Effective Treatment With Oral Sulfonylureas in Patients With Diabetes Due to Sulfonylurea Receptor 1 (SUR1) Mutations

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OBJECTIVE — Neonatal diabetes can result from mutations in the Kir6.2 or sulfonylurea receptor 1 (SUR1) subunits of the ATP-sensitive K^+ channel. Transfer from insulin to oral sulfonylureas in patients with neonatal diabetes due to Kir6.2 mutations is well described, but less is known about changing therapy in patients with SUR1 mutations. We aimed to describe the response to sulfonylurea therapy in patients with SUR1 mutations and to compare it with Kir6.2 mutations.

RESEARCH DESIGN AND METHODS — We followed 27 patients with SUR1 mutations for at least 2 months after attempted transfer to sulfonylureas. Information was collected on clinical features, treatment before and after transfer, and the transfer protocol used. We compared successful and unsuccessful transfer patients, glycemic control before and after transfer, and treatment requirements in patients with SUR1 and Kir6.2 mutations.

RESULTS — Twenty-three patients (85%) successfully transferred onto sulfonylureas without significant side effects or increased hypoglycemia and did not need insulin injections. In these patients, median A1C fell from 7.2% (interquartile range 6.6–8.2%) on insulin to 5.5% (5.3–6.2%) on sulfonylureas ($P = 0.01$). When compared with Kir6.2 patients, SUR1 patients needed lower doses of both insulin before transfer (0.4 vs. 0.7 units $\cdot$ kg^{-1} $\cdot$ day^{-1}; $P = 0.002$) and sulfonylureas after transfer (0.26 vs. 0.45 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}; $P = 0.005$).

CONCLUSIONS — Oral sulfonylurea therapy is safe and effective in the short term in most patients with diabetes due to SUR1 mutations and may successfully replace treatment with insulin injections. A different treatment protocol needs to be developed for this group because they require lower doses of sulfonylureas than required by Kir6.2 patients.

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Activating mutations in the Kir6.2 and sulfonylurea receptor 1 (SUR1) subunits of the pancreatic ATP-sensitive K^+ channel, coded for by the genes *KCNJ11* and *ABCC8*, are recently identified major causes of both transient and permanent neonatal diabetes (1–3). To date, over 40 different heterozygous activating mutations have been reported in the *KCNJ11* gene and are thought to account for between 25 and 55% of all cases of neonatal diabetes (1,4–6). *ABCC8* gene mutations may be either dominantly or recessively acting, and ~40 different mutations have been reported in patients with neonatal diabetes (7,8). Mutations in the *ABCC8* gene are thought to account for ~10% of all cases of neonatal diabetes (9) and frequently cause transient neonatal diabetes (3,9,10).

In the normal pancreatic β-cell, metabolism results in increased cellular ATP, which binds to Kir6.2 to close the potassium channel and hence depolarizes the membrane and, through increased calcium entry, initiates insulin release (11,12). Conversely, increased cellular ADP acts on SUR1 to open the channel and prevent insulin release (11). Activating mutations in these channels reduces sensitivity to the inhibitory actions of ATP and increases sensitivity to the stimulatory actions of ADP (2,9). This causes the ATP-sensitive K^+ channel to remain open, even in the presence of glucose, therefore preventing insulin release.

Sulfonylureas act by an ATP-independent mechanism to close these channels even when mutations are present (2,9,13). They result in insulin release and are therefore a potential treatment option in neonatal diabetes caused by mutations in these channels. The effective replacement of insulin treatment by high-dose sulfonylureas has been shown to be successful in 90% of patients with Kir6.2 mutations and results in improved glycemic control in a series of 49 patients described by Pearson et al. (14).

There is far less information on sulfonylurea use in patients with SUR1 mutations. Successful transfer from insulin to oral sulfonylureas has been described in eight patients with neonatal diabetes due to SUR1 mutations (9,10,15–17). This study will examine the treatment response to sulfonylureas in a cohort of 27 patients with diabetes due to SUR1 mutations to identify whether they can be used effectively and how their transfer and treatment differ from that in Kir6.2 patients.

RESEARCH DESIGN AND METHODS

— We studied an international series of 27 patients with ages ranging from 2 months to 46 years, with a genetic diagnosis of diabetes due to an *ABCC8* gene mutation (or mutations), identified by sequencing in Exeter, U.K. Genetic information on 23 of these muta-

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Abbreviations: SUR1, sulfonylurea receptor 1.

