXPHOS complexes, and other proteins involved in OXPHOS complexes assembly, mtDNA maintenance, mtDNA genes expression, mitochondrial fission and fusion, in addition to several cofactors required for proper mitochondrial function [1,2]. As mitochondria are important for energy production through OXPHOS complexes, energy failure contributes to multi-organ involvement usually seen in mitochondrial disorders. Mitochondria also carry other biological functions, including calcium homeostasis, steroid synthesis, and apoptosis and these also likely contribute to the pathophysiology in various mitochondrial disorders [1,3].

The advent of deep, high-throughout, in-parallel DNA sequencing technologies has enabled a better understanding of the bases and mechanisms of a growing list of mitochondrial disorders. In a recent nosology of inborn errors of metabolism, 244 well-characterized disorders are listed under the category of mitochondrial disorders of energy metabolism (http://www.iembase.org/iem-nosology.asp; accessed on 4/18/2020) [4]. Furthermore, a recently published multicenter epidemiological study has provided invaluable data on the natural history of mitochondrial disorders [5] that could lay the foundation for planning randomized clinical trials.

Treatment of mitochondrial disorders has been challenging though. These challenges stem from the ubiquitous nature of mitochondria, genetic complexity with dual genome control, the presence of heteroplasmy associated with most variants in mtDNA, and the heterogeneous clinical presentations associated with multi-organ involvement in various mitochondrial disorders [6]. Therapeutic approaches have been mostly limited to symptom specific therapies and supportive measures including treatment of catabolic stress and infections, exercise, and the use of vitamins, cofactors, and antioxidants [7,8].

Recently, the number of preclinical and clinical trials in mitochondrial disorders has been increasing. These efforts will open venues for more specific and effective treatment modalities for mitochondrial disorders. In this review, various therapeutic modalities currently used or trialed in different mitochondrial disorders are presented, with a focus on recent and ongoing clinical trials.

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2. Modulation of oxidative stress

Mitochondrial disorders are associated with oxidative stress due to the imbalance between the production of reactive oxygen species (ROS), and antioxidant systems [9]. Increased ROS production can result in protein oxidative modification, lipid peroxidation, and DNA damage, eventually leading to cellular dysfunction. Therefore, one of the strategies in treating mitochondrial disorders has relied on the use of antioxidants, which are agents that significantly delay or prevent oxidation of substrates, therefore ameliorating the impaired oxidative stress and promoting cell survival and endurance [10].

Coenzyme Q_{10} (CoQ_{10}) and its analogs have gained attention in the last few decades due to their antioxidant properties. Coenzyme Q is a ubiquitous, lipophilic molecule and is located mainly in the inner mitochondrial membrane where it shuttles electrons from complexes I and II to complex III. It also cycles from an oxidized to a reduced form, therefore buffering free electrons as a direct antioxidant and also restoring other cellular antioxidants [11,12]. Therapeutic supplementation with CoQ_{10} leads to a favorable outcome in primary CoQ_{10} deficiency [13]. The use of CoQ_{10} in a randomized clinical trial in 30 patients with mitochondrial disorders (15 patients with Mitochondrial Lactic Acidosis and Stroke-like Episodes (MELAS) and the rest with other mitochondrial disorders) showed minor effects on cycle exercise aerobic capacity and post-exercise lactate [14]. In a phase 3, randomized, double-blind, cross-over trial in children with mitochondrial diseases and documented deficiency of respiratory chain complexes or a molecular diagnosis, no statistically significant difference was documented with CoQ_{10} compared to placebo in achieving the primary outcome measures; McMaster gross motor function and pediatric quality of life scales (https://clinicaltrials.gov/ct2/show/NCT00432744).

Idebenone is a CoQ_{10} analogue that shares the quinone moiety with CoQ_{10} but has a shorter lipophilic tail. This distinct chemical structure results in better bioavailability and allows idebenone to cross the blood–brain barrier and mitochondrial membranes more easily [15]. Idebenone also acts as an electron carrier in the mitochondrial electron transport chain (ETC). While its original properties were promising, the results of clinical trials using idebenone in humans have not demonstrated significant efficacy. In patients with MELAS syndrome, a phase 2a, randomized, double blind, placebo-controlled, dose finding study did not show a statistically significant difference between idebenone versus placebo on the primary outcome (mean change in cerebral lactate concentration)[16](https://www.clinicaltrials.gov/ct2/show/NCT00887562) (Table 1). A randomized, double-blinded, placebo-controlled study (RHODOS) evaluating idebenone in patients with Leber hereditary optic neuropathy (LHON) did not demonstrate a statistically significant difference in recovery of visual acuity but it showed that patients with discordant visual acuities were more likely to benefit from idebenone, in whom secondary end-points were significantly different between the idebenone and the placebo group (https://clinicaltrials.gov/ct2/show/NCT00747487) [17]. A follow up report for this study demonstrated that the beneficial effect from idebenone persisted despite discontinuation of therapy [18]. LHON is the only mitochondrial disease for which idebenone has been recently approved by the European Medicines Agency (EMA). An open-label interventional phase IV trial to further assesses the efficacy and safety of idebenone (Raxone) in the long-term treatment of LHON patients is currently active but not recruiting as it reached recruitment target with 197 patients enrolled (https://clinicaltrials.gov/ct2/show/NCT02774005).

Cysteamine bitartrate is an aminothiol used as an approved therapy for nephropathic cystinosis [19]. Cysteamine breaks the disulfide bond of cystine, forming cysteine–cysteamine disulfide and cysteine, the latter of which is a precursor of glutathione biosynthesis [20,21]. Thus, a delayed release form of cysteamine bitartrate was repurposed and used as RP103 in an open label, dose-escalating study to assess its safety and efficacy in children with mitochondrial diseases. This initial study was followed by a long-term extension study that was terminated due to lack of efficacy (https://clinicaltrials.gov/ct2/show/NCT02023866 and https://clinicaltrials.gov/ct2/show/NCT02473445).

EPI-743 (now known as PTC-743) is a para-benzoquinone analog that exerts its antioxidant effects through repletion of reduced intracellular glutathione [22]. In an open-label study in patients with a heterogeneous group of mitochondrial disorders, EPI-743 was associated with clinical improvement in most subjects treated [22]. Another open-label study in children with Leigh syndrome showed that treatment with EPI-743 was associated with reversal of disease progression [23]. Similarly, EPI-743 arrested disease progression and reversed vision loss in 4 out of 5 treated patients with LHON [24]. Moreover, EPI-743 has been trialed in a randomized, double-blind, placebo-controlled trial in children with Leigh syndrome (https://clinicaltrials.gov/ct2/show/NCT01721733 and https://clinicaltrials.gov/ct2/show/NCT02352896). Treatment with EPI-743 led to fewer patients necessitating admission to hospital or showing serious adverse events when compared to the placebo arm (11.8% vs 42.8%). During the extension phase, there was a decline in hospital admissions and serious adverse events. The number of hospital admissions per patient declined by 40% [25]. In another open-label study, five children with a mitochondrial syndrome named RARS2 deficiency received EPI-743 during a year with an extension phase that is still ongoing. Two children showed resolution of status epilepticus whereas the other three had a decrease in the frequency and duration of seizures [25]. EPI-743 prevented ferroptosis in cells derived from patients with mitochondrial disease-associated epilepsy [26]. Ferroptosis is a form of iron-dependent programmed cell death associated with glutathione depletion and production of lipid peroxides. It has been implicated in a number of disorders, including epilepsy [26]. A randomized trial to assess the efficacy and safety of EPI-743 for the treatment of mitochondrial disease subjects with refractory epilepsy is active but not recruiting yet (https://clinicaltrials.gov/ct2/show/NCT04378075).

