CASE REPORT

Development of type 1 diabetes in a patient treated with anti-interleukin-6 receptor antibody for rheumatoid arthritis

Eiji Kawasaki* iD, Takahiro Fukuyama, Aira Uchida, Yoko Sagara, Yuko Nakano, Hidekazu Tamai, Masayuki Tojikubo, Yuji Hiromatsu, Nobuhiko Koga

Department of Diabetes and Endocrinology, Shin-Koga Hospital, Kurume, Japan

ABSTRACT

Interleukin-6 is a pleiotropic cytokine that plays a pathogenic role in type 1 diabetes. Therefore, anti-interleukin-6 receptor antibody, tocilizumab, used for the treatment of rheumatoid arthritis, is considered a candidate for immune intervention in type 1 diabetes. Here, we report the case of a 73-year-old woman (HLA-DR9-DQ3 homozygote) with well-controlled rheumatoid arthritis who developed type 1 diabetes while receiving tocilizumab treatment. At 57 years-of-age, the patient was diagnosed with rheumatoid arthritis, for which she underwent tocilizumab therapy that enabled complete suppression of her joint inflammation. A total of 17 months after starting tocilizumab therapy, she noticed polydipsia, polyuria, general fatigue and weight reduction (−2 kg/month), and was diagnosed with type 1 diabetes with diabetic ketoacidosis based on an arterial pH of 7.26, serum ketone body of 7,437 μmol/L, blood glucose level of 925 mg/dL, glycated hemoglobin of 13.2% and the presence of anti-islet autoantibodies. This case report shows valuable insight regarding the effect of anti-interleukin-6 receptor antibody therapy on type 1 diabetes prevention.

INTRODUCTION

Interleukin (IL)-6 is a key pro-inflammatory cytokine that mediates the development and progression of chronic inflammatory and autoimmune diseases, including type 1 diabetes[1]. The expression of IL-6 in pancreatic islets correlates with insulitis/β-cell destruction in non-obese diabetic mice, and overexpression of IL-6 in pancreatic β-cells is associated with marked insulitis[2]. Besides this, reports state that the systemic administration of anti-IL-6 monoclonal antibody reduces the incidence of diabetes in non-obese diabetic mice[3], indicating that IL-6 has an essential role in the pathogenesis of β-cell destruction.

Tocilizumab is a humanized monoclonal antibody that acts as an IL-6 receptor antagonist, and is used in the treatment of various autoimmune disorders and inflammatory conditions, including rheumatoid arthritis (RA), Castleman's disease and coronavirus disease 2019[4,5]. Currently, a clinical study investigating the efficacy of tocilizumab in preserving β-cell function in new-onset patients with type 1 diabetes is being explored (NCT02293837). Based on our literature search, there have

been few reports of tocilizumab-related autoimmune endocrine disease and none involving type 1 diabetes. Here, we present the first report, to our knowledge, of type 1 diabetes developing during tocilizumab therapy.

CASE REPORT

A 73-year-old woman was diagnosed with RA (anti-citrullinated peptide antibody-positive) at the age of 57 years. She had no family history of diabetes or autoimmune diseases, including RA. Over the years, the patient's RA was treated with several antirheumatics showing resistance to sulfasalazine, methotrexate and prednisone. At aged 70 years, methotrexate and sulfasalazine regimens were discontinued due to adverse gastrointestinal effects and chronic kidney disease, respectively.

In January 2019, she was started on tocilizumab at a dose of 162 mg once every 2 weeks delivered via subcutaneous autoinjector. This treatment led to a remission of her arthritis, allowing for the successful tapering and eventual complete discontinuation of her prednisone treatment in August 2019 (Table S1). After discontinuing prednisone, the patient continued to experience beneficial effects on her arthritis and

complete suppression of inflammation while treated with tocilizumab. Furthermore, her urine glucose had been consistently negative and glycated hemoglobin was 5.5% in May 2019 (Table S1).

However, in June 2020, the patient complained of hyperglycemic symptoms, such as thirst, polydipsia, polyuria, generalized fatigue and a 2 kg loss of bodyweight. She visited Shin-Koga Hospital, Kurume, Japan, and was admitted for diabetic ketoacidosis. Her height, bodyweight and body mass index were 153 cm, 43.1 kg and 18.4 kg/m^2, respectively. On admission, her blood glucose level was 925 mg/dL, and glycated hemoglobin was 13.2% (Table 1). She tested positive for urinary ketone bodies, and her venous blood gas analysis showed metabolic acidosis. Serum C-peptide was 0.05 ng/mL, and serum β-hydroxybutyrate concentration was 6,154 μmol/L. The levels of autoantibodies to glutamic acid decarboxylase, insulinoma-associated antigen-2 and zinc transporter 8, determined by enzyme-linked immunosorbent assay (RSR Ltd., Cardiff, UK), were high at 241 U/mL (normal range <5 U/mL), >30 U/mL (normal range <0.6 U/mL) and 80.2 U/mL (normal range <10 U/mL), respectively. Insulin autoantibodies were negative. Human leukocyte antigen class II genotype was DRB1*09:01/*09:01-DQB1*03:03/*03:03, which is a strong susceptive genotypic combination of the DRB1-DQB1 haplotype in Japanese patients with type 1 diabetes[6]. Subsequently, the patient was diagnosed as having autoimmune type 1 diabetes in an insulin deficient-state and was started on insulin injection therapy. Ultimately, the patient was put on multiple daily insulin injection therapy using a combination of insulin lispro and insulin degludec. The current daily insulin requirement is ~0.35 U/kg.

