Meglitinide Analogues in Adolescent Patients With HNF1A-MODY (MODY 3)

abstract

For pediatric patients with hepatocyte nuclear factor-1A (HNF1A)—maturity-onset diabetes of the young (MODY 3), treatment with sulfonylureas is recommended. In adults with HNF1A-MODY, meglitinide analogues achieve lower postprandial glucose levels and pose a lower risk of delayed hypoglycemia compared with sulfonylureas. This therapy has not yet been reviewed in pediatric patients. We report on meglitinide analogue treatment in 3 adolescents with HNF1A-MODY. Case 1 (14-year-old girl) was diagnosed asymptptomatically but had an hemoglobin A1c (HbA1c) level of 7.4%; her father had been recently diagnosed with HNF1A-MODY. With repaglinide, her HbA1c level decreased to 5.5%, with no hypoglycemic episodes. Case 2 (14-year-old boy) was diagnosed incidentally with glucosuria (HbA1c level: 7.0%) and was treated with insulin. After the HNF1A-MODY diagnosis, he was switched to glibenclamide. Due to several hypoglycemic episodes, treatment was changed to nateglinide and his HbA1c level decreased to 6.2% with no further hypoglycemic episodes. Case 3 (11-year-old girl) presented with polyuria and polydipsia (HbA1c level: 10.1%) and was initially treated with insulin. After the HNF1A-MODY diagnosis, treatment was changed to repaglinide. She was obese (BMI: 28.8 kg/m²; z-score: +2.2), and glucose control with repaglinide alone was insufficient. Therefore, neutral protamine Hagedorn insulin (0.27 U/kg per day) was added. With this combination therapy, her HbA1c level decreased to 8.2%. The use of meglitinides in these 3 adolescent patients was well tolerated and effective. Furthermore, hypoglycemic episodes were rare compared with treatment with insulin or sulfonylureas. We therefore suggest considering meglitinides as the primary oral treatment option for adolescents suffering from HNF1A-MODY. Pediatrics 2014;133:e775–e779
Hepatocyte nuclear factor-1A (HNF1A)–maturity-onset diabetes of the young (MODY) (also known as MODY 3 [maturity-onset diabetes of the young type 3], phenotype MIM #600496) is a rare disease that accounts for ~0.3% of all diabetes cases with pediatric onset. It is caused by a heterozygous gene defect of the transcription factor HNF1α that leads to a progressive malfunction of glucose-dependent insulin secretion. HNF1α is part of a complex, islet cell–specific regulatory circuit that is formed of the transcription factors HNF4α, HNF6, and HNF1β. Overall, HNF1α regulates >100 islet cell–specific genes. HNF1α has an impact on insulin transcription, β-cell–specific glucose sensing, and insulin secretion (Fig 1). If not treated sufficiently, patients with HNF1A-MODY are at an increased risk for developing microvascular and macrovascular complications of diabetes.

Patients with HNF1A mutations are very sensitive to sulfonylureas, as tested by intravenous administration of tolbutamide. As a consequence, the current International Society for Pediatric and Adolescent Diabetes consensus guideline recommends careful introduction of sulfonylureas as first-line therapy in children and adolescents with HNF1A-MODY. Nevertheless, the use of any drug that can stimulate insulin secretion in diabetes is still an off-label therapy in children and adolescents, and it requires individual informed consent.

In adult patients with type 2 diabetes, use of meglitinides to target insulin secretion has become an established treatment option. Meglitinides lead to a rapid and transient increase in insulin secretion. In healthy subjects, as well as in middle-aged patients with type 2 diabetes, treatment with repaglinide (meglitinide) compared with glibenclamide (sulfonylurea) results in an earlier peak of insulin secretion, reduced postprandial glucose levels, and an insulin profile that is closer to normal insulin secretion. However, elevated insulin levels may cause postprandial hypoglycemic episodes. Due to a shorter duration of action, this phenomenon is thought to occur less frequently when meglitinides are used.

In pediatric patients, the use of meglitinides has not yet been reviewed.

**CASE REPORTS**

We report on our follow-up results of successful meglitinide analogue treatment in 3 adolescent patients with the molecular diagnosis of HNF1A-MODY (Table 1). The patients were otherwise healthy and had normal liver and kidney function. Common adverse effects of meglitinides include abdominal pain and diarrhea; a more rare effect is transient elevation of liver enzyme levels.

