Optimal Glycemic Control in a Patient With HNF1A MODY With GLP-1 RA Monotherapy: Implications for Future Therapy

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We present the case of a 27-year-old woman with inadequately controlled HNF1A maturity-onset diabetes of the young (MODY) who was successfully transitioned from sulfonylurea therapy to once-weekly monotherapy with dulaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA). More than a decade from diabetes diagnosis, she has maintained optimal glycemic control without hypoglycemia for >12 months while receiving GLP-1 RA therapy alone. This case illustrates the potential for successful use of GLP-1 RA monotherapy in patients with HNF1A MODY.

Freeform/Key Words: monogenic diabetes, HNF1A MODY, GLP-1 receptor agonist

Maturity-onset diabetes of the young (MODY) accounts for at least 1% to 2% of diabetes cases. The various MODY phenotypes form part of a heterogenous group of monogenic diabetes phenotypes transmitted in an autosomal dominant fashion. Individuals are often misdiagnosed as having type 1 or type 2 diabetes, depending on the age at diagnosis and clinical presentation. Along with mutations in the glucokinase gene, mutations in the hepatocyte nuclear factor 1α (*HNF1A*) gene account for most cases [1]. Individuals with HNF1A MODY typically demonstrate marked sensitivity to sulfonylureas, which are recommended as first-line therapy [2]. However, hypoglycemia related to sulfonylurea use may become problematic in certain individuals. When added to the potential for weight gain with this class of medications, this raises the question of whether nonsulfonylurea therapies may have a role to play. Given the glucose-dependent mechanism of action and widespread efficacy of GLP-1 RA in type 2 diabetes, in addition to low hypoglycemia risk with use as monotherapy, beneficial effects on body weight, and evidence supporting cardiovascular benefit in type 2 diabetes, this class of medications holds potential that is yet to be fully explored in certain MODY phenotypes.

To date, there are limited data on the use of GLP-1 RA in patients with confirmed HNF1A MODY. One a short-term, 6-week clinical trial examined liraglutide as monotherapy, and several case reports have documented GLP-1 RA as adjunctive therapy [3, 4]. To our knowledge, no prior reports have addressed the use of weekly dulaglutide therapy in patients with confirmed HNF1A MODY or the long-term use of incretin monotherapy in this population.

Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; MODY, maturity-onset diabetes of the young.

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1. Clinical Case

A lean white woman with presumed type 1 diabetes since age 14 years presented to our institution for diabetes care at age 23 years during pregnancy on full basal-bolus insulin therapy. She was diagnosed with diabetes with serum glucose >600 mg/dL, without evidence of diabetic ketoacidosis, and was immediately started on full insulin replacement therapy. She has a family history of type 2 diabetes in her mother, who is obese, was diagnosed with diabetes in her fourth decade, and is well managed with metformin monotherapy. She has no personal or family history of autoimmune disease. Her examination was notable for weight of 66 kg, with a body mass index of 25 kg/m^2.

In the immediate postpartum period, a diagnosis of MODY was suspected given frequent hypoglycemia while she was receiving a total daily dose of insulin <0.2 U/kg/day with minimal basal insulin requirement, no diabetic ketoacidosis in the setting of complete insulin cessation for several days, random C-peptide concentration of 2.15 ng/mL (reference range, 0.80 to 3.10 ng/mL) and a concurrent serum glucose level of 181 mg/dL, and lack of glutamic decarboxylase-65 and islet cell antibodies. Genetic sequencing performed at the University of Chicago Kovler Diabetes Center demonstrated a heterozygous missense mutation, c.827C>A; p.Ala276Asp in exon 4 of the *HNF1A* gene. Given the patient's clinical phenotype, and without available genetic data from her mother, who had a distinct diabetes phenotype, her presentation was thought to be consistent with a *de novo* case of HNF1A MODY.

