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Precision Medicine: Long-Term Treatment with Sulfonylureas in Patients with Neonatal Diabetes Due to *KCNJ11* Mutations

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Abstract

Purpose of Review—The goal of this review is to provide updates on the safety and efficacy of long-term sulfonylurea use in patients with *KCNJ11*-related diabetes. Publications from 2004 to the present were reviewed with an emphasis on literature since 2014.

Recent Findings—Sulfonylureas, often taken at high doses, have now been utilized effectively in *KCNJ11* patients for over 10 years. Mild-moderate hypoglycemia can occur, but in two studies with a combined 975 patient-years on sulfonylureas, no severe hypoglycemic events were reported. Improvements in neurodevelopment and motor function after transition to sulfonylureas continue to be described.

Summary—Sulfonylureas continue to be an effective, sustainable, and safe treatment for *KCNJ11*-related diabetes. Ongoing follow-up of patients in research registries will allow for deeper understanding of the facilitators and barriers to long-term sustainability. Further understanding of the effect of sulfonylurea on long-term neurodevelopmental outcomes, and the potential for adjunctive therapies, is needed.

Keywords

KCNJ11; Sulfonylurea; Glyburide; Neonatal diabetes; Monogenic diabetes; DEND syndrome

Introduction

Using sulfonylureas (SU) to treat *KCNJ11*-related diabetes is arguably the best example of personalized genetic medicine in diabetes. Mutations in *KCNJ11* are the most common cause of permanent neonatal diabetes and were initially found to be responsive to SU about 15 years ago. Since that time, numerous *KCNJ11* patients have successfully transitioned from insulin to these oral medications, often with improvements in glycemia, decrease in healthcare costs, and increases in quality of life. SU have been used for the treatment of type

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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2 diabetes worldwide for many years, although the rates of secondary failure and side effects such as hypoglycemia and cardiovascular risk have been notable concerns [1–3]. Questions have remained regarding the long-term efficacy and safety of these medications in patients with *KCNJ11* mutations, particlarly in those taking high doses and off-label use for children. This review will focus on literature surrounding SU use in patients with *KCNJ11* mutations, particularly those related to efficacy, sustainability, and safety with a focus on publications from the last 5 years.

Overview of KCNJ11 Neonatal Diabetes

Mechanism of Mutations

KCNJ11 encodes the protein Kir6.2, which forms the inner membrane, or pore, of the ATP-dependent potassium channel (KATP channel). The other subunit is an outer regulatory complex formed by SUR1 proteins, encoded by the *ABCC8* gene. Mutations in *ABCC8* can be clinically similar to mutations in *KCNJ11,* but they will not be focused on in this review. KATP channels are critically important for insulin release in beta cells. Heterozygous activating mutations in *KCNJ11* cause the channel to stay in the open, active position by reducing the sensitivity of the channel to inhibition [4, 5]. This dysfunction ultimately prevents cell membrane depolarization and calcium influx, thus inhibiting the release of insulin from the beta cell. Severity of the clinical phenotype and level of channel dysfunction are directly related [4, 6]. Some *KCNJ11* mutations cause a transient diabetes phenotype, due to a less severe reduction in sensitivity to inhibition [7].

Initial Identification and Diabetes Presentation

KCNJ11 mutations were first identified as a cause of permanent neonatal diabetes (PNDM) in 2004 and transient neonatal diabetes (TNDM) in 2005; they remain the most common cause of PNDM 15 years after their initial discovery [7, 8]. Clinically, patients are most often diagnosed with diabetes in the first 6 months of life, with occasional cases diagnosed beyond 6 months [9–11]. Diabetes onset characteristics can be variable but are frequently severe and may include long-lasting complications [12]. A study of 41 patients with *KCNJ11* or *ABCC8* mutations (median age at diabetes diagnosis 9.6 weeks) indicated 79% were in diabetic ketoacidosis (DKA) at diagnosis with median initial blood glucose levels of 717 mg/dL [13•].

