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Case Report

The Role of Imatinib in Pediatric Type 1 Diabetes

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Abstract

We report the first case of imatinib use in an adolescent with diabetes and suggest that it impacts the natural course of disease. A 14-year-old male patient presented in diabetic ketoacidosis (DKA) and was diagnosed with presumed autoantibody-negative type 1 diabetes (T1D) as well as myeloid neoplasm with platelet-derived growth factor receptor beta (PDGFRB) rearrangement. After starting exogenous insulin and imatinib, he experienced a 1.7-point reduction in glycated hemoglobin (HbA1c) and a 71% reduction in insulin requirement with sustained partial diabetes remission. Our case suggests imatinib as a potential therapeutic agent for pediatric T1D.

Key Words: imatinib, pediatric, diabetes, case report

Abbreviations: DKA, diabetic ketoacidosis; G6PD, glucose-6-phosphate dehydrogenase; HbA1c, glycated hemoglobin; MODY, maturity-onset diabetes of the young; PDGFRB, platelet-derived growth factor receptor beta; T1D, type 1 diabetes.

Introduction

With the rising incidence of both type 1 and 2 diabetes in children and adolescents, efforts to mitigate this disease are needed more than ever. A growing body of evidence suggests that imatinib may attenuate or even reverse diabetes in both mice and adults (1-7). In children with diabetes, however, the role of imatinib has not yet been evaluated. We report a case of pediatric diabetes in which sustained partial remission was achieved and demonstrate that imatinib may play an important role.

Case Presentation

A 14-year-old previously healthy Black male presented to the hospital with a 2-week history of polydipsia, polyuria, and weight loss. He had no family history of diabetes or autoimmunity. On admission, his weight was at the 45th percentile ($Z = -0.11$) with a body mass index (BMI) of 15 kg/m^2 ($Z = -1.62$) and no acanthosis nigricans was noted on exam. He was found to be in diabetic ketoacidosis (DKA), with serum pH 7.15 (normal reference range, 7.31-7.47), glucose 560 mg/dL (31.1 mmol/L [normal reference range 65-99 mg/dL; 3.6-5.5 mmol/L]), HCO_3 9.7 mEq/L or mmol/L (normal reference range, 20-28 mEq/L or mmol/L), urine ketones 4+, glycated hemoglobin (HbA1c) 12.3% (0.12 proportion of total hemoglobin [normal reference range, < 5.7%; < 0.057 proportion of total hemoglobin]). He was also COVID-19 positive and glucose-6-phosphate dehydrogenase (G6PD) deficient with white blood cell count (WBC) 137.8 TH/mm^3 (0.14×10^9/L [normal reference range, 5-10 TH/mm^3; $0.005\text{-}0.01 \times 10^9$/L]). He has had mild anemia with hemoglobin level ranging from 9.2 to 12.2 gm/dL (92-122 g/L [normal reference range 13.3-16.6 gm/dL; 133-166 g/L]) and mean corpuscular volume (MCV) < 80 μm^3 or fL (normal reference range 79-95 μm^3 or fL). Both anti-thyroglobulin and anti-thyroid peroxidase antibodies were negative at the time of diagnosis, and he has remained euthyroid.

Diagnostic Assessment

After discharge, islet autoantibodies (glutamic acid decarboxylase, islet cell antigen 512, insulin, and zinc transporter 8) returned negative (Barbara Davis Core Lab, University of Colorado). Whole exome sequencing (modified from Roche NimbleGen SeqCap EZ Exome Library workflow (8)) was performed and mutations in genes linked to monogenic diabetes (including monogenic type 1 diabetes, maturity onset diabetes of the young [MODY], neonatal diabetes and hereditary pancreatitis) were ruled out, but he was found to have a pathogenic G6PD variant and alpha thalassemia trait. His lipid profile 3 months after diagnosis did not reveal any dyslipidemia: high-density lipoprotein 51.3 mg/dL (1.33 mmol/L [35-60 mg/dL; 0.91-1.6 mmol/L]), low-density lipoprotein 73.5 mg/dL (1.9 mmol/L [< 100 mg/dL; <2.59 mmol/L]), and triglycerides 57 mg/dL (0.64 mmol/L [36-138 mg/dL; 0.41-1.6 mmol/L]). He has also remained normotensive. Oncologic testing returned positive for somatic myeloid neoplasm with ETV6-PDGFRB fusion (UCSF500 Gene Panel (9)).

