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CASE REPORT

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Successful treatment of a patient with refractory adult Still's disease by tacrolimus

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Abstract Adult Still's disease (ASD) is a systemic rheumatic disease characterized by high spiking fever, erythema, polyarthritis, and increased levels of C-reactive protein, ferritin, and interleukin (IL)-18. Recently, biological agents targeting proinflammatory cytokines such as tumor necrosis factor (TNF) α, IL-1, and IL-6 have been described as effective treatments for refractory ASD. Herein, we present a patient with ASD, who was successfully treated by tacrolimus concomitant with corticosteroid, while infliximab and etanercept were not effective. Tacrolimus may be one of the drugs for the ASD patients refractory to the conventional treatments including TNF inhibitors.

Key words Adult Still's disease · Interleukin-18 · Interleukin-6 · Tacrolimus · Tumor necrosis factor · Tumor necrosis factor inhibitors

Introduction

Adult Still's disease (ASD) is a systemic rheumatic disease characterized by high spiking fever, evanescent rash, polyarthritis, and leukocytosis, and it sometimes results in life-threatening complications such as adult respiratory distress syndrome.[1] No immunological abnormality specific for ASD has been clarified yet, whereas markedly increased level of serum interleukin (IL)-18[2] and activation of a certain subset of γδT cells[3] have been reported. Proinflammatory cytokines such as IL-6 are involved in the pathogenesis of ASD,[4] and anakinra (IL-1 receptor antagonist)[5] and humanized antihuman IL-6 receptor monoclonal antibody (tocilizumab)[6] may be effective for ASD. However, both agents cannot as yet be used for patients with ASD in Japan. The favorable effects of TNF inhibitors such as infliximab and etanercept have been also noticed in patients with refractory ASD,[7–9] whereas the serum tumor necrosis factor α (TNFα) levels appeared not to correlate with ASD activity.[4,10] We experienced a Japanese patient with intractable ASD, in whom tacrolimus concomitant with corticosteroids, but not a high dose of methotrexate (MTX) and/or TNF inhibitors, were effective. Our case indicates that tacrolimus may have a favorable effect for patients with refractory ASD.

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Case report

In August 1997, a 16-year-old man came to Kyoto University Hospital suffering from spiking fever, polyarthralgia, evanescent rash, and leukocytosis. His blood tests revealed a high level of C-reactive protein (CRP) but negative rheumatoid factor and antinuclear antibodies. He was diagnosed as having ASD according to the preliminary criteria of ASD proposed by Yamaguchi et al.[11] Although 10 mg of prednisolone (PSL) was started daily, his symptoms did not disappear completely. After methotrexate (MTX, 10 mg weekly) was initiated concomitant with PSL, his clinical manifestations were well controlled.

In September 2001, he was admitted to our hospital because of high spiking fever and polyarthralgia. Steroid pulse therapy (methylprednisolone 500 mg for 3 days) was administered and he then continued treatment with 3.5 mg of betamethasone daily. In February 2002, he had a left total hip arthroplasty, and in July 2002 he underwent arthrodesis of both ankle joints.

In February 2003, he was admitted to our hospital again because of high fever and general malaise, although he continued receiving 10 mg of MTX weekly concomitant with betamethasone 3.75 mg daily. Blood examination showed marked leukocytosis (27 900/mm^3), and increased levels of CRP (19.8 mg/dl, normal range <0.2) and serum ferritin (758 ng/ml, normal range <150). After the betame-

thasone dose was increased to 7.0 mg daily, these symptoms disappeared.

In March 2004, cyclosporine (200 mg daily) was added to MTX and betamethasone because of high fever along with the increased level of CRP (3.2 mg/dl). However, because CRP and ferritin levels failed to decrease, cyclosporine was discontinued. In September 2004, according to the protocol for rheumatoid arthritis, infliximab (3 mg/kg) was administered along with 15 mg of MTX weekly. Infliximab was used five times, but his CRP level did not normalize. In July 2005, he was admitted again because of fever and general malaise. On admission, his bilateral wrist joints were ankylotic and the limitation of right hip joint motion had deteriorated. Laboratory data were as follows: white blood cell (WBC) count 17 600/mm^3 with 83% neutrophils, CRP 5.3 mg/dl, erythrocyte sedimentation rate 59 mm/h, and serum ferritin level 182 ng/ml. The activity of ASD appeared not to be well controlled in spite of combination treatment with 3 mg of betamethasone daily and 15 mg of MTX weekly.

