Efficacy and Safety of Sirolimus (mTOR Inhibitor) in Two Patients with Diazoxide-Unresponsive Hyperinsulinemic Hypoglycemia

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Although sirolimus is a novel treatment option for congenital hyperinsulinism (CHI), which often requires surgery, its immune suppressive and toxic side effects may limit its usage. We present the efficacy and safety of sirolimus in two patients with diazoxide-unresponsive CHI.

Case 1: A male presented at the first postnatal day with hypoglycemic convulsions and a diagnosis of CHI was confirmed. Genetic analysis identified two homozygous mutations, p.L270M and p.E288K in the *KCNJ11* gene. Despite maximum doses of diazoxide, octreotide, and glucagon, the requirement of 18 mg/kg/min glucose infusion suggested medically unresponsive CHI. At postnatal day 15, sirolimus was commenced at a dose of 0.5 mg/m^2/day which was gradually increased and glucose infusion was tapered accordingly. Blood sirolimus level of 27.9 ng/mL (N: 5-15 ng/mL) was attained at a dose of 2 mg/m2/day and normoglycemia was achieved with no need for treatment. The patient however developed renal and hepatic failure which recovered spontaneously following withdrawal of sirolimus. When sirolimus level dropped to therapeutic range, hypoglycemia episodes recurred. He also had three episodes of blood culture-confirmed sepsis. He was referred to another center for surgery.

Case 2: A 5-year-old male was admitted with a history of CHI diagnosed at postnatal day 45 having previous partial (80%) pancreatectomy. Following the identification of homozygous p.R1494W mutation in the *ABCC8* gene, diazoxide was stopped and sirolimus was commenced. Dose was gradually increased to 1.0 mg/m^2/day and the patient showed a good glycemic response. Octreotide dose was reduced from 20 µg/kg/day to 6.6 µg/kg/day with no hypoglycemia episode and excellent fasting tolerance up to 10 hours. Except for mild elevation of liver enzymes, no side effects were observed. In conclusion, we present two distinct experiences on the efficacy and safety of sirolimus. These findings suggest a comprehensive need for identifying the optimal doses and therapeutic blood level in addition to careful monitoring for side effects.

Key words: Congenital hyperinsulinism, diazoxide, sirolimus, immunosuppression, toxic side effects

Successful Transfer from Insulin to Oral Sulphonylurea in an Infant and His Mother with Monogenic Diabetes Due to a Heterozygous Missense Mutation in the *ABCC8* Gene

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Neonatal diabetes mellitus (NDM) which can be transient or permanent is a rare form of monogenic diabetes which usually presents in the first 6 months of life. Mutations in the KATP channel genes (*ABCC8* and *KCNJ11*) are the most common cause of NDM. NDM due to *ABCC8* and *KCNJ11* mutations can be sulphonylurea-responsive. Herein, we present the successful transfer from insulin therapy to sulphonylureas following the identification of an ABCC8 mutation in a patient with NDM and his affected mother who was on insulin therapy for 8 years.

Case: A 7-month-old male presented with hyperglycemia. He was born at term by caesarean delivery to non-consanguineous parents after an uneventful gestation with a birth weight of 2750 gr. His mother and two aunts had diabetes and were on insulin therapy. On physical examination, his length was 66 cm (-1.56 SD) and weight was 8.4 kg (0.1 SD). Other physical findings were normal. In laboratory examination, blood glucose was 304 mg/dL, insulin: 1.9 µU/mL, C-peptide: 0.38 ng/mL, and hemoglobin A1c (HbA1c) was 8.4%. In urine analysis, he had (+++) glycosuria and mild ketonuria. He had no acidosis in blood gas analysis, and anti-glutamic acid decarboxylase antibodies were negative. Normoglycemia was achieved by insulin therapy. Molecular genetic analysis identified a heterozygous missense mutation, p.E208K (c.622G>A) in exon 5 of *ABCC8* gene. The patient's mother was heterozygous for the same mutation. A trial of sulphonylurea therapy in the patient and his mother has shown a satisfactory glycemic response. Insulin therapy was weaned successfully in both the patient and his mother. HbA1c level declined from 8.4% to 6.0% with sulphonylurea therapy. In conclusion, mutation analysis in patients with monogenic diabetes can provide fundamental changes in management of their diabetes and allows for genetic counseling in the family.

Key words: Monogenic diabetes, sulphonylurea, *ABCC8* gene