We screened for adverse effects by using targeted interviews at every visit and by analyzing liver enzyme levels 1 month after the start of meglitinides and then annually. All parents and children provided their written informed consent for the off-label use of either repaglinide or nateglinide for the treatment of HNF1A-MODY. The first week of meglitinide treatment was assessed by using continuous glucose monitoring. To evaluate severity and number of subsequent hypoglycemic episodes, patients were asked to document symptomatic, hypoglycemic episodes that were confirmed by a blood glucose test result of <60 mg/dL.

**Case 1**

The 14-year-old girl was diagnosed by genetic testing of the family (her father had recently been diagnosed with HNF1A-MODY). Up to then, she had had no overt symptoms of diabetes, but postprandial blood glucose values peaked at >200 mg/dL, and her hemoglobin A1c (HbA1c) level was 7.4%. Dietary changes were insufficient to prevent postprandial glucose peaks. She was started on repaglinide after detailed discussion of treatment options with her and her parents. The start of repaglinide therapy was monitored by continuous glucose monitoring, and glucose values normalized with 0.5 mg of repaglinide taken before main meals (Fig 2).
Case 2
This 14-year-old boy was incidentally diagnosed with glucosuria, and insulin treatment was started when he had an HbA1c level of 7.0%. When the genetic diagnosis of HNF1A-MODY was made 12 months later, his treatment was first changed to glibenclamide. Despite titrating his regimen to a daily dose of 2.5 mg, he continued to have elevations in postprandial glucose levels and suffered from several hypoglycemic episodes (>20 per month), which occurred predominantly at night. The hypoglycemic episodes were uncomfortable, but none led to convulsions or unconsciousness. His treatment was changed to nateglinide (starting dose: 60 mg 3 times daily; final dose: 180 mg 3 times daily), resulting in excellent glucose control (HbA1c level:

### TABLE 1 Clinical and Genetic Characteristics of the 3 Adolescents With HNF1A-MODY Switched to Meglitinide Analogue Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation nucleotide (protein)</td>
<td>c.872dupC (p.Gly292ArgfsX25)</td>
<td>c.1627T&gt;G (p.Leu54Pro)</td>
<td>c.1192C&gt;T (p.Gln398Stop)</td>
</tr>
<tr>
<td>Age at diabetes onset, y</td>
<td>12.6</td>
<td>14.1</td>
<td>11.1</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>HbA1c at diabetes onset, %</td>
<td>7.4</td>
<td>7.0</td>
<td>10.1</td>
</tr>
<tr>
<td>HbA1c, mean (range), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6–0 before meglitinides</td>
<td>NA</td>
<td>8.5 (8.5–8.6)</td>
<td>8.6 (7.8–9.2)</td>
</tr>
<tr>
<td>Month 0–6 with meglitinides</td>
<td>5.6 (5.3–6.0)</td>
<td>6.2 (6.0–6.4)</td>
<td>8.2 (8.0–8.6)</td>
</tr>
<tr>
<td>Hypoglycemic episodes (symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and blood glucose &lt;50 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6–0 before meglitinides</td>
<td>NA</td>
<td>&gt;20/mo, predominantly</td>
<td>0–2/mo (insulin)</td>
</tr>
<tr>
<td>at night (glibenclamide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1–6 with meglitinides</td>
<td>None</td>
<td>None</td>
<td>0–2/mo (none severe)</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At change to meglitinides</td>
<td>23.7 (+1.5)</td>
<td>19.2 (+0.8)</td>
<td>28.8 (+2.2)</td>
</tr>
<tr>
<td>Month 1–6 with meglitinides</td>
<td>23.7 (+1.4)</td>
<td>19.6 (+0.8)</td>
<td>28.4 (+2.0)</td>
</tr>
<tr>
<td>Medication (daily dose)</td>
<td>Repaglinide 0.5 mg TID</td>
<td>Nateglinide 180 mg TID</td>
<td>Nateglinide (1.5 mg, 0.5 mg, 2 mg); NPH (10 U am, 11 U pm)</td>
</tr>
</tbody>
</table>

**FIGURE 2**
Continuous glucose monitoring (CGM; Guardian Real-Time CGM System [Medtronic, Northridge, CA]) before (A) and after the start of repaglinide therapy (B) in case 1. Blue line: CGM tissue glucose levels. Green arrows indicate when repaglinide was taken. Meals are documented by the amount of grams of carbohydrates (CHO) consumed.
Overall, we observed no adverse effects. In accordance with results in adult patients with HNF1A, \( \text{we found a marked reduction of hypoglycemic episodes, especially compared with the recommended therapy with a sulfonylurea (Table 1). The 2 patients with meglitinide analogue treatment alone had excellent glucose control without any hypoglycemic episodes within the 6-month follow-up period. Only 1 patient (case 3) required additional basal insulin treatment and experienced rare and mild hypoglycemic episodes. These episodes were considerably less than with insulin therapy alone.}

