Elamipretide treatment in an infant with Sengers syndrome

Rognvaldsson I., Stephensen S.S.(1), Oskarsson G.(1), Gunnarsdottir B.B.(2), Marelsson S.(1), Jonsson J.J.(2,3), Bjornsson H.T. (1,2,4)
Department of Pediatrics, Barnaspitali Hringsins, Reykjavik, Iceland (1); Department of Genetics and Molecular Medicine, Landspitali University Hospital, Reykjavik, Iceland (2); Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Iceland (3); McKusick-Nathans Institute of Genetics Medicine, Johns Hopkins University, Baltimore, MD, USA. (4)

Introduction: Sengers syndrome (SS) is a rare cause of early onset cardiac failure, congenital cataracts and hypotonia caused by homozygous disease-causing variants in the AGK gene. We recently diagnosed a boy that was homozygous for a founder mutation (p.Ile348AsnfsTer38) carried by approximately 1% of Icelanders. In the first few months he was noted to have severe hypertrophic cardiomyopathy, bilateral cataracts and significant hypotonia, but average published survival of children presenting at this age is 4.2 months. SS and Barth syndrome have overlapping phenotypes and both are thought to lead to depletion of mitochondrial cardiolipin. Elamipretide is a tetrapeptide which is known to target the inner mitochondrial membrane and thought to bind and reduce cardiolipin damage, and thus theoretically may be of use to both syndromes.

Methods: In collaboration with Stealth BioTherapeutics we have treated our patient with elamipretide for ~6 months (starting at 3 months) through a compassionate care protocol, in addition to established beta-blocker treatment. Here we summarize data from weekly clinical global impression evaluations and bi-weekly echocardiograms during the 6 months of treatment.

Results: Pharmacokinetic studies indicated that drug exposure was similar to other elamipretide trials. Our patient showed subjective improvement from the prior week evaluation in 13/21 visits (~62%) and only was felt to worsen on one occasion. His global score went from markedly ill to borderline ill during the treatment period. Specifically, our patient’s cardiac condition improved in the first few weeks of treatment and has remained stable, with 53% increase in left ventricular internal dimension in end-diastole and stabilization of left ventricle septal and posterior wall thickness despite a 40% weight gain due to normal growth. There have been no obvious side effects that are attributable to elamipretide. The patient has demonstrated intermittent lactic acidosis and neutropenia which are thought to be related to his condition. The patient has now been discharged to home.

Conclusions: Our treatment of a single individual with SS suggests that elamipretide is well tolerated in SS and that treatment may have helped stabilized our patients cardiac function. Further studies are required to definitely define the role of elamipretide in SS.