Soon afterward, in 2014, insulin was discontinued and sulfonylurea therapy with glimepiride, 2 mg daily, was started, with hemoglobin A1c (HbA1c) ranging from 7.1% to 8.8% over the following 2 years in the setting of variable adherence to medications. Despite reported increased adherence to sulfonylurea therapy, her HbA1c remained elevated at 8.8%; glimepiride was increased to 4 mg daily, and HbA1c decreased to 7.9%. Given consistently elevated HbA1c, as well as previously published case reports and short-term crossover trials using GLP-1 RA therapy in patients with HNF1A MODY, dulaglutide, 0.75 mg weekly, was added to glimepiride in 2017, with subsequent improvement in HbA1c [3, 4]. However, hypoglycemia developed with use of the combination, prompting a decrease in sulfonylurea dose to glimepiride, 2 mg daily. In early 2018, sulfonylurea therapy was discontinued given continued hypoglycemia with glimepiride, 1 mg daily, and dulaglutide, 0.75 mg weekly. After sulfonylurea discontinuation, dulaglutide was increased to 1.5 mg weekly without adverse events, including gastrointestinal upset. Four months after initiation of GLP-1 RA monotherapy, HbA1c had improved to 7.1% and she had a documented 6-kg weight loss. At 9 months, her HbA1c was 6.6% without apparent hypoglycemia, as assessed by self-monitored capillary blood glucose, and she had lost an additional 2.9 kg; her weight was now 57.6 kg, and her BMI was 21.47 kg/m^2. She has maintained improved glycemic control for 18 months since initiation of dulaglutide monotherapy. Her most recent HbA1c was 7.2%, and she has lost a total of 12.5 kg during this time frame, now weighing 54 kg (BMI, 20.13 kg/m^2).

2. Discussion

Nine years following an initial diagnosis of type 1 diabetes, our patient was diagnosed with HNF1A MODY, successfully transitioned from full insulin replacement therapy to sulfonylurea therapy, and eventually transitioned to GLP-1 RA monotherapy. As was the case in this patient, individuals with MODY are frequently misdiagnosed with type 1 or type 2 diabetes depending on their clinical presentation and underlying genotype. HNF1A MODY is one of the two most common monogenic diabetes phenotypes and is characterized by marked postprandial hyperglycemia that is often severe and progressive, resulting in rates of vascular complications similar to those seen with both type 1 and type 2 diabetes. In direct contrast, heterozygous mutations in the glucokinase gene (GCK MODY) result in modest HbA1c elevations and stable, regulated fasting hyperglycemia that is present from birth and does not result in clinically meaningful microvascular complications [1, 5].

HNF1A MODY should be suspected in lean individuals with normal insulin sensitivity, who often have relatively normal fasting glucose concentrations early on in the disease, but who typically develop substantial hyperglycemia after an oral glucose challenge, as a result of a progressive insulin secretory defect. They often have other suggestive features, which may help suggest this particular diagnosis, such as absence of β-cell autoantibodies, ability to omit insulin without development of ketoacidosis, glucosuria at near-normal serum glucose concentrations, high normal HDL cholesterol concentrations, and detectable C-peptide concentrations many years after diabetes diagnosis [1]. In this case, an atypical diabetes phenotype was considered based on age at diagnosis, lean habitus, ability to omit insulin without development of ketosis, minimal basal insulin requirement, substantial residual endogenous insulin concentrations, and negative β-cell autoantibodies 12 years after diagnosis of diabetes.

Individuals with HNF1A MODY typically demonstrate sulfonylurea sensitivity, and some may be exquisitely sensitive to even low sulfonylurea doses, which may result in hypoglycemia that limits their usefulness. Although many patients retain long-term sensitivity to sulfonylureas, HNF1A MODY is characterized by a progressive insulin secretory deficit; additional secretagogue or insulin therapy may be required to meet glycemic targets over time.

