



Long-Term Efficacy of Glibenclamide and Sitagliptin Therapy in Adult Patients With KCNJ11 Permanent Diabetes

Julia Sastre,¹ Alessandra Luque,¹
Florentino del Val,¹ Angel Aragonés,²
and José López¹

Diabetes Care 2014;37:e55–e56 | DOI: 10.2337/dc13-2280

Permanent neonatal diabetes (PND) is a rare disease characterized by hyperglycemia diagnosed within the first 6 months of life (1). Activating mutation of the KCNJ11 gene encoding Kir6.2 subunit of the ATP-potassium (K_{ATP}) channel has been described as the most frequent cause of PND. Under physiologic circumstances, K_{ATP} channel closure plays a central role in glucose-stimulated insulin secretion from pancreatic β -cells. Sulfonylureas (SUs) stimulate insulin secretion by closing K_{ATP} channels via an ATP-independent mechanism. Since 2004, SUs are best choice of treatment in PND with such mutations and allow better glycemic control in children and adults than insulin (2).

Some authors report that adult patients are unable to switch successfully from insulin to SU and that the doses required to get the insulin independence are higher (3,4). We present our experience in switching the treatment from insulin to SU and the usefulness of adding sitagliptin.

We describe an 18-year-old Spanish girl with PND due to the previously reported H46Y mutation in the KCNJ11 gene. No history of epilepsy or developmental delay was present. Clinical characteristics are shown in Table 1.

After discovering the etiology of the diabetes, switching from insulin to SU

Table 1—Clinical characteristics of patient

| | |
|---|----------|
| Birth weight (g) | 2,400 |
| Age diabetes diagnosed (days) | 28 |
| Age at examination (years) | 18 |
| Height (cm) | 162 |
| Weight (kg) | |
| At study entry | 59 |
| At 6 months | 60 |
| At 15 months (insulin discontinuation) | 58 |
| 3 years after insulin independence | 51 |
| HbA _{1c} (%) (mmol/mol) | |
| At study entry | 8.9 (74) |
| At 6 months | 8.1 (65) |
| At 15 months (insulin discontinuation) | 7.0 (53) |
| 3 years after insulin independence | 6.3 (45) |
| Glibenclamide dose (mg/kg/day) | |
| At study entry | 1.0 |
| At 6 months | 0.8 |
| At 15 months (insulin discontinuation) | 0.6 |
| 3 years after insulin independence | 0.3 |
| Sitagliptin | |
| Initiation after glibenclamide (months) | 12 |
| Dose (mg/day) | 100 |
| Fasting C-peptide level (ng/mL) | |
| At study entry | 0.05 |
| At 6 months | 1.46 |
| At 15 months (insulin discontinuation) | 1.60 |
| At 24 months | 2.10 |
| Glucagon-stimulated C-peptide level (ng/mL) | |
| At study entry | 0.15 |
| At 6 months | 2.59 |
| At 15 months (insulin discontinuation) | 2.69 |
| At 24 months | 4.10 |

was attempted. Informed consent was obtained from the patient. We started glibenclamide (GB) therapy according

to a standardized protocol at initial dose of 0.2 mg/kg/day and then gradually increased it until she reached a dose of

¹Endocrinology Department, Complejo Hospitalario de Toledo, Toledo, Spain

²Pediatrics Department, Complejo Hospitalario de Toledo, Toledo, Spain

Corresponding author: Julia Sastre, jsastrem@sescam.jccm.es.

© 2014 by the American Diabetes Association. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

1 mg/kg/day. Insulin was progressively reduced. Four weeks after the beginning of the transition, the glycemic control was poor, so we decided to continue with insulin and SU at high doses. Six months after initiating GB, she was receiving basal insulin (20 units/day) and GB (0.8 mg/kg/day) with little improvement of glycemic control, but, in agreement with the patient, we decided to continue with this compound treatment. Twelve months after the start of SU treatment, her HbA_{1c} was high and we decided to add sitagliptin (100 mg/day). After 3 months with GB (0.6 mg/kg/day) plus sitagliptin and glargine (16 units/day), HbA_{1c} was 7% (53 mmol/mol) and insulin was discontinued. After 3 years of insulin independence, the patient has good glycemic control and has reduced the dose of GB to 0.3 mg/kg/day. She continues with sitagliptin combined with SU.

To our knowledge, this is the first report of sitagliptin as a possible therapeutic tool in PND with mutations in the KCNJ11 gene. Today, we know that patients with KCNJ11 mutations who are

receiving SU have marked insulin secretion in response to oral glucose (2). This finding is consistent with the hypothesis that improved glycemic control in PND treated with SU could be, in part, mediated by incretin effects. SUs close the K_{ATP} channel and depolarize the membrane of β -cells, so that they are able to respond to glucagon-like peptide 1 and other secretagogues (3). Glucagon, like glucagon-like peptide 1, does not stimulate insulin secretion in PND unless SUs are present. In adult patients with PND with KCNJ11 mutations unable to switch from insulin to SU or with long transitions, dipeptidyl peptidase 4 inhibitors could be an option of treatment.

Acknowledgments. The authors thank L. Castaño (Hospital Universitario de Cruces, Spain), who provided sequence analysis of the KCNJ11 gene.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. J.S. took care of the patient, researched data, and wrote the manuscript. A.L. and F.d.V. took care of the

patient, researched data, and contributed to the writing of the manuscript. A.A. took care of the patient since diagnosis to adult age, contributed to discussion, and reviewed the manuscript. J.L. contributed to discussion and reviewed the manuscript. J.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Greeley SA, Tucker SE, Worrell HI, Skowron KB, Bell GI, Philipson LH. Update in neonatal diabetes. *Curr Opin Endocrinol Diabetes Obes* 2010;17:13–19
2. Pearson ER, Flechtner I, Njølstad PR, et al.; Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006;355:467–477
3. Malecki MT, Skupien J, Klupa T, et al. Transfer to sulphonylurea therapy in adult subjects with permanent neonatal diabetes due to KCNJ11-activating mutations: evidence for improvement in insulin sensitivity. *Diabetes Care* 2007;30:147–149
4. Heo JW, Kim SW, Cho EH. Unsuccessful switch from insulin to sulfonylurea therapy in permanent neonatal diabetes mellitus due to an R201H mutation in the KCNJ11 gene: a case report. *Diabetes Res Clin Pract* 2013; 100:e1–e2