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Given the lack of family history and autoimmunity, as well as the clinical picture of DKA at presentation and weight loss in the setting of a viral trigger without signs of insulin resistance, he was diagnosed with type 1B diabetes (T1D) (10). Furthermore, known monogenic drivers of T1D (11), MODY mutations (12), and genetic variations that predispose to ketosis-prone diabetes such as *PAX4* (13) were negative. Of note, myeloid neoplasm with PDGFRB rearrangement has been associated with hypereosinophilic syndrome that can rarely affect the pancreas; however, our patient had only mild eosinophilia and no evidence of pancreatitis (14). Because patients with G6PD are at higher risk of developing impaired fasting glucose (15) and diabetes (16), his pathogenic G6PD variant may have played a role in his development of diabetes.

Treatment

During his initial admission, the patient was started on a multiple daily insulin injection regimen; he was requiring 0.7 u/kg/day upon discharge, and this decreased in the ensuing months to his present dosing of 0.2 u/kg/day. He was readmitted for initiation of imatinib 400 mg/day 3 months after diagnosis of diabetes. After repeat bone marrow biopsy demonstrated negative fluorescence in situ hybridization (FISH) for the PDGFRB rearrangement, his imatinib dose was decreased to 100 mg/day 6 months later.

Outcome and Follow-Up

Since starting imatinib, the patient's HbA1c has decreased from 6.3% to 4.6% (Fig. 1A) and his insulin use has lowered from 0.7 u/kg/day to 0.2 u/kg/day (Fig. 1B) without significant weight change (Fig. 1C); he has achieved sustained partial diabetes remission. Additionally, he has been in range > 90% of the time via continuous glucose monitoring (CGM) on a non-restricted diet of > 200 g carbohydrates per day without hypoglycemia (Fig. 2). His random, nonfasting C-peptide level 9 months after starting imatinib and 12 months post-diagnosis was 2.2 ng/mL (0.73 nmol/L [normal reference range, 1.1-4.4 ng/mL; 0.36-1.45 nmol/L]). He has been adherent to both insulin and imatinib, and both have been well-tolerated without any adverse or unanticipated events.

Discussion

We report an unusual case of type 1B diabetes in an adolescent in which partial diabetes remission was sustained for at least 6 months after initiating imatinib therapy. Because the impact