Table 1—*Clinical characteristics of patients with SUR1 mutations according to success of treatment with sulfonylureas*

Characteristic	All patients	Patients with successful sulfonylurea treatment	Patients with unsuccessful sulfonylurea treatment	*P**
n	27	23	4	
Mutation (number of patients)	NA	V86G†, P45L/G1401R- (2)†, D209E (3)†, T229I/V1523L†, Q211K†, V86A (2)†, E1507G, V215I/V607M, E208K/Y263D†, R1380L (2)‡, D212I (3)§, T229I/T229I‡, R1183W§, L225P†, R826W, and D209N	F132L (2)†, F132V†, and N72S† (mosaic).	NA
Classification: TNDM initial/TNDM relapse/ PNDM/non-neonatal diabetes	2/6/17/2	2/6/13/2	0/0/4/0	NA
Neurological features	6 (22)	4 (17)	2 (50)	0.20
Male sex	10 (37)	8 (35)	2 (50)	0.61
Birth weight (g)	2,675 (1,470–3,870)	2,675 (1,470–3,500)	2,670 (2,440–3,870)	
Birth weight (SD score)	−1.3 (−2.8 to 0.64)	−1.3 (−2.8 to −0.1)	−1.1 (−1.4 to 0.64)	0.22
Age at diagnosis (weeks)	6 (0–30)	5 (0–30)	17 (5–26)	0.046
Age at start of sulfonylurea treatment (years)	7.8 (0.2–46.5)	7.1 (0.2–46.5)	14.9 (0.4–28.5)	0.52
A1C before sulfonylurea treatment (%)	7.5 (5.0–21.0)	7.1 (5.0–21.0)	10.0 (7.5–12.0)	0.11
Insulin dose (units · kg^{-1} · day^{-1})	0.5 (0.2–1.2)	0.4 (0.2–0.9)	0.8 (0.4–1.2)	0.097
Equivalent dose of glyburide (mg · kg^{-1} · day^{-1})	0.28 (0.07–2.80)	0.26 (0.07–2.80)	1.00 (1.00–1.12)	NA

Data are median (range), *n* (%), or *n* unless otherwise indicated. Percentages are rounded up to the nearest whole number. **P* values are for comparison of the patients with a successful switch with patients with an unsuccessful switch and were calculated by the Mann-Whitney *U* test or Fisher's exact test for categorical data. †Reported in Ellard et al., 2007 (ref. 7); ‡reported in Patch et al., 2007 (ref. 8); §reported in Flanagan et al., 2007 (ref. 3). NA, not applicable.

tions has previously been published (3,7) (Table 1). Most patients were referred based on membership in the International Society of Pediatric and Adolescent Diabetes. All of the patients attempted transfer from treatment with insulin to a sufficient dose of sulfonylureas except two, who were initially on no treatment and then treated with sulfonylureas when treatment was required. The dose of sulfonylurea was considered to be sufficient if equivalent to at least 0.6 mg · kg body wt^{-1} · day^{-1} of glyburide use; this is the highest reported dose required in previously published cases with patients with *ABCC8* gene mutations (9). No other selection criteria were applied, and all patients were included when there was outcome data for the attempted transfer. The observation period was at least 2 months after commencing sulfonylureas in all patients. Treatment details for two patients have been described previously (8,15,17).

Switch to sulfonylureas

For this study, clinicians were provided with two recommended protocols for the transfer to the sulfonylurea glyburide (also known as glibenclamide) as used for Kir6.2 patients (see www.diabetesgenes.org and 14). One was for a rapid inpatient transfer, where the glyburide dose was increased by 0.2 mg · kg^{-1} · day^{-1} every day and the other for a slower outpatient transfer, where the glyburide dose was increased by 0.2 mg · kg^{-1} · day^{-1} every week. Both involved the gradual withdrawal of insulin as sulfonylurea was introduced depending on blood glucose. These protocols were modified by the treating clinicians. In seven patients, as a result of physician choice, the recommended sulfonylurea, glyburide, was not used: three patients used gliclazide, three used glipizide, and one used tolbutamide. For these patients, equivalent doses of glyburide were calculated to allow inclusion of these results. This, as previously described (14), was done by expressing the sulfonylurea dose as a percentage of the maximum recommended dose (according to the British National Formulary 2007) and converting this to an equivalent dose of glyburide. Transfer was considered a success if the patient was able to completely stop insulin at any dose of sulfonylurea and was considered unsuccessful if insulin was still required with a dose of sulfonylurea equivalent to at least 0.6 mg · kg^{-1} · day^{-1} glyburide.