Neurodevelopmental and Behavioral Difficulties

Because KATP channels are widely expressed within the brain, patients with *KCNJ11* mutations may also have a range of neurodevelopmental and behavioral difficulties. The severity of difficulties is directly related to the functional severity of the mutations [6, 14]. Central nervous system features of any severity appear to be relatively common, with one study describing such problems in 64% of permanent diabetes cases with *KCNJ11* mutations (n = 52/81) [15••]. Studies of cells expressing mutations suggest that the most damaging mutations are more likely to cause the most severe phenotype, termed DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome, with patients often being unable to ambulate or speak [8, 16–18, 19•, 20]. Other mutations such as V59M are associated with a slightly less severe phenotype sometimes called “intermediate DEND”

characterized by global developmental delay and severe cognitive dysfunction but often without seizures [16, 18, 19•, 20]. Compared with siblings without *KCNJ11*-related diabetes, even children with "mild" mutations (such as R201H) may still display significant differences on measures including IQ, academic achievement, and executive function [19•, 20]. Children with *KCNJ11* were reported to have difficulties with inattention and attention-deficit/hyperactivity disorder (ADHD), anxiety, autism spectrum disorder, behavior challenges, and sleep issues, which were often significantly different than sibling controls [21•, 22]. Examination of adults with *KCNJ11* mutations revealed similar features, such as autism spectrum disorder, as well as difficulties in coordination, motor sequencing, inattention, and lower IQ [23•].

Sulfonylurea Responsiveness and Efficacy

SU responsiveness in patients with *KCNJ11* mutations was first demonstrated in 2004, in the first report of *KCNJ11* mutations as a cause of PNDM [8]. These drugs increase the sensitivity of the KATP channels to inhibition, allowing them to close, and thus permitting insulin secretion. Both inpatient and outpatient transitions have been successful [24, 25]. Published protocols and expert centers are available to help guide healthcare providers in most appropriate use of SU medications and the process of reducing insulin doses [24] (monogenicdiabetes.org, diabetesgenes.org).

Transition from Insulin to Sulfonylurea

Large cohort studies have found that up to 90% of patients will be able to fully transition onto SU and discontinue insulin [24, 26•, 27]. These patients often require higher SU doses than are typically used in type 2 diabetes. Significant initial reductions in glycated hemoglobin (HbA1c) after transition to SU ranging from 1.3 to 2.5% have been reported in several cohorts [15••, 24, 28–32].

Barriers to Transition

While most patients will be able to fully transition off of insulin therapy, some will not. Some cases may be entirely unable to transition due to severely activating mutations that have minimal to no responsiveness to SU, such as two *KCNJ11* patients (G334D and C166Y) that were completely unresponsive to SU trial [27]. In the case of the patient with G334D mutation, C-peptide levels before and after treatment with SU therapy as high as 1.8 mg/kg/day were barely detectable [33]. Others may respond to SU but have difficulty achieving sufficient glycemic control on SU monotherapy. Target glycemia may be achievable with additional glucose-lowering medications.

In vitro functional studies that include tests of SU responsiveness by mutated channels have generally correlated well to clinical responsiveness to SU therapy [4, 5, 8]. However, among patients with the same mutation, differences in responsivity to SU exist. Age at transition to SU has emerged as a potential barrier to complete transition to SU monotherapy without the need for insulin or other medications (Fig. 1). Of 58 patients studied in our US cohort, 10 (17%) required additional glucose-lowering medications beyond SU, and they had all been transitioned at age 13 years old or later (metformin: $n = 5$, sitagliptin: $n = 6$, exenatide: $n = 1$,

insulin: $n = 2$). Age of SU initiation was also significantly correlated with dose required at long-term follow-up [27]. Similarly, in a separate study of 127 patients with *KCNJ11* mutations, 15 (12%) were unable to fully discontinue insulin, although several were able to decrease their insulin dose. There was a significant difference in age at the time of SU initiation for those who required additional medications [26•]. In a single case report of a mother and child who carried the R201C mutation, the child was able to successfully transition at age 8.5 years while the mother was unable to fully transition and remained on short-acting insulin with high-dose SU [34]. An 18-year-old patient with H46Y mutation was able to discontinue insulin and continue on SU after adding sitagliptin [35]. Some older patients may exhibit at least partial SU response only after being treated over several months [36], which may relate to a delayed effect of SU on cellular channel function, but may also be due to adverse effects of hyperglycemia on beta-cell function (such as altering gene expression, increasing glycogen accumulation, and increasing beta-cell apoptosis), as suggested in mouse models ofKCNJ11 diabetes [37, 38]. These adverse effects were modifiable with glucose-lowering medications, and improvements occurred faster with SU therapy than with insulin therapy [37, 38].

