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 Center[1], King Saud bin Abdulaziz University for Health science[2], King Abdulla International Medical Research Center[2], 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 pancreactomy for patients who are not responding to maximum doses of Diazoxide and Octreotide. A previous study has shown that the Sirolimus, a mammalian target of Rabamycin (mTOR) inhibitor has been used successfully to treat four 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 ABCC8 genes that resulted in poor glycemic response to Sirolimus in the 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 ABCC8 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 ABCC8 or KCNJ11 genes mostly unresponsive to medical therapy and near total pancreacteomy is the final treatment option which has a lot of morbidities. Based on these outcomes, a study by Sanda Alexandrescu et al evaluating the histologic finding of two infants have diffuse CHI, resulted in a novel finding of the constitutive activation with overexpression of the mTORC1 pathway in the acinar cells and a reaffirming transdifferentiation of acinar-to-islet cells and possible mechanism 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 (2) 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 days of life, diagnosis of CHI was confirmed biochemically and by gene test (clinical characteristic shown in table-1).
Consents were signed and pharmacist was contacted for formulation and drug preparation. Sirolimus started according to the protocol (3).

Results

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

Table-1: Patients Clinical Characteristics

Infant No.	Sex	Gestational Age (weeks)	Birth Weight (Kg)	Family History	Hypoglycemia Onset	Genetic Characteristic	Histopathology characteristic	Glucose infusion rate (mg/kg/min)
1	Female	38	3.59	1st cousin with CHI	Few hours postnatal	Mutation: c.902G>C (p.Arg301 pro) in exon1 of *KCNJ11 gene* homozygous	Diffuse	9
2	Male	36	3.65	-Positive consanguinity -Sibling with diffuse CHI	Few hours postnatal	Mutation: c.1090delp.Ala365Profs*23 *ABCC8* homozygous	Diffuse	14
3	Female	38	4.17	Index case	Few hours postnatal	Result: Pending	Diffuse	14.6

Table-2: Sirolimus Treatment and Response:

Infant	Daily Sirolimus Dose	Sirolimus Level (ng/ml)	Response	Duration of therapy (days)	Maximum Sirolimus Dose (mg/m2 /day)	Insulin Level (Uiu/ml) C-Peptide Level (ng/ml) (at glucose <2.4mmol/l)	Complications	Outcome
1	Day 1 0.16 mg Last day 3mg	4 9	-Daily intractable Hypoglycemia -Poor glycemic response	47	9	Insulin= 10.10 C- Peptide= 3.32	Mild leukocytosis Mildly increase LDL	• Sirolimus discontinued after 47 days of treatment • Near total pancrectomy complicated by residual pancreatic cyst. • Feeding difficulties • On Octreotide • Occasional hypoglycemia
2	D1 0.1mg Last day 3mg	4 14	-Daily frequent intractable Hypoglycemia -Poor glycemic response	60	13	Insulin = 4.1 C-peptide= 0.81	Leukocytosis	• On octerotide Occasional hypoglycemia • Near total pancreactomy done before starting Sirolimus • Feeding difficulties • Occasional hypoglycemia
3	D1 0.16 mg Last day 12 mg	2 8	-Daily frequent intractable Hypoglycemia -Poor glycemic response	58	35	Insulin = 60.30 C-peptide= 7	Mildly increased LDL	• Near total pancreactomy • No post OP complication • No hypoglycemia • Feeding difficulties

Discussion & Conclusion

Sirolimus (mTOR inhibitor) is a promising drug for treatment of severe form of CHI based on the study by Senniappan S etal(2), the genetic characteristic of the four infants show no mutation in ABCC8, KCNJ11, or HNF4A for the first patient, maternally inherited heterozygous ABCC8 mutation for the second patient, maternally inherited heterozygous ABCC8 mutation for 3rd patient and homozygous ABCC8 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 ABCC8 (c.1467+5G→A).
In our trial, all infants have KCNJ11or ABCC8 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 sever type of mutations (homozygous).

Sirolimus (mTOR inhibitor) is a promising drug for treatment of severe form of CHI based on the study by Senniappan S etal(2), the genetic characteristic of the four infants show no mutation in ABCC8, KCNJ11, or HNF4A for the first patient, maternally inherited heterozygous ABCC8 mutation for the second patient, maternally inherited heterozygous ABCC8 mutation for 3rd patient and homozygous ABCC8 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 ABCC8 (c.1467+5G→A).
In our trial, all infants have KCNJ11or ABCC8 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 sever type of mutations (homozygous).

References

1. Persistent hyperinsulinemic hypoglycemia of infancy: constitutive activation of the mTOR pathway wit associated exocrine-islet transdifferentiation and therapeutic implication ,Alexandrescu S etal .Int Jou Of Clin and and Exper Path.2010 ,3(7) 691-705.
2. Sirolimus Therapy in Infants with Severe Hyperinsulinemic Hypoglycemia, Senniappan S etal, N Eng J Med 2014 ;370:1131-1137.
3. Protocol for: Senniappan Set al. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia,N Eng J Med 2014.
4. Senniappan S et al the role of mTORC1/Rag GTPase and IGF1R/mTCR2/akt pathways and the response of diffuse congenital hyperisnulinism to sirolimus,ESPE 2014.

ESPE 2015
1072--P3
Misc 3
Angham Al Mutair
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com