Despite normal serum incretin levels, individuals with HNF1A MODY demonstrate exaggerated postprandial glucagon responses and increased fasting dipeptidyl peptidase-4 enzymatic activity, which may represent a therapeutic target and rationale for the use of incretin-based therapy [5]. After a liquid meal challenge, individuals with HNF1A MODY develop postprandial hyperglucagonemia despite similar plasma GLP-1 and glucose-dependent insulinotropic polypeptide concentrations when compared with healthy controls and patients with GCK MODY [5]. Additionally, GLP-1 RAs may potentiate insulin secretion and enhance β-cell sensitivity of the K_{ATP} channels to the effect of ATP [6]. In a short term, 6-week study of 16 patients with HNF1A MODY, these preclinical observations were extended as glimepiride was compared with liraglutide in a double-blind, crossover manner. Glimepiride resulted in slightly improved glucose lowering at the expense of a 10-fold increase in mild hypoglycemic events. However, liraglutide was effective in lowering both postprandial and fasting glucose concentrations [3]. Augmentation of sulfonylurea therapy (with possible dose reduction) after addition of GLP-1 RA therapy may be a reasonable consideration in individuals who struggle with hypoglycemia or weight gain on sulfonylurea monotherapy. The two drug classes may act synergistically to overcome the β-cell secretory defect in HNF1A MODY with less risk for hypoglycemia and weight gain. It is still not clear whether long-term GLP-1 RA monotherapy will result in a durable glycemic effect because most of the literature to date reports on individual cases or series in which GLP-1 RAs or DPP-4 inhibitors were used in combination with other diabetes therapies. Given the limitations of these observational reports and the relative rarity of this diagnosis, which has precluded completion of large-scale, controlled studies thus far, many questions still remain.

This case adds to the observational evidence base by showing that the once-weekly GLP-1 RA dulaglutide resulted in durable 18- month glycemic control when used as monotherapy in an individual with HNF1A MODY. We are not aware of any reports of long-term use of GLP-1 RA monotherapy or the use of once-weekly dulaglutide in this population. Additionally, in this individual case, dulaglutide appeared to be more effective than glimepiride monotherapy despite the long duration of diabetes, in which β-cell dysfunction with worsening insulin secretory deficit may have been expected.

However, there are limitations to this conclusion, including the uncontrolled nature of this case report and multiple potential confounders. These include varying patient motivation levels throughout the treatment period, uncontrolled variations in diet, and the effect of a 12.5-kg weight loss after initiation of dulaglutide, a medication known to decrease appetite and stimulate weight loss. To address these issues and to definitively determine whether

GLP-1 RAs are effective in HNF1A MODY, an ambitious multicenter, large-scale prospective trial would be required.

Conclusion

Dulaglutide monotherapy was more effective than glimepiride monotherapy in achieving glycemic targets for more than 1 year in an individual with HNF1A MODY.

Additional Information

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References and Notes

1. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic β-cell diabetes. *Nat Clin Pract Endocrinol Metab*. 2008;**4**(4):200–213.
2. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet*. 2003;**362**(9392):1275–1281.
3. Østoft SH, Bagger JI, Hansen T, Pedersen O, Faber J, Holst JJ, Knop FK, Vilsbøll T. Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. *Diabetes Care*. 2014;**37**(7):1797–1805.
4. Docena MK, Faiman C, Stanley CM, Pantalone KM. Mody-3: novel HNF1A mutation and the utility of glucagon-like peptide (GLP)-1 receptor agonist therapy. *Endocr Pract*. 2014;**20**(2):107–111.
5. Østoft SH, Bagger JI, Hansen T, Hartmann B, Pedersen O, Holst JJ, Knop FK, Vilsbøll T. Postprandial incretin and islet hormone responses and dipeptidyl-peptidase 4 enzymatic activity in patients with maturity onset diabetes of the young. *Eur J Endocrinol*. 2015;**173**(2):205–215.
6. de Heer J, Holst JJ. Sulfonylurea compounds uncouple the glucose dependence of the insulinotropic effect of glucagon-like peptide 1. *Diabetes*. 2007;**56**(2):438–443.