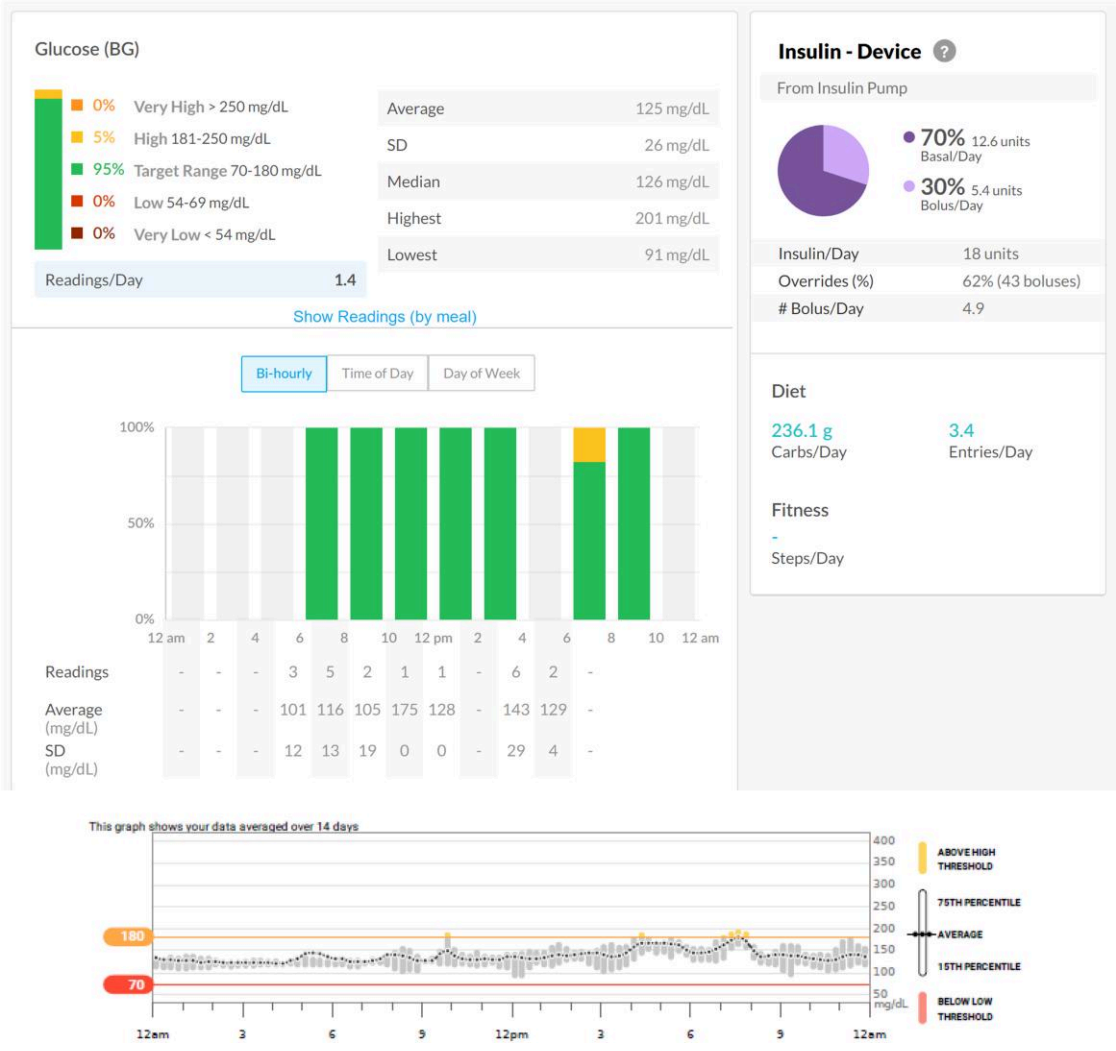

Figure 1. 2-week Dexcom G6 CGM/OmniPod 5 download with daily trends from approximately 15 months post-diagnosis and 12 months after starting imatinib.

