Tyrosine Kinase Inhibitor Sunitinib Allows Insulin Independence in Long-standing Type 1 Diabetes

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Diabetes Care 2014;37:e87–e88 | DOI: 10.2337/dc13-2132

Sunitinib, a tyrosine kinase inhibitor (TKI), along with other TKIs, is reported to lower blood glucose in type 2 diabetes and in recent-onset type 1 diabetes (T1D) (1,2). We report a case of sunitinib apparently inducing remission in long-standing T1D.

A 48-year-old woman, with T1D diagnosed at age 9 and requiring lifelong insulin therapy, presented in 2004 with a pancreatic neuroendocrine tumor secreting gastrin. She proceeded to pancreaticoduodenectomy with adjuvant 5-fluorouracil chemotherapy. She had retinopathy, peripheral neuropathy, and impaired hypoglycemia awareness. Diabetes treatment included insulin aspart and glargine, total daily dose (TDD) of 25–35 units. Her pancreatic neuroendocrine tumor remained in clinical and radiological remission until 2007 when multiple liver and pancreatic metastases were found on surveillance imaging. Octreotide was introduced, and due to subsequent hypoglycemia, her insulin TDD was progressively reduced to 6–7 units. HbA_{1c} remained between 7–7.5% (53–58 mmol/mol).

Her metastatic disease progressed, and sunitinib 50 mg per day was commenced in June 2011, with later dose reduction to 25 mg per day after gastrointestinal side effects. Hypoglycemia worsened, and insulin was reduced from 7 units TDD to 1 unit TDD over 2 months, stopping completely after 3 months. Thyroid, renal, adrenal function, and IGF-1 were within normal limits. For the next 3 months, she was ambulant, eating regular small meals, and insulin independent, without hyperglycemia or ketosis, and preprandial capillary blood glucose readings were between 90–144 mg/dL (5–8 mmol/L). HbA_{1c} was 7.9% (62.8 mmol/mol) on starting sunitinib and decreased to 6.7% (49 mmol/mol) after 5 months of treatment. During that time period, her body weight also steadily increased from 62.5 kg to 76.8 kg with no edema, due to improved appetite and well-being. Fasted serum C-peptide after 5 months of sunitinib treatment was 69.5 ng/mL (0.21 nmol/L), with corresponding glucose 129.6 mg/dL (7.2 mmol/L). In December 2011, 3 months after stopping insulin, she died of pneumonia and severe sepsis.

To our knowledge, this is the first report of a TKI allowing a patient with a 40-year duration of T1D to discontinue insulin for several months. Studies in a rodent autoimmune diabetes model have shown that imatinib and sunitinib can both induce long-term remission (3). Imatinib induces diabetes remission in the *db/db* mouse, possibly by increasing β-cell mass (4). Dasatinib given for 2 weeks in a patient with type 2 diabetes and chronic myelogenous leukemia resulted in doubling of fasted C-peptide levels (5).

Remission of T1D in this patient might have arisen due to promoting insulin release or through an insulin-like effect on target tissues through activation of downstream signaling pathways. After 5 months of sunitinib, our patient had detectable C-peptide production. However, using an accepted cutoff for fasted C-peptide of $>$0.3 nmol/L, she remained in the range associated with insulin-deficient T1D. Somatostatin analogs may suppress ketogenesis and counterregulatory responses, leading to insulin reduction but not remission. Taken together, this case and the extant literature suggest that further research into the effect of TKIs on the insulin signaling pathway and the effect on patients with T1D would be of value.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.S.B.H. wrote the initial main text of the manuscript. S.A.A., P.R., and S.J.B.A. contributed to editing and preparing the manuscript for submission. M.S.B.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes

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responsibility for the integrity of the data and the accuracy of the data analysis.

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