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

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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 diabetes1. 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 insulitis2. Besides this, reports state that the systemic administration of anti-IL-6 monoclonal antibody reduces the incidence of diabetes in non-obese diabetic mice3, 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 20194.5. 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 arthritis 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/m², 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. 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 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, 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. Thus, anti-IL-6 therapy using IL-6-neutralizing antibodies or tocilizumab results in marked suppression of insulin, as well as the restoration of normoglycemia in these animals. 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 × 10¹²/μL |
| Hb 15.7 g/dL | Hct 44.9% |
| Hct 44.9% | Hb 15.7 g/dL |
| Hb 15.7 g/dL | PLT 8.9 × 10⁹/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 80 mg/dL | |
| AST 47 U/L | |
| ALT 28 U/L | |
| γ-GTP 17 U/L | |
| TP 7.1 g/dL | |
| Amy 35 U/L | |
| CRP <0.02 mg/dL | |
| Venous blood gas | |
| pH 7.248 | |
| PO₂ 30.1 mmHg | |
| PCO₂ 37.9 mmHg | |
| HCO₃⁻ 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 | |
| IA-2 <125 U/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 *0201/*2402 | |
| HLA-B *3501/*5401 | |
| HLA-C *0102/*0303 | |
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. 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. 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. Therefore, clinicians charged with patients undergoing anti-IL-6 therapy 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 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; CI, chlorine; CRE, creatinine; CREP, C-reactive protein; FT4, free-thyroxine; GA, glycoalbumin; GAD, glutamic acid decarboxylase; γ-GTP, γ-glutamyltransferase; Hb, hemoglobin; HBAlc, 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.

**DISCLOSURE**

The authors declare no conflict of interest. Approval of the research protocol: N/A. Informed consent: Informed consent was obtained from the patient. Registry and the registration no. of the study/trial: N/A. Animal studies: N/A.

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