

Case Report

Insulin Independence in a GAD-65 Positive Patient Utilizing a Proton-Pump Inhibitor

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Abstract

Proton-pump inhibitors (PPI) are known to increase gastrin levels up to 9 fold. Gastrin subsequently works to promote islet cell neogenesis via the stimulation of the Reg gene receptor on progenitor cells within the human pancreatic ductal cells. We detail the case of a 56 year-old woman with a thin body habitus (BMI 22) and positive GAD65 antibodies who presented with diabetic ketoacidosis with a glucose of 771 mg/dL. Her baseline hemoglobin A1C was 11.1% with a C-peptide of 1.7 ng/mL before insulin was initiated at the time of her hospitalization. She had been maintained on 18- 20 units of insulin per day (0.35 units/kg/day) for two years since her hospitalization with hemoglobin A1C levels consistently <6.0%. This patient was successfully transitioned off of basal and bolus insulin therapy following the initiation of 40mg of omeprazole twice daily. Having successfully transitioned a patient off of insulin for more than 16 weeks, we believe that PPI therapy may offer future insight into an innovative treatment for some patients with diabetes.

INTRODUCTION

Diabetes is a disease characterized by an absolute deficiency of insulin due to autoimmune attack, as in type 1, or insulin resistance and subsequent insulin deficiency resulting from beta cell apoptosis, as seen in type 2. Current treatment of diabetes focuses on improving insulin sensitivity, increasing endogenous insulin secretion in existing beta cells, or replacing insulin via injections. However none of these therapies address the underlying absolute deficiency of beta cells and subsequent hyperglycemia resulting from inadequate insulin production.

It has long been known that gastrin, a peptide hormone produced in the antrum of the stomach, duodenum, and pancreas, stimulates hypertrophy of pancreatic beta cells. Patients who have undergone resection of the antrum, duodenum, and proximal jejunum have a decreased insulin response to glucose challenges [1]. Conversely, patients with Zollinger-Ellison syndrome who have gastrin secreting tumors, have been shown to have islet cell hyperplasia [2,3]. Proton pump inhibitor (PPI) therapy has been shown to indirectly increase gastrin levels in a dose-dependent fashion [4,5]. There is new data suggesting that gastrin works through the Reg receptor in human pancreatic ductal tissue where progenitor cells can be stimulated to transform into fully functional islets containing new beta cells populations [6-8].

In the clinical realm a recent clinical study examined the effects of 12 weeks of pantoprazole therapy in patients with

Type 2 diabetes and demonstrated increases in plasma insulin and gastrin levels along with improvements in hemoglobin A1C (A1C) [9].

We present the case of a 56-year old woman with positive GAD-65 antibodies and a two-year history of insulin dependence at a dose of 0.35 units/kg/day, who was successfully tapered off of insulin therapy after initiating therapy with omeprazole 40mg twice daily. This patient has remained off of insulin therapy for 16 weeks and is being maintained exclusively on omeprazole with fasting glucose levels remaining less than 100 mg/dL with maximal glucose levels of 125 mg/dL.

CASE REPORT

LC is a 56-year-old woman who presented in diabetic ketoacidosis on 4/9/11. Her past medical history included a thirty-year history of sarcoidosis and a history of diabetes for which she was on no diabetes medications until two days prior to admission. Approximately four months prior to admission, LC was treated for a sarcoidosis flare with methylprednisone 16mg every other day and afluticasone and salmeterol (500/50) inhaler twice daily. Ten days prior to hospital presentation, she developed polydipsia and polyuria, which prompted the patient to discontinue her oral steroids. Two days prior to admission, due to persistent symptoms, her primary physician began metformin 500 mg twice daily.

At presentation, LC's initial laboratory studies demonstrated

the following: blood glucose 774 mg/dL, pH 7.35, anion gap 14, bicarbonate 24 mmol/L, positive serum acetone, and positive urine ketones. Her chest X-Ray demonstrated bilateral fibrosis of the upper lung fields consistent with chronic sarcoidosis. LC's A1C was 11.1% at the time of admission. Glutamic acid decarboxylase antibody levels were 2.2 U/mL (reference range: <1.0 U/mL), Insulinoma-Associated Antibody-2 (IA-2) levels were <0.8 U/mL (reference range: <0.8 U/mL), and Insulin Autoantibodies were <0.4 U/mL (reference range: <0.4 U/mL).

LC was treated with aggressive fluid repletion and a Regular insulin drip before being transitioned to subcutaneous insulin. At the time of discharge, she was on a regimen of 6 units of glargine at bedtime and 4 units of lispro with meals and sliding scale to correct for hyperglycemia (0.35 units/kg/day). Metformin was discontinued upon admission to the hospital and was not resumed. After consultation with pulmonology the fluticasone and salmeterol inhaler was discontinued and methylprednisone was decreased to 8mg every other day with plans to taper as tolerated. **** months following her discharge LC stopped her oral steroids and has not required any since.