Etanercept (25 mg twice a week) was then initiated from June 2005. The weekly dose of concomitant MTX was gradually increased up to 25 mg, but the clinical manifestations and the high level of CRP were not well controlled. Therefore, etanercept was discontinued and 1.5 mg of tacrolimus daily was initiated. After the daily dose of tacrolimus was increased up to 3 mg concomitant with betamethasone and MTX, the patient's clinical features and laboratory findings markedly improved. The immunosuppressive treatments including TNF inhibitors and tacrolimus were started after the informed consent for these treatments were obtained from the patient and his family.

On December 16, 2005, he underwent total right hip arthroplasty. Prior to the operation, MTX was discontinued. After the operation, 2.75 mg of betamethasone daily and 3 mg of tacrolimus daily were continued. His clinical manifestations and CRP level were completely normalized without MTX, and no serious adverse reactions have been recognized until now. Daily betamethasone was decreased to 2 mg on May 17, 2006 (Fig. 1).

The serum concentrations of TNFα, IL-6, IL-18, and IL-1β in the patient's preserved sera were determined by enzyme-linked immunosorbent assay kits according to the manufacturer's instructions (eBioscience, San Diego, CA, USA) (Table 1). Unfortunately, no serum samples between February 1, 2003 and August 29, 2005 were stored. On February 1, 2003, when the patient had high disease activity, IL-6 and IL-18 were markedly elevated. On August 29 and September 29, 2005, when etanercept was used with 3 mg of betamethasone daily and 15–20 mg of MTX weekly, TNFα, IL-6, and IL-18 were still increased. On October 27, 2005, 10 days after tacrolimus was initiated, IL-6 and IL-18 concentrations had decreased, although TNFα had not changed. Of note, IL-18 was normalized along with the marked decreases in CRP, serum ferritin, and erythrocyte sedimentation rate by tacrolimus (Fig. 1), even when MTX was discontinued. Interleukin-1β could not be determined by our system.

