

BSPED RESEARCH AWARD REPORT

EVALUATION OF EFFICACY AND SAFETY OF mTOR INHIBITORS IN THE MANAGEMENT OF SEVERE CONGENITAL HYPERINSULINISM

Congenital hyperinsulinism (CHI) is the commonest cause of recurrent and persistent hypoglycaemia in the infancy and childhood period. CHI is characterized by the inappropriate and often excessive secretion of insulin from the pancreatic β -cells in relation to the blood glucose concentration. Histologically there are two distinct types of CHI, focal and diffuse. The medical therapy for diffuse CHI involves diazoxide, glucagon and octreotide. The patients who are unresponsive to medical therapy require near total pancreatectomy. However, this often fails to provide the best outcome as some patients continue to have recurrent hypoglycaemia whilst others develop diabetes mellitus and exocrine pancreatic insufficiency in the long term. Hence there is a need to identify novel therapeutic strategies for the management of severe CHI.

We studied the gene expression pattern in the pancreatic tissues of the patients with diffuse CHI so as to identify novel mechanism(s) and therapeutic options. Gene expression microarray using RNA extracted from fresh frozen pancreatic tissue samples (obtained from children who underwent pancreatectomy) revealed significant overexpression of mammalian target of rapamycin (mTOR) and insulin-like growth factors in the diffuse CHI patients in comparison with normal controls. Immunostaining suggested an activation of mTOR pathway (which regulates cellular proliferation) in diffuse CHI and transdifferentiation of exocrine pancreatic elements into insulin producing cells, contributing to β -cell hyperplasia.

We recruited 4 patients with severe CHI unresponsive to maximal doses of diazoxide and octreotide (who would have required pancreatectomy as per our standard protocol) and commenced them on the mTOR inhibitor Sirolimus. We did note a good glycaemic response and these children were able to come off intravenous fluids as well as glucagon and octreotide infusions. This facilitated discharge home on enteral feeds and prevented the need for a major surgery. Subsequent follow up to 12 months revealed that these patients were normoglycaemic on sirolimus therapy without any major side effects.

Further morphoproteomic studies were undertaken and the genomic overexpression of MTOR, IGF1, IGF2 and IGF2BP3 and downregulation of TSC2 was noted in diffuse CHI. Correspondingly, morphoproteomics revealed: (a) strong plasmalemmal expression of phosphorylated (p)-mTOR (Ser 2448) in the exocrine pancreas; (b) p-Akt (Ser473) in the nuclear compartment and cytoplasm of the insulin-producing islet cells with variable expression of p-mTOR (Ser 2448); and (c) insulin and IGF-1R expression in the expanded islet cells in the context of minimal progression into the mitotic phase.

Genomic and morphoproteomic findings indicate that the IGF-1R/mTORC2/Akt pathway is overexpressed in the expanded beta cell population in the absence of significant progression into the mitotic phase and a mass effect. These suggest that the observed efficacy of sirolimus in diffuse CHI could be the result of mTORC1 inhibition thereby reducing exocrine transdifferentiation to beta cells, and contributing to the disassembly of the mTORC2/Akt pathway, resulting in reduced insulin secretion and a propensity for increased apoptosis of insulin-producing beta cells.

Benefits of the Award

The award has helped to complete the microarray and morphoproteomic elements of the study thereby enabling the understanding of the efficacy of mTOR inhibitors in CHI. It has helped the applicant to complete the proposed study and the institution by enabling newer treatment options for the children with the rare disorder (CHI). The treatment with mTOR inhibitors is an option now considered for patients with severe diffuse CHI patients around the world.

Publications

1. Sirolimus Therapy in Infants with Severe Hyperinsulinemic Hypoglycemia. Senthil Senniappan, M.D., Sanda Alexandrescu, M.D., Nina Tatevian, M.D., Pratik Shah, M.D., Ved Arya, M.D., Sarah Flanagan, Ph.D., Sian Ellard, Ph.D., Dyanne Rampling, F.I.B.M.S., Michael Ashworth, M.D., Robert E. Brown, M.D., and Khalid Hussain, M.D. N Engl J Med 2014; 370:1131-1137 March 20, 2014 DOI: 10.1056/NEJMoa1310967
2. Genomic and morphoproteomic correlates implicate the IGF-1/mTOR/Akt pathway in the pathogenesis of diffuse congenital hyperinsulinism Senthil Senniappan, Robert E Brown, Khalid Hussain. Int J Clin Exp Pathol 2016;9(2):548-562 www.ijcep.com /ISSN:1936-2625/IJCEP0013812.