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ORIGINAL ARTICLE

Neonatal diabetes due to potassium channel mutation: Response to sulfonylurea according to the genotype

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Abstract

Objective: A precision medicine approach is used to improve treatment of patients with monogenic diabetes. Herein, we searched SU efficiency according to the genotype-phenotype correlation, dosage used, and side effects.

Research Design and Methods: Systematic review conducted according the PRISMA control criteria identifying relevant studies evaluating the in vivo and in vitro sensitivity of ATP-dependent potassium channels according to the characteristics of genetic mutation.

Results: Hundred and three selected articles with complete data in 502 cases in whom 413 (82.3%) had mutations in *KCNJ11* (#64) and 89 in *ABCC8* (# 56). Successful transfer from insulin to SU was achieved in 91% and 86.5% patients, respectively, at a mean age of 36.5 months (0-63 years). Among patients with *KCNJ11* and *ABCC8* mutations 64 and 46 were associated with constant success, 5 and 5 to constant failure, and 10 and 4 to variable degrees of reported success rate, respectively. The glibenclamide dosage required for each genotype ranged from 0.017 to 2.8 mg/kg/day. Comparing both the in vivo and in vitro susceptibility results, some mutations appear more sensitive than others to sulfonylurea treatment. Side effects were reported in 17/103 of the included articles: mild gastrointestinal symptoms and hypoglycaemia were the most common. One premature patient had an ulcerative necrotizing enterocolitis which association with SU is difficult to ascertain.

Conclusions: Sulfonylureas are an effective treatment for monogenic diabetes due to *KCNJ11* and *ABCC8* genes mutations. The success of the treatment is conditioned by differences in pharmacogenetics, younger age, pharmacokinetics, compliance, and maximal dose used.

KEYWORDS

monogenic diabetes, precision medicine, genotype-phenotype correlation

1 | INTRODUCTION

Precision diabetes refers to the concept of the incorporation of a wide array of individual data, including clinical, lifestyle, genetic, and further biomarkers beyond signs and symptoms, which might add substantial information to improve treatment of patients with monogenic diabetes. Monogenic diabetes includes maturity-onset diabetes of the young (MODY), early-infancy onset and neonatal diabetes mellitus (NDM), and many rare forms of atypical diabetes. Neonatal diabetes is a monogenic disease defined by the onset of persistent hyperglycemia in the first 6 months of life with an incidence of 1/150 000 to 1/90 000. Before genetic diagnosis, neonatal diabetes was classified solely on the clinical

Laure Garcin and Veronica Mericq have contributed equally to this study.

course of disease as transient neonatal diabetes (TNDM), permanent neonatal diabetes (PNDM), or by the specific syndrome when associated. Up to date we know of 19 different genetic causes of neonatal diabetes.[1] Genetic diagnosis in monogenic diabetes disorders impacts therapy choices, gives explanation of associated clinical features, anticipates clinical features, and drives therapeutics.

The TNDM represents about 50% of neonatal diabetes and is characterized by frequent diagnosis in the first few weeks of life, remission in childhood, and very frequent relapse later in life.[2] Most TNDM are due to abnormalities of chromosome 6, that is, paternal uniparental isodisomy of chromosome 6, 6q24 duplication on the paternal allele and loss of methylation at 6q24 on the maternal allele. The most common causes of PNDM is the presence of mutations in the *KCNJ11* (75%) and *ABCC8* genes (15%) which encode for the proteins constituting the KIR 6.2 and SUR1 subunits, of the ATP-dependent potassium channel of the β-cells of the pancreas. Increases in intracellular ATP concentration close the potassium channel causing the accumulation of intracellular potassium, membrane depolarization, an open maintenance of the voltage regulated calcium channel and thus the exocytosis of insulin.[3] Gain of function mutations in *KCNJ11* and *ABCC8* genes cause more K(ATP) channels to remain open, thereby decreasing insulin secretion. Mutations in *KCNJ11* can modify the ATP fixation site on the KIR 6.2 subunits or the protein parts forming the channel itself. *ABCC8* mutations can change the activity of SUR1 subunits: that is, they can help reduce the fixation of ATP to KIR 6.2.[3]

