Sitagliptin (DPP-4 Inhibitor)-induced Rheumatoid Arthritis in Type 2 Diabetes Mellitus: A Case Report

Kazuki Yokota and Naoya Igaki

Abstract

A dipeptidyl peptidase (DPP)-4 inhibitor, commonly used to treat patients with type 2 diabetes, has caused concern because of immune system side effects. We report a 48-year-old woman with type 2 diabetes who was diagnosed with rheumatoid arthritis (RA) after continued polyarthritis and an increase in rheumatoid factor up to 86 IU/mL after three months of treatment with sitagliptin, a DPP-4 inhibitor. The shared epitope (SE)-containing human leukocyte antigen (HLA)-DRB1 alleles, which are important predisposing factors for RA, were positive. RA might have been triggered by sitagliptin due to a predisposing condition.

Key words: dipeptidyl peptidase (DPP)-4 inhibitor, rheumatoid arthritis, human leukocyte antigen (HLA)

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Introduction

Dipeptidyl peptidase (DPP)-4 degrades the incretin hormones glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), which decreases their stimulatory effects on insulin secretion by beta-cells. In patients with type 2 diabetes, meal-related GLP-1 secretion is reduced. DPP-4 inhibitors block GLP-1 degradation, thus prolonging the incretin effect and enhancing glucose homeostasis. DPP-4 is a ubiquitous atypical serine protease family member and has physiological functions beyond incretin degradation, including effects on the endocrine and immune systems. As oral DPP-4 inhibitors are commonly used to treat patients with type 2 diabetes, there has been concern about side effects of the immune system. Recent studies in DPP-4 homozygous knockout mice and rheumatoid arthritis (RA) patients suggest that DPP-4 activity is inversely correlated with the severity of RA (1). Thus, a DPP-4 inhibitor might be involved in the pathogenesis of RA. Here, we report the case of a patient with type 2 diabetes who was treated with sitagliptin, a DPP-4 inhibitor, and developed RA.

Case Report

In January 2009, a 48-year-old woman had an HbA1c level of 6.9% (NGSP) (2) during a medical checkup. When the patient underwent a 75 g oral glucose tolerance test (OGTT) in accordance with the National Diabetes Data Group recommendations at a later date, her fasting, 0.5, 1, 1.5 and 2 hours plasma glucose levels were 128, 216, 247, 259 and 256 mg/dL, respectively. She had a personal history of obesity (BMI 26.4 kg/m²), the diabetics in her family history included her mother and maternal uncle, and her anti-gluutamic acid decarboxylase (GAD) antibody test was negative. Therefore, she was diagnosed with type 2 diabetes. She was prescribed nateglinide (270 mg t.i.d.) and miglitol (150 mg t.i.d.), which maintained her HbA1c level between 6.1% and 6.4%. In June 2010, her medications were changed to sitagliptin (50 mg per day), as it was expected that incretin therapy would improve important parameters, including body weight and beta-cell function (the patient’s BMI was 24.8 kg/m² and the HOMA-beta was 42.8% at the start of sitagliptin treatment), with a low risk for hypoglycemia. In September 2010, headaches and a low-grade fever developed daily in the evenings, with temperatures up to 37.2°C. The patient awoke frequently at night because of both joint swel-
Table 1. Results of Laboratory Tests of the Patient

<table>
<thead>
<tr>
<th>Peripheral blood count</th>
<th>Blood biochemistry</th>
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<tbody>
<tr>
<td>WBC 4,210 /mm$^3$</td>
<td>TP 6.9 g/dL</td>
</tr>
<tr>
<td>RBC 424×10$^6$ /mm$^3$</td>
<td>Alb 4.1 g/dL</td>
</tr>
<tr>
<td>Hb 13.1 g/dL</td>
<td>AST 22 IU/L</td>
</tr>
<tr>
<td>Ht 38.1%</td>
<td>ALT 23 IU/L</td>
</tr>
<tr>
<td>Plt 18.3×10$^4$ /μL</td>
<td>BUN 8.9 mg/dL</td>
</tr>
<tr>
<td>ESR 42 mm/hour</td>
<td>Cre 0.50 mg/dL</td>
</tr>
<tr>
<td>Urinalysis (-)</td>
<td>Fasting plasma glucose 121 mg/dL</td>
</tr>
<tr>
<td>Occult blood (-)</td>
<td>HbA1c (NGSP) 6.6 %</td>
</tr>
<tr>
<td>Prot (-)</td>
<td>T-Chol 161 mg/dL</td>
</tr>
<tr>
<td>Glu (-)</td>
<td>HDL-Chol 43.8 mg/dL</td>
</tr>
<tr>
<td></td>
<td>TG 122 mg/dL</td>
</tr>
</tbody>
</table>

Immunologic blood tests

- C-reactive protein 2.66 mg/dL
- MMP-3 51 ng/mL
- IgG 1.043 mg/dL
- IgA 159 mg/dL
- IgM 82 mg/dL
- IgE 244 IU/mL
- C3 143 mg/dL
- C4 41.7 mg/dL
- CH50 57.3 U/mL

Anti-nuclear antibody 10.2 index
Rheumatoid factor 86 IU/mL
Anti-CCP antibody <0.6 U/mL
Anti-DNA antibody <2.0 U/mL
Anti-Sm antibody <7.0 U/mL
Anti-SS-A antibody <10.0 index
Anti-SS-B antibody <10.0 index
Anti-RNP antibody <7.0 U/mL
Anti-GAD antibody <0.3 U/mL

