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CASE REPORT

Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab

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Abstract We report a 29-year-old Japanese woman with disseminated intravascular coagulation (DIC) and adult onset Still's disease (AOSD). Her disease was refractory to high-dose glucocorticoids, two courses of steroid pulse therapy, and addition of cyclosporine (3.5 mg/kg/day). The serum interleukin-6 level was markedly elevated. Therefore, we administered an anti-interleukin-6 receptor antibody (tocilizumab, 8 mg/kg fortnightly), which dramatically improved her symptoms and the levels of acute-phase proteins. In addition, rapid tapering of the glucocorticoid dose was possible. Four months later, she was maintained on tocilizumab infusion once a month with low-dose steroid therapy. Cyclosporine is one of the first-line immunosuppressants for AOSD, especially when associated with DIC, hepatic failure, or hemophagocytic syndrome. In patients with cyclosporine-resistant AOSD, tocilizumab may be another useful option.

Keywords Adult onset Still's disease · Disseminated intravascular coagulation · Interleukin-6 · Tocilizumab

Introduction

Adult onset Still's disease (AOSD) is an uncommon disorder that typically features an evanescent rash, sore throat, intermittent spiking fever, and polyarthritis. Glucocorticoids are the mainstay of treatment, but some patients require additional immunosuppressants, including methotrexate, cyclosporine, anti-TNF agents, or the IL-1 receptor antagonist anakinra [1]. Here, we report a patient with treatment-resistant AOSD complicated by disseminated intravascular coagulation (DIC), successfully managed with tocilizumab, a humanized monoclonal anti-IL-6 receptor antibody.

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Case report

A 29-year-old Japanese woman was admitted to her local hospital with a high fever, sore throat, and arthritis. Bacterial infection was suspected due to elevation of the leukocyte count and C-reactive protein (CRP). Administration of imipenem (1 g/day) was immediately started, but symptoms and laboratory findings did not improve. Spiking fever (maximum: 40°C) continued for 2 weeks. No evidence of infection or connective tissue disease was obtained. AOSD was suggested by an elevated serum ferritin level, so she was referred to our hospital.

On admission, she had an evanescent rash on her anterior chest, upper arms, and thighs. Cervical lymph nodes were palpable, and she complained of arthralgia in the shoulders, knees, and ankles. Laboratory tests showed a leukocyte count of 14.7×10^9/l (93% neutrophils), hemoglobin of 10.6 g/dl, platelet count of 87×10^9/l, and ESR of 35 mm/h (normal <15). Aspartate aminotransferase was 213 U/l (normal range 11–30), alanine aminotransferase was 65 U/l (4–30), lactate dehydrogenase was 1,690 U/l (109-216), CRP was 26.1 mg/dl, and serum ferritin was 34,891.5 ng/ml (3.0–59.4). Serum IL-6 was markedly elevated to 52 pg/ml (normal <4). Fibrinogen was 270 mg/dl, fibrin degradation products (FDP) were 119.2 μg/ml

(normal <5.0), and D-dimer was 99.2 μg/ml (0.5–1.5). Her chest X-ray film and abdominal computed tomography (CT) demonstrated bilateral pleural effusions and mild splenomegaly, respectively. From these findings, a diagnosis of AOSD with DIC was made.

Intravenous methylprednisolone (1 g/day) was given for 3 days, followed by oral prednisolone at 60 mg/day (1 mg/kg). Continuous intravenous infusion of heparin was also done (Fig. 1). On the next day, fibrinogen decreased to 77 mg/dl, and purpura appeared on her chest and abdomen. Fresh frozen plasma was administered, and heparin was changed to nafamostat mesilate. Oral cyclosporine (2.5 mg/kg/day) was added for worsening of liver dysfunction. Two days after finishing methylprednisolone, spiking fever recurred and CRP rebounded. Prednisolone was changed to oral dexamethasone at 6 mg/day (0.12 mg/kg), cyclosporine was increased to 3.5 mg/kg/day, and intravenous dexamethasone (100 mg/day) was added for 3 days. DIC and liver function tests improved with resolution of her fever, but arthralgia and a high CRP persisted.