Approximately 25% of patients with neonatal diabetes have developmental delay, epilepsy, and neonatal diabetes termed DEND syndrome, or intermediate DEND [I-DEND], in case they have all features except for epilepsy, likely related to the expression of mutated channels in the brain.[4] Moreover, up to 85% of patients have neuropsychological features when tested properly with accurate tests.[2,5] There is a strong genotype-phenotype relationship with the mutation being an important determinant of associated neurological features. Disease severity is correlated with the extent of reduction in ATP sensitivity; Kir6.2 mutations associated with DEND syndrome are less sensitive to ATP than those causing isolated diabetes.[6-8]

Sulfonylureas (SU) are oral antidiabetics used in the treatment of type 2 diabetes.[9] They allow the maintenance of a glycemic balance by stimulating insulin-secretion. Of note, in patients with HNF1A-MODY or HNF4A-MODY, some patients are hypersensitive to sulfonylurea and we usually start with a low dose. Both are monogenic diabetes. However, the exact mechanism is not well clarified yet.[10] In case of KATP-channel diabetes, sulfonylureas are used with higher dose than for type 2 diabetes, including for adults. The mechanism of action is through attachment to the high-affinity fixation site of the sulfonylurea of the subunit SUR1, suppressing the activator effect of ADP and the inhibitory effect of ATP on KIR 6.2, and inducing potassium channel closure.[11]

Their use in the treatment of monogenic diabetes is a therapeutic pathway that has seemed rational with recent marketing authorization (MA), given by the EMA to AMGLIDIA, a suspension of glibenclamide (glyburide) designed for children, once the genetic cause has been highlighted.[12] Treatment with sulfonylurea stimulates insulin secretion in patients with a potassium channel whose genetic mutation inhibits spontaneous closure.[3] In 2006, our group together with some other teams reported that in those patients the switch from insulin to SU restored insulin secretion and dramatically improved glycemic control.[13]

Hence the aims of this study were 2fold: (a) report SU efficiency according to the genotype based on the data from the literature and (b) analyze the dosage used for a successful switch, reported side effects and neurological effects.

2 | SUBJECTS AND METHODS

This study was a systematic review conducted according to the PRISMA control criteria. To identify relevant studies, a comprehensive electronic search of PubMed and Cochrane databases was performed from their inception to December 2018. The bibliographies of all included studies were checked carefully for identifying additional studies. The research was carried out in two stages. The first step was to select the articles describing one or more patients who had been treated with sulfonylurea at a time of the evolution of their neonatal diabetes and in whom a mutation of the genes *ABCC8* or *KCNJ11* was diagnosed. In addition, in these patients we analyzed the dosage used for a successful switch, reported side effects and neurological effects. The keywords used, identified the different combinations of "sulfonylurea", "neonatal diabetes", "monogenic diabetes", "*ABCC8*", and "*KCNJ11*". The second part selected the articles reporting the in vitro sensitivity of mutated potassium channels to the sulfonylurea from the following keywords: "sulfonylurea sensitivity", "in vitro", "*KCNJ11*", "Diabetes", and "tolbutamide".

All observational studies (cohort, case reports) published in English, German, or French were eligible for inclusion if they provided the required information. Exclusion criteria were duplicated cases, absence of genotype or information on treatment course. On the basis of pre-specified inclusion criteria, one reviewer (L.G.) scrutinized titles and abstracts to exclude apparently ineligible studies, and then read the full text carefully to further exclude ineligible studies. Any discrepancies were resolved by collegial discussion.

2.1 | Data extraction

One reviewer (L.G.) extracted data through a standardized data collection form, and then another reviewer (J.B./M.P.) checked the data for accuracy. All data had been verified four times. Any inconsistent results were handled by discussion. We next extracted for each selected item, the published data concerning: general data (year of publication, first author), the characteristics of patients (number, age and symptoms of diagnosis, and neurological status), the characteristics of the treatment (possible duration and dose of insulin before switch, age at switch, time to stop insulin from the onset of treatment with sulfonylurea, dose of SU used), the success rates and presumed causes of switch failure, the type of genetic mutations, HbA1c before and after switch, presence of adverse reactions.

The main judgment criterion was the evaluation of the in vivo and in vitro sensitivity of ATP-dependent potassium channels according to the type of genetic mutation. The secondary judgment criterion was the tolerance of the treatment.

The success of the switch was defined, when mentioned, as achieving a minimum 5-year Glycemic balance without insulin treatment. In other cases, success of the switch has been assessed when good glycemic control was described with a satisfactory level of HbA1c. Adjuvant therapy with other oral antidiabetic drugs was not a failure criterion.

