

A Case of Slowly Progressive Type 1 Diabetes with Insulin Independence Maintained for 10 Years with α -glucosidase Inhibitor Monotherapy

Yuichiro Munakata¹, Tetsuya Yamada¹, Kazuma Takahashi², Sohei Tsukita¹, Kei Takahashi¹, Shojiro Sawada¹, Junta Imai¹, Yasushi Ishigaki¹, Yoshitomo Oka¹ and Hideki Katagiri¹

Abstract

Slowly Progressive Type 1 Diabetes (SPT1D) is characterized by the absence of insulin dependence at the onset of diabetes and persistent detection of islet cell autoantibodies. These patients with high titers of glutamic acid decarboxylase autoantibodies (GADA) are known to progress to insulin dependence within several years. Low-dose insulin injections have been reported to prevent or delay the decline of insulin secretion in SPT1D patients. We experienced the case of an SPT1D patient with preserved endogenous insulin secretion and good glycemic control achieved with α -glucosidase inhibitor (α -GI) treatment alone for 10 years despite having continuously elevated GADA titers. The details of this case suggest that α -GI treatment might have preventive effects on SPT1D progression.

Key words: α -glucosidase inhibitor, slowly progressive type 1 diabetes, glutamic acid decarboxylase autoantibodies

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Introduction

Slowly Progressive Type 1 Diabetes (SPT1D), also known as latent autoimmune diabetes in adults, is characterized by the absence of insulin dependence at the onset of diabetes and persistent detection of islet cell autoantibodies such as glutamic acid decarboxylase autoantibodies (GADA) and islet cell antibodies (ICA) (1, 2). Most SPT1D patients experience gradual declines in the numbers of pancreatic β cells and finally, after a mean period of three years, become insulin dependent (3, 4). A 5-year prospective study revealed high GADA titers [>10 U/mL] to be a risk factor for progression to an insulin-dependent state (5). In another prospective study, the fasting plasma C-peptide levels in patients with high GADA titers [>10 U/mL] on diagnosis of diabetes became undetectable within 12 years (4). The prevalence of SPT1D is reported to be as high as 10% among non-insulin-dependent diabetes mellitus patients in

certain ethnic groups, including Caucasian, Japanese, Chinese, Indonesian and Thai populations (3). Therefore, examining the levels of GADA and ICA is highly recommended in diabetic patients who are not yet in an insulin-dependent state in order to predict future insulin dependence (i.e. the need for insulin treatment) (6). Insulin therapy can reportedly prevent continuous declines in endogenous insulin secretion in SPT1D patients, although sulfonylureas (SUs) do not (5). In addition, two reports suggest that thiazolidinediones delay becoming insulin deficient in SPT1D patients. Kawano et al. reported a case in which pioglitazone might have prevented the loss of insulin secretion for four years in an SPT1D patient (7). Another 3-year prospective study suggested that rosiglitazone preserves insulin secretion (8). We herein report the case of an SPT1D patient with fair glycemic control whose endogenous insulin secretion was well preserved for 10 years with α -glucosidase inhibitor (α -GI) monotherapy. We discuss the mechanisms whereby β cell defect progression was suppressed in this case and outline

¹Department of Diabetes and Metabolism, Tohoku University Hospital, Japan and ²Division of Diabetes and Metabolism, Department of Internal Medicine, Iwate Medical University School of Medicine, Japan

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Correspondence to Dr. Tetsuya Yamada, yamatetsu-ky@umin.ac.jp

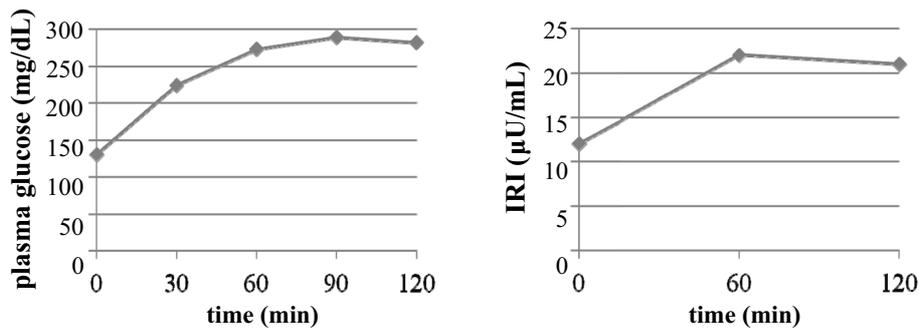


Figure 1. 75 g OGTT performed at the first visit.