Elamipretide is a mitochondrial-targeted tetrapeptide that associates with cardiolipin in the inner mitochondrial membrane. It maintains mitochondrial cristae, promotes oxidative phosphorylation, and reduces production of ROS [27,28]. A phase 3 trial to evaluate the efficacy of elamipretide in subjects with primary mitochondrial myopathy (MMPOWER-3) was recently terminated as it did not meet its primary endpoints assessing changes in the six-minute walk test and primary mitochondrial myopathy symptom assessment (PMMSA) total fatigue score (https://clinicaltrials.gov/ct2/show/NCT03323749). A clinical trial evaluating safety and efficacy of a topical ophthalmic solution of elamipretide in subjects with LHON was completed recently, but no results are available (https://clinicaltrials.gov/ct2/show/NCT02693119). There is an active trial also to evaluate safety and efficacy of subcutaneous injections of elamipretide (MTP-131) in subjects with Barth Syndrome (https://clinicaltrials.gov/ct2/show/NCT03098797). The study consists of a 12 weeks cross-over phase followed by an open-label extension. Primary endpoints assessed included 6-Minute Walk Test (6MWT) and Barth Syndrome Symptom Assessment (BTHS-SA) Total Fatigue Score. Results from 12 patients showed that elamipretide was well tolerated but primary endpoints were not statistically significant in the blinded portion. After the 36-week open label phase, eight remaining subjects demonstrated improvements in 6MWT ($p = 0.02$), BTHS-SA Total Fatigue Score ($p = 0.03$), and a trend toward increased left ventricular end-diastolic volume [29].

Sonlicromanol (KH176) is a recently developed orally bioavailable small molecule that works as an antioxidant as well as a redox modulator [30]. A randomized, double-blind, crossover phase IIA study of Sonlicromanol in patients harboring the m.3243A > G mutation in *MT-TL1* was completed (The KHENERGY study; https://clinicaltrials.gov/ct2/show/NCT02909400). Twice daily oral dose of 100 mg Sonlicromanol was well tolerated. No significant improvement in gait parameters or other outcome measures were obtained, except for a positive effect on alertness and mood [31]. A Phase IIb double-blind, randomized, placebo-controlled trial is currently evaluating the effect of Sonlicromanol on cognitive function in patients with the m.3243A > G

Table 1
Summary of recent and ongoing clinical trials in mitochondrial Disorders.

Agent	Clinical Trials	Primary Outcome	Status
Modulation of Oxidative Stress			
Coenzyme Q_{10}	Phase 3 trial of coenzyme Q_{10} in mitochondrial disease (NCT00432744)	- McMaster gross motor function (GMFM 88) (Time frame: 6 and 12 months) - Pediatric quality of life scale (Time frame: 6 and 12 months)	Completed, no statistically significant difference in primary outcomes measures
Idebenone	A phase IIa double-blind, randomized, placebo-controlled, dose-finding study of Idebenone in the treatment of MELAS (NCT00887562)	Cerebral lactate concentration as measured by brain magnetic resonance spectroscopy (Time frame: up to 4 weeks)	Completed, no statistically significant difference in primary outcome measures
	External natural history controlled, open-label intervention study to assess the efficacy and safety of long-term treatment with Raxone® in LHON (LEROS) (NCT02774005)	Recovery or stabilization of visual acuity from baseline up to one year after the onset of symptoms, compared to matching external natural history control group (Time frame:12 months)	Active, not recruiting
	A non-interventional study of clinical experience in patients prescribed Raxone® for the treatment of LHON (PAROS) (NCT02771379)	Long-term safety profile assessed by incidence of adverse events (Time frame: up to 5 years)	Active, recruiting
	A double-blind, randomized, placebo-controlled study of the efficacy, safety and tolerability of idebenone in the treatment of patients with LHON (NCT00747487)	Best recovery of logMAR visual acuity in either right or left eye (Time frame: 24 weeks)	Completed, no statistically significant difference in primary outcome; secondary end-points were significantly different between the idebenone and the placebo group in patients with discordant visual acuities
Cysteamine bitartrate	A long-term open-label extension study of RP103-MITO-001 (NCT02023866) to assess the safety, tolerability and efficacy of cysteamine bitartrate delayed-release capsules (RP103) for treatment of children with inherited mitochondrial disease (NCT02473445)	NPMDS Score (Time frame: every 3 months, study exit up to 24 months)	Terminated due to lack of efficacy
EPI-743	An open-label phase 2 safety and efficacy study of EPI-743 (vatiquinone) in children with Pearson syndrome (NCT02104336)	Occurrence of episodes of sepsis, metabolic crisis or hepatic failure (Time frame: one year)	Terminated (Results from other studies didn't support continuation of this trial)
	Efficacy and safety study of vatiquinone for the treatment of mitochondrial disease subjects with refractory epilepsy (NCT04378075)	Change from baseline in umber of observable motor seizures per 28 days (Time frame: 24 weeks)	Not yet recruiting
	Emergency use protocol for EPI-743 in acutely ill patients with inherited mitochondrial respiratory chain disease within 90 days of end-of-life care (NCT01370447)	Incidence of adverse events events (Time frame:13 weeks)	Active, not recruiting
	Therapeutic trial of EPI -743 In patients with disorders of energy utilization or oxidation-reduction (NCT01642056)	Quality of life based NPMDS Score (Time frame: every 6 months)	Completed, no results yet
	A phase 2B randomized, placebo controlled, double blind clinical trial of EPI-743 in children with Leigh syndrome (NCT01721733)	NPMDS sections 1–3 score (Time frame: 6 months)	Completed, no results yet
	EPI743-13-023: long-term safety and efficacy evaluation of EPI-743 in children with Leigh syndrome (NCT02352896)	- NPMDS sections 1–3 score (Time frame: up to 36 months) - Dose-limiting serious adverse events (Time frame: up to 36 months)	Active, not recruiting
Elamipretide	A phase 3 randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of daily subcutaneous injections of elamipretide in subjects with primary mitochondrial myopathy followed by an open-label treatment extension (MMPOWER-3) (NCT03323749)	- 6MWT (Time frame:24 weeks) - Mitochondrial Myopathy Symptom Assessment (PMMSA) total fatigue score (Time frame: 24 weeks)	Terminated (part 1, double blind portion of the trial did not meet the primary end points)
	A prospective, randomized, double-masked, vehicle controlled, phase 2 clinical study to evaluate the safety, tolerability and efficacy of elamipretide (MTP-131) topical ophthalmic solution in subjects with LHON (NCT02693119)	Incidence and severity of adverse events (Time frame: 56 weeks)	Completed, no results available
	A Phase 2 randomized, double-blind, placebo-controlled crossover trial to evaluate the safety, tolerability, and efficacy of subcutaneous injections of E elamipretide (MTP-131) in subjects with genetically confirmed Barth Syndrome followed by an open-label treatment extension (TAZPOWER) (NCT03098797)	6MWT (Time frame: 12 weeks)	Active, not recruiting
	A multicenter, open-label phase 2 extension trial to characterize the long-term safety and tolerability of subcutaneous - elamipretide in subjects with genetically confirmed primary mitochondrial myopathy (NCT02976038)	Incidence of adverse events (Time frame: up to 260 weeks)	Terminated (Registration trial did not meet the primary end points)