The in vitro susceptibility to sulfonylurea of mutated potassium channels was defined by a percentage of the current block of ATP-dependent potassium channels >75% in Xenopus oocytes ([6,14]), the intermediate sensitivity was defined between a 65% and 74% block. Other methods for quantifying the sensitivity of potassium channels to sulfonylurea consisted of identification of the required ATP concentration in the presence of a given amount of tolbutamide for 50% inhibition of the potassium channel,[15] or quantification of the inhibition of rubidium efflux, reflecting potassium channel activity, in the presence of sulfonylurea.

3 | ANALYSIS

The success rate of in vivo SU treatment of patients with neonatal diabetes due to a known mutation of potassium channels was calculated globally for all patients as well as for each genetic mutation identified.

4 | RESULTS

Initial research on databases highlighted 2759 articles for the "in vivo" aim and 1460 for the "in vitro" second aim. After applications of the exclusion criteria, 103 articles were retained with complete reports describing 502 cases (Figure 1).

The switch from insulin to SU was reported to be successful in 453 patients (90%) of patients. Median age at diagnosis was 42 days, with a range from birth to 20 years of age. Median age at SU introduction was 36.5 months (range = 0-63 years). Although, SU was mostly introduced in infants and children, it was introduced in adulthood in 32 patients. The later patients presented either with a PNDM treated by insulin for years or a TNDM that relapsed in adulthood. Time to stop insulin was most of the time very short (mean switch duration was 13 days) although it could last longer than 1 year. HbA1c changed from 8.37% (range = 6.7-15.3) to 6.2% (range = 3-10.8) after SU treatment (Table 1).

4.1 | Mutation characterization according to success to SU treatment

Mutations in *KCNJ11* were reported in 413 patients and in *ABCC8* in 89 patients. Among the cases with *KCNJ11* mutations 376 (91.0%) were successfully transferred to SU. There were 64 reported mutations among whom 48 were associated with constant success whereas five mutations (C166Y, G334D, G334V, I296L, and L164P) associated with constant failure. Furthermore, 11 *KCNJ11* mutations were associated with variables degrees of reported success rate (Table 2).

Among the patients with *ABCC8* 77 (86.5%) were successfully transferred to SU. There were 56 reported mutations; 46 mutations were associated with constant success whereas five mutations (F132V, I395F, N72S, R1182W, and R825W) associated with constant failure. In addition, four other mutations were associated with partial success (Table 2). Ten *ABCC8* mutations were compound heterozygous mutations. It is of interest to note that, as shown by Ellard et al.,[16] the compound heterozygous SUR1 mutations were sensitive to SU as demonstrated on Table 2.

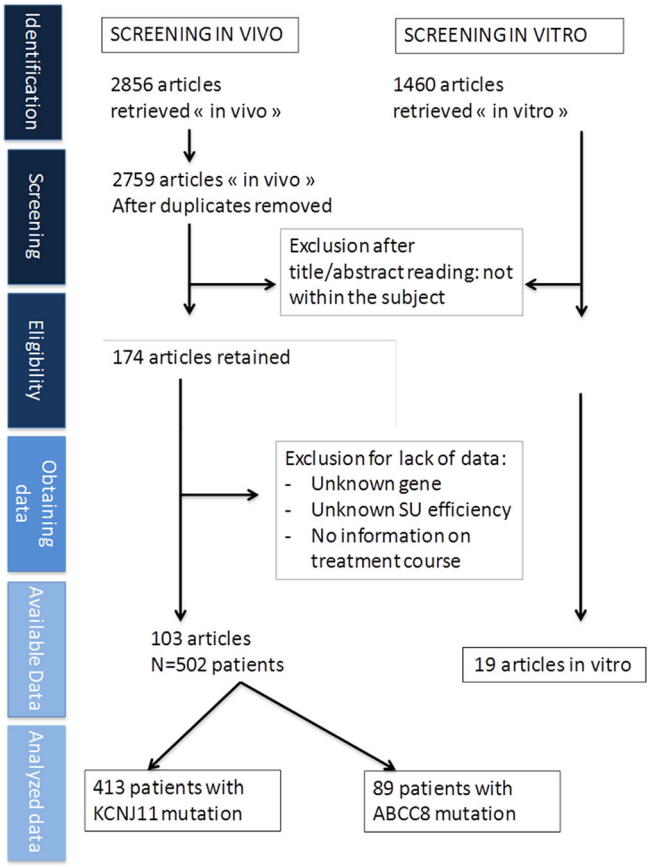

FIGURE 1 Flowchart of meta-analysis

TABLE 1 Diagnosis and SU switch information

	Median	Maximal
Age at diagnosis (days)	42	7300
Insulin dose before switch (UI/kg/d)	0.7	2.1
Age of SU switch (months)	36.5	756
Delay to stop inuslin (days)	13	397
	Before switch	After switch
HbA1c (%)	8.375	6.2