DISCUSSION

Type 1 diabetes is an organ-specific autoimmune disease in which pancreatic β-cells are destroyed by autoreactive T cells. There is an accumulation of evidence that cytokines play crucial roles in the development of type 1 diabetes[1] and are thus potential immunotherapeutic targets for this disease. The pro-inflammatory cytokines, such as interferon-γ, tumor necrotic factor-α, IL-17 and IL-21, promote the differentiation and function of diabetogenic autoreactive T cells. In contrast, cytokines, such as IL-2, IL-10, transforming growth factor-β and type 2 cytokines, lead to immunosuppressive effects and prevent β-cell damage. IL-6 is a multifactorial cytokine that has a significant influence on both immunoregulation and non-immune events. IL-6 induces T helper 17 cells, important pathogenic T cells in type 1 diabetes, in coordination with IL-23, and inhibits the differentiation of transforming growth factor-β-induced regulatory T cells that play a protective role in β-cell destruction[7], suggesting that IL-6 might play a pivotal and pathogenic role in the development of type 1 diabetes. Studies on animal models of type 1 diabetes have shown that the expression of IL-6 in the islets correlates with insulitis/β-cell destruction, and β-cell-specific overexpression of IL-6 promotes islet inflammation[2,8]. Thus, anti-IL-6 therapy using IL-6-neutralizing antibodies or

tocilizumab results in marked suppression of insulitis, as well as the restoration of normoglycemia in these animals[3,9]. Based on this evidence, the EXTEND study is currently investigating

Table 1 | Laboratory data on admission

Urinalysis	
pH	5.5
Protein	(−)
Sugar	(4+)
Ketone	(+)
CBC	
WBC	6,900/μL
RBC	4.99×10^6/μL
Hb	15.7 g/dL
Hct	44.9%
PLT	8.9×10^4/μL
Biochemistry	
Na	122 mEq/L
K	5.3 mEq/L
Cl	81 mEq/L
BUN	61.9 mg/dL
CRE	2.61 mg/dL
UA	8.0 mg/dL
AST	47 U/L
ALT	28 U/L
γ-GTP	17 U/L
T.P.	7.1 g/dL
Amy	35 U/L
CRP	<0.02 mg/dL
Venous blood gas	
pH	7.248
PO$_2$	30.1 mmHg
PCO$_2$	37.9 mmHg
HCO$_3^-$	16.2 mmol/L
BE	−10.3 mmol/L
Glucose metabolism	
Glucose	925 mg/dL
HbA1c	13.2%
GA	63.8%
IRI	0.37 μU/mL
C-peptide	0.05 ng/mL
GAD antibody	241 U/mL
IA-2 antibody	>30 U/mL
ZnT8 antibody	80.2 U/mL
IAA	<125 nU/mL
Total ketone body	7,437 μmol/L
Acetoacetate	1,283 μmol/L
β-Hydroxybutyrate	6,154 μmol/L
Others	
TPO antibody	(−)
Tg antibody	(−)
TSH	0.37 μU/mL
FT4	1.74 ng/dL
HLA-A	*02:01/*24:02
HLA-B	*35:01/*54:01
HLA-C	*01:02/*03:03

Table 1 (*Continued*)

HLA-DRB1	*09:01/*09:01
HLA-DQB1	*03:03/*03:03

ALT, aspartate aminotransferase; Amy, amylase; AST, alanine aminotransferase; BE, base excess; BUN, blood urea nitrogen; Cl, chlorine; CRE, creatinine; CRP, C-reactive protein; FT4, free-thyroxine; GA, glycoalbumin; GAD, glutamic acid decarboxylase; γ-GTP, γ-glutamyltransferase; Hb, hemoglobin; HbA1c, glycated hemoglobin; Hct, hematocrit; HLA, human leukocyte antigen; IA-2, insulinoma-associated antigen-2; IAA, insulin autoantibodies; IRI, immunoreactive insulin; K, potassium; Na, sodium; PLT, platelets; RBC, red blood cells; Tg, thyroglobulin; T.P., total protein; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; UA, uric acid; WBC, white blood cells; ZnT8, zinc transporter 8.

whether tocilizumab can preserve β-cell function in new-onset patients with type 1 diabetes.

The present case report shows valuable insight regarding the protective effect of anti-IL-6 therapy in the context of the development of type 1 diabetes. In conclusion, the present study reveals that although tocilizumab therapy had a beneficial effect on the patient's rheumatoid arthritis, it did not prevent the development of type 1 diabetes. Despite this, although the transgenic expression of IL-6 in β-cells has been shown to have an association with marked insulitis in non-obese diabetic mice, these mice do not develop diabetes[8]. This suggests that IL-6 might contribute to, but is likely neither necessary nor sufficient for inducing or promoting β-cell destruction. We propose that the use of anti-IL-6 therapies, such as tocilizumab, might be ineffective in preventing type 1 diabetes, and that although there is currently no evidence that anti-IL-6 therapy precipitates type 1 diabetes, this possibility cannot be ruled out, because it has been reported that the IL-6 expression is highly reduced in insulin-deficient islets of patients with type 1 diabetes[10]. Furthermore, based on the patient's genetic background (strong susceptible human leukocyte antigen class II genotype) and the longer duration of tocilizumab therapy (17 months), there is a possibility that such a therapy delayed the onset of type 1 diabetes in the present patient. This case report offers a crucial insight, as a growing number of patients are currently treated with tocilizumab[11]. Therefore, clinicians charged with patients undergoing anti-IL-6 treatment should consider the need for careful monitoring of patients' blood glucose levels and glycated hemoglobin during its use.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Change over time of dosage of prednisone and parameters of glucose metabolism before development of type 1 diabetes.

DISCLOSURE

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