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Table 1 (*continued*)

Agent	Clinical Trials	Primary Outcome	Status
Sonlicromanol (KH176)	An exploratory, double-blind, randomized, placebo-controlled, single-center, two-way cross-over study with KH176 in patients with the mitochondrial DNA tRNALeu$^{(UUR)}$ m.3243A > G mutation and clinical signs of mitochondrial disease (The KHENERGY study) (NCT02909400)	Motor abnormalities and movement characteristics (Time frame: one month)	Completed; no significant improvement in gait parameters or other outcome measures, except for a positive effect on alertness and mood
	A phase IIb double-blind, randomized, placebo-controlled, multi-centre, confirmative three-way cross-over study on cognitive function with two doses of KH176 in subjects with a genetically confirmed mitochondrial DNA tRNALeu$^{(UUR)}$ m.3243A > G mutation (The KHENERGYZE study) (NCT04165239)	The attention domain score of cognitive functioning, as assessed by the visual identification test of the Cogstate computerized cognitive testing battery (Time frame: one month)	Active, recruiting
Augmentation of Mitochondrial Biogenesis			
Exercise	Effects of resistance exercise training on cardiac, metabolic and muscle function and quality of life in Barth syndrome (NCT01629459)	Peak oxygen consumption, exercise time and exercise work during graded exercise test on cycle ergometer (Time frame: 3 months)	Completed, no results available
Bezafibrate	A feasibility study of bezafibrate in mitochondrial myopathy (NCT02398201)	Respiratory chain enzyme activity (Time frame: 12 weeks)	Completed; reduction in complex IV-deficient muscle fibers and improvement in cardiac function. No change in exercise testing parameters, accelerometry, and NMDAS score. Increase in FGF-21 andGDF-15 levels
Resveratrol	Resveratrol supplementation in patients with mitochondrial myopathies and skeletal muscle fatty acid oxidation disorders: A double-blind, placebo-controlled, cross over study (NCT03728777)	Decrease in heart rate during constant load cycling exercise (Time frame: 20 weeks)	Completed, no results available
Omaveloxolone	A phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of mitochondrial myopathy (MOTOR) (NCT02255422)	Change of peak workload (in watts/kg) during exercise testing (Time Frame: 12 weeks)	Completed; no differences in peak cycling exercise workload (primary outcome) or in 6MWK (secondary outcome). Reduced heart rate and lactate levels during submaximal exercise (exploratory outcomes)
NAD^+ precursors/ modulators	The role of nicotinamide riboside in mitochondrial biogenesis (NCT03432871)	- Bioavailability - Safety (incidence of adverse events, blood analytes, vital signs) - Mitochondrial biogenesis (31P-MRS measurement of mitochondrial function, respiratory chain enzyme analysis, and mtDNA quantification) (Time frame: 4 weeks)	Active, recruiting
	The effect of niacin supplementation on systemic Nicotinamide Adenine Dinucleotide (NAD^+) metabolism, physiology and muscle performance in healthy controls and mitochondrial myopathy patients(NiaMIT) (NCT03973203)	Change in concentrations of NAD^+ and related metabolites in blood and muscle (Time Frame: 4 months and 10 months)	Completed; Niacin supplementation increased blood and muscle NAD^+ of patients to the level of their controls. Muscle strength and mitochondrial biogenesis increased in all subjects. Muscle metabolome shifted toward controls and liver fat decreased
	Acipimox in adults with mitochondrial myopathy and m.3243A > G mutation or single large-scale mtDNA deletion (AIMM) (ISRCTN12895613)	ATP content in skeletal muscle (Time frame: 12 weeks)	Active, recruiting
	A Phase Ia/Ib, multiple-site study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of KL1333 after a single and multiple ascending oral doses in healthy subjects and patients with primary mitochondrial disease (NCT03888716)	Safety (incidence of adverse events, laboratory analytes, EKG, vital signs, and physical exam) (Time frame: 15 days)	Active, recruiting
REN001	An open-label study to evaluate the safety and tolerability of 12 weeks treatment with oral REN001 in patients with primary mitochondrial myopathy (PMM), with an optional extension of treatment (NCT03862846)	Incidence of adverse events (Time frame:12 weeks)	Terminated because of COVID-19 pandemic but sufficient data gathered to achieve the objectives. Preliminary results showed the drug to be safe and well tolerated
Modulation of Mitochondrial Autophagy			
Rapamycin	A Phase 2a, open-label study to evaluate the safety, tolerability, and clinical activity of ABI-009 (Nab-sirolimus) in patients with genetically-confirmed Leigh or Leigh-like syndrome (NCT03747328)	- Incidence of adverse events (Time Frame: up to 24 weeks) - Gross Motor Function Measure (GMFM) (Time Frame: up to 24 weeks)	Not yet recruiting
Restoration of Nitric Oxide			
	Phase-1, dose finding and safety study on L-citrulline treatment of nitric oxide deficiency in MELAS (NCT03952234)	Incidence of dose limiting toxicities to establish maximum tolerated dose (Time frame: 8 weeks)	Not yet recruiting
	The effect of arginine and citrulline supplementation on endothelial dysfunction in mitochondrial diseases (NCT02809170)	Reactive hyperemic index (RHI) (Time Frame: 2 years)	Completed, RHI increased with arginine or citrulline supplementation

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Table 1 (*continued*)