Information was collected from clinicians regarding treatment before and after transfer, clinical features, and details of the transfer. Clinical features were compared between patients who successfully transferred onto sulfonylureas and patients whose transfer was unsuccessful. Fisher's exact test for categorical data and the Mann-Whitney *U* test for continuous data were used because the data were not normally distributed. Glycemic control before and after sulfonylurea therapy was compared by analyzing the A1C values using Wilcoxon's signed-rank test. Doses

of insulin and sulfonylurea used in Kir6.2 and SUR1 patients who successfully transferred from insulin to sulfonylurea therapy were compared using the Mann-Whitney *U* test. All tests were two sided. Data are expressed as median (range). Differences with a *P* value <0.05 were considered statistically significant.

This study was conducted in accordance with the Declaration of Helsinki as revised in 2000. Informed consent was obtained from all participating patients, with parental consent given on behalf of children.

RESULTS

Successful transfer

Of the 27 patients who attempted transfer onto sulfonylureas at an adequate dose, 23 (85%) were successful in being able to be treated with sulfonylureas alone. Successful transfer occurred with all the different sulfonylureas used, suggesting that choice of agent was not critical. The clinical characteristics of these patients are shown in Table 1. The ages of these patients at transfer ranged from 2 months to 46 years. All eight patients with transient neonatal diabetes were successfully treated with sulfonylureas: six were treated having relapsed, and two were treated in the initial diabetic phase before they went into remission ~11 months after transfer. Four patients with neurological features successfully transferred onto sulfonylureas; all of these had developmental delay, and one also had generalized seizures. Median A1C level dropped from 7.2% (interquartile range 6.6–8.2) on insulin to 5.5% (5.3–6.2) on sulfonylureas ($P = 0.011$) (see Fig. 1*A*) in the 10 patients in whom A1C measurements were available before and at least 4 weeks after transfer (median 15 weeks).

In the five patients for whom follow-up data were available for >6 months following transfer onto sulfonylurea, glycemic control continued to improve despite decreasing sulfonylurea doses, with a mean drop in A1C levels of 1.86% (95% CI 0.2- 3.5) from after transfer to the most recent value (Fig. 1*B*).

Unsuccessful transfer

Four patients were unable to completely stop treatment with insulin despite receiving an adequate dose of at least 1 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} of sulfonylurea (Table 1). Two of these patients with F132V and F132L mutations had increased C-peptide levels following the transfer, but it was decided that the response was insufficient to discontinue insulin. Two of the patients had neurological features, including one patient who had severe developmental delay, epilepsy, and neonatal diabetes (2).

Clinical features of the patients according to whether transfer was successful are shown in Table 1. Unsuccessful patients were diagnosed as diabetic later: median age at diagnosis 17 weeks (range 5–26) compared with 5 weeks (0–30) ($P = 0.046$).

