HHS Public Access

Author manuscript

Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Lancet Diabetes Endocrinol. 2018 August ; 6(8): 594–595. doi:10.1016/S2213-8587(18)30138-4.

Precision medicine in *KCNJ11* permanent neonatal diabetes

Siri Atma W Greeley, **Lisa R Letourneau**, and **Louis H Philipson**

Departments of Medicine and Pediatrics, University of Chicago, Chicago, IL, USA; and Kovler Diabetes Center, University of Chicago, Chicago, IL 60637, USA

One of the most important advances towards personalised genetic medicine for diabetes was the discovery that nearly half of neonatal diabetes is caused by de-novo (usually) or inherited mutations in the subunits of the pancreatic β-cell ATP-sensitive potassium (K_{ATP}) channel.[1] These activating mutations in the *KCNJ11* and *ABCC8* genes shift the probability of the K_{ATP} channels to have an open configuration, causing plasma membrane hyperpolarisation, thereby inhibiting insulin secretion, and causing permanent or transient neonatal diabetes. With most of these mutations, channel function can be restored by blockade with sulfonylurea tablets. This simple and low-cost treatment allows most patients to achieve substantially improved glycaemic control— with minimal hypoglycaemia— compared with insulin injections.[2,3] Identification and appropriate treatment of these individuals with sulfonylureas is also remarkably cost-effective over their lifetime.[2] In many cases, the K_{ATP} subunit mutations also cause a spectrum of sometimes severe neurological defects that often (but not always) correlate with the open probability of the mutant channels and the ability of sulfonylurea drugs to block the channel.[3] Despite this profoundly insightful set of discoveries, some concern has remained about the safety and durability of sulfonylurea treatment in these patients, which often requires higher than approved doses and is given off-label in most countries when used in children.

In *The Lancet Diabetes & Endocrinology,* Pamela Bowman and colleagues[4] report findings from long-term follow-up of an international cohort of patients with neonatal diabetes due to *KCNJ11* mutations who were switched from insulin to sulfonylurea treatment. After about 10 years of follow-up, 75 (93%) of 81 participants remained on sulfonylurea therapy alone. Very good glycaemic control was maintained for patients for whom paired data were available on HbA_{1c} and sulfonylurea at all time points (ie, pre-transfer [for HbA_{1c}], year 1, and most recent follow-up; n=64), with median HbA_{1c} 6.4% at most recent follow-up, compared with 5.9% at 1 year and 8.1% before transfer to sulfonylurea therapy. There were no reports of severe hypoglycaemia in 809 patient-years of follow-up for the whole cohort. We agree that these positive long-term findings confirm this approach to be one of the best examples of precision genetic medicine in all medical practice.

In type 2 diabetes, sulfonylurea drugs are associated with hypoglycaemia and failure to durably maintain improvements in glucose control, and have also been associated with increased all-cause mortality and cardiovascular events in adults with type 2 diabetes.[5,6] Additional concerns exist about the use of glibenclamide specifically in type 2 diabetes.[7]

We declare no competing interests.

These concerns might contribute to reluctance among some clinicians to pursue sulfonylurea therapy in patients known to have *KCNJ11* or *ABCC8* mutations causing neonatal diabetes. However, compared with adults with type 2 diabetes, most individuals with K_{ATP} mutation-related diabetes are children or young adults who are non-obese and insulin sensitive, without confounding or contributory histories of coronary artery disease, hyperlipidaemia, hypertension, and renal insufficiency, among other issues more common in type 2 diabetes. The evidence that HbA_{1c} is improved by sulfonylurea treatment more than with insulin is robust,[8,9] and the results of Bowman and colleagues' study,[4] together with previous research,[10] show that hypoglycaemia is mild and other side-effects of high-dose sulfonylureas are not clinically significant. Some evidence exists that sulfonylurea therapy might have a beneficial effect on the neurological features seen in patients with more severe mutations, but treatment might need to start at an early age and the benefit might be small.[11] Bowman and colleagues report that,[4] despite some initial improvement in some patients, neurological features persisted in their international cohort of long-term sulfonylurea-treated patients.

Bowman and colleagues' findings[4] show that during more than 10 years of treatment there was no loss of the effect of sulfonylurea therapy on insulin secretion; rather, there was a small but detectable continued lowering of the dose (expressed as dose per kg bodyweight) necessary to maintain normal glycaemia. Why this might be the case is unclear, but several possibilities exist. It could be that there is continued improvement of the capacity of β cells for glucose-stimulated insulin secretion during sulfonylurea treatment, or that sulfonylureas, often hydrophobic in nature, can accumulate in tissues over time. This theory might also explain why we have heard anecdotally from patients that occasional doses can be missed without a prompt rise in blood sugar.

