Diabetol Int
DOI 10.1007/s13340-010-0010-y

CASE REPORT

Acute onset of rheumatoid arthritis associated with administration of a dipeptidyl peptidase-4 (DPP-4) inhibitor to patients with diabetes mellitus

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Received: 16 August 2010 / Accepted: 8 November 2010
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Abstract We describe the first case of a 63-year-old male patient with type 2 diabetes mellitus who was newly diagnosed with definitive rheumatoid arthritis (RA) 2 months after starting medication with a dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin. We subsequently performed a survey to determine if other such cases existed among patients who started taking sitagliptin at our university hospital and at hospitals in the Kashiwa and Noda districts. A survey of 147 patients treated with sitagliptin revealed an additional patient whose arthritis was also linked to the use of the DPP-4 inhibitor. This second patient had maintained her RA in a state of remission with diabetes for 15 years; however, 2 months after beginning sitagliptin therapy for control of diabetes, her arthritis relapsed as definitive RA. A recent study on patients with RA and on animals deficient in DPP-4 suggests that a decrease or absence of DPP-4 activity might be associated with cytokine-induced arthritis. On the other hand, a pooled analysis in the United States and a post-marketing monitoring in Japan have revealed that the occurrence of arthritis linked to pharmacologic inhibition of DPP-4 by sitagliptin is rare. Because DPP-4 might possibly be involved in the pathogenesis of RA, and the use of sitagliptin in our cases is linked to activation of RA, it is important to carefully follow patients treated with DPP-4 inhibitor to monitor for onset of RA, although the incidence rate of this adverse event is low.

Keywords DPP-4 · Adverse event · Stromal cell-derived factor-1 · Incretin · Chemokine · Oral hypoglycemic agent

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A dipeptidyl peptidase-4 (DPP-4) inhibitor is an oral agent used to treat type 2 diabetes mellitus by extending the half-life of glucagon-like peptide-1 (GLP-1) and enhancing its effects on glucose metabolism by DPP-4 inhibition. Similar to GLP-1, several cytokines, including stromal cell-derived factor-1 (SDF-1), have an identical X-Ala/X-Pro motif at their N terminus; this motif is a target for degradation and inactivation by DPP-4 [1]. Therefore, pharmacologic inhibition of DPP-4 activity may potentially cause adverse events related to cytokine-induced inflammation [2]. Despite numerous theoretical implications [3, 4], an association between DPP-4 inhibition and occurrence of arthritis has not yet been reported. We describe the first case of acute-onset rheumatoid arthritis (RA) linked to the use of a DPP-4 inhibitor for treatment of diabetes.

In May 2010, a 63-year-old man with type 2 diabetes presented at the outpatient clinic of the Jikei University

Published online: 07 December 2010

Kashiwa Hospital because of severe joint pain. He had been diagnosed with diabetes at the age of 45 years and treated with sulfonylurea (glimepiride, 3 mg/day) at Kobari hospital in recent years. In February 2010, his glycemic control was fair (HbA1c, 6.9%), but his postprandial glucose level was not well controlled; usually, it reached as high as 200 mg/dl. In addition, the patient sometimes experienced hypoglycemia in the evening with the original treatment with glimepiride. In order to improve the postprandial hyperglycemia and possible inadequate hypoglycemia, the doctor at the above-mentioned hospital decided to replace glimepiride by sitagliptin (50 mg/day), a specific inhibitor of DPP-4. He was in good health until early March 2010. Until that time, the patient's HbA1c level had decreased to 6.5%, but he subsequently experienced swelling of the knees, wrists, and metacarpal joints of the left hand. In May, our examination showed swelling, spontaneous pain, and flare on the metacarpal joints of the left hand, both wrist joints, both knee joints, the proximal interphalangeal joint of the second toe, and the metatarsal phalangeal joint of the right leg. Further examination indicated that he had neither diabetic microangiopathy nor atherosclerosis obliterans in the extremities. Anti-GAD autoantibody was not detected. His renal function appeared normal with a serum creatinine level of 0.90 mg/dl, but the results of laboratory tests were positive for RA (Table 1). Consequently, the patient was diagnosed with definitive RA, with a 28-joint disease activity score calculated using C-reactive protein (DAS28-CRP) of 4.57. Because the symptoms were serious, sitagliptin was discontinued, and insulin therapy combined with salazosulfapyridine, and a corticosteroid was initiated without observation of simple washout. In August, his RA activity was decreased by this treatment, but the activity still remained 3.42 points on the DAS28-CRP. The signs and symptoms of RA have not yet disappeared even 3 months after discontinuation of the treatment with sitagliptin.

Because RA onset in this case was related to administration of a DPP-4 inhibitor, we subsequently conducted a hospital-based survey to determine the presence of other such cases among 147 patients who started sitagliptin between February and May 2010 in the Jikei University Kashiwa Hospital and hospitals in the region of Kashiwa and Noda. We found an additional patient who exhibited recurrence of RA approximately 2 months after initiation of sitagliptin administration. This second patient, a 65-year-old woman, had been maintained in a state of RA remission (<2.60 points on the DAS28-CRP) for 15 years. She was diagnosed as having diabetes mellitus in November 2009. At that time, she weighed 61.2 kg and was 157 cm tall (BMI 24.8). Her laboratory tests indicated that her renal function was normal (serum creatinine 0.55 mg/dl; UN 18 mg/dl; urine protein and ketones negative), she had no anemia (RBC 520 $\times$ 10^4/μl, Hb 15.5 g/dl, Ht 46.4%), but chronic hyperglycemia with FPG 9.27 mmol/l, serum insulin 2.6 μU/ml, and HbA1c 7.1%. Anti-GAD autoantibody was not detected. In February, treatment with sitagliptin (50 mg/day) was initiated. Two months later, however, she experienced arthralgia and swelling of both wrist joints. In April, she was diagnosed with disease relapse as definitive RA (6.14 points).