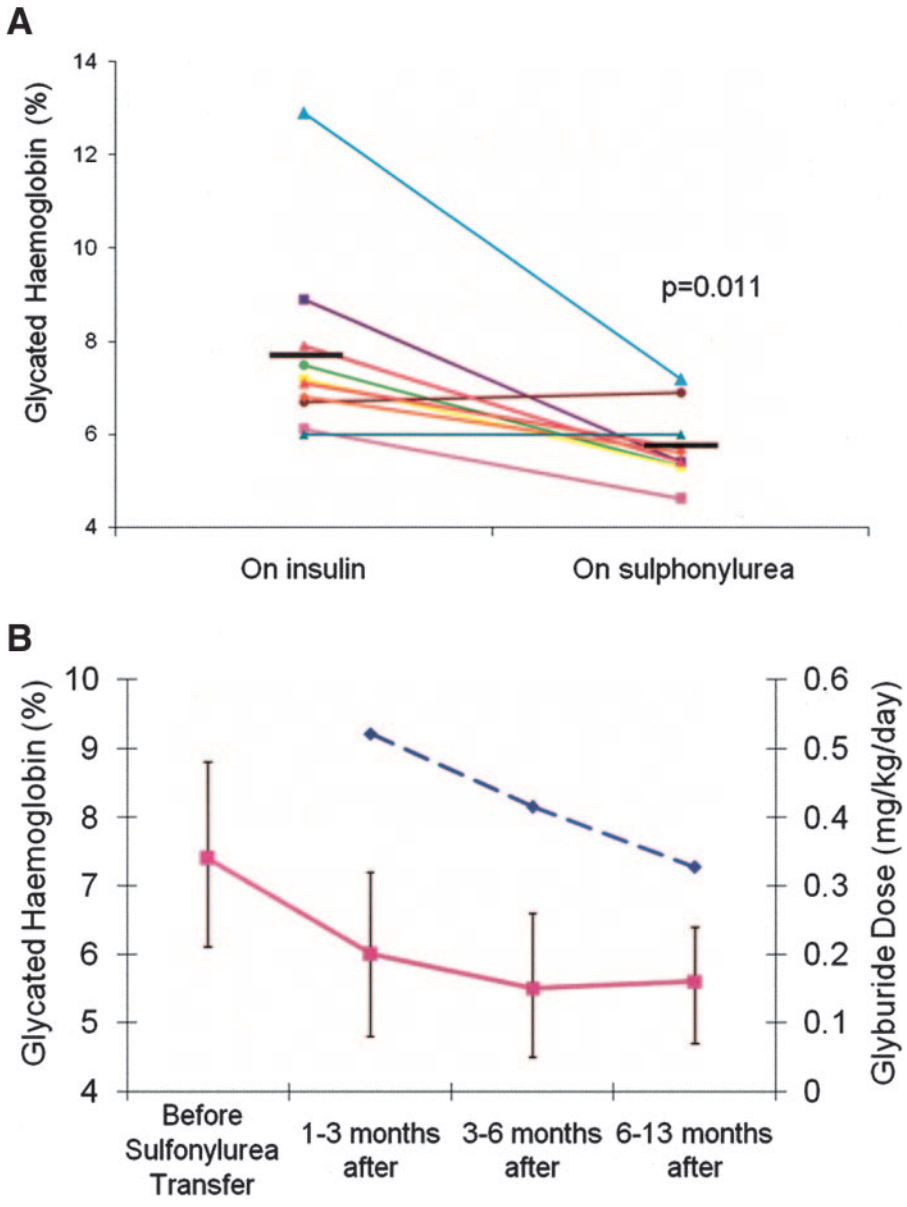

Figure 1—*Initial reduction in A1C levels following transfer from insulin to sulfonylurea.*

Side effects

Three patients reported side effects during treatment with sulfonylureas. One patient had mild transitory diarrhea on glyburide, which has been previously reported (15), but when transferred to tolbutamide, another sulfonylurea, no further side effects were experienced. Another patient had morning nausea while on glyburide, which may have been a side effect of the sulfonylurea therapy but resolved without discontinuing treatment. Transitory nausea has been previously reported in patients on glyburide (18). One severe hypoglycemic episode (grade three in the International Society of Pediatric and Adolescent Diabetes 2000 consensus guidelines) was reported in a patient, requiring a reduction in dosage of sulfonylureas. This patient also experi-

Table 2—*Comparison of clinical characteristics of patients with SUR1 and Kir6.2 mutations who successfully transferred from insulin to sulfonylureas*

Characteristic	SUR1 patients with successful sulfonylurea treatment	Kir6.2 patients with successful sulfonylurea treatment*	*P*†
n	21	44	
Neurological features	4 (19)	6 (14)	0.72
Male sex	8 (38)	24 (55)	0.16
Birth weight (g)	2,700 (1,470–3,500)	2,740 (1,871–3,570)	0.27
Birth weight (SD score)	−1.3 (−2.79 to −0.1)	−1.0 (−3.7 to 1.3)	0.46
Age at diagnosis (weeks)	5 (0–30)	6 (0–152)	0.52
Age at start of sulfonylurea treatment (years)	7.2 (0.2–46.5)	6 (0.2–36.0)	0.55
Days to transfer	3.5 (1–107)	12 (0–170)	0.12
A1C before sulfonylurea treatment (%)	7.1 (5.0–21.0)	8.1 (6.3–13.1)	0.062
Insulin dose (units · kg^{-1} · day^{-1})	0.4 (0.2–0.9)	0.7 (0.1–1.2)	0.002
Equivalent dose of glyburide (mg · kg^{-1} · day^{-1})	0.26 (0.07–2.8)	0.45 (0.05–1.5)	0.005