In individuals showing signs of developmental delay and neurological dysfunction due to K_{ATP} mutations, there might only be a modest effect on improving the neurological features with sulfonylurea drugs.[11–14] CNS effects are clearly variable in their response and might depend on getting the drug to affected individuals as early as possible,[9] and in a way that overcomes the low concentration of sulfonylurea in the CNS itself.[15]

Overall, Bowman and colleagues' findings[4] illustrating the durability of sulfonylurea therapy without substantial off-target effects will be of general interest, not only to those following advances in this field, but as an exemplar of precision medicine. These results also suggest that there are important differences between sulfonylurea therapy in type 2 diabetes and neonatal K_{ATP}-related diabetes, the mechanisms of which remain to be fully elucidated.

Acknowledgments

Our work is supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the US National Institutes of Health (grant numbers R01 DK104942 and K23 DK094866).

References

1. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N EnglJ Med 2004; 350: 1838–49. [PubMed: 15115830]

2. Greeley SAW, John PM, Winn AN, et al. The cost-effectiveness of personalized genetic medicine: the case of genetic testing in neonatal diabetes. Diabetes Care 2011; 34: 622–27. [PubMed: 21273495]

3. Proks P, Antcliff JF, Lippiat J, Gloyn AL, Hattersley AT, Ashcroft FM. Molecular basis of Kir6.2 mutations associated with neonatal diabetes or neonatal diabetes plus neurological features. Proc Natl Acad Sci USA 2004; 101: 17539–44. [PubMed: 15583126]

4. Bowman P, Sulen A, Barbetti F, et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to *KCNJ11* mutations: an international cohort study. Lancet Diabetes Endocrinol 2018; published online 6 1 10.1016/S2213- 8587(18)30106–2.

5. Riddle MC. Modern sulfonylureas: dangerous or wrongly accused? Diabetes Care 2017; 40: 629–31. [PubMed: 28428320]

6. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. Diabetes Care 2017; 40: 706–14. [PubMed: 28428321]

7. Tuccori M, Wu JW, Yin H, Majdan A, Azoulay L. The use of glyburide compared with other sulfonylureas and the risk of cancer in patients with type 2 diabetes. Diabetes Care 2015; 38: 2083–89. [PubMed: 26341130]

8. Pearson ER, Flechtner I, Njolstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006; 355: 467–77. [PubMed: 16885550]

9. Thurber BW, Carmody D, Tadie EC, et al. Age at the time of sulfonylurea initiation influences treatment outcomes in *KCNJ11* -related neonatal diabetes. Diabetologia 2015; 58: 1430–35. [PubMed: 25877689]

10. Lanning MS, Carmody D, Szczerbinski k, Letourneau LR, Naylor RN, Greeley SAW. Hypoglycemia in sulfonylurea-treated *KCNJ11*-neonatal diabetes: mild-moderate symptomatic episodes occur infrequently but none involving unconsciousness or seizures. PediatrDiabetes 2017; 49: 405.

11. Shah RP, Spruyt K, Kragie BC, Greeley SAW, Msall ME. Visuomotor performance in *KCNJ11* -related neonatal diabetes is impaired in children with DEND-associated mutations and may be improved by early treatment with sulfonylureas. Diabetes Care 2012; 35: 2086–88. [PubMed: 22855734]

12. Mlynarski W, Tarasov AI, Gach A, et al. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in *KCNJ11*. Nat Clin Pract Neurol 2007; 3: 640–45. [PubMed: 17982434]

13. Fendler W, Pietrzak I, Brereton MF, et al. Switching to sulphonylureas in children with iDEND syndrome caused by *KCNJ11* mutations results in improved cerebellar perfusion. Diabetes Care 2013; 36: 2311–16. [PubMed: 23462667]

14. Busiah K, Drunat S, Vaivre-Douret L, et al. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study. Lancet Diabetes Endocrinol 2013; 1: 199–207. [PubMed: 24622368]

15. Lahmann C, Kramer HB, Ashcroft FM. Systemic administration of glibenclamide fails to achieve therapeutic levels in the brain and cerebrospinal fluid of rodents. PLoS One 2015; 10: e0134476. [PubMed: 26225433]