Impact of Sulfonylurea Treatment on Neurodevelopmental Outcomes

Neurodevelopment

Several case studies highlighting improvements for individual patients in either parent/caregiver-reported measures or standardized assessments have been reported (Fig. 1). Improvements in motor function [11, 39–41], cognition [11, 41, 42], communication [41], attention [10, 41], and behavior [10] have been attributed to SU transitions. A study by Beltrand and colleagues included several pre- and post-SU transfer measures for 16 children with *KCNJ11* mutations. Significant improvements were noted in hyperactivity and motor skills, whereas sociability, language, and intelligence scores did not improve [31]. In a recent study of 81 *KCNJ11* participants on long-term SU therapy, 47% of those with central nervous system (CNS) features reported improvements after transfer to SU in areas such as muscle tone and strength, concentration and attention, motor function, and speech [15••].

Early SU treatment appears to impact neurodevelopmental outcomes more strongly, perhaps due to treatment timing during critical windows of brain development. A cohort of 19 children with varying *KCNJ11* mutations found that age of SU initiation was inversely correlated with visual-motor integration (VMI) scores for participants carrying the V59M or V59A mutation [43].

Imaging

Changes in neuroimaging before and after transition to SU were assessed for five participants with varying *KCNJ11* mutations using single-photon emission computed tomography (SPECT). Significant improvements in cerebellar perfusion were noted after SU transfer in both hemispheres [44], and concurrent improvements in motor skills, attention, coordination, hyperactivity-impulsivity, and cognition (IQ) were noted in a previous description of one participant [45].

Limitations

While significant improvements have been noted through both parent/caregiver report and by standardized assessments, most patients with notable neurological dysfunction will continue to exhibit significant struggles after switching to SU therapy. Noticeable improvement in symptoms such as attention, motor coordination, and behavior are often seen, but complete reversal of physical challenges or full resolution of neurodevelopment difficulties is not common. Out of 18 participants who reported improvements in CNS features after SU treatment, 94% reported incomplete improvements with challenges remaining [15••]. Earlier treatment with SU leads to better neurodevelopmental outcomes, and so identifying patients with *KCNJ11* mutations very early on, such as through standardized newborn screening programs or prenatal screening, would allow for earlier treatment and increased potential for improvements before brain development is complete. Limitations of SU treatment exist. A recent animal study sought to quantify the concentration of SU in plasma, cerebrospinal fluid, and brain tissue of treated and control rats and mice. While the plasma concentration of SU was high in the treated animals, SU was not detectable in either the cerebrospinal fluid (CSF) or brain tissue, suggesting that SU may be rapidly removed from CSF [46]. This highlights the need for additional medications that may more directly impact brain tissue and could have additional positive impacts on neurodevelopment.

Clinical Use of Sulfonylurea for KCNJ11 Diabetes

Sulfonylurea Dosing and Other Medications

As a result of the above factors, there is a wide range of SU dose requirements for *KCNJ11* patients and it may take weeks before the effectiveness of any dose (especially the initial dose) is fully apparent. We thus recommend careful blood sugar monitoring during any periods of SU dose initiation or escalation, as well as monitoring of adherence, while utilizing published protocols for transition to SU [24] (monogenicdiabetes.org, diabetesgenes.org). Some patients have found continuous glucose monitoring to be helpful, although this may also reveal relative hypoglycemia that does not appear to be dependent on SU dose [47•]. The goals for SU dosing in these patients are distinct from more common forms of diabetes, in that they require a much higher dose for effective insulin secretion, but they subsequently may have some lower blood sugar numbers similar to individuals without diabetes [48, 49]. A dose of at least 1.0 mg/kg/day is typically required for most patients, but doses up to 2 mg/kg/day or more may be needed in some cases. Patients who are older at the time of transition may have had more time for beta-cell destruction or dedifferentiation, and thus less ability to respond to SU. For patients that are unable to fully transition onto SU after a trial with sufficiently high SU dose, the addition of other glucose-lowering medications may assist with lowering HbA1c, reducing insulin requirements, decreasing risk for hypoglycemia, and even improving hypoglycemic awareness [50]. It is imperative to continue SU at a maximal dose even after other medications are utilized to help achieve glycemic targets, as the endogenous insulin secretion is only possible through high-dose SU and the resulting benefits include reducing the dose of any exogenous insulin that may still be required, as well as possible beneficial effects on brain function (such as those discussed above) [34, 51, 52].