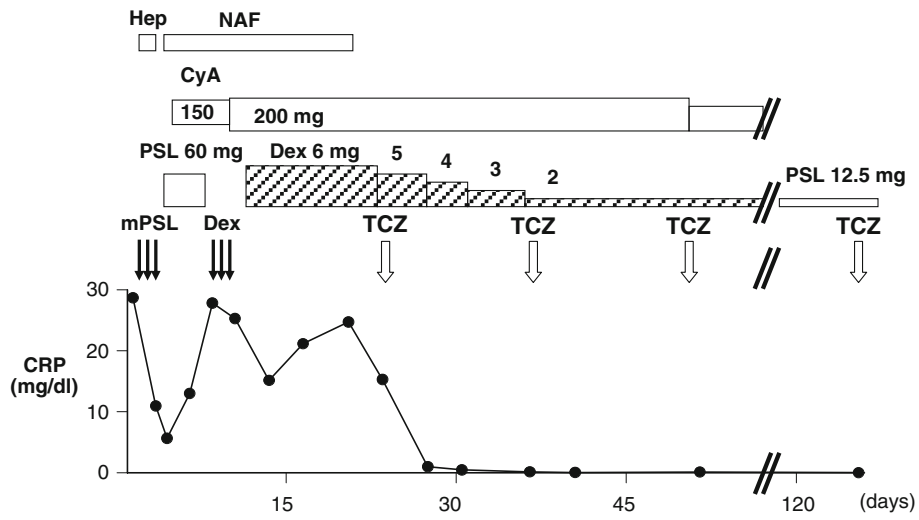
Since we had previously achieved dramatic improvement of intractable AOSD by using tocilizumab, we decided to try it. After oral informed consent was obtained, we administered 400 mg (8 mg/kg) of tocilizumab intravenously. On the next day, fatigue and arthralgia were markedly improved, and CRP was almost normalized within 1 week. Fortnightly administration of tocilizumab was continued, and dexamethasone was tapered to 2 mg/day at discharge. Three months later, cyclosporine has been discontinued, and 4 months later, she was maintained on tocilizumab every 4 weeks with prednisolone 10 mg/day.

Discussion

Various cytokines, including TNF-α, IFN-γ, IL-1β, IL-6, and IL-18, are elevated in AOSD [1]. Although IL-6 is thought to be important in this disease, its elevation is not observed consistently [2–6]. High circulating levels of a cytokine do not necessarily reflect its importance for AOSD [2]. Anti-TNF agents are less effective in patients with refractory AOSD [7]. A causative role of IL-1 in AOSD has been demonstrated through the response to its direct inhibition by anakinra [2, 3, 8]. We previously encountered a patient with refractory AOSD who responded to treatment with an anti-IL-6 receptor monoclonal antibody [9]. A role of IL-6 in AOSD could also be confirmed by direct blockade of its receptor.

The role of a cytokine cascade in AOSD was proposed by Fitzgerald et al. [2]. It is considered that TNF-α induces IL-1, which stimulates the production of IL-6. Accordingly, it may be better to directly inhibit IL-6, the downstream cytokine, by using tocilizumab than to block IL-1 with anakinra. A prospective study could properly define the most effective agents for treating AOSD that is refractory to current immunosuppressants, but its low prevalence precludes such an investigation. Tocilizumab may be more convenient than anakinra for clinical use because of less frequent administration, since daily subcutaneous injection of anakinra is needed, and interruption of therapy can trigger recurrence [2].

Efficacy of cyclosporine has been reported in patients with treatment-resistant AOSD [10, 11]. It is also effective for AOSD associated with DIC or hemophagocytic



ferritin	(ng/ml)	34891.5	4684	1923	270	19.7
IL-18	(pg/ml)	220,000	77,100		16,900	7,000
IL-1β	(pg/ml)	<10	<10		<10	<10
TNF-α	(pg/ml)	6.3	2.4		0.9	0.6
IL-6	(pg/ml)	52	68.1		373	10.6
IFN-γ	(IU/ml)	16.3	<0.1		<0.1	<0.1

Fig. 1 Summary of the clinical course. *Hep* heparin, *NAF* nafamostat mesilate, *mPSL* methylprednisolone, *PSL* prednisolone, *CyA* cyclosporine, *Dex* dexamethasone, *TCZ* tocilizumab. Reference values are as follows: IL-18 (normal <259.4), IL-1β (normal <10), TNF-α (normal <2.8), IL-6 (normal <4), and IFN-γ (normal <1.2)

syndrome [12, 13], and we have previously obtained dramatic improvement of AOSD associated with hepatic failure by administration of cyclosporine [14]. In the present patient, we added cyclosporine due to worsening of liver function tests. Although her fever, DIC, and liver function tests improved to some extent, cyclosporine did not improve arthralgia or the levels of acute-phase proteins. Thus, cyclosporine is not always effective for steroid-resistant AOSD.

Long-term tocilizumab therapy can induce remission of AOSD. Although spontaneous disease remission also occurs, our first patient has been disease-free with no medications for 7 years after 18 months of tocilizumab therapy (unpublished observation). Remission has also been achieved in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab [15], but it remains unclear how long anti-cytokine therapy should be continued for AOSD.

Disclosures Dr. Iwamoto and Minota have received royalties from Chugai Pharmaceutical Company, Ltd., Tokyo, Japan (less than $10,000). The other authors have disclosed no conflicts of interest.

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