In our cases, arthritis exhibited acute onset approximately 2 months after commencement of sitagliptin administration without any other apparent cause. Therefore, the occurrence and reactivation of RA were linked to the use of DPP-4 inhibitor in the time course analysis, and inhibition of DPP-4 could be related to the pathophysiology of

Table 1 Results of laboratory tests of the patient

Variable (units, reference range)	Results	
	12 May 2010	3 June 2010
Peripheral blood count		
White blood cell count (per mm^3)	7,700	12,700
Red blood cell count ($\times 10^4$/μl)	449	460
Hemoglobin (g/dl)	13.1	13.3
Hematocrit (%)	38.5	39.8
Platelet count ($\times 10^4$/μl)	27.9	23.7
ESR (mm/h)	29	17
Urinalysis		
Protein (mg/day)	0.1	0.1
Ketones	(−)	(−)
Blood biochemistry		
UN (mg/dl)	19	12
Se-Cre (mg/dl)	0.90	0.87
Fasting plasma glucose (mmol/l)	7.78	7.1
HbA1c (NGSP, %)	7.3	7.3
C-peptide (nmol/l)	0.57	n.t.
Immunologic blood tests		
Anti-GAD antibody (IU/ml, <0.3)	<0.3	n.t.
C-reactive protein (mg/dl)	0.6	0.1
Rheumatoid factor (IU/ml, <18)	137	n.t.
Rheumatoid factor-IgG index	9.8	n.t.
Anti-CCP antibody (IU/ml, <4.5)	43.2	n.t.
Anti-nuclear antibody (ELIS, IU/ml)	6.9 (−)	n.t.
MMP-3 (ng/ml, 17.3–59.7)	80.1	n.t.
IgG (mg/dl)	1,357	1,078
IgA (mg/dl)	457	395
IgM (mg/dl)	71	71
C3 (mg/dl)	139	102
C4 (mg/dl)	39	28
CH50 (mg/dl)	61	52

HbA1c (%) was converted from Japan Diabetes Society (JDS) value to National Glycohemoglobin Standardization Program (NGSP) value using the method of the Japan Diabetes Society

RA in these cases. Busso et al. [3] investigated the critical role of DPP-4 in RA. In the clinical study [4, 5], the plasma DPP-4 levels of RA patients were autonomously decreased when compared to those of osteoarthritis patients and were inversely correlated with C-reactive protein levels. In the experimental study, the endogenous level of intact SDF-1, a proinflammatory chemokine causing RA, was dependent on DPP-4 activity; mice genetically deficient for DPP-4, DPP-4(−/−) showed increased severity of antigen-induced arthritis. From these findings, we analyzed whether reduced degradation of SDF-1 by pharmacologic inhibition of DPP-4 caused the onset of arthritis by measuring the concentration of SDF-1α (by Quantikine^{R}, R&D Systems, Inc.) in preserved serum from our first case. The result showed no increase in the level of SDF-1α (1,127 pg/ml) in the sample of the period of therapy with sitagliptin compared to control samples and the reference range in the condition that the assay was not for intact SDF-1α nor performed under the in vitro inhibition of DPP-4. Thus, we failed to obtain direct evidence of SDF-1 having a role in the triggering mechanism of the development of RA in patients with type 2 diabetes treated with the DPP-4 inhibitor sitagliptin. DPP-4 has many physiological substrates, including peptides of the glucagon superfamily, some hormones, and chemokines. Among these, at least 15 chemokines are considered to be inactivated by DPP-4 through cleaving the characteristic peptide sequence, although many of these peptides are inactivated by more than one enzyme. Thus, many of these peptides are not influenced by one-enzyme inhibition. Among these substrates, however, SDF1a/b is thought to be physiologically catalyzed by DPP-4. Therefore, a decrease in the activity of DPP-4 might contribute to the development of RA in addition to possible activation of multiple cytokines other than SDF-1.

Currently, large-scale studies are being conducted on the safety and adverse events of sitagliptin. A pooled analysis of data from 10,246 patients in the US has recently been published [6]. Among the reported adverse events that might be related to sitagliptin, arthralgia occurred at a frequency of 0.2 incident events per 100 patient-years in the US, which was not significantly different compared with that in patients who were non-exposed. In addition, a recently published report on post-marketing information in Japan [7] showed that of the 967 adverse events observed during 6 months in Japan, only three patients, including our two, presented with occurrence or reactivation of RA; six patients showed arthralgia, and the other patients developed joint swelling related to sitagliptin use. Therefore, the adverse events of the two cases reported here should be considered as relatively rare and observed only in individuals with susceptibility to the disease, that is, those with a tendency to have occurrence or reactivation of RA associated with DPP-4 inhibition. Susceptible patients administered DPP-4 inhibitor must be carefully observed to prevent acute onset of RA.

Because DPP-4 might be involved in the pathogenesis of RA and the use of sitagliptin was linked to activation of RA in our cases, it is important that patients receiving treatment with DPP-4 inhibitor be carefully followed, although the incidence rate of this adverse event is low.

Acknowledgments The value for HbA1c (%) is estimated as NGSP equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS)(%) + 0.4%, considering the relational expression of HbA1c (JDS)(%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP) [8]. We have reported these cases to the office of Ministry of Health, Labor and Welfare. We thank Ms. Kumiko Nezu for her help in editing the manuscript. We declare that we have no conflicts of interest.

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