Consideration of Sulfonylurea Trial Before Genetic Testing Results Are Available

Some countries experience significant difficulty and/or delay in obtaining genetic testing. It may therefore be appropriate to consider trialing SU before genetic testing results are available in patients diagnosed with diabetes under 6 months of age who have no other ongoing medical difficulties, have no evidence for consanguinity, and have imaging evidence of normal pancreatic tissue [53, 54•]. However, it is imperative that comprehensive genetic testing be performed in all cases to confirm the underlying defect, whether SU was effective or not. If financial limitations to genetic testing exist, connecting with centers who may have resources to support testing is recommended (monogenicdiabetes.org, diabetesgenes.org, and additional local research groups in many different countries).

Choice of Sulfonylurea

Several different SU drugs are available for clinical use; however, glyburide—also called glibenclamide in some countries—has been the primary SU used in this patient population. Differences in efficacy based on SU drug choice have been described in a few instances that support the specific use of glyburide both for diabetes and potential neurological benefit. A patient with G53D mutation experienced no change in C-peptide levels (undetectable) with the addition of gliclazide, while restoration of C-peptide occurred with glyburide treatment. Motor function improved with the addition of gliclazide, with a slightly additional improvement seen after switching from gliclazide to glyburide [40]. Because glyburide is the most commonly used medication in patients with *KCNJ11* mutations, it remains unclear how important differences between medications may be for glycemic and developmental improvements.

Safety

SU use in patients with *KCNJ11* mutations is generally safe and imparts less risk than insulin use.

Hypoglycemia

Some cases require high-dose SU therapy, and therefore, questions about the potential for hypoglycemia are frequently raised by both families and clinicians. Mild and moderate hypoglycemia can occur in these patients, but severe hypoglycemia has not been reported. In one study of 166 patient-years on SU across 30 participants, 89% reported hypoglycemia (< 70 mg/dl) once per month or less frequently [47•]. However, three participants reported hypoglycemia once weekly or more frequently. Mild-moderate hypoglycemia does not appear to be dose-dependent; SU dose of the three participants reporting frequent hypoglycemia ranged from 0.386 to 2.354 mg/kg/day. No hypoglycemic episodes met criteria for severe hypoglycemia (involving seizures or unconsciousness) [47•]. In a 10-year multicenter follow-up study, data from 81 patients were examined. Across 809 patients-years, there were no reports of severe hypoglycemia [15••]. While any concern for hypoglycemia should be closely monitored, decreasing SU dose does not appear to eliminate mild-moderate hypoglycemia. Anecdotal reports of decreasing SU dose to avoid any blood sugar levels below 70 mg/dL have in some cases resulted in significant worsening of

glycemic control, whereas with a sufficient dose, most patients will achieve HbA1c levels well within goal.

Other Side Effects

In general, other reported side effects from SU therapy are mild. The most commonly reported side effects include gastrointestinal issues including diarrhea [15••, 27, 30], initial hepatic steatosis [15••], and tooth discoloration (particularly in those who chewed glyburide tablets or used a concentrated solution instead of swallowing the tablets whole) [15••, 27, 55]. No cardiac side effects have been reported, and it is important to recognize that this unique patient population carrying mutations whose defect is directly addressed by high-dose SU treatment is completely distinct from those with type 2 diabetes who have extremely high baseline cardiovascular risk likely related to insulin resistance and other factors, regardless of which diabetes medications they are treated with. Indeed, most studies suggesting increased cardiovascular risk in type 2 diabetes treated with SU have been in comparison with met-formin and may reflect the benefit of year-long reduction of insulin exposure that would not be applicable to the KCNJ11 diabetes patient population [56].