Our rationale for using meglitinides was that patients with HNF1A are hypersensitive to sulfonylureas but possibly not to meglitinides, \( \text{although meglitinides have a similar mechanism of action. The mechanism behind this hypersensitivity is not yet totally understood.}

In general, patients with HNF1A-MODY are more sensitive to insulin compared with patients with type 2 diabetes or latent autoimmune diabetes in adults. \( \text{Both drugs (sulfonylureas and meglitinides) cause an increase in insulin secretion by specific binding to the sulfonylurea receptor (SUR) subunit of the K\text{ATP} channel.}\)

However, certain specific differences might partly explain the difference in the glucose-lowering effect in HNF1A-MODY. First, the binding properties to the A- and B-binding sites of SUR1 differ: glibenclamide binds to both the A and B site, whereas repaglinide binds predominantly to the B site and nateglinide to the A site of SUR1. \( \text{Second, sulfonylureas (but not glinides) activate the K\text{ATP} modulator Epac2A. This is a cyclic adenosine monophosphate–binding protein that potentiates glucose-induced insulin secretion.}\)

Whether HNF1A-MODY patients hypersecrete insulin by an Epac2A activation needs further functional investigation.

Moreover, mouse pharmacodynamic studies suggest that glibenclamide’s half-life in serum is increased approximately fourfold in Hnf-1alpha(−/−) mice compared with wild-type littermates. \( \text{However, whether this mechanism also affects meglitinides, which are subject to hepatic glucuronidation as well, remains unclear.}

If hypoglycemia is present with glibenclamide, use of other sulfonylureas with different kinetics could be considered. Gliclazide has a shorter plasma half-life, but it is still longer than that of the meglitinides, and it interacts with elimination pathways of many other drugs. \( \text{Glimepiride is a third-generation sulfonylurea preparation, and an additional, extrapancreatic glucose-lowering effect has been suggested with its use.}\)

It displays a lower incidence of hypoglycemia than gliclazide because it has a lesser effect on fasting insulin levels. \( \text{Glimepiride’s plasma half-life is almost equal to that of gliclazide, and it can also be given once daily. In summary, we favored changing therapy to meglitinides for 2 reasons: first, because of the hypersensitivity to sulfonylureas exhibited by HNF1A patients and second, because all types of sulfonylureas cannot be adjusted well to the lifestyle demands of adolescents with diabetes.}

Our cases highlight that meglitinides can achieve very good metabolic control and reduced hypoglycemia in adolescents with HNF1A-MODY. Limitations for this might be insufficient compliance and obesity-associated, increased insulin resistance. There is considerable genetic and phenotypic heterogeneity in HNF1A-MODY patients, which might explain the observed worse response to meglitinide analogue therapy in our third patient. Therapy for HNF1A-MODY should therefore be individualized and adapted to each patient’s needs. This modification may require combination therapy with basal insulin treatment to achieve sufficient glucose control. In addition, meglitinides did not change the patient’s initial BMI-SDS and thus helped to maintain weight.
A recent, representative survey from the German/Austrian DPV database has identified 44 HNF1A-MODY patients, of whom 43% were treated with oral antidiabetic drugs (OADs), 15.9% with a combination therapy of insulin and OADs, 20.5% with lifestyle intervention, and 35.3% with insulin alone. The OADs were not further subclassified, but these data demonstrate that one-third of all adolescents with HNF1A-MODY in Germany and Austria are still treated with insulin. Meglitinides seem to be safer than sulfonylureas and insulin because the risk for hypoglycemic episodes is apparently lower. They improve the quality of life compared with insulin because they are available as tablets; a change of treatment should therefore be offered to these patients.

CONCLUSIONS

We suggest considering meglitinides as a primary oral treatment option in adolescent patients with HNF1A-MODY or at least in those with recurrent hypoglycemic episodes who are undergoing sulfonylurea treatment. This report on 3 patients from our center is preliminary, and further studies evaluating the safety and efficacy of meglitinides in adolescent patients with HNF1A-MODY are needed to confirm our findings.

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