TPOA (IU/mL) 105.0 219.1
 GADA (U/mL) 14 19.2 23.1 23.0 33.3 31.9 23.5 147

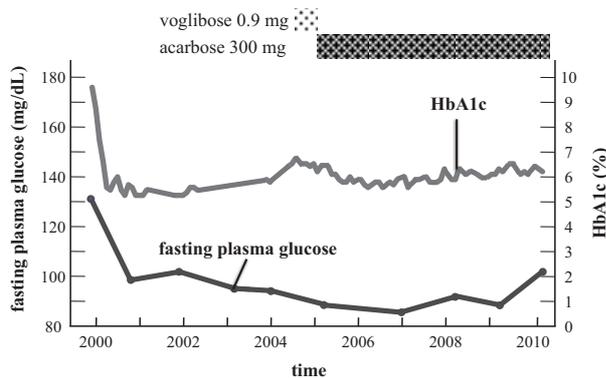


Figure 2. The clinical course of the patient.

the effectiveness of α -GIs in particular.

Case Report

The patient was a 27-year-old Japanese woman. In April 2000, at the age of 17, she was found to be asymptotically positive for urinary sugar during a high school medical checkup. She had no family history of diabetes mellitus. On her first visit to a local hospital, her body mass index (BMI) was 27.6 kg/m² and her HbA1c (NGSP) level was 9.9%.

She was diagnosed as having diabetes mellitus and started diet therapy without the administration of any other treatments. A 75 g oral glucose tolerance test (OGTT) revealed slight impairment of insulin secretion after glucose loading (Fig. 1). During the first three months of the diet therapy, her weight decreased from 63.0 to 59.5 kg and her HbA1c (NGSP) level decreased from 9.9 to 7.1%. In August 2000, she was hospitalized at Tohoku University Hospital for further education and examination.

On admission, the patient's BMI was 25.7 kg/m², her fasting plasma glucose level was 94 mg/dL and her fasting IRI level was 9.0 μ U/mL. In addition, she was positive for GADA (14 U/mL). Nevertheless, her insulin secretion was preserved (24-h urinary C-peptide excretion: 46 μ g/day and Δ CPR after 1 mg glucagon challenge: 2.1 ng/mL). Her serological human leukocyte antigen (HLA) types were A2, B54 (22)/B61 (40), Cw1 and DR4/DR9. Among these, DR4/DR9

is associated with susceptibility to type 1 diabetes (9). Taking these findings together, she was diagnosed with SPT1D. In 2001, she was found to be positive for anti-thyroid peroxidase antibody (TPOA) (105.0 IU/mL). In addition, we confirmed that she was negative for both insulinoma-associated antigen-2 autoantibodies (IA-2A) and insulin autoantibodies (IAA) throughout her clinical course.

We recommended that she start insulin therapy to prevent or delay progression to an insulin-dependent state. However, she chose to continue diet therapy alone. Her HbA1c (NGSP) levels remained below 6.9% for four years after discharge (Fig. 2). In 2005, her postprandial glucose level was found to be slightly increased (her blood glucose levels after evening meals exceeded 200 mg/dL according to self-monitoring data) and her HbA1c (NGSP) level had risen to 7.2%. Therefore, treatment with voglibose, an α -GI, was started at a dose of 0.9 mg/day. Later, voglibose was switched to another α -GI, acarbose, at a dose of 300 mg/day. To date, i.e. 10 years after the onset of diabetes, her HbA1c (NGSP) levels have remained within a range of 6.1 to 7.0% and her GADA titers have persistently been above 10 U/mL (Fig. 2). She was still positive for TPOA (219.1 IU/mL) in 2010 (Fig. 2). Repetitive oral glucose tolerance tests performed during the 10 years revealed that her glucose tolerance did not worsen (Fig. 3a). In addition, the Σ IRI, defined as $\{\Sigma\text{IRI} = \text{IRI} (0') + \text{IRI} (60') + \text{IRI} (90') + \text{IRI} (120')\}$, did not decrease after the initiation of α -GI treatment (Fig. 3b, c). These data indicate no apparent worsening of either glucose tolerance or insulin secretion during the patient's clinical course (Fig. 3). Therefore, in this case, endogenous insulin secretion remained fairly well preserved and an acceptable glycemic control was maintained for 10 years despite persistently elevated high GADA titers [>10 U/mL], positive TPOA and the lack of insulin therapy.

Discussion

Most SPT1D patients experience gradual decreases in insulin secretion over several years, and ultimately, after a mean period of three years, progress to insulin dependence (3, 4). According to previous reports, the risk factors for progression to an insulin-dependent state include SU treatment, high GADA titers [>10 U/mL], low C-peptide

