

## Guidance for transferring patients with a disease-causing variant in the *ABCC8* or *KCNJ11* gene causing transient neonatal diabetes (TNDM) and/or later adult-onset diabetes from insulin to a sulphonylurea

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### What is a pathogenic TNDM causing variant and how does diabetes present in these patients?

Pathogenic variants in the potassium channel ( $K_{ATP}$ ) genes *ABCC8* and *KCNJ11* can lead to transient neonatal diabetes (TNDM) and/or later adult onset diabetes as well as permanent neonatal diabetes (PNDM). There is usually a close relationship between the genetic change and the clinical presentation, so specific pathogenic variants found in patients with TNDM are also likely to result in TNDM in other patients.

In  $K_{ATP}$  gene variants that result in TNDM, the typical pattern is of:

- diabetes being diagnosed in early infancy, typically 4 weeks (range 0-16);
- and then going into remission in early childhood – typically at 8 months (range 0.5-48);
- and then relapse with diabetes again typically at around 15 years (range 2 – 45)

We know from our earlier work (Flanagan S. *et al*, Diabetes 2007) that in some families a child presented with TNDM but a parent was not known to have diabetes in infancy and presented later in life – typically around 30-35 years (range 5 – 50 years). We found that the characteristics of the diabetes in these patients were similar to those who had relapsed having presented in infancy and then remitted. It is as if the patients who presented in adulthood did not present in the initial neonatal phase that then remitted but went straight to the “relapse” phase.

One interesting feature of  $K_{ATP}$  channel TNDM is that patients can present in ketoacidosis but still remit. Mild developmental features are seen in some children with TNDM (more frequently *ABCC8* variants) but these are not well characterised.

### Our experience to date:

We have received feedback on over 100 patients with *KCNJ11* or *ABCC8* variants resulting in TNDM who have transferred from insulin to a sulphonylurea.

These TNDM patients, unlike those with PNDM, are likely to have significant endogenous insulin production; regardless of whether in the initial neonatal phase, in the relapse phase or whether diagnosed in childhood/ adulthood only. This is shown by C peptide being clearly measurable and patients getting good glucose control with less than a replacement dose of insulin (often < 0.5U/kg/day). As these patients with TNDM have significant endogenous insulin, they are much more responsive to sulphonylureas (than patients with PNDM) and may need very low doses (unlike patients with PNDM that need a very high dose of sulphonylurea).

### Switching from insulin in infancy or very early childhood (<2 years)

Once a molecular genetic diagnosis establishes that a patient has a TNDM causing variant in one of the  $K_{ATP}$  genes then most patients can switch from insulin to sulfonylureas. Patients with TNDM only need hypoglycaemic agents (insulin or sulfonylurea) for the first few weeks to months post-diagnosis until they go into remission. The aim of a switch to a sulfonylurea is to prevent the need to inject the infant with insulin. It is also likely to allow improved glycaemic control before the diabetes remits but hypoglycaemia can easily occur as the diabetes remits so glucose should be carefully monitored.

### Switching from insulin to a sulfonylurea in later childhood or early adulthood

Patients whose TNDM relapses or those that just present for the first time typically develop diabetes between the ages of 10 and 40 years. They are often thought to have Type 1 diabetes and hence treated with insulin. The correct diagnosis is often only considered when a child or other family members are diagnosed with TNDM. The dominant inheritance of diabetes in early adulthood can also mean they can be thought have MODY (Bowman *et al* Diabetologia 2012, Bonnefond *et al* PloS One 2012).

The identification of an activating *KCNJ11* or *ABCC8* variant means that a trial of sulfonylureas is appropriate. If the patient is on insulin, it is best to confirm first that they are making their own insulin by measuring a fasting or post meal C-peptide. When this is confirmed then a trial of low dose sulfonylurea is appropriate.

### Dose of sulfonylurea

In both infants with neonatal diabetes pre-remission and older children/adults with relapsed/adult onset diabetes with TNDM  $K_{ATP}$  variants, once it is established that they have endogenous insulin production, they should be treated initially with a low dose of a sulfonylurea.

In contrast to PNDM where high doses are used (up to 3 x the maximum dose used in Type 2 diabetes); we recommend a starting total daily dose of 0.05mg/kg/day glibenclamide divided into two doses. Some patients have become hypoglycaemic on this low dose, so close monitoring and adjustment of the dose is necessary. At first the dose may need to be slowly adjusted upwards to ensure glycaemic control. However weeks to months after initial transfer, glycaemic control will improve, the diabetes will remit and the dose will need to be decreased and stopped.

As some patients with adult onset diabetes and a TNDM causing variant are very sensitive to sulfonylureas (Bowman *et al* Diabetologia 2012), in adults we recommend starting a quarter of a tablet of glibenclamide or gliclazide and increasing from that dose – as in HNF1A MODY (see our website [www.diabetesgenes.org](http://www.diabetesgenes.org) in the section on HNF1A MODY <http://www.diabetesgenes.org/content/guidance-transferring-hnf1a-or-hnf4a-patients-insulin-sulphonylureas>).

In the relapsed/adult onset patients, after decades of success with sulfonylurea treatment the response to sulfonylureas may reduce. This will require the sulfonylurea to be increased up to the maximum adult dose (which is approximately 0.4mg/kg/day Glibenclamide) with next option being adding in background insulin or possibly a DPP4 inhibitor (gliptin).

### Choice of sulfonylurea

Theoretically any sulfonylurea should be as effective as any other in treating the diabetes. Gliclazide only binds to SUR1 (pancreas/neurons) whereas glibenclamide binds to cardiac and muscle (SUR2A) as well. We have used glibenclamide in most cases of TNDM/PNDM and so have the most experience of this. Other sulfonylureas have been successfully used. As patients only require a low dose the fact that it is less effective than glibenclamide in some patients is not critical.

### Adverse reactions

The doses of sulfonylureas required are below the normal maximum adult dose (if you allow for the weight difference) however, no sulfonylureas are licensed for use in children although they are widely used. Reported side effects from glibenclamide are listed on the drug information.

The commonest known side effects are: skin allergies (1-5%) which may resolve and gastrointestinal including diarrhoea (1-2%). Blood disorders – anaemia, leucopenia and thrombocytopenia – are rare. Sulfonylureas can occasionally cause a disturbance in liver function.

### Further information

We hope clinicians will follow the protocols outlined below **and will then give us feedback on how the transfer went**. We would request as much feedback as possible, especially if there are any problems as well as annual updates on patient treatment via the FIND database: <https://penctu.pcmd.ac.uk/find>.

If you have previously diagnosed a patient with neonatal diabetes, you may already have access to this site; otherwise we will send you log-in details.

For specific advice regarding individual patients please contact Prof Andrew Hattersley on 01392 408260 [a.t.hattersley@exeter.ac.uk](mailto:a.t.hattersley@exeter.ac.uk) or Prof Maggie Shepherd on 01392 408261 [m.h.shepherd@exeter.ac.uk](mailto:m.h.shepherd@exeter.ac.uk).