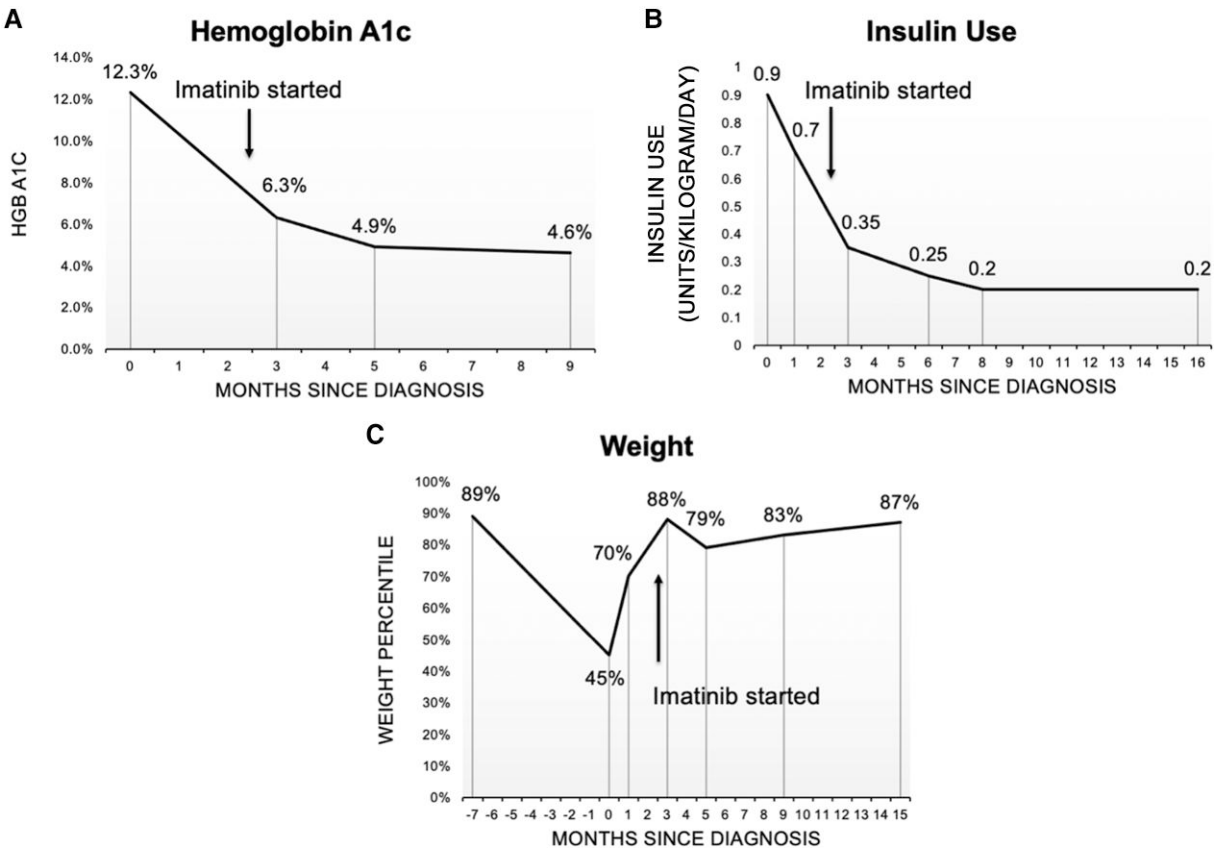

Figure 2. A) HbA1c over time in months since diabetes diagnosis with imatinib initiation indicated by arrow. B) Insulin use in units/kilogram/day over time in months since diabetes diagnosis with imatinib initiation indicated by arrow. C) Weight percentile over time in months since diabetes diagnosis with imatinib initiation indicated by arrow.

of imatinib in pediatric diabetes has not yet been evaluated, our case provides an initial opportunity to understand its potential role in diabetes management.

Imatinib is a tyrosine kinase inhibitor first approved for treatment of chronic myeloid leukemia. Various preclinical studies have demonstrated that it targets antidiabetic pathways as well: imatinib inhibits c-Abl in pancreatic beta cells, thereby blunting endoplasmic reticulum stress responses and reducing apoptosis (1, 2, 17). Imatinib also inhibits platelet-derived growth factor receptors, thereby increasing adiponectin and improving insulin sensitivity (18). Mouse studies have shown prevention of TID (1) and reversal of both T1D and type 2 diabetes with imatinib (2, 3, 6).

In adults, there have been several case reports demonstrating improved glycemic control with lowering or elimination of antihyperglycemic medications in type 2 diabetes with imatinib use (4). Similar effects have also been reported in T1D. After a 5-month course of imatinib 400 mg/day, a patient with T1D and TEL-PDGFRB rearrangement experienced a sustained 56% reduction in insulin dose and 2.2-point reduction in A1c with no change in weight (7). In a prospective multicenter, randomized placebo-controlled phase 2 trial in adults with new-onset T1D, subjects treated with imatinib 400 mg/day for 6 months showed preservation of beta cell function out to 12 months (5). While receiving imatinib, participants also exhibited lower Hgb A1c, less insulin use, higher adiponectin and lower proinsulin:C-peptide ratio, and improved beta cell glucose sensitivity when compared to the placebo group.

Our patient similarly has reduced HbA1c and insulin requirements with improved estimated beta cell function in the absence of weight change on imatinib. After starting imatinib, his HbA1c decreased from 6.3% to 4.6% over 6 months, and his insulin use decreased from 0.7 u/kg/day to 0.2 u/kg/day over 7 months. We defined partial remission as glycated hemoglobin level of 6.5% or less and insulin use per kilogram of 0.25 or less (19). Based on this definition, our patient achieved partial remission within 4 months after starting imatinib, and he has continued to sustain this. Notably, his HbA1c and insulin use initially dropped and then continued to decrease, indicating an ongoing improvement in beta cell function.