TABLE 2 In vivo success rate of SU switch in glycemic control of monogenic diabetes due to *KCNJ11* or *ABCC8* mutations. Success number = number of patients who achieved success in the report , patient number = number of patients reported, red: mutations for whom SU are never efficient

KCNJ11	Success Number	Patients Number	Efficiency	ABCC8	Success Number	Patients Number	Efficiency
S3C	2	2	100.00%	N23H/R826W	1	1	100.00%
F35V	1	1	100.00%	P45L/G1401R	2	2	100.00%
K39R	1	1	100.00%	I49F	3	3	100.00%
C42R	2	2	100.00%	N72S	0	2	0.00%
H46L	4	5	80.00%	V86A	5	5	100.00%
H46Y	6	6	100.00%	V86G	1	1	100.00%
N48D	1	1	100.00%	R118W	1	1	100.00%
E51A	1	1	100.00%	F132L	1	3	33.33%
R50P	6	6	100.00%	F132V	0	2	0.00%
R50Q	9	9	100.00%	R186C/G1256S	1	1	100.00%
Q51G	1	1	100.00%	D209E	5	5	100.00%
Q52L	1	1	100.00%	D209N	1	1	100.00%
Q52R	2	5	40.00%	Q211K	2	2	100.00%
G53D	13	13	100.00%	D212I	3	3	100.00%
G53N	1	1	100.00%	D212Y	1	1	100.00%
G53R	3	5	60.00%	L213P	2	2	100.00%
G53S	2	3	66.67%	L213R	1	1	100.00%
V59A	1	3	33.33%	L225P	2	2	100.00%
V59M	51	54	94.44%	T229I/T229I	1	1	100.00%
F60Y	1	1	100.00%	T229N	1	1	100.00%
W68G	1	1	100.00%	E280K/Y623D	1	1	100.00%
I82T	1	1	100.00%	R306H	1	1	100.00%
W86G	1	1	100.00%	V324M	1	1	100.00%
A161T	1	1	100.00%	V324M/R1394L	1	1	100.00%
L164P	0	5	0.00%	E382K	1	2	50.00%
C166Y	0	3	0.00%	E382V	2	2	10.00%
I167F	1	1	100.00%	I395F	0	1	0.00%
I167L	1	1	100.00%	C435R	1	1	100.00%
A174G	1	1	100.00%	T488L	1	2	50.00%
K170N	5	5	100.00%	I544T/R1215W	1	1	100.00%
K170R	2	2	100.00%	F577L	1	1	100.00%
K170T	2	2	100.00%	V587G	1	1	100.00%
E179A	3	3	100.00%	E747*	2	2	100.00%
K179R	1	1	100.00%	G832C	2	2	100.00%
I182T	1	1	100.00%	G832D	1	1	100.00%
K185Q	1	1	100.00%	R825W	0	1	0.00%
K185T	1	1	100.00%	R826W	1	2	50.00%
H186D	4	4	100.00%	H1023R	1	1	100.00%
R201C	48	53	90.57%	H1024Y	1	1	100.00%
R201G	1	1	100.00%	F1164L	1	1	100.00%
R201H	137	140	97.86%	R1182W	0	1	0.00%
R201L	5	5	100.00%	R1183W	4	4	100.00%
R201S	1	1	100.00%	P1198L	2	2	100.00%
S225T+pro226_pro232del	1	1	100.00%	P1199L	2	2	100.00%
E227K	13	13	100.00%	A1263V/I196N	1	1	100.00%
G228A	1	1	100.00%	R1380C	1	1	100.00%
E229K	8	9	88.89%	R1380H	2	2	100.00%

TABLE 2 (Continued)