Data are median (range) or *n* (%) unless otherwise indicated. Data from the Kir6.2 patients are taken from ref. 14. *Data from Pearson et al. (ref. 14). †*P* values are for comparison of the patients with SUR1 mutations with patients with Kir6.2 mutations and were calculated by the Mann-Whitney *U* test or Fisher's exact test for categorical data.

enced abdominal discomfort, which started before the transfer but may have worsened during treatment with glyburide. No other severe hypoglycemic episodes were reported before or after the transfer onto sulfonylureas in any patients, and no other side effects were reported.

Comparison with patients with Kir6.2 mutations who successfully transferred to sulfonylureas

Our SUR1 patients who successfully transferred from insulin to sulfonylureas were compared with the previously published series of patients with Kir6.2 mutations published by Pearson et al. (14) (Table 2). Comparison of treatment in SUR1 patients with Kir6.2 patients showed different treatment requirements (Fig. 2). The SUR1 patients needed a lower dose of insulin before transfer (median of 0.4 units · kg^{-1} · day^{-1} ([0.2–0.9]) compared with that in Kir6.2 patients (0.7 units · kg^{-1} · day^{-1} [0.1-1.2]) ($P = 0.002$). SUR1 patients also required a lower dose of sulfonylurea after transfer, with a median of 0.26 mg · kg^{-1} · day^{-1} (0.07–0.63) compared with 0.45 mg · kg^{-1} · day^{-1} (0.05–1.50) in Kir6.2 patients ($P = 0.005$). In four SUR1 patients, the dose of sulfonylurea required was less than 0.1 mg · kg^{-1} · day^{-1}, and these patients all had A1C levels on insulin treatment <7%.

CONCLUSIONS — We found that the majority of patients (85%) with diabetes due to *ABCC8* gene mutations could be successfully treated with oral sulfonylurea treatment even if they had previously been treated with insulin. As with those with Kir6.2 mutations (14), patients who transferred from insulin showed markedly improved glycemic control, and the good control was maintained over the first year. There was no evidence that despite the improved control, there was an increase in hypoglycemia.

Lower doses of sulfonylureas were needed in the SUR1 patients compared with the Kir6.2 patients. This meant that doses were closer to those used in type 2 diabetic patients if calculated as dose corrected for body weight, while those used in patients with Kir6.2 mutations were considerably higher. It is likely that this reduced dose of sulfonylureas represented increased endogenous insulin secretion, as the patients also required less insulin before transfer. Further support that the degree of endogenous insulin secretion determines the sulfonylurea dose came from the four patients with excellent control on insulin (A1C <7%), who all required very low doses of sulfonylureas (<0.1 mg · kg^{-1} · day^{-1}). The lower sulfonylurea requirements suggest that a different protocol for transfer onto sulfonylureas is needed for SUR1 patients than for Kir6.2 patients. We suggest that in SUR1 patients, the gradual increase in glyburide dose recommended during inpatient transfer should be 0.1 mg · kg^{-1} · day^{-1}, which is one-half the increase per day used for Kir6.2 patients. Particular care should be taken when attempting transfer in patients with evidence of existing endogenous insulin secretion. These patients are likely to already have good glycemic control, with A1C levels <7%, insulin doses <0.5 units · kg^{-1} · day^{-1}, and measurable C-peptide. It is likely that these patients will need lower doses of sulfonylureas; they should be monitored closely to avoid hypoglycemic episodes, and an even slower increase in glyburide should be considered. Despite this, some

