Sirolimus in Treatment of Three Infants with Diffuse Type of Congenital Hyperinsulinism

Angham Al-Mutair, M.D.1,2, Rana Al-Balawi, M.D.1, Ahlam Al-Otibi, M.D.1, Mohsen Al-Atawi, M.D.1,2, Omar Babaker, M.D.1

King Abdullah Children Specialty Hospital and Research Center1, King Saud bin Abdulaziz University for Health sciences2, King Abdullah International Medical Research Center2, National Guard, Riyadh, KSA

Abstract

Congenital hyperinsulinism (CHI) is the major cause of persistent hypoglycemia and brain damage that requires immediate medical treatment. It has been a challenge to find a new medical treatment to avoid near total pancreatectomy for patients who are not responding to maximum doses of Diazoxide and Octreotide. A previous study has shown that Sirolimus, a mammalian target of Rapamycin (mTOR) inhibitor has been used successfully to treat infants with congenital hyperinsulinism. We therefore tried Sirolimus to treat three infants with medically unresponsive severe diffuse type of congenital hyperinsulinism with homozygous mutations involving KCNJ11 and ABCB8 genes that resulted in poor glycemic responses in these three infants. We suggest that Sirolimus in treatment of homozygous type of mutation might not be as effective as in treatment of heterozygous or compound heterozygous type of CHI.

Background

CHI represents a group of clinically and genetically heterogeneous disorders characterized by dysregulated insulin secretion and resulting in severe and persistent hypoglycemia. Nine genes expressed in the beta cell have been involved in the pathophysiology of CHI. Mutations in ABCB8 and KCNJ11 are associated with severe CHI that is unresponsive to medical treatment with Diazoxide and Octreotide. Children with diffuse CHI (60%) have homozygous recessive or compound heterozygous mutations in the ABCB8 or KCNJ11 genes mostly unresponsive to medical therapy and near total pancreatectomy is the final treatment option which has a lot of morbidity. Based on these outcomes, a study by Sandra Alexandreus et al evaluating the histologic finding of two infants have diffuse CHI, resulted in a novel finding of the constitutive activation of the mTORC1 pathway in the islet cells and a reprogramming of the transcriptional program of acinar-to-islet cells and possible mechanisms of hyperinsulinism and beta cell hyperplasia in diffuse hyperinsulinemic hypoglycemia involves the constitutive activation of the mTOR pathway (1). Further study to show the effect of the mTOR inhibitor therapy on four infants with severe CHI was done, resulted in remarkable good glycemic control in all of the four infants that raised the option to use mTOR inhibitor as a therapy to treat severe, diffuse form of CHI.

Aim

Reporting our experience with Sirolimus in three infants with diffuse types of CHI with refractory hypoglycemia and not responding to maximum doses of Diazoxide and Octreotide.

Methods

Three infants were presented with severe symptomatic hypoglycemia during first four days of life, diagnosis of CHI was confirmed biochemically and by genetic test (clinical characteristic shown in table-1). Consents were signed and pharmacist was consulted for formulation and drug preparation. Sirolimus started according to the protocol (3).

Results

Sirolimus doses with incremental changes, trough level and glycemic response in these three infants are shown (Table 2).

Discussion & Conclusion

Sirolimus (mTOR inhibitor) is a promising drug for treatment of severe form of CHI based on the study by Senniappan S et al (2), the genetic characteristic of the four infants show no mutation in ABCB8, KCNJ11 or HNF4A for the first patient, maternally inherited heterozygous ABCB8 mutation for the second patient, maternally inherited heterozygous ABCB8 mutation for 3rd patient and homozygous ABCB8 mutation for the 4th patient and as noticed all these mutations are not in a homozygous state except for the 4th patient where the mutation involves ABCB8 (c.1467G>A). In our trial, all infants have KCNJ11 or ABCB8 gene mutations in a homozygous state that failed good glycemic response to the Sirolimus therapy. Comparing our result to the previous study result (2), we suggest that the Sirolimus might not be effective in CHI with severe type of mutations (homozygous).

Table 1: Patients Clinical Characteristics

<table>
<thead>
<tr>
<th>Infant No.</th>
<th>Sex</th>
<th>Age (mo)</th>
<th>Impaired Glycogen Storage (Igs)</th>
<th>Birth Weight (kg)</th>
<th>Family History</th>
<th>Hypoglycemia (mo)</th>
<th>Genetic Characteristic</th>
<th>Hemopathy Abnormalities</th>
<th>Glucose infusion (mg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>26</td>
<td>No (unconfirmed)</td>
<td>3.16</td>
<td>No</td>
<td>12</td>
<td>KCNJ11 mutation</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>36</td>
<td>No (unconfirmed)</td>
<td>2.95</td>
<td>No</td>
<td>18</td>
<td>ABCB8 mutation</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>30</td>
<td>No (unconfirmed)</td>
<td>3.16</td>
<td>No</td>
<td>8</td>
<td>ABCB8 mutation</td>
<td>Yes</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 2: Sirolimus Treatment Response:

<table>
<thead>
<tr>
<th>Infant</th>
<th>Daily Dose (mg/kg)</th>
<th>Serial Dose (mg)</th>
<th>Glycemic Response</th>
<th>Major Adverse Events</th>
<th>Insulineant Level (ug/ml)</th>
<th>Complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15 mg/kg</td>
<td>0.15 mg</td>
<td>Poor glycemic response</td>
<td>No</td>
<td>30 mg</td>
<td>Hyperglycemia</td>
<td>Sirolimus discontinued after 47 days.</td>
</tr>
<tr>
<td>2</td>
<td>0.05 mg/kg</td>
<td>0.05 mg</td>
<td>Poor glycemic response</td>
<td>No</td>
<td>50 mg</td>
<td>Hyperglycemia</td>
<td>Sirolimus discontinued after 47 days.</td>
</tr>
</tbody>
</table>


4. Senniappan S et al at the role of mTORC1/Rag ST/Pase and IGF1R/mTORC2/Skt pathways and the response of diffuse congenital hyperinsulinism to sirolimus, ESPE 2014.