Pioglitazone Might Prevent the Progression of Slowly Progressive Type 1 Diabetes

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Abstract

Although recent studies recommended that insulin should be administered to patients with slowly progressive type 1 diabetes, even those with non-insulin dependent status, patients prefer oral hypoglycemic agents to insulin injections. We report a slowly progressive type 1 diabetic patient whose insulin production was preserved for 4 years (ΣC-peptide from 29.48 ng/mL to 24.58 ng/mL) using pioglitazone despite a high titer of anti-GAD antibody (GADA; 120.7 U/mL). This case suggests that pioglitazone might prevent or delay the loss of insulin secretion and insulin dependency in slowly progressive type 1 diabetic patients.

Key words: pioglitazone, slowly progressive type 1 diabetes, PPAR-γ, anti-GAD antibody

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Introduction

Patients with slowly progressive type 1 diabetes (1) (SPT1D) or latent autoimmune diabetes in adults (LADA) (2) are characterized as non-insulin dependent at the onset of diabetes, are positive for β cell antibody(ies), and become insulin dependent after a few years. Although the Tokyo Study showed that low-dose insulin injections prevent or delay the decline of insulin secretion in SPT1D patients (3), patients prefer oral agents to insulin injection. Of the available oral hypoglycemic agents, thiazolidines have anti-inflammatory activities and may have beneficial effects for SPT1D patients.

Here we report a SPT1D patient whose insulin secretion was preserved using a thiazolidine.

Abbreviation: SPT1D: slowly progressive type 1 diabetes

Case Report

A 61-year-old Japanese man was referred to our hospital for surgery for ureterolithiasis and ureterectasia in April 2004. He had been properly treated for hypertension and dyslipidemia with valsartan and atorvastatin, respectively. He had no family history of diabetes. At the first visit, his body mass index (BMI) was 27.2 kg/m² and his fasting plasma glucose was 325 mg/dL and HbA1c was 8.3%. He had no diabetic complications and no sign of thyroid diseases. Before the operation, he reduced his body weight from 74.0 to 71.0 kg by lifestyle modification, and glycemic control was improved (HbA1c level improved from 8.3 to 7.4%).

Laboratory examination revealed that he was positive for the anti-GAD antibody (GADA; 120.7 U/mL), but his insulin secretion was preserved. Anti-insulinoma associated protein 2 (IA-2) antibody was negative. For a 75-g oral glucose tolerance test, his glucose values were 121 mg/dL (0 minute), 195 mg/dL (30 minutes), 262 mg/dL (60 minutes), 282 mg/dL (90 minutes), 284 mg/dL (120 minutes) and C-peptide values were 1.90 ng/mL (0 minute), 3.28 ng/mL (30 minutes), 6.41 ng/mL (60 minutes), 7.59 ng/mL (90 minutes), 10.3 ng/mL (120 minutes), and ΣC-peptide was 29.48 ng/mL.

Although we strongly recommended that he start insulin therapy to prevent or delay insulin dependency, he refused insulin injection; therefore we started pioglitazone 15 mg/day to relieve β cell overload (4). Within 7 months, HbA1c levels had decreased, and were within the normal range (Fig. 1). Although the titer of GADA exceeded 10 U/mL (575 U/mL in December 2005 and 286 U/mL in July 2007), the ΣC-peptide (24.58 ng/mL in May 2008) was preserved for 4 years with the administration of 15 mg/day pioglitazone. For the 75 g-OGTT, glucose values were 98 mg/dL (0
Figure 1. Clinical course of a case of slowly progressive type 1 diabetes in which pioglitazone prevented insulin deficiency.

Discussion

Recently, Maruyama et al showed that a low dose of insulin administration prevented or delayed insulin deficiencies in SPT1D patients (3). This intervention was most beneficial in patients with both a high titer of GADA (over 10 U/mL) and preserved insulin secretion, i.e. ΣC-peptide over 10 ng/mL. Based on their hypothesis, we recommended insulin administration for the present patient, but he chose the treatment with oral hypoglycemic agent.

Thiazolidinediones are peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists. PPAR-γ is a ligand-activated nuclear receptor and controls the expression of metabolic and immune response genes including nuclear factor (NF)-κB. Trans-repression of NF-κB leads to low interferon (IFN)-γ expression, and prevents T-helper1 (Th1) skewing of the Th1/Th2 balance (5). In fact, troglitazone was shown to ameliorate experimental autoimmune encephalomyelitis, which is thought to be a Th1 disease (6).

Of the available oral hypoglycemic agents, thiazolidinediones have been shown to prevent insulin deficiency. Fukuda et al first reported that troglitazone prevented cyclophosphamide induced type 1 diabetes (7) and Beales et al showed similar results (8). These findings were further confirmed by other groups (9, 10) and another thiazolidinedione was also reported to prevent the type 1 diabetes (11, 12). It was proposed that thiazolidinediones might be considered for β cell protection in LADA patients (12). In humans, Zhou et al (13) reported that rosiglitazone combined with insulin may be beneficial to preserve β cell function compared with insulin alone, but this study did not clarify the effect of monotherapy of thiazolidinedione.

Conclusion

To our knowledge, this is the first report of SPT1D in which thiazolidinedione monotherapy might prevent or delay the progression of insulin deficiency. Of course, the disease preventive HLA haplotype, DRB1 1501- DQB1 0602, might affect natural history of β cell in this case. To clarify whether prevention of insulin deficiency seen in this case was due to pioglitazone or not, therefore, diabetologists should consider a clinical trial of thiazolidinedione as a treatment option to prevent insulin deficiency in SPT1D patients.

References