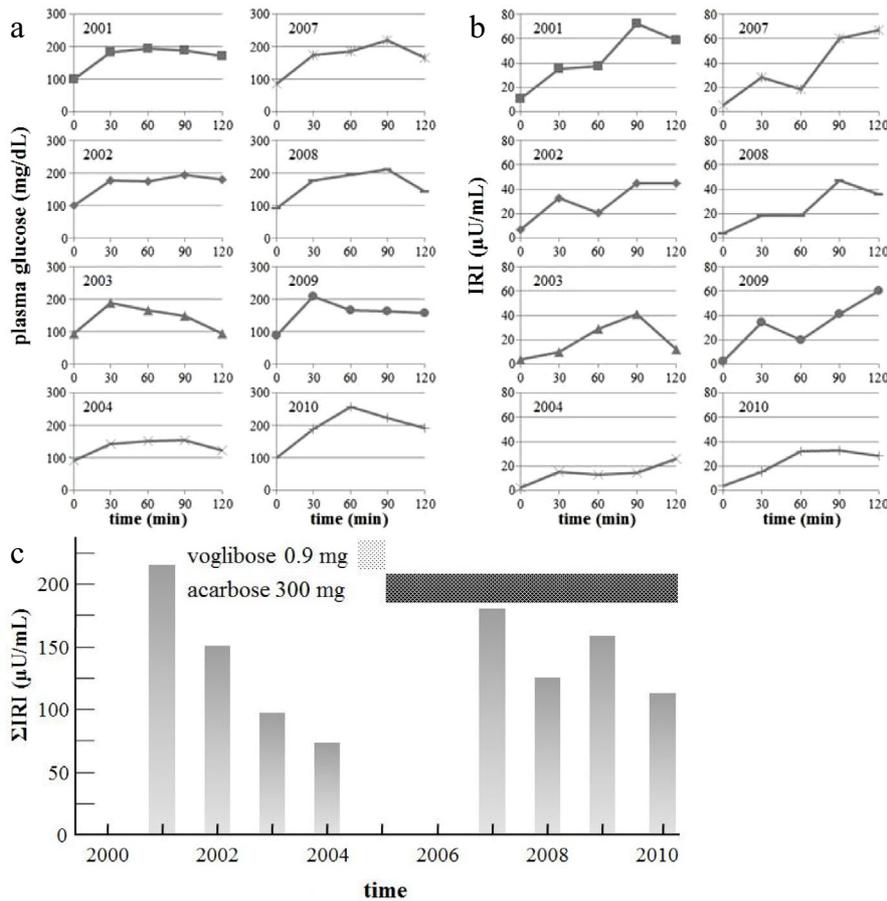


Figure 3. 10-year follow-up 75 g OGTT studies. a, b and c show the levels of plasma glucose, plasma IRI and Σ IRI respectively.

values [Σ C-peptide < 10 ng/mL] (3, 5) and the presence of other islet autoantibodies or TPOA (10, 11). Furthermore, in a prospective study (4), a 12-year follow-up revealed insulin secretion in the aforementioned patients with high GADA titers [>10 U/mL] on diagnosis of diabetes to have progressively worsened to complete β cell failure.

However, our present SPT1D patient, who had persistently elevated GADA and TPOA titers, has shown preserved endogenous insulin secretion for 10 years without the use of insulin therapy. Many analyses have focused on how to prevent or delay progression to an insulin-deficient state. The early initiation of insulin therapy (3, 5) and thiazolidinediones (7, 8) in SPT1D patients have been proposed as potential strategies, although one report showed that insulin intervention failed to delay insulin deficiency (12). In particular, among patients with SPT1D whose β cell function is preserved and who have high GADA titers [>10 U/mL] on initiation of insulin therapy, insulin intervention may be effective for preventing gradual β cell failure (3, 5). Exogenous insulin administration is reported to diminish β cell overload, resulting in β cell rest together with subsequent protection from damage via immunological and/or metabolic mechanisms. Conversely, high glucose concentrations and/or the use of SU therapy may thus lead to antigen expression by β cells and thereby increase their vulnerability to immu-

nological attacks (5). Although our present patient had persistently elevated GADA titers, her endogenous insulin secretion was preserved. In this case, good glycemic control, achieved with diet therapy and α -GI administration, is assumed to have prevented declines in endogenous insulin secretion, the natural course otherwise generally seen in SPT1D patients. Fig. 3c shows that the Σ IRI levels decreased between 2001 and 2004; however, after the initiation of α -GI treatment, the Σ IRI levels were persistently higher than those measured in 2003 and 2004, suggesting that α -GI treatment exerts protective effects on endogenous insulin secretion. α -GI treatment reportedly delays the development of type 2 diabetes in patients with impaired glucose tolerance (13). The preventive mechanisms of α -GI are considered to involve suppression of postprandial rises in plasma glucose, leading to decreased toxic effects induced by glucose and reduced stress on β cells (13). Furthermore, Suzuki et al. reported that α -GI neutralizes oxidative stress by increasing the production of H_2 , which acts as an antioxidant, in the gastrointestinal tract (14). Since oxidative stress is known to correlate with the loss of β cell function (15), increased H_2 production occurring in response to α -GI administration might also contribute to preserving the function of surviving β cells by directly reducing oxidative stress.

Clearly, further studies are needed before it can be con-

cluded that α -GI therapy contributes to preventing insulin deficiency in SPT1D patients. However, to our knowledge, this is the first report of an SPT1D patient with high GADA titers who was protected from progression to insulin deficiency for a long period (10 years) with α -GI monotherapy.

The authors state that they have no Conflict of Interest (COI).

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