Agent	Clinical Trials	Primary Outcome	Status
	A phase 2a safety, tolerability, pharmacokinetic, and pharmacodynamic study in individuals with MELAS (NCT04475549)	Incidence of adverse events (Time frame: 43 days (± 4)	Not yet recruiting
Modulation of the Mitochondrial Genome			
Allotopic Expression	An open-label dose escalation study of an adeno-associated virus vector (scAAV2-P1ND4v2) for gene therapy of LHON caused by the m.11778G > A mutation in mitochondrial DNA (NCT02161380)	Incidence of adverse events (Time frame: 1 year)	Active, recruiting (Initial results: no serious safety problems were observed in the first 5 participants)
	Safety and efficacy study of gene therapy for the treatment of LHON (NCT03153293)	- Best corrected visual acuity (Time frame: 12 months) - Computerized visual field (Time frame: 12 months)	Active, not recruiting
	Efficacy and safety of bilateral intravitreal injection of GS010: A randomized, double-masked, placebo-controlled trial in subjects affected with m.11778G > A mutation in the mitochondrial *ND4* gene associated with LHON for up to one year (REFLECT) (NCT03293524)	Best corrected visual acuity (Time frame: 18 months)	Active, not recruiting
	An open - label dose escalation clinical trial to evaluate the safety and the tolerability of GS010 (rAAV2/2-ND4) in patients with LHON due to mutations in the mitochondrial *ND4* gene (NCT02064569)	Incidence of adverse events (Time Frame: Up to 48 weeks)	Completed, no results yet
	Efficacy study of gene therapy for the treatment of acute LHON onset within three months (NCT03428178)	Best corrected visual acuity (Time frame: 12 months)	Active, not recruiting
	A randomized, double-masked, sham-controlled clinical trial to evaluate the efficacy of a single intravitreal injection of GS010 in subjects affected for 6 months or less by LHON due to the m.11778G > A mutation in the mitochondrial *ND4* gene (RESCUE) (NCT02652767)	Visual acuity according to ETDRS chart (Time Frame: 48 weeks)	Completed, on average, treated eyes gained +26 ETDRS letters at week 96 compared with their nadir best corrected visual acuity. A clinically relevant response from the nadir was observed in at least one eye of 63% of subjects
	Randomized, double-masked, sham-controlled clinical trial to evaluate the efficacy of a single intravitreal injection of GS010 in subjects affected for more than 6 months and to 12 months by LHON due to the m.11778G > A mutation in the *ND4* gene (REVERSE) (NCT02652780)	Visual acuity according to ETDRS chart (Time Frame: 48 weeks)	Completed, on average, treated eyes gained +15 ETDRS letters at week 96 compared with baseline. A clinically relevant response from the nadir was observed in at least one eye of 78% of subjects
	Long-term follow-up of *ND4* LHON subjects treated with GS010 ocular gene therapy in the RESCUE or REVERSE Phase III clinical trials (NCT 03406104)	Incidence of adverse events (Time frame: up to 5 years)	Active, not recruiting
Restoration of nucleotides pool			
	Deoxythymidine and deoxycytidine treatment for thymidine kinase 2 (TK2) deficiency (NCT03639701)	Safety (blood analytes, EKG, and severity of diarrhea) (Time frame: up to 60 months)	Active, enrolling by invitation
	A phase 2 open-label study of continuation treatment with combination pyrimidine nucleosides in patients with thymidine kinase 2 deficiency (TK2) (NCT03845712)	Safety (incidence of adverse events, blood analytes, and EKG) (Time frame: approximately 3 years)	Active, not recruiting
Enzyme Replacement Therapy for MNGIE			
	The safety, tolerability, pharmacodynamics, and efficacy of Erythrocyte Encapsulated Thymidine Phosphorylase (EE-TP) in patients with MNGIE (TEETPIM) (NCT03866954)	- Safety (incidence of adverse events, blood analytes, vital signs, EKG) (Time frame: 31 months) - Pharmacodynamics (Time frame: 31 months) - Efficacy as measured by change in body mass index (BMI) (Time frame: 24 months)	Active, not yet recruiting
Mitochondrial Augmentation Therapy			
	A phase I/II, open label, single dose clinical study to evaluate the safety and therapeutic effects of transplantation of MNV-BM-BLD (autologous cd34+ cells enriched with blood derived mitochondria) in pediatric patients with Pearson syndrome (NCT03384420)	- Incidence of adverse events (Time frame: one year) - IPMDS score (Time frame: one year)	Active, enrolling by invitation
Solid Organ and Stem Cell Transplantation			
AHSCT	MNGIE allogeneic hematopoietic stem cell transplant safety study (MASS)(NCT02427178)	Engraftment success (neutrophil count) (Time frame: 42 days)	Active, recruiting
Prevention of mitochondrial disease			

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Table 1 (*continued*)

Agent	Clinical Trials	Primary Outcome	Status
	Mitochondrial donation: An 18 month outcome study (NCT04113447)	Neurodevelopmental quotient scored using a Bayley-III score (Time frame: 18 months)	Active, recruiting

AHSCT: Allogeneic hematopoietic stem cell transplant; EKG: Electrocardiogram; ETDRS: Early Treatment Diabetic Retinopathy Study; IPMDS: International Pediatric Mitochondrial Disease Scale; LHON: Leber Hereditary Optic Neuropathy; LogMAR: Logarithm of the minimum angle of resolution; MELAS: Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like Episodes; MNGIE: Mitochondrial neurogastrointestinal encephalomyopathy; MRS: Magnetic resonance spectroscopy; 6MWT: Six minute walk test; NMDAS: Newcastle Mitochondrial Disease Scale for Adults; NPMDS: Newcastle Pediatric Mitochondrial Disease Scale.

pathogenic variant (The KHENERGYZE study; https://clinicaltrials.gov/ct2/show/NCT04165239)

3. Augmentation of mitochondrial biogenesis

One of the aims for several agents trialed in mitochondrial disorders is the enhancement of mitochondrial biogenesis. Mitochondrial biogenesis is defined as growth and division of pre-existing mitochondria, thereby increasing the number, size, and mass of mitochondrial population and enhancing the mitochondrial function [32]. One of the key regulators of mitochondrial biogenesis is PGC-1α (peroxisome proliferator-activated receptor (PPAR) γ coactivator 1α). PGC-1α is a transcriptional coactivator that augments mitochondrial biogenesis through activation of different transcriptional factors among which are nuclear respiratory factor 1(NRF1) and nuclear respiratory factor 2(NRF2) [33,34]. These factors in turn control the expression of nuclear-encoded mitochondrial proteins, such as the OXPHOS proteins, as well as transcription factor A mitochondrial (TFAM), which regulates mtDNA transcription and replication [35].

PGC-1α is regulated at transcriptional and post-translational levels to meet the dynamic cellular energetic needs [36]. AMP-activated protein kinase (AMPK) is a major energy sensor that is released in response to high AMP/ATP ratio reflecting energy deficiency [37]. It helps restore the energy balance through several mechanisms, one of which is the activation PGC-1α through direct phosphorylation [38]. AMPK, through the increase of cellular NAD^+ levels, also enhances SIRT1(NAD^+-dependent deacetylase sirtuin-1) activity, thereby causing deacetylation and activation of PGC-1α[39].