From composite type 1 diabetes TrialNet data and others, we know that beta cell function declines after diagnosis. In 2012, Greenbaum et al showed that C-peptide level decreases with a slope of −0.0245 pmol/mL/month (95% CI −0.0271 to −0.0215) through the first 12 months after diagnosis in subjects aged 7 to 45 years; the rate of decline is even greater for adolescents younger than 21 (20). Further, it is uncommon to still be in partial remission at 12 months; only 18% of children at least 10 years of age will be in partial remission at 12 months (21). Hao et al then demonstrated a mean C-peptide AUC of 0.4 pmol/mL for T1D adolescents aged 12 to 17 (22). Not only was our patient in partial remission at 12 months, but his estimated pancreatic beta cell function improved over the year. This is a significant deviation from the expected natural history of beta cell function after diagnosis and suggests that imatinib is likely having a positive effect.

Since this patient appears to have benefited from imatinib, it is important to try to define the underlying pathophysiology of his diabetes to identify future potential responders to this

therapy. For example, a patient with T1D who was found to have a STAT1 gain of function mutation experienced reversal of his diabetes with JAK inhibition (23). If we could similarly clarify the pathway that contributed to our patient's diabetes, then we could better understand the exact role that imatinib is playing and then extend this to others moving forward. We have taken initial steps to uncover this by performing whole exome sequencing, which did not reveal any clear diabetogenic mutations. We plan to pursue whole genome sequencing in future analysis.

One additional aspect of interest is the accuracy of the HbA1c% measurement in this patient. While persons with G6PD deficiency may experience underestimated HbA1c levels due to reduced erythrocyte lifespan (24), our patient had no evidence of ongoing hemolysis. He did, however, develop mild, chronic microcytic anemia, possibly due to iron deficiency. Untreated iron-deficient patients can have falsely high levels of HbA1c (25). If this were the case, then it is possible our patient in fact had lower HbA1c levels and entered partial diabetes remission even earlier, though it would not affect the argument that he was able to sustain it following imatinib therapy. Regardless, the observation that this adolescent patient has an HbA1c in the lower range of normal and time in range of > 90% on such low exogenous insulin doses while 16 months out from diagnosis, at a time of typical increased insulin resistance from puberty, suggests robust underlying beta cell function.

In summary, we present a unique case of an adolescent with type 1B diabetes in partial remission while treated with imatinib. This experience further supports the prior observations in preclinical and clinical settings in adult diabetes that imatinib therapy might benefit children and adolescents with diabetes by altering the natural course of disease. Further studies in prospective randomized trials are warranted to clarify the efficacy and safety of imatinib in pediatric diabetes.

Learning Points

- Imatinib is a tyrosine kinase inhibitor that targets antidiabetic pathways to prevent and reverse both type 1 and 2 diabetes in mice.
- Imatinib has been shown in case reports and in a phase 2 trial to alter the natural course of disease in adults with type 1 diabetes.
- Imatinib may also impact the natural course of type 1 diabetes in the pediatric population; future studies in prospective randomized trials are warranted.

Contributors

All authors made individual contributions to authorship. A.N. was responsible for clinical diabetes management. C.C. performed whole exome sequencing. K.L. was responsible for patient chart review. K.L., A.N., M.G., M.A., and S.G. were involved with diagnostic assessment. K.L. and S.G. submitted the manuscript. All authors reviewed and approved the final draft.

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Disclosures

S.E.G. has served on advisory boards for Abata, Avotres, Genentech, GentiBio, Provention Bio, SAB Biotherapeutics, Sana Biotechnology, and Sanofi. He has received support from Provention Bio and NIH for roles as an investigator in clinical trials. He serves on data and safety monitoring boards for Diamyd, Juvenile Diabetes Research Foundation, and INNODIA.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability

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

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