Tocilizumab Improved both Clinical and Laboratory Manifestations Except for Interleukin-18 in a Case of Multiple Drug-Resistant Adult-Onset Still’s Disease

Yoshihiro Yoshida, Mayuko Sakamoto, Kazuhiro Yokota, Kojiro Sato and Toshihide Mimura

Abstract

A patient with adult-onset Still’s disease (AOSD) resistant to multiple drugs was treated in our hospital. Even biologics that block tumor necrosis factor (TNF) were ineffective. However, this patient responded quite well to tocilizumab, an interleukin (IL)-6 receptor blocker, suggesting that it is among the promising candidate drugs for multiple-drug resistant AOSD. Although the serum levels of most inflammatory markers such as C-reactive protein (CRP) and ferritin were reduced promptly by tocilizumab, that of IL-18 remained high. Thus, IL-18 is considered to have a further upstream position than IL-6 or to be at the same level as IL-6 in the inflammatory cascade of AOSD. This finding casts light on the pathogenesis of AOSD, and drugs that target IL-18 may prove beneficial in the treatment of this inflammatory disease.

Key words: adult-onset Still’s disease, IL-6, IL-18, tocilizumab

Introduction

Adult-onset Still’s disease (AOSD) is a systemic inflammatory disease characterized by a high spiking fever, arthritis, evanescent rash, and certain laboratory findings including abnormal liver function and elevated acute-phase proteins (1). AOSD is of unknown etiology although infectious triggers have been suggested (2, 3). The mainstay of treatment is glucocorticoids and/or non-steroidal anti-inflammatory drugs (NSAIDs) (4), but in addition, immunosuppressants, such as methotrexate (MTX) (5), cyclosporine A (CyA) (6), TNF blockers (7-10) or an IL-1 blocker (11), are sometimes necessary. Some patients are refractory even to the combination of the drugs mentioned above.

Recently, an IL-6 receptor blocker has been developed and made available in the clinical field. This agent, called tocilizumab, is a humanized anti-IL-6 receptor (IL-6R) antibody; it is used for Castleman’s disease (12), juvenile idiopathic arthritis (JIA) (13), and rheumatoid arthritis (14). As IL-6 is a key player in the induction of various acute-phase proteins (15) and AOSD shares some characteristics with JIA, tocilizumab is promising as an agent for multiple-drug refractory AOSD. Indeed, we successfully treated such a patient with tocilizumab, for whom even treatment with the TNF blockers, infliximab and etanercept, had not proven effective. In the course of the treatment, the levels of both CRP and ferritin decreased rapidly, but interestingly, that of IL-18 did not. We discuss the implication of this phenomenon in light of certain reports in the literature.

Case Report

A 25-year-old man was admitted to a local hospital with fever and arthritis of the knees. As he exhibited marked leukocytosis (>20,000/μL) along with an elevated level of CRP (>20 mg/dL), infectious diseases were suspected at first. Treatment with various antibiotics did not ameliorate the symptoms, and no bacterium or virus was detected. Eventually, an evanescent salmon-colored rash appeared on his trunk. Rheumatoid factor, anti-nuclear antibody and anti-neutrophil cytoplasmic antibody (ANCA) were all negative. AOSD was suspected and the patient was treated with (i) prednisolone (PSL, 40 mg/day), (ii) intravenous methylpred-
nisolone 1 g/day for 3 days (steroid pulse) ×2 times, (iii) azathioprine (100 mg/day), and (iv) MTX (8 mg/week), but the levels of CRP, ferritin, and white blood cells (WBCs) did not normalize. He was referred and admitted to this hospital about 2 months after the onset of the symptoms.

On examination, the patient presented as obviously ill. His body temperature was 37.1°C, pulse 89 beats per minute, and blood pressure 125/62 mmHg. His weight was 60.0 kg and height 169 cm. Chest sounds were normal. The abdomen was flat and soft and bowel sounds were normal. The liver and spleen were not palpable. Skin rash was not observed. The leukocyte count was 25.37×10³/μL (92.9% neutrophil), hemoglobin level 13.8 g/dL, and platelet count 266×10³/μL. The CRP level was 7.19 mg/dL, ferritin 1890 ng/mL, and matrix metalloproteinase-3 (MMP-3) 339.0 ng/mL. The aspartate aminotransferase level was not increased (16 IU/L, normal range 10.0-37.0) but lactate dehydrogenase (LDH) was slightly elevated (237 IU/L, normal range 107.0-220.0). No bone erosion was observed by X-ray. The patient was treated with PSL (60 mg/day) and MTX (8 mg/week), and one course of steroid pulse was performed again, followed by tacrolimus (3 mg/day). General fatigue persisted.
and the level of CRP remained high, as well as that of ferritin (Fig. 1A). The dose of MTX was increased to 10 mg/week and then to 12.5 mg/week with no evident improvement. As the blood levels of tacrolimus remained low, it was discontinued and infliximab (3 mg/kg, 165 mg in total) was begun with the result of a decrease in the CRP level. After the second infusion of infliximab (200 mg), however, the CRP level rebounded. Infliximab was switched to etanercept and the patient was discharged. However, the CRP level did not normalize in the outpatient clinic of this hospital and it was difficult to taper the dose of PSL. CyA (75 mg/day) was added and etanercept was discontinued. The dose of CyA was increased to 200 mg/day, without notable benefit. Finally, after discussion with the patient and his family, we decided to use tocilizumab. After the first treatment with tocilizumab (480 mg, 8 mg/kg), the level of CRP dropped to below 0.1 mg/dL. The patient also reported that his general fatigue disappeared. He was treated with tocilizumab every 4 weeks and the levels of ferritin and MMP-3 gradually and consecutively came into the normal range (Fig. 1B). As reported previously (16), the level of IL-6 elevated after the initiation of tocilizumab therapy, however, the level of IL-18 remained extremely high (more than 5,000 pg/mL, Fig. 1C). Almost 16 months have passed since the first treatment with tocilizumab, however, the level of IL-18 plays in AOSD, it appears to afford collateral evidence that IL-18 is involved in the pathogenesis of the disease.

This case reveals the potential of tocilizumab to be a quite effective drug for refractory AOSD. It is also possible, however, that tocilizumab may have to be continued as long as the level of serum IL-18 remains high. In such a case, drugs that target IL-18 may prove beneficial to the patients.

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References