For a long time, exercise has been well known to augment mitochondrial biogenesis [40]. In rats, bouts of swimming resulted in increased expression of PGC-1α, NRF1 and NRF2 in skeletal muscle [41]. Besides modulating AMPK levels, exercise activates PGC-1α expression through other factors like Ca^{2+}/calmodulin-dependent protein kinase IV (CamKIV) and p38 MAPK [42]. Interestingly, Rowe et al. showed that in mice lacking PGC-1α specifically in skeletal muscle; exercise still induced mitochondrial biogenesis suggesting that other factors could play a role in mitochondrial biogenesis [43]. Exercise can also reduce the percentage of mutated mtDNA through mtDNA shifting [44]. Endurance and resistance exercise were found to be safe for patients with mitochondrial myopathy [45]. A trial to evaluate the effect of resistance exercise training on patients with Barth Syndrome is completed, but results are not available yet. The primary outcome measure is the change in exercise tolerance whereas secondary outcomes include change in muscle strength, quality of life, and left ventricular systolic strain (https://clinicaltrials.gov/ct2/show/NCT01629459).

Another compound that is being evaluated to promote mitochondrial biogenesis is bezafibrate. Bezafibrate, an amphipathic carboxylic acid, is a pan-PPAR agonist and therefore it activates the PGC-1α axis [46]. In HeLa cell line, bezafibrate significantly increased PGC-1α and OXPHOS proteins levels [47]. Bezafibrate treatment in fibroblasts from a patient with *DNM1L* pathogenic variant resulted in normalized ATP production and oxygen consumption and it improved mitochondrial morphology [48]. However, in vivo studies in mouse models showed little change in mitochondrial biogenesis and OXPHOS proteins levels [49,50]. Very recently, the results of an open-label study of six patients with mitochondrial myopathy caused by the common m.3243A > G *MTTL1* pathogenic variant who were treated with 600–1200 mg bezafibrate daily for 12 weeks were published (https://clinicaltrials.gov/ct2/show/NCT02398201) [51]. Bezafibrate was well tolerated and it resulted in a reduction in the number of complex IV-deficient muscle fibers and an improvement in end-systolic volume and end-systolic index. There was no change in other outcomes including exercise testing parameters, accelerometry, and the Newcastle mitochondrial disease scale for adults (NMDAS) score. Bezafibrate treatment was found to be associated with an increase in biomarkers of mitochondrial disease, including fibroblast growth factor 21 (FGF-21), growth and differentiation factor 15 (GDF-15), and dysregulation of fatty acid and amino acid metabolism, raising concerns over long term use [51].

Resveratrol (RSV) is a naturally occurring polyphenol found in large quantities in the skin of red grapes [52]. Treatment of mice with RSV was associated with increased expression of OXPHOS proteins and mitochondrial biogenesis. RSV, through activation of SIRT1, resulted in deacetylation-mediated activation of PGC-1α [53]. In another study in mice, RSV was associated with an increase in oxygen consumption, skeletal muscle mRNA levels of mitochondrial enzymes, and suppression of the aging-related decline in physical performance [54]. RSV can also activate SIRT1 indirectly by increasing cyclic AMP levels [55]. Mizuguchi et al. showed that low dose of RSV ameliorated mitochondrial dysfunction in patient-derived fibroblasts carrying homoplasmic mtDNA pathogenic variants (m.3243A > G, m.8344A > G, or m.8993T > G) [56]. Besides direct effect through SIRT1 activation, RSV could also improve cellular conditioning through SIRT3 activation, which in turn upregulates mitochondrial superoxide dismutase [56,57]. In a randomized controlled trial, exercise added to RSV treatment in elderly subjects improved mitochondrial density and muscle fatigue resistance compared to placebo and exercise treatments [58]. A randomized-controlled trial to evaluate RSV supplementation on physical ability and muscle metabolism in patients with mitochondrial myopathy and patients with VLCAD and CPTII deficiencies was recently completed but results are not available. The primary outcome was decrease in heart rate during exercise, whereas secondary outcomes included peak oxygen utilization, fatty acid oxidation, perceived exertion, and self-rated fatigue (https://clinicaltrials.gov/ct2/show/NCT03728777).

AICAR (5-aminoimidazole-4-carboxamide ribonucleotide), an adenosine analog, is a known activator of AMPK [59], making it a potential therapeutic target in mitochondrial disorders. Studies in animal models and human cells though revealed inconsistent effects of AICAR treatment on mitochondrial biogenesis and function [60–64]. Epicatechin is a naturally occurring molecule that belongs to the flavonoids family. It is found in high concentrations in cocoa [65]. Mice fed with (−)-epicatechin showed increased mitochondrial biogenesis in hindlimb and heart muscles and better exercise performance [66]. In a randomized-controlled trial, dark chocolate (epicatechin rich cocoa) intake in sedentary subjects was associated with better exercise performance and mitochondrial biogenesis [67]. Mitochondrial biogenesis augmentation was attributed to increase concentration of upstream inducers like AMPK [67,68] and nitric oxide synthase [69]. Moreover, Moreno-Ulloa et al. showed that treatment of mouse skeletal muscle cells with

(−)-epicatechin stimulated mitochondrial biogenesis through activation of G-protein coupled estrogen receptor (GPER1) [70]. No human trials in mitochondrial disorders have been conducted so far with AICAR or epicatechin.

Omaveloxolone (RTA 408) is a semi-synthetic triterpenoid that prevents ubiquitination of NRF2 and therefore potentiates its action [71,72]. In neural cells from mouse models and fibroblasts from patients with Friedreich ataxia (FA), omaveloxolone restored substrate availability and complex I activity and was able to protect the cells against oxidative stress [73]. Recently, the results of the MOTOR trial were published. Fifty-three patients with mitochondrial myopathy caused by known nuclear or mitochondrial DNA pathogenic variants participated in a double-blind study and were randomized to either 12 weeks of escalating doses of omaveloxolone or placebo. Overall, omaveloxolone was well tolerated. No statistically significant differences in peak cycling exercise workload (primary outcome) or in 6-min walk test (secondary outcome) were observed after treatment. However, treatment resulted in reduced heart rate and lactate levels during submaximal exercise, indicating improved mitochondrial function and submaximal exercise tolerance. The authors suggested further studies need to be conducted with a more homogenous population, and a larger number of patients [74] (https://clinicaltrials.gov/ct2/show/NCT02255422).