Long-Term Sustainability

Since the initial discovery of *KCNJ11* mutations causing diabetes in 2004, there have now been several longer term outcome studies of a relatively large number of patients who have been treated with SU for many years (Table 1). Eleven patients in a 2010 report who had transitioned to SU a median of 34 months prior were noted to have an initial reduction in HbA1c of 1.68%, as well as an overall decrease in SU dose of 0.24 mg/kg/day from initial transfer to follow-up. A case report of 30-month follow-up on a patient with G53D mutation similarly noted HbA1c reduction and SU dose reduction over the follow-up period [57]. Iafusco and colleagues reported on 11 patients in 2011 that had been followed for a median of 68 months after SU transfer [30]. Mean HbA1c decreased from 8.4% prior to transition, to 5.9% after 3 months of glyburide, to 6.0% after a median of 68 months after transition, suggesting excellent sustainability of SU. The longest follow-up study reported outcomes for 81 participants over a median duration of 10.2 years of SU treatment [15••]. At follow-up, 93% of the cohort remained on SU alone with a median HbA1c of 6.4%. The six patients who still required daily insulin in addition to SU also reported a higher HbA1c at follow-up (8.5%). These patients had similar ages at SU initiation and similar current ages. Oral and intravenous glucose tolerance tests on a small subset of participants ($n = 6$) suggested preservation of insulin response to oral glucose that may depend at least in part on the incretin effect.

Diabetes-Related Complications

Diabetes-related complications in patients with *KCNJ11* mutations have been reported only rarely. Examinations for retinopathy were conducted in 11 participants in a Polish cohort prior to SU transfer [58]. Two participants had retinopathy at baseline. One was non-proliferative, did not progress during the 3-year follow-up period, and did not require laser therapy. The other participant, who was known to have proliferative retinopathy at baseline, also exhibited microalbuminuria, peripheral polyneuropathy, and cardiovascular autonomic

neuropathy and hypertension. Of the cohort, she had been exposed to the highest HbAlc values (some > 13%) for many years while on insulin and had preexisting hypertension. Transfer to SU resulted in rapid improvement of glycemic control, and when the retinopathy also rapidly progressed, she required several rounds of laser therapy. She did achieve stabilization [59], and the rapid progression was not shown to be associated with her SU therapy. One patient out of 58 (7%) in a US cohort was found to have retinopathy, which was thought to be influenced by his later age of transition to SU and years of suboptimal HbAlc [27]. In a recent long-term follow-up study by Bowman and colleagues, after a median of 10 years on SU therapy, 9% of patients (n = 7/81) had microvascular complications, including retinopathy, microalbuminuria, proteinuria, and neuropathy [15••]. These patients were significantly older at the time of SU transfer, and likely had been exposed to non-optimal blood sugars for longer periods of time than those without complications. No macrovascular complications were reported.

Conclusions

Several studies demonstrate that high-dose SU treatment is a sustainable and safe treatment for patients with *KCNJ11-relat*ed diabetes. SU treatment specifically corrects the molecular defect in these patients, and the majority will exhibit significant restoration of endogenous insulin production that results in vastly improved and excellent glycemic control for most patients. Initiating SU therapy as early as possible is critical for optimizing both glycemic and neurodevelopmental outcomes. Additional studies are needed to better understand the potential for additional therapies to improve neurodevelopmental outcomes. Systematic efforts are needed to more consistently identify patients with neonatal diabetes as early as possible. Possible approaches such as broad newborn screening programs, easier access to affordable genetic testing, as well as better implementation of genomic information into clinical practice will be crucial for optimizing patient outcomes.

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Abbreviations

KATP channel	ATP-dependent potassium channel
SU	Sulfonylurea
PNDM	Permanent neonatal diabetes
TNDM	Transient neonatal diabetes
DKA	Diabetic ketoacidosis

DEND	Developmental delay, epilepsy, and neonatal diabetes
CNS	Central nervous system
SPECT	Single-photon emission computed tomography
CSF	Cerebrospinal fluid