Three months later after the initiation of insulin, LC's A1C was 6.5% and six months later it had fallen to 5.7%. Over the course of two years her A1C's consistently remained <6.0% while on insulin therapy. Just over two years after insulin was started, LC was treated with omeprazole 40 mg twice daily. Within two weeks of initiation of omeprazole, her basal and bolus insulin was tapered and discontinued. She communicated her blood sugars to the medical team as requested and reported no glucose levels, including postprandial levels that were above 120 mg/dL. Prior to discontinuation of insulin, after 16 months of insulin therapy, LC's C-peptide was 1.7 ng/mL (NR: 0.8-3.1 ng/mL).

Since that time her A1C has been monitored at three-month intervals and consistently remained ≤6.0% again without diabetes medications. Her most recent C-peptide was 3.12ng/mL sixteen weeks after the discontinuation of insulin with a concomitant glucose of 76 mg/dL. GAD antibodies remained elevated at 2.1 U/mL.

DISCUSSION

Mefford recently described improved glycemic control and insulin production after starting treatment with omeprazole in a 43-year old man with type 2 diabetes [10]. A randomized trial by Singh demonstrated marked improvement in glycemic control using the PPI, pantoprazole. Patients with type 2 diabetes received 40mg of pantoprazole twice daily over the course of twelve weeks and their A1C's improved from 7.6% to 6.8% ($p < 0.001$) [9]. The decrease in A1C significantly correlated with an increase in gastrin and insulin levels and beta cell function as measured by HOMA assessment [10].

A recent randomized study by Hove and colleagues using treatment with esomeprazole over 12 weeks did not improve insulin secretion or glycemic control. However patients in the control group had a significant 16.3% reduction ($p = 0.002$) in insulin production, whereas the esomeprazole treated patients had no decline [11]. Given the natural history of 2 diabetes characterized by the progressive loss of insulin secretion, its maintenance utilizing a PPI may demonstrate the potential role

for such an agent to preserve or enhance beta cell regeneration. In this respect the effect of proton pump inhibitors might be also of interest in type 1 diabetes.

Preliminary studies combining gastrin with epidermal growth factor resulted in up to a 75% reduction in insulin requirements among existing type 1 diabetes patients [13]. While regenerating islet cells alone has significant potential in patients with type 2 diabetes, patients with type 1 diabetes and ongoing autoimmune destruction of the islet cells will likely require additional treatment to protect the newly generated islet cells. By using combination therapy, and combining a PPI with an immune tolerance agent, there is the potential to increase beta cell mass among patients with type 1 diabetes.

A recent BrdU study, considered to be the gold-standard for determining if new insulin-producing cells are derived from ductal cells versus existing beta cells, found that two Reg peptides resulted in a 2-fold increase in the volume of small new islets derived from ductal cells after five days of treatment ($p < 0.05$) [12]. In addition to increased new islets, there was upregulation of pancreatic transcription factors including Ngn3, Nkx6.1, Sx9 and Ins. The ability of gastrin to stimulate the Reg gene receptor, which is located exclusively in pancreatic ductile tissue, holds potential for novel therapeutic approaches in the field of diabetes.

In type 1 diabetes mouse models, both PPI's and immune tolerance agents used alone have rendered mice insulin independent. Rodents, however, have the capacity to regenerate beta cells faster than in man and have less complex vascular, neural, and paracrine systems. Contributing factors may include their continuous patterns of eating and their islets having a higher percentage of beta cells and lower percentage of alpha, delta, pancreatic polypeptide and ghrelin-secreting epsilon cells. Perhaps these differences and complexities help explain why diabetes can be "cured" in a mouse with immunosuppression or PPI's alone. In man reversal of type 1 diabetes may require both islet regeneration in addition to immune protection.

Interestingly the patient we present did not require an immune tolerance agent. Her age, lean build and persistent presence of GAD65 antibodies suggest that her presentation may also be consistent with latent autoimmune diabetes of adulthood. Although LC did require significant doses of steroids to control her sarcoidosis the persistent need for insulin therapy after steroids were discontinued and the presence of GAD65 antibodies argue against steroid induced diabetes. It will be interesting to see whether a PPI alone will provide adequate glycemic control as more time passes.

The fact that she had detectable C-peptide at the time of hospital admission and PPI initiation may hold the key to LC's insulin independence. In spite of persistently elevated GAD65 antibodies, LC's C-peptide levels nearly doubled over the course of 16 weeks after insulin was discontinued. These findings suggest that LC had enough residual islet function for the PPI stimulated regeneration of islet cells to outpace autoimmune beta cell destruction.

The presence of C-peptide at the time of initiation of the PPI may be a caveat in her success. It is also possible that the type of

PPI utilized may have an impact; pantoprazole and omeprazole may have a more positive impact on glycemic control than esomeprazole.

Further study is needed to determine if PPI's may be a safe, effective and novel approach to patients with both type 1 and type 2 diabetes. We hypothesize that early treatment with PPI's shortly after diagnosis when there are still significant levels of C-peptide present will contribute to greater success. We also hypothesize that PPI therapy used in combination with an immune tolerance agent will lead to greater success in some patients who present with a more traditional type 1 picture.

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