NAD^+ (nicotinamide adenine dinucleotide) is a cofactor for SIRT1, which then activates PGC-1α and mitochondrial biogenesis [75]. The NAD^+/NADH ratio is also essential for several metabolic pathways including citric acid cycle and fatty acid oxidation [75]. Oral administration of nicotinamide riboside (NR), an NAD^+ precursor, in the Deletor mouse model resulted in increased mitochondrial biogenesis and delayed myopathy progression [76]. In the *Sco2* knockout/knockin mouse, NR supplementation and reduction of NAD^+ consumption by inhibiting the poly(ADP-ribose) polymerases (PARP1), significantly improved the mitochondrial respiratory chain defects and exercise intolerance [77]. An ongoing open label trial is investigating the effects of NR supplementation on patients with progressive external ophthalmoplegia (PEO) and exercise intolerance/fatigue caused by a single deletion of mtDNA; and in patients with mitochondrial disease caused by the m.3243A > G pathogenic variant. The primary outcomes are to evaluate safety, bioavailability, and effects of NR on mitochondrial biogenesis. Secondary outcomes are related to impact on symptoms (https://clinicaltrials.gov/ct2/show/NCT03432871).Very recently, the results of an open label study evaluating niacin supplementation, an NAD^+ precursor, in healthy controls and patients with pure mitochondrial myopathy and single or multiple deletions of mtDNA (NiaMIT trial) were published [78]. Systemic NAD^+ deficiency was documented in mitochondrial myopathy patients. With niacin supplementation, muscle NAD^+ of patients reached the level of their controls. Muscle strength and mitochondrial biogenesis increased in all subjects (https://clinicaltrials.gov/ct2/show/NCT03973203). An ongoing study (AIMM trial), is evaluating acipimox, a niacin derivative, in adults with mitochondrial myopathy and m.3243A > G mutation or single large-scale mtDNA deletion (http://www.isrctn.com/ISRCTN12895613) [79]. KL1333 is an NAD^+ modulator that increases intracellular NAD^+ levels via NADH oxidation and was shown to improve mitochondrial dysfunction in MELAS fibroblasts [80]. There is an ongoing phase one study to assess safety and tolerability of KL1333 in healthy subjects and patients with primary mitochondrial disease (https://clinicaltrials.gov/ct2/show/NCT03888716).

Taurine is a sulfur-containing amino acid that can augment mitochondrial biogenesis via PGC-1α activation and it is also essential for mitochondrial protein synthesis through modifications of taurine-containing uridines of the anticodon in a subset of mitochondrial tRNAs [81,82]. This taurine modification is defective in patients with MELAS syndrome and other mitochondrial disorders. An open-label, phase III trial was conducted to evaluate taurine supplementation over 52 weeks in 10 patients with MELAS and recurrent stroke-like episodes. Sixty percent of patients had complete prevention of stroke-like episodes during the evaluation period and taurine reduced the annual relapse rate of stroke-like episodes from 2.22 to 0.72 ($P = 0.001$) [83].

Finally, REN001 is a recently developed drug that works as PPAR-δ agonist. It was found to be safe and well tolerated in 23 adult patients with primary mitochondrial myopathies in a 12-week open label trial. A multicenter placebo controlled clinical trial is expected to start in 2021 (https://clinicaltrials.gov/ct2/show/NCT03862846).

4. Modulation of mitochondrial autophagy

Mitochondrial autophagy, or mitophagy, allows for mitochondrial turnover through lysosomal degradation of aged and dysfunctional mitochondria, thereby protecting the body from harmful effects of such mitochodria [84].

Rapamycin is a mammalian target of rapamycin (mTOR)-inhibitor which was found to enhance survival and attenuate disease progression in an *Ndufs4* knockout mouse model of Leigh disease [85]. Rapamycin treatment restored autophagic flux and enhanced lysosomal biogenesis and in doing so both mechanisms contributed to the clearance of dysfunctional mitochondria [86]. Treatment with everolimus, a rapamycin analogue, in a child with Leigh syndrome resulted in sustained benefit whereas another child with MELAS failed to respond and died of progressive disease [87]. A phase 2a, open-label study to evaluate the safety and efficacy of ABI-009 (Nanoparticle albumin-bound sirolimus) in patients with Leigh or Leigh-like syndrome is active but not yet recruiting (https://clinicaltrials.gov/ct2/show/NCT03747328).

Urolithin A is a gut microbiota-generated small metabolite that can induce mitophagy [88]. In a recent trial, urolithin A was evaluated in healthy, sedentary elderly individuals. It was found to be safe and also it modulated plasma acylcarnitines and skeletal muscle mitochondrial gene expression with improved mitochondrial and cellular health [89]. No human trials in mitochondrial disorders have been conducted so far using this compound.

5. Restoration of nitric oxide

Nitric oxide (NO) is produced by vascular endothelial cells and it relaxes vascular smooth muscles and maintains patency of small blood vessels and blood flow through microvasculature [90,91]. NO deficiency in mitochondrial diseases can contribute to the pathogenesis of several complications observed in these conditions including stroke-like episodes, myopathy, and lactic acidosis [3,92,93].

NO is formed from arginine via the enzyme NO synthase, which catalyzes the conversion of arginine to citrulline. Citrulline can be converted back to arginine via argininosuccinate synthase and argininosuccinate lyase [94]. Both NO production impairment and post-production sequestration cause the deficiency in mitochondrial disorders. NO production can be reduced because of NO synthase inhibition and decreased intracellular availability of NO precursors arginine and citrulline. Postproduction NO sequestration occurs due to NO shunting into reactive nitrogen species formation and binding to cytochrome C oxidase [93].

The administration of intravenous arginine to subjects with MELAS syndrome during stroke-like episodes was shown to improve the clinical symptoms associated with these episodes, and oral arginine supplementation at the interictal phase was shown to decrease the frequency and severity of stroke-like episodes [95–97]. The use of arginine intravenously during stroke-like episodes and orally as maintenance therapy has been recommend in treating individuals with MELAS syndrome [98]. In a recent report, a trough plasma arginine level of ≥168 μmol/L was found to be optimal for prevention of stroke like episodes [99].

Stable isotope studies have demonstrated that arginine and citrulline supplementation can increase NO production in children and adults with MELAS syndrome [100,101]. These studies also found that citrulline supplementation induced a greater increase in NO synthesis

rate than arginine supplementation indicating that citrulline is a more effective NO precursor, and therefore may have a better therapeutic effect than arginine. This can be due to the superiority of citrulline in raising plasma and intracellular arginine levels, leading to more arginine availability for NO synthesis [93,100,101]. A new open-label dose-finding and safety clinical trial will soon be started with the primary outcome measure being the establishment of the maximum tolerated dose of citrulline in individuals with MELAS syndrome by measuring the incidence of dose limiting toxicities. The study will also evaluate changes in cerebral blood flow and cerebrovascular reactivity by using arterial spin-labeling (ASL) magnetic resonance imaging (MRI) as secondary outcome measures (https://clinicaltrials.gov/ct2/show/NCT03952234).

The effect of arginine and citrulline supplementation on endothelial dysfunction in children with mitochondrial disease was investigated using peripheral arterial tonometry which measures the reactive hyperemic index (RHI). The results demonstrated low RHI in these children indicating endothelial dysfunction. RHI increased with arginine or citrulline supplementation suggesting that supplementation with NO precursors can improve endothelial dysfunction by enhancing NO production [102].