KCNJ11	Success Number	Patients Number	Efficiency	ABCC8	Success Number	Patients Number	Efficiency
L233F	2	2	100.00%	R1380L	2	2	100.00%
V252L	1	1	100.00%	G1401R	1	1	100.00%
V252M	3	3	100.00%	I1425V	1	1	100.00%
E292G	1	1	100.00%	E1507G	1	1	100.00%
T293N	1	2	50.00%	V1523M	2	2	100.00%
I296L	0	2	0.00%	A1537P	1	1	100.00%
E322A/D352H	1	1	100.00%	V2151I/V607M	1	1	100.00%
E322K	5	5	100.00%	T2291I/V1523L	1	1	100.00%
G324R	1	1	100.00%				
Y330C	2	2	100.00%	Locus 11p15.1	0	1	0.00%
Y330S	2	2	100.00%				
F333I	2	2	100.00%				
F333L	2	2	100.00%				
P333L	1	1	100.00%				
G334C	1	3	33.33%				
G334D	0	1	0.00%				
G334V	0	2	0.00%				
Total	376	413	91.04%	Total	77	89	86.52%

Considering only the available data on the dosage required for each genotype, the median dose of SU needed to treat monogenic diabetes was 0.48 mg/kg/day (0.017-2.8 mg/kg/day). We present the data divided into first quartile with low required doses and a high dose quartile (Table 3). The median daily intakes of sulfonylurea was 3 (1-5 intakes per day).

4.2 | In vitro sensitivity of mutant potassium channels to sulfonamides

We found 19 reports which investigated the in vitro susceptibility of mutant potassium channels to sulfonylurea. They concern 52 different mutations of the *KCNJ11* gene using three different types of tests as described in Methods. Forty-two different mutations are responsible for potassium channels sensitive in vitro to sulfonylurea, three relate to channels with an intermediate susceptibility to tolbutamide, and eight mutations showed a lack of sensitivity: C166Y, G334D, I296L, L164P, Q52R, S225T, T293N, and V59G (Table 4).

4.3 | Comparison in vivo/in vitro sensitivity of mutant potassium channels to sulfonylurea

Taking into account both the in vivo and in vitro susceptibility results of potassium channels modified by mutation of the *KCNJ11* and *ABCC8* genes, some mutations appear more sensitive than others to sulfonylurea treatment.

Mutant channels from 29 different mutations are always sensitive to sulfonylurea treatment in vivo or in vitro: A161T, C42R, E227K, E229G, E322K, F333I, F35V, F60Y, G324R, G53D, G53N, H46Y, I167L, K170N, K170R, K170T, K185Q, K185T, L233F, N48D, R201S, R50P, R50Q, S3C, V252M, W68G, W86G, Y330C, and Y330S (Table 4).

Conversely, the channels resulting from four mutations of *KCNJ11* seem to be never sensitive, both in vivo and in vitro: C166Y, G334D, I296L, and L164P.

On the other hand, there are cases of discrepancy between the in vivo efficacy of the treatment and the in vitro sensitivity to sulfonylurea for certain mutations. For example, only 1/3 of the patients carrying the *KCNJ11* G334C mutation can be successfully treated with sulfonylurea for their diabetes, whereas the mutated channels are sensitive in vitro to sulfonylurea (Tables 2 and 4).

4.4 | Beneficial effect on the neurological examination of patients with neonatal diabetes and neurological involvement (DEND or iDEND syndromes)

Our review of the literature showed that 40/55 published patients, showed an improvement in their neurological examination after initiation of treatment with sulfonylurea in motor or attention skills.[14,17-20] Although their existence is proven by numerous studies, the neurological progress was variable in nature and intensity. Nevertheless, the neurodevelopmental disability may be ameliorated by early sulfonylurea treatment.[21]

TABLE 3 SU doses needed to obtain good glycemic control in monogenic diabetes due to a *KCNJ11* or *ABCC8* mutation

	KCNJ11	ABCC8
HIGH	R50P	R118W
	Q52L	Q211K
	Q52R	L213P
KCNJ11: >0,95mg/kg/j	V59A	T229N
ABCC8: >0,725mg/kg/d	I82T	R306H
	I167L	V324M/R1394L
	E179A	E382K
	T293N	V587G
	P333L	A1263V/I196N
MEDIUM	K39R	V86A
	C42R	F132L
	H46L	R186C/G1256S
	H46Y	D212Y
	R50Q	L213R
	G53D	I544T/R1215W
	G53S	F577L
	V59M	E747*
	W68G	G832C
	K170N	G832D
	K170R	H1023R
	K179R	F1164L
	R201C	P1198L
	R201G	P1199L
	R201H	I1425V
	R201L	
	L233F	
	F333L	
LOW	N48D	I49F
	I167F	D209E
	A174G	V324M
KCNJ11: <0,385mg/kg/d	H186D	E382V
ABCC8: <0,22mg/kg/d	E227K	T488L
	E229K	H1024Y
	S225T +pro226_ pro232del	R1380C
	V252L	
	E322A/D352H	
	E322K	
	G324R	
	Y330C	