Human lymphocyte antigen (HLA) typing

<table>
<thead>
<tr>
<th>HLA - A locus</th>
<th>HLA - B locus</th>
<th>HLA - DR locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A<em>11 , A</em>26)</td>
<td>(B<em>07 , B</em>54)</td>
<td>(DRB1<em>0101 , DRB1</em>0405)</td>
</tr>
</tbody>
</table>

The value for HbA1c (%) was estimated as an NGSP equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4% using the relational expression of HbA1c (JDS) (%) measured according to the previous Japanese standard substance and measurement methods and HbA1c (NGSP) (2).

ling and arthralgias in her hands, knees and ankles, which were the most painful after waking up in the morning. Laboratory results at that time were as follows: anti-nuclear antibody (ANA) 10.2 index, rheumatoid factor (RF) 86 IU/mL, C-reactive protein (CRP) 2.66 mg/dL and erythrocyte sedimentation rate (ESR) 42 mm/hour (Table 1). Analysis of the synovial-fluid revealed sterile cultures with no crystals. A radiographic skeletal survey and computed tomography (CT) of the chest, hands, knees, and ankles did not show sclerotic or lytic lesions or other evidence of a malignant condition. Although treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was initiated, the joint symptoms did not improve over the course of the following six weeks. The patient’s illness was differentiated from infections such as a bacterial endocarditis or a urinary-tract infection and various cultivation surveys were negative. She also did not have collagen diseases such as systemic lupus erythematosus or Sjögren’s syndrome-A/B, Anti-Smith, Anti-RNP: anti-ribonucleoprotein, Anti-GAD: anti-glutamic acid decarboxylase

Discussion

Previously, it has been reported that the number of peripheral T lymphocytes expressing DPP-4 is increased in the peripheral blood of RA patients (4). In contrast, soluble DPP-4 levels were reduced in RA patients compared with controls and were inversely correlated with the number of swollen joints (5, 6). Some reports indicate that RANTES (regulated upon activation, normal T-cell expressed and secreted) and stromal cell-derived factor (SDF)-1α actively participate in RA pathogenesis, and they have been shown to be substrates of DPP-4 activity (7, 8). The lower levels of soluble DPP-4 in RA patients may be matched by a reciprocal increase in T lymphocyte membrane expression of DPP-
Although the RF was negative in May 2009, approximately three months after sitagliptin use began in June 2010, the patient began to have headaches and polyarthritis, and the RF increased to 86 IU/mL. Sitagliptin was discontinued in December 2010, and the patient returned to nateglinide and miglitol after drug-induced arthritis was suspected. Ten days later, the joint swelling, arthralgia, and low-grade fever improved in the patient, and one month later, the CRP was negative. Additionally, the RF also declined, although it remained positive throughout the observation period.

Figure 1. Although the RF was negative in May 2009, approximately three months after sitagliptin use began in June 2010, the patient began to have headaches and polyarthritis, and the RF increased to 86 IU/mL. Sitagliptin was discontinued in December 2010, and the patient returned to nateglinide and miglitol after drug-induced arthritis was suspected. Ten days later, the joint swelling, arthralgia, and low-grade fever improved in the patient, and one month later, the CRP was negative. Additionally, the RF also declined, although it remained positive throughout the observation period.
associated with ACPA than with RA itself (12, 13). The present patient was HLA-DRB1 SE-positive and ACPA-negative, so this association was not applicable. However, Balsa et al. has described that SE-containing HLA-DRB1 alleles are positive in 35% of ACPA-negative RA patients (14). They hypothesized that the lack of association may be due to the influence of environmental factors. Two independent studies have reported an increased risk of ACPA-negative RA associated with HLA-DR3 (15, 16). In contrast, Balsa et al. did not support the association between ACPA-negative RA and HLA-DR3 but, rather, they suggested that this allele reduces the risk of ACPA-positive RA (14). More case studies will be necessary to confirm whether RA is triggered by sitagliptin in patients that are positive for SE-containing HLA-DRB1 alleles with or without ACPA.

In the post-marketing surveillance study of sitagliptin in Japan, approximately 243,500 patients were administered this drug for an investigational period of six months. Among these patients, only three developed RA. The RA was in remittance for each patient, and they all experienced acute exacerbation. In the present case, the patient was newly diagnosed with RA, as the RF test was confirmed to be negative prior to the onset of the arthritis. In addition, this patient had no signs or symptoms of RA before the administration of sitagliptin. We propose that susceptible HLA-DRB1 alleles are sufficient for RA to develop in patients after the administration of sitagliptin, even if these patients have no signs of RA. To the best of our knowledge, this is the first reported case of an individual developing newly diagnosed RA as a result of a predisposing condition, such as the presence of SE-containing HLA-DRB1 alleles, after the administration of a DPP-4 inhibitor.

Clinicians must utilize caution when prescribing DPP-4 inhibitors for the treatment of type 2 diabetes, as the effect of DPP-4 inhibition on the immune system is unclear. Caution should be exercised when prescribing sitagliptin alone with agents that are known to cause RA and when prescribing sitagliptin to high-risk patients with predisposing genes such as SE-containing HLA-DRB1 alleles.

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

References