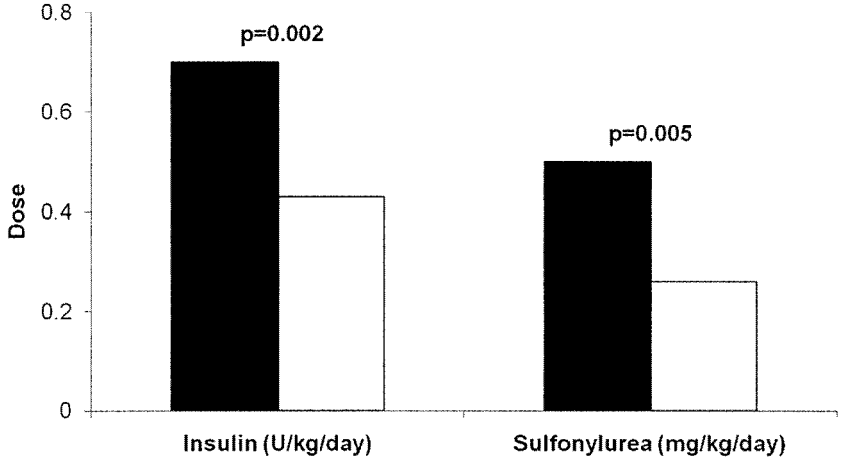

Figure 2—*Lower treatment doses are needed in patients with SUR1 mutations □ compared with those with Kir6.2 mutations ■. Median insulin and sulfonylurea doses are shown for 21 patients with SUR1 mutations and 44 with Kir6.2 mutations who successfully transferred from insulin to sulfonylurea therapy.*

patients may still need high doses of sulfonylureas, particularly if transferred outside childhood.

The prevalence of side effects was low. There was only one severe hypoglycemic episode reported in our cohort, but this is further evidence that caution and close blood glucose monitoring is needed during transfer to avoid hypoglycemic episodes. Despite this, sulfonylurea use in this group appears to be safe, with the only other side effects reported being mild transitory diarrhea, morning nausea, and abdominal discomfort. Sulfonylurea doses of over 1 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} were used in this study with no reported adverse effects. Continued close follow-up is recommended in view of the high doses used.

Four patients in our study were unable to completely stop insulin and successfully transfer onto sulfonylureas. Patients who could not transfer were diagnosed with diabetes later in life than those who did transfer. This might suggest that in addition to the characteristics of the mutation, exposure before diagnosis of the pancreatic islet to untreated hyperglycemia might alter response to sulfonylureas. Two of the patients who could not transfer also have neurological complications, including one case of developmental delay, epilepsy, and neonatal diabetes, which is the most severe form of neonatal diabetes (DEND syndrome). Previous studies have shown that patients with neurological complications and Kir6.2 mutations are less likely to successfully transfer onto sulfonylureas (14). This can be explained by in vitro studies that found that mutations associated with neurological symptoms are less responsive to sulfonylureas as well as responding less to ATP (19,20). Despite this, four patients in our study who had neurological features successfully transferred onto sulfonylureas. This indicates that presence of neurological complications in patients with diabetes due to SUR1 mutations should not act as a barrier to attempting sulfonylurea therapy.

Our study had some limitations. At present, it is only possible to comment that transfer to sulfonylureas is successful in the short term, as we do not have follow-up data outside the immediate starting of sulfonylurea treatment. It is encouraging that the few patients with data over the first year maintained excellent glycemic control despite a decreasing sulfonylurea dose over time. The transfer was performed in multiple centers throughout the world; hence, it is not possible to ensure a standard protocol, as shown by the choice of medication varying. Finally, it is not possible to be certain about the prevalence of hypoglycemia before and after transfer, as this were not formally studied using techniques such as 24-h glucose monitoring.

We conclude that most patients with *ABCC8* gene mutations can successfully transfer onto sulfonylureas. This treatment has been shown to be safe and achieve improved glycemic control in the short term. Long-term follow up is needed in a large cohort of patients to see whether trends in improved glycemic control and decreased sulfonylurea dose continue. In comparison with Kir6.2 patients, lower doses of both insulin and sulfonylurea were found in SUR1 patients, suggesting that they have greater endogenous insulin secretion. We recommend that patients with diabetes diagnosed before 6 months of age should undergo genetic testing for *ABCC8* gene mutations if they do not have a *KCNJ11* mutation encoding Kir6.2 and if positive transfer onto oral sulfonylureas be attempted but using a different protocol than that for Kir6.2 patients.

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APPENDIX

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