Many of the physiological functions of NO are mediated through its primary receptor, soluble guanylyl cyclase (SGC) [103]. Following a dose determination study in healthy volunteers, a phase 2a study to assess safety and tolerability of a CNS penetrant-SGC stimulator (IW-6463) in patients with MELAS is planned to start, but not recruiting yet (https://clinicaltrials.gov/ct2/show/NCT04475549).

6. Modulation of the mitochondrial genome

Gene therapy for mitochondrial disorders is challenging. The mitochondria are under dual genome control and they contain their own DNA (mtDNA); however, most of the mitochondrial proteins are encoded by nuclear genes [104]. Most mitochondrial disorders have clinical features consistent with multi-organ disease, and therefore for a gene therapy trial to be successful, the vector should be expressed throughout the body and should be able to cross the blood-brain barrier [105]. In a mouse model with ethylmalonic encephalopathy, AAV2/8 *ETHE1*-gene transfer to the liver resulted in full restoration of sulfur dioxygenase, normalization of plasma thiosulfate levels and clinical improvement [106]. AAV2/8-mediated transfer of *TYMP* transgene normalized deoxycytidine triphosphate and deoxythymidine triphosphate levels in a mouse model of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) [107]. The effect of this gene therapy persisted long term in treated mice [108].

Allotopic expression, which is the nuclear expression of mitochondrial genes followed by mitochondrial targeting of expressed proteins, is a way to overcome the difficulty of targeting genes into the mitochondria [109]. Results from in vitro and in vivo studies in mouse models are variable [110–114]. LHON is the only mitochondrial disorder for which there is an active gene therapy clinical trial. In a prospective open-label trial that is still ongoing (https://clinicaltrials.gov/ct2/show/NCT02161380), unilateral intravitreal injection of AAV was found to be safe and resulted in visual acuity improvement with treatment relative to baseline [115]. In another open-label trial (https://clinicaltrials.gov/ct2/show/NCT01267422), 8 patients with LHON from China received unilateral intravitreal injection of AAV. At 36 months follow up, visual function improvement was observed in the treated eye in 4 patients but 4 patients also showed improvement in the untreated eye [116]. Recently, the results from randomized-controlled phase 3 trials (REVERSE and RESCUE trials) to evaluate the efficacy of intravitreal injection of AAV in patients with LHON and the m.11778G > A mutation in the *ND4* showed a clinically relevant response from the nadir in at least one eye of 78% of REVERSE subjects and 63% of RESCUE subjects, compared to 28% in the natural history study of LHON subjects [117]. (https://clinicaltrials.gov/ct2/show/study/NCT02652780 and https://clinicaltrials.gov/ct2/show/NCT02652767).

As most mitochondrial disorders caused by defects in mtDNA are characterized by heteroplasmy, the disease burden can be ameliorated through reduction of the percentage of a deleterious variant, i.e. heteroplasmy shifting [118,119]. In cells heteroplasmic for the m.8993T > G mutation in *MT-ATP6*, mitochondrially targeted restriction endonucleases resulted in selective destruction of mutant mtDNA [120]. However, for most mutations in mtDNA, no appropriate restriction endonucleases are available. This limitation was overcome with the development of mitochondrial zinc finger nucleases (mitoZFNs) and transcription activator-like effector nucleases (mitoTALENs) which showed encouraging results in preclinical studies [119]. In proof of concepts studies, expression of mtZFN in hybrid cell lines harboring the m.8993T > G mutation and in a mouse model with m.5024C > T mutation in $tRNA^{Ala}$ led to a reduction in mutant mtDNA load [121,122]. MitoTALENs successfully eliminated the m.3243A > G mutation in induced pluripotent stem cells [123]. In NZB/BALB heteroplasmic mice, mitoTALENs led to a significant reduction of NZB mtDNA levels in oocytes. Furthermore, fusion of human cells carrying mtDNA mutations to mouse oocytes followed by injection of mitoTALENs against human mtDNA mutations resulted in reduction in the levels of mutated mtDNA [124].

7. Restoration of nucleotides pool

The maintenance of mtDNA depends on a number of nuclear DNA-encoded proteins that play roles in either mtDNA synthesis or in the provision of a constant and balanced supply of nucleotides. The latter is achieved by nucleotide recycling inside the mitochondria and nucleotide import from the cytosol. Mitochondrial DNA maintenance defects are a group of diseases caused by mutations in the nuclear genes involved in mtDNA maintenance resulting in impaired mtDNA synthesis leading to quantitative (mtDNA depletion) and qualitative (multiple mtDNA deletions) defects in mtDNA [125].

As a constant and balanced supply of nucleotides is crucial for mtDNA maintenance, mtDNA maintenance defects associated with nucleotide metabolism defects can be amenable to therapeutic administration of nucleotides. This approach aims to restore the imbalanced mitochondrial nucleotide pools which can improve mtDNA maintenance and the clinical manifestations associated with these diseases including the deficiencies of thymidine kinase 2 and thymidine phosphorylase [126].

Thymidine kinase 2 (TK2) is a key enzyme in the mitochondrial pyrimidine nucleotide salvage pathway. TK2 deficiency causes a depletion of mitochondrial nucleotides leading to impairment of mtDNA synthesis and a myopathic mtDNA depletion syndrome [127]. In Tk2 deficient mice, the administration of deoxythymidine(dT) and deoxycytidine(dC) was found to delay the onset of disease, prolong the life span of Tk2-deficient mice, and restore mtDNA content as well as ETC complexes activities and levels [128]. A multicenter study evaluating the effect of deoxynucleoside administrations to individuals with TK2 deficiency has been recently published. This study showed that survival and motor functions improve in individuals with early onset and severe disease. Individuals with childhood and adult onset disease demonstrated improvement or stabilization in clinical measures including motor, respiratory, and nutrition evaluations [129]. On a compassionate use, 38 patients with TK2 deficiency who were treated with combination of dC and dT survived and most showed stabilization or improvement in feeding, respiratory, and motor domains [130] (https://clinicaltrials.gov/ct2/show/NCT03701568). A phase 2 prospective, open-label study of the safety and efficacy of MT1621 (dC/dT) in TK2 deficient patients is currently active but not recruiting (https://clinicaltrials.gov/ct2/show/NCT03845712).

In MNGIE, the deficiency of thymidine phosphorylase (TP) leads to increased deoxythymidine and a secondary decrease in mitochondrial

deoxycytidine which results in mtDNA depletion [131]. Deoxycytidine is rapidly deaminated by the ubiquitous enzyme cytidine deaminase. In a MNGIE mouse model, co-administration of deoxycytidine and tetrahydrouridine (a cytidine deaminase inhibitor) prevented tetrahydrouridine deamination and plasma deoxycytidine significantly increased. More importantly, mitochondrial deoxycytidine levels increased in response to the elevated systemic deoxycytidine concentrations. Furthermore, thymidine-induced mtDNA depletion in cultured fibroblasts was used as a cell model of MNGIE. The administration of deoxycytidine and tetrahydrouridine to this cell model was also able to prevent mtDNA depletion [132].