4.5 | Side effects

Three reports involving altogether 26 patients, described the presence of hypoglycemia in five patients, which however remained always moderate or asymptomatic. In all cases a SU dosage adaptation made it possible to solve this side effect. Another known side effect of sulfonylurea is the presence of digestive disorders, which was described in 13 publications (n = 20 out of 112 patients), including diarrhea, usually occurring in the first days after treatment or nausea. No dehydration was recorded, and the treatment never had to be interrupted for any of these reasons. One severe side effect was described by Marshal et al.[22] in 2015: one patient (0.02%) formerly premature developed at the age of 1 month, 10 days after the introduction of glycazide, an ulcerative necrotizing enterocolitis (UNEC).

5 | DISCUSSION

The present report provides information on tailored medicine using sulfonylurea therapy in patients with monogenic diabetes which has important clinical implications. Overall these drugs demonstrate to allow a satisfactory glycemic control in 90% of treated patients with monogenic diabetes by mutation of the potassium channel genes, which concerns the majority of PNDM patients and agrees with a recent meta-analysis in a smaller group of subjects of (n = 285).[23] Importantly current data show that the metabolic benefit is maintained over time under SU therapy, in a series of 90 patients with a mean follow-up of 10.2 years.[24] Furthermore, an oral treatment to replace the subcutaneous insulin injections leads to a clear improvement in the quality of life of the patients.

This study is, to our knowledge, the only review of the literature aimed at identifying the sulfonylurea sensitivity of the mutant potassium channels in vivo and in vitro. Our analysis provides a dosage guide necessary for the glycemic control of the affected patients according to their genetic mutations, which we believe will be of great clinical help when making the switch from insulin and for treatment efficacy evaluation. Mutations in the *KCNJ11* gene show a concordance in sensitivity both in vivo and in vitro. Nevertheless, the degree of sensitivities may vary in vivo vs in vitro. For instance, in patients bearing the G53R mutation, only 60% of the carriers could be weaned off insulin, while the mutation is 100% sulfonylurea sensitive in vitro. On the other hand, when the mutated channels have low sensitivity in vitro, the success rate of the switch in vivo is greater. However, sulfonylurea treatment is sometimes ineffective while the mutant channel is sensitive in vitro. This is due to the existence of other factors influencing the efficacy of the treatment. Indeed, as described by Thruber et al.,[25] sulfonylurea treatment of monogenic diabetes is most effective when started young. This is probably due to the gradual destruction of the β cells of the pancreas during the evolution of diabetes. Chronic hyperglycemia (glucotoxicity) leads to destruction of the β cells by stimulation of various complex mechanisms: pro-apoptotic process,[26] oxidative,[27] and protein glycation. The study of treatment within families supports this theory.[13] Furthermore, beta cell de-differentiation is also one of the proposed additional mechanisms.

On the other hand, the failure of sulfonylurea treatment may be favored by poor glycemic control prior to the start of treatment[28] or

TABLE 4 Success rate of SU block of ATP-dependent potassium channels on in vitro channels with a *KCNJ11* mutation red: mutations for whom SU are never efficient in vivo nor in vitro, green: mutations for whom SU have always been efficient in vivo and in vitro

