

Other potential modes of metabolic therapy include: 1. Supplementation of the missing compound, e.g. CoQ10 which is effective only in primary Q10 deficiency and is given to most patients with mitochondrial disorders even if deficiency is not tested; 2. Pharmacologically increasing the oxidative capacity of muscle (by giving various 'cocktails' of oxygen species scavengers that include: carnitine, vitamin C, riboflavin, and extra creatine); 3. Changing the diet composition in order to increase the availability of compensatory fuel sources (e.g. sucrose or a carbohydrate rich diet given before exercise in MacArdle's disease). Because of the rarity of metabolic myopathies no proper double blind studies were performed to assess these therapeutic modalities.

Hereditary inclusion body myopathy (HIBM) is a destructive muscle disease due to mutations in GNE, an enzyme in the synthetic pathway of sialic acid. Part of the pathogenic mechanism is thought to be sialylation deficiency so correcting it may affect the disease course. Providing orally a metabolic intermediate that is downstream to the defective site in the sialic acid pathway (e.g. ManNac) or sialic acid itself was shown to be effective in a mouse model of HIBM. With these considerations in mind, planned therapy of this progressive metabolic myopathy is now reaching human trials. Human and animal toxicity studies with various compounds are now in progress.

I-3

Treatment of CPT2 deficiency with bezafibrate

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The most prevalent fatty acid oxidation disorders (FAO) in adults are carnitine palmitoyl transferase II (CPTII), very-long chain Acyl-CoA-dehydrogenase (VLCAD) and multiple Acyl-CoA dehydrogenase (MAD) deficiencies.

Proposed treatment strategies for FAO defects include avoidance of exacerbating factors, carnitine supplementation, riboflavin treatment and dietary modifications (medium-chain triglycerides and triheptanoin). Riboflavin treatment may induce a dramatic improvement of muscle symptoms and encephalopathy in some patients with riboflavin-responsive MAD deficiency.

Children with long-chain FAO defects are generally treated with a low long-chain fat diet and supplements of MCT, but the evidence for benefit is less convincing in patients whose problems are recurrent rhabdomyolysis. A remarkable improvement of cardiac and muscular symptoms occurred in three children with VLCAD deficiency and in seven patients with CPTII deficiency after dietary supplementation with triheptanoin, a seven-carbon medium-chain fatty acid, which supposed mechanisms are the production of C5 ketone bodies and propionyl-CoA, allowing to replenish the pool of catalytic intermediates of the citric acid cycle. Further clinical trials and prolonged clinical follow-up are needed to confirm the benefit of these treatments.

A recently tested alternative way to treat FAO disorders are agonists of peroxisome proliferators-activated receptors

(PPARs), that are potent pharmaceutical tools stimulating FAO enzymes in a wide variety of cells. Recent data showed in vivo correction of CPT II and VLCAD deficiency in cultured patients' fibroblasts, with bezafibrate a widely prescribed hypolipidemic drug. The potential for bezafibrate to correct inborn FAO disorders, has already conducted to the achievement of a pilot clinical trial in 6 adults with CPT II deficiency showing a clear improvement of FAO in muscle.

Another potential target for improving FAO oxidation is AMP-activated protein kinase (AMPK). Exercise, some drugs (metformine, rosiglitazone), and hormones such as leptin and adiponectine are known activators of AMPK in skeletal muscle and increase FAO in muscle. The development of new drugs modulating the activity of AMPK could also open new avenues for the treatment of FAO disorders.

I-4

Long-term follow-up effects on enzyme replacement treatment of adult form of acid maltase deficiency myopathy

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We evaluated the clinical efficacy of alglucosidase alpha enzyme replacement therapy (ERT) in 77 patients with late-onset glycogen storage disease type 2 (GSDII) at various stages of disease progression. Previous studies on efficacy led to demonstrate ERT efficacy against placebo in a 18 months study (LO-TOS van Der Ploeg, NEJM, 2010).

Seventy-seven juvenile or adult patients were treated with ERT in a multi-centre open label non-randomized study with regular clinical assessment for up to 54 months. Recombinant human alpha glucosidase (rh-GAA) was injected by intravenous route at 20 mg/kg i.v. every second week. For analysis, patients were divided in three groups: one group received ERT treatment for 12-18 months, a second group received ERT treatment for 24-30 months, and a third group patients were treated for over 36 months. Clinical assessment included a 6-minute walk test (6MWT), the Walton and Gardner-Medwin scale, forced vital capacity (FVC) and blood creatine kinase (CK). All tests were performed at baseline and every three months thereafter.

ERT was associated with a longer walking distance on the 6MWT. FVC was stabilized in most patients, and a significant decrease in number of hours off the ventilator was found in several patients. Few adverse effects were observed, leading to discontinuation of treatment in 1 patient.

ERT appears a long term reasonable safe treatment for all patients examined. The response pattern in a single patient was variable and not always correlated with treatment duration.