8. Hypoxia

Jain et al. performed a genome-wide, Cas9-mediated screen to identify factors that could protect against ETC inhibition and identified Von Hippel-Lindau (VHL) to be the most effective genetic suppressor of mitochondrial disease. This effect stems from the important role of VHL in degrading hypoxia inducible transcription factors (HIF) and therefore, suppression of VHL allows for continues activation of the HIF[133]. The protective effect of hypoxia was further explored in *vhl*-null zebrafish which had better survival when exposed to ETC inhibitors like antimycin compared to heterozygous and wild-type controls. Furthermore, chronic hypoxia was found to prevent or even reverse neurological dysfunction in *Ndufs4* knockout mice [133,134]. In a subsequent study, the same group showed that interventions that normalize brain tissue hyperoxia, rather than those that activate HIF, reverse the neurological disease, indicating that unused oxygen could be the likely culprit in the disease pathology [135]. No clinical trials evaluating hypoxia have been conducted so far in patients with mitochondrial disorders.

9. Enzyme replacement therapy for MNGIE

In an adult with MNGIE, erythrocyte encapsulated recombinant *Escherichia coli* thymidine phosphorylase (EE-TP) was associated with a decrease in the plasma concentrations of deoxythymidine and deoxyuridine and the urinary excretion of deoxythymidine and deoxyuridine. Furthermore, significant clinical improvements were noted suggesting a greater muscle mitochondrial oxidative function [136]. A study on MNGIE is currently recruiting to evaluate the natural history of the disease as an initial step for a trial using recombinant form TP delivered with endosomal escape vehicle technology (https://clinicaltrials.gov/ct2/show/NCT04245917). A phase 2 trial to determine the safety, tolerability, action, and effectiveness of repeated doses of EE-TP for the treatment of individuals with this disorder is currently active but not recruiting yet. The primary outcome measures will determine the safety, pharmacodynamics, and efficacy of EE-TP. Efficacy will be measured by a change in body mass index. (https://clinicaltrials.gov/ct2/show/NCT03866954).

10. Mitochondrial augmentation therapy

Mitochondrial augmentation therapy (MAT) is transplantation of healthy mitochondria into affected patients through enrichment of patient's peripheral stem cells with healthy mitochondria derived from donor white blood cells or placenta. Several preclinical studies have demonstrated that isolated mitochondria can re-enter cells and that mesenchymal stem cells and stromal cells are able to transfer mitochondria into recipient neighboring cells, thereby rescuing diseased tissues [137–141]. Based on this finding, there is currently an ongoing phase 1/2 clinical trial to evaluate the safety and therapeutic effects of autologous CD34+ cells enriched with blood derived mitochondria (MNV-BM-BLD) in children with Pearson syndrome (https://www.clinicaltrials.gov/ct2/show/NCT03384420). Initial results on three patients with Pearson syndrome treated with MAT showed that the procedure was well tolerated with only leukapheresis related adverse events. In 2 patients with more than 3 months follow up, in vivo mitochondrial enrichment was observed 3–4 months after therapy. Mitochondrial function and quality of life, as measured by the International Pediatric Mitochondrial Disease Score (IPMDS), improved after treatment [142]. In addition, similar approach has been trialed in a 14-year-old child with Kearns-Sayre syndrome who also showed marked neurological and functional improvement over 7 months [143].

11. Solid organ and stem cell transplantation

Allogenic hematopoietic stem cell transplant (AHSCT) has been tried as a measure to restore TP activity in MNGIE patients [144]. In a retrospective review of 24 patients with MNGIE who had AHSCT, only 9 (37.5%) were alive at last follow- up. Death was attributed to transplant (9/15) and to the primary disease (6/15). In all survivors, TP activity normalized after transplant. Survival was found to be associated with human leukocyte antigen match 10/10; and absence of liver disease, history of gastrointestinal pseudo-obstruction or both [145]. Currently, there is an active trial to assess the safety of AHSCT in patients with MNGIE (https://clinicaltrials.gov/ct2/show/NCT02427178).

Due to the multi-organ nature of mitochondrial disorders, the options for organs and stem cell transplantation are limited. The 5-year survival rate post orthotopic liver transplantation (OLT) in 14 patients with hepatocerebral mitochondrial DNA depletion syndrome due to deoxyguanosine kinase (DGUOK) deficiency transplanted in infancy was 36% [146]. In the presence of abnormal neurological features in DGUOK deficiency, liver transplantation was not associated with increased survival and therefore should not be considered [147]. In 6 patients with MNGIE, including one child, OLT was associated with 100% survival, significant improvement in nucleosides levels, and stabilization of clinical course with short term follow up [148–150]. OLT also led to clinical and biochemical improvement in three patients with ethylmalonic encephalopathy [151,152]. Cardiac transplantation has been performed in some patients with Barth syndrome [153]. The outcomes of solid organ transplant in subjects with mitochondrial diseases could be comparable with those with non-mitochondrial disease provided there is good selection and preparation of patients [154].

12. Prevention of mitochondrial disease

Mitochondrial diseases caused by defects in nuclear mitochondrial genes follow Mendelian inheritance and prevention in these disorders can be achieved through prenatal testing or preimplantation genetic testing (PGT) [2]. The situation is more daunting in mtDNA-related disorders in which counseling and prevention are complicated by maternal inheritance of mtDNA, heteroplasmy, and the presence of the mitochondrial genetic bottleneck. PGT can be used in these situations to select embryos with low level heteroplasmy [155]. This option is not suitable in mothers with homoplasmic mutations or those unable to produce embryos with low mutation load [156]. Mitochondrial donation or mitochondrial replacement therapy is a method in which the nuclear DNA from a mother with mtDNA mutation is transferred to an oocyte or zygote that contains normal mtDNA from a healthy donor [156]. Techniques utilized in mitochondrial replacement therapy include pronuclear transfer, maternal spindle transfer, and polar body transfer [157]. Mitochondrial replacement therapy is not approved in the United States but it is approved in the United Kingdom with special requirements [158]. An observational study is currently active and recruiting participants with primary aim to evaluate the neurodevelopment of children conceived using mitochondrial donation at 18 months of age (https://clinicaltrials.gov/ct2/show/NCT04113447).

13. Conclusion

In this review, we discuss the various modalities used in the treatment of mitochondrial disorders and we focus on the recent and the

ongoing clinical trials. While the treatment of mitochondrial disorders still lags behind in comparison to the advances in the diagnosis of these disorders, recent efforts in this field to provide a more targeted approach are promising. The better understanding of the pathophysiologic mechanisms in mitochondrial disorders, recently acquired knowledge of the epidemiology and natural history of these disorders, and the establishment of collaborative, multi-center consortia, will allow for the design of more efficient clinical trials. The use of metabolomics in mitochondrial disorders may also help in identifying disease specific biomarkers that could potentially be used to monitor the effects of investigational drugs.

Declaration of Competing Interest

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