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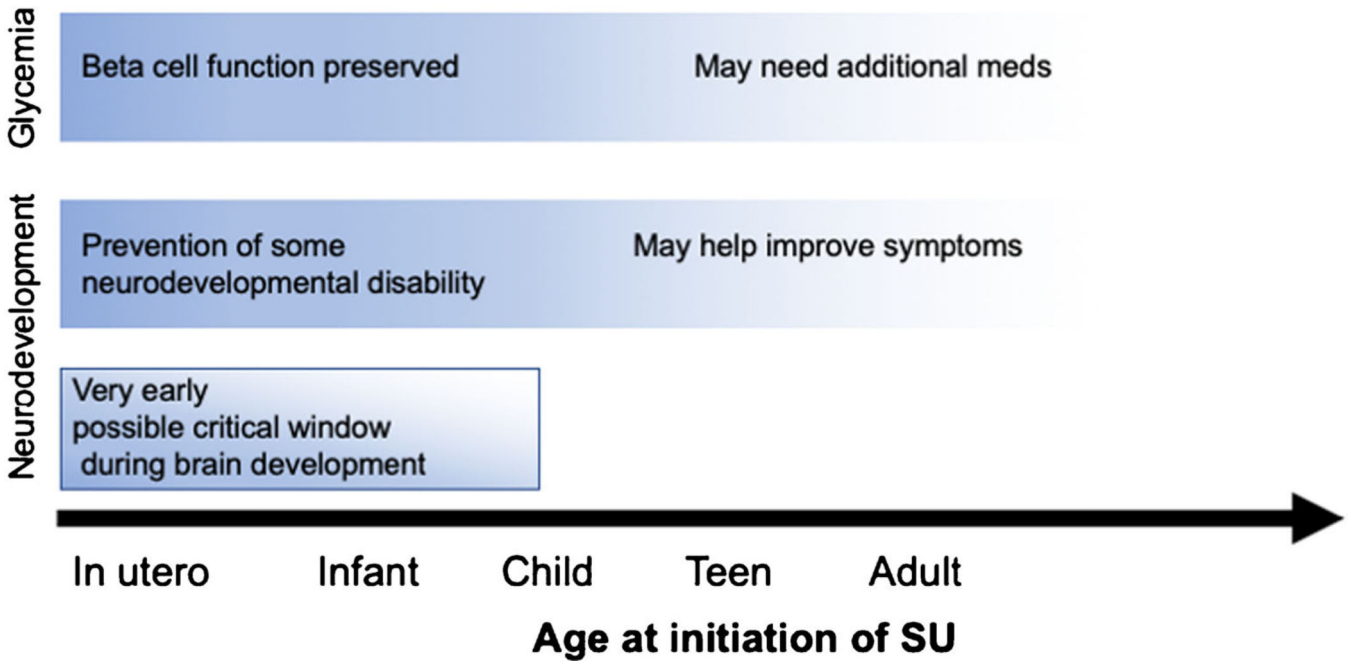

Fig. 1.
Age at initiation of sulfonylurea therapy impacts both glycemia and neurodevelopment

Table 1

Longitudinal studies on sulfonylurea use in *KCNJ11* patients

Author	Year published	Number of KCNJ11 cases	Years of SU f/up	SU monotherapy at f/up	Glycemic impact for SU monotherapy	SU dose change	Needed addt meds	Unable to transition, non-responsive to SU	Hypoglycemia	Other side effects	Complications
Bowman	2018	81	Median f/up duration: 10.2 years	93% (75/81)	Pre-transfer: median A1c 8.1% 1 year after: 5.9% Most recent f/up: 6.4%	SU dose fell over	7% (6/81) req. daily insulin	NR	No severe hypoglycemia reported in 809 pt-years of f/up	Reported in 14% (11/81)—diarrhea, nausea, abdominal pain, reduced appetite, hepatic steatosis, tooth discoloration	9% (7/81)—retinopathy, microalbuminuria, proteinuria, neuropathy
Iatusco	2011	11	Median f/up duration: 68 months	100% (11/11)	Pre-transfer: mean Alc 8.4% 3 months after: 5.9% Most recent f/up: 6%	SU dose fell over time	NR	NR	NR	Diarrhea	NR
Li	2018	5 PNDM KCNJ11 with SU trial	Mean f/up duration 3.6 years	5/5 (100%)	“More stable glucose”	SU dose over time	2 additional KCNJ11 participants chose not to trial SU so remained on insulin	0%	NR	Transient diarrhea, poor feeding	NR
Laiming	2016	30	Age at SU initiation: median 1.2 years. Age at assessment: median 8 years	97% (29/30)	NR	NR	3% (1/30)—sitagliptin, metformin, insulin	NR	Mild to moderate hypoglycemia reported once per month or less frequently in 89.3% No severe hypoglycemia in 166 pt-years of f/up	NR	NR

Defined as reports with follow-up sulfonylurea data on at least five cases followed for a median or mean of least 3 years

SU sulfonylurea, *NR* not reported, *PNDM* permanent neonatal diabetes mellitus