	In vivo		In vitro			Success	
KCNJ11 mutation	Success	Total	Success	Intermediate	Total	In vivo	In vitro
A161T	1	1	1	0	1	100.00%	100.00%
A174G	1	1				100.00%	
C166Y	0	3	0	0	1	0.00%	0.00%
C42R	2	2	1	0	1	100.00%	100.00%
E179A	3	3				100.00%	
E227K	13	13	3	0	3	100.00%	100.00%
E229K	8	9	3	0	3	88.89%	100.00%
E292G	1	1	1	0	1	100.00%	100.00%
E322A/D352H	1	1				100.00%	
E322K	5	5	2	0	2	100.00%	100.00%
E51A	1	1	0	1	1	100.00%	0.00%
F333I	2	2	1	0	1	100.00%	100.00%
F333L	2	2				100.00%	
F35L			1	0	1		100.00%
F35V	1	1	2	0	2	100.00%	100.00%
F60Y	1	1	1	0	1	100.00%	100.00%
G324R	1	1	1	0	1	100.00%	100.00%
G334C	1	3	1	0	1	33.33%	100.00%
G334D	0	1	0	0	2	0.00%	0.00%
G334V	0	2	1	0	1	0.00%	100.00%
G53D	13	13	2	0	2	100.00%	100.00%
G53N	1	1	1	0	1	100.00%	100.00%
G53R	3	5	4	0	4	60.00%	100.00%
G53S	2	3	3	0	3	66.67%	100.00%
H1023Y			1	0	1		100.00%
H186D	4	4				100.00%	
H46L	4	5	2	0	2	80.00%	100.00%
H46Y	6	6	4	0	4	100.00%	100.00%
I1424V			1	0	1		100.00%
I167F	1	1				100.00%	
I167L	1	1	2	0	2	100.00%	100.00%
I182V			2	0	2		100.00%
I296L	0	2	0	0	6	0.00%	0.00%
I82T	1	1				100.00%	
K170N	5	5	1	0	1	100.00%	100.00%
K170R	2	2	1	0	1	100.00%	100.00%
K170T	2	2	3	0	3	100.00%	100.00%
K179R	1	1				100.00%	
K185Q	1	1	1	0	1	100.00%	100.00%
K185T	1	1	1	0	1	100.00%	100.00%
K39R	1	1				100.00%	
L164P	0	5	0	0	3	0.00%	0.00%
L225P			1	0	1		100.00%
L233F	2	2	1	0	1	100.00%	100.00%
N48D	1	1	2	0	2	100.00%	100.00%

(Continues)

TABLE 4 (Continued)

	In vivo		In vitro			Success	
KCNJ11 mutation	Success	Total	Success	Intermediate	Total	In vivo	In vitro
P333L	1	1				100.00%	
Q52L	1	1				100.00%	
Q52R	2	5	0	0	5	40.00%	0.00%
R201C	48	53	4	0	4	90.57%	100.00%
R201G	1	1				100.00%	
R201H	137	140	4	0	4	97.86%	100.00%
R201L	5	5	0	2	2	100.00%	0.00%
R201S	1	1	1	0	1	100.00%	100.00%
R333I			1	0	1		100.00%
R50P	6	6	2	0	2	100.00%	100.00%
R50Q	9	9	3	0	3	100.00%	100.00%
S225T			0	0	1		0.00%
S225T+pro226_pro232del	1	1				100.00%	
S3C	2	2	1	0	1	100.00%	100.00%
T293N	1	2	0	0	2	50.00%	0.00%
V252A			2	0	2		100.00%
V252L	1	1				100.00%	
V252M	3	3	1	0	1	100.00%	100.00%
V59A	1	3				33.33%	
V59G			0	0	1		0.00%
V59M	51	54	3	1	5	94.44%	60.00%
W68G	1	1	1	0	1	100.00%	100.00%
W86G	1	1	1	0	1	100.00%	100.00%
Y330C	2	2	1	0	1	100.00%	100.00%
Y330S	2	2	1	0	1	100.00%	100.00%
G228A	1	1				100.00%	
I182T	1	1				100.00%	
Q51G	1	1				100.00%	
Total	**376**	**413**	**78**	**4**	**104**	91.04%	75.00%

differences in pharmacogenetics and pharmacokinetics of the sulfonylurea. Glibenclamide is completely metabolized by the liver mainly by CYP3A4 and CYP2C9. In 18 children aged between 2.4 and 12.8 years, body weight was the most significant parameter affecting drug clearance. In addition, those subjects carrying a variant genotype of CYP2C9 (ie, *1/*2 and *1/*3; slow metabolizers) had a clearance decreased by 45%.[12,29]

Finally, the success of the treatment is largely conditioned by the patient's good compliance with the treatment as well as the dietary and hygiene rules and maximal dose used. On the molecular level, the genetic mutations affecting certain amino acids of the protein seem both very pathogenic and determinant for the sensitivity to treatment with sulfonylurea. Particularly, mutations affecting residues H46, R50, G53, W86, K170 K185, R201, V252, F333, and Y330 of the KCNJ11 gene are particularly sensitive to glibenclamide and tolbutamide. The Kir 6.2 protein forms, through a tetrameric structure, the pores of the ATP-dependent potassium channel. Each Kir6.2 protein has a pocket for attachment to ATP molecules, as well as helices for channel formation. The mutations of residues R50, K185, R201, Y330, F333, G334, and R201 directly affect the spatial conformation of the ATP binding pocket and thus the sensitivity of the molecule to ATP. The sulfonylurea, therefore, allow a closure of the channel despite the lack of efficacy of the increase of intracellular ATP on the potassium channel.[30-33] Conversely, mutations affecting residues G334 and C166Y seem relatively insensitive to sulfonylurea, regardless of the amino acid substitution. The prospects for oral treatment of these children are therefore more uncertain. Trapp et al.[34] have shown that mutations at residue 166 replacing cysteine, a hydrophobic amino acid, with a larger and less hydrophobic amino acid increases the probability of opening the channel. Altered intrinsic kinetics of the canal and/or an altered conformation could explain

non-response to sulfonylurea. Trends in mutations that are more or less sensitive to sulfonylurea thus seem to emerge from this meta-analysis.

The doses of sulfonylurea required for good glycemic control in ND are higher than those used in adults. Hence before declaring the failure of SU treatment, it is necessary to justify a high-dose treatment trial for several weeks. Rafiq et al. [35] observed that the SU doses used for the treatment of monogenic diabetes were lower in patients with mutations in the *ABCC8* gene, than for the *KCNJ11* mutations, 0.26 mg/kg/d (0.07-0.63) vs 0.45 mg/kg/d (0.05-1.5), respectively. In our literature review, this difference was less significant. Indeed, the median dose required for good glycemic balance in patients with *ABCC8* mutations was 0.43 mg/kg/d (0.07-1.8 mg/kg/d) vs 0.50 mg/kg/d (0.03-3.0) for *KCNJ11* mutations.

Sulfonylurea is currently used outside the marketing authorization for the treatment of monogenic and neonatal diabetes in most countries. The available form is a tablet treatment that is poorly adapted for newborns and children. A therapeutic trial concerning an oral suspension of treatment AMGLIDIA has proven successful and easy to use in newborn and children.[12]

Our results need to be balanced against the limitations of the study. On the one hand, the treatment success rates, whether in vitro or in vivo, were calculated from very small numbers per mutation that could be found in the literature. The statistical power of these success rates is therefore relative. In addition, this analysis is exposed to the bias of publications inherent to this type of study: the cases concerning rare/new mutations are more easily published than the cases concerning known mutations. Moreover, some factors external to the characteristic of the genetic mutation can influence the sensitivity in vivo to the sulfonylurea of certain patients, as reviewed above.

Genetic explorations of patients with diabetes diagnosed before the age 12 months or with the discovery of diabetes later, but that may correspond to a relapse of neonatal diabetes, are warranted. These studies must be carried out early, allowing the initiation of treatment as soon as possible. However, the results of these genetic analyzes should not be expected before initiating treatment with sulfonylurea.

In addition, the real nature (disease causing or variants of unknown significance) of the mutations should be assessed by electrophysiology tests and these data are not available for all mutations. Hence, we are not able to make further comments about the pathogenicity of all mutations.

In summary hypoglycemic sulfonylurea such as glibenclamide is an effective treatment for monogenic diabetes due to *KCNJ11* and *ABCC8* gene mutations, both at the diagnostic phase and in later stages of diabetes progression. The treatment is more or less effective depending on the genetic mutations found but caution must be exerted before ruling out a therapeutic effect of glibenclamide, based on the observation of some mutations with discrepancy in vitro and in vivo effect. Hence pushing an empirical attitude to test the effect of sulfonylurea in such neonatal diabetes mellitus.

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CONFLICT OF INTEREST

Pr Michel Polak is the scientific advisor of AMMTeK. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

L.G. involved in collection, analysis, interpretation of data, reading final manuscript, and edition. V.M. involved in analysis, interpretation of data and manuscript writing reading final manuscript and edition. A.L.F.A. involved in genetic analysis and interpretation of the genetic data, corrected the manuscript. H.C. involved in genetic analysis and interpretation of the genetic data, corrected the manuscript. M.P. involved in study design, analysis and interpretation of data reading final manuscript and edition. J.B. involved in study design, analysis, and interpretation of data reading final manuscript and edition.

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