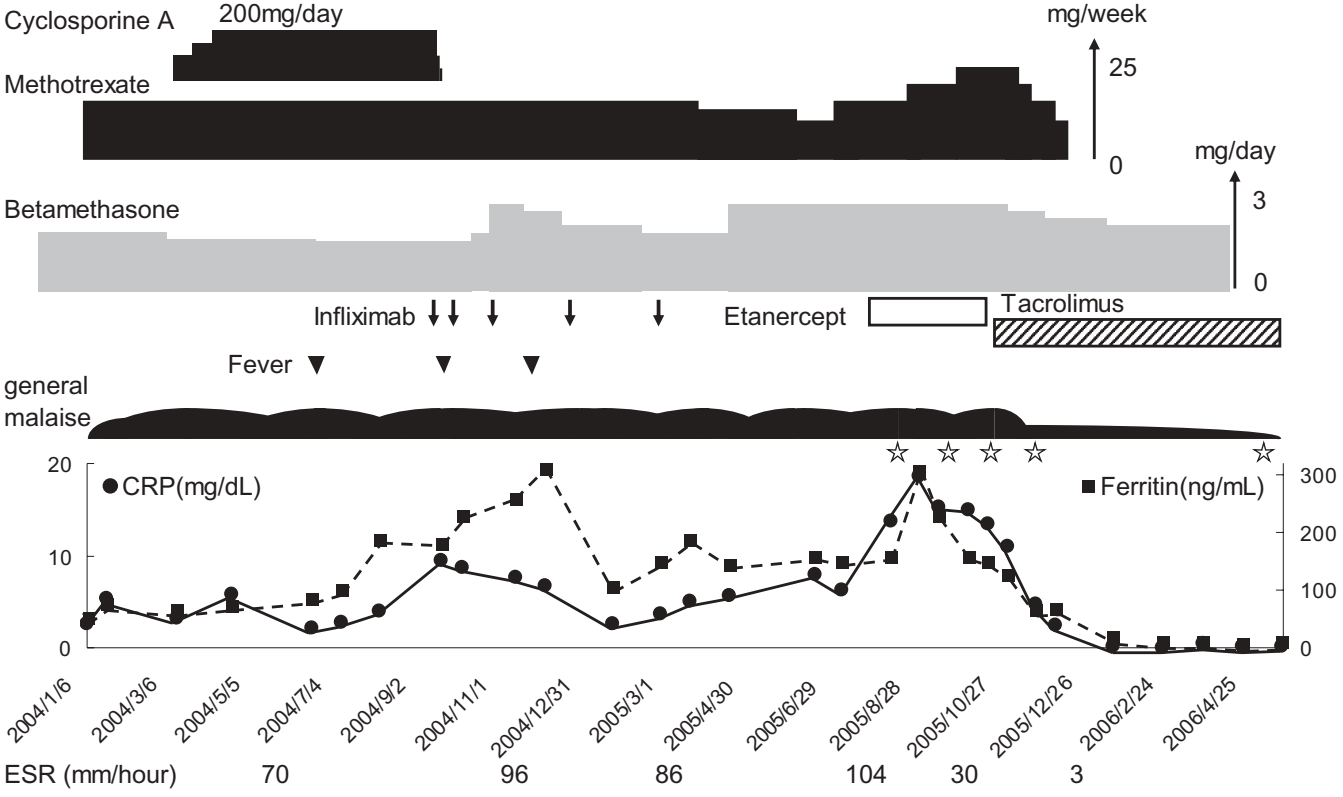

Fig. 1. The clinical course of our patient. Tacrolimus (1.5 mg daily) was started from October 17 and the dose was increased to 3.0 mg daily from October 24. Both C-reactive protein (*CRP*) and serum ferritin levels were completely normalized by tacrolimus even after methotrexate was discontinued. *Open stars* indicate days on which serum cytokine concentrations were determined

Table 1. Serum cytokine levels and treatment in our patient

	01-Feb-03	29-Aug-05	29-Sep-05	27-Oct-05	21-Nov-05	17-May-06
Treatments						
Betamethasone (mg/day)	3.75	3.0	3.0	3.0	3.0	2.0
Methotrexate (mg/week)	10	15	20	25	15	–
Etanercept (mg/week)	–	50	50	–	–	–
Tacrolimus (mg/day)	–	–	–	3.0	3.0	3.0
Cytokines						
TNFα (pg/ml, normal < 5)	<5	195	94	90	<5	<5
IL-6 (pg/ml, normal < 4)	164.0	8.6	8.8	4.4	<4	<4
IL-18 (pg/ml, normal < 180)	10360	4476	4694	2898	2413	<180

TNF, tumor necrosis factor; IL, interleukin

Discussion

We present herein a patient with ASD successfully treated with tacrolimus, which is an orally available macrolide calcineurin inhibitor. To the best of our knowledge, this is the first report that clearly shows the efficacy of tacrolimus in patients with refractory ASD. Our case suggests that tacrolimus may be useful for such patients even though the standard doses of infliximab and etanercept were not effective. Whereas the usefulness of infliximab and etanercept has been suggested, most patients failed to have complete remission and discontinued these agents.[8,9] As in the cases experienced by Husni et al.,[8] a higher dose of etanercept may be required for the management of ASD than for rheumatoid arthritis.

Tacrolimus diminishes the ability of calcineurin to dephosphorylate and translocate the nuclear factor of activated T cells that initiate gene transcription for the synthesis of Th cell-producing cytokines such as IL-2 and interferon (IFN)-γ. Previously, we reported that the serum levels of soluble IL-2 receptors correlated with the activity of chronic arthritis in the patients with ASD.[4] In addition, recent studies have indicated that Th1/Th2 cytokines may play a critical role in the pathogenesis of ASD.[4,10,12,13] Chen et al. demonstrated that IFNγ-producing Th cells in the peripheral blood of patients with ASD, but not IL-4-producing Th cells, were increased more than in the healthy controls.[12] Whereas the importance of Th1/Th2 imbalance in ASD remains unclear, including in our case, some previous studies also indicated that the suppression of Th cell is useful in the treatment of active ASD.

An extremely high level of serum IL-18 has been reported as a hallmark of ASD.[2] The serum IL-18 in ASD sometimes remained elevated even when the disease activity was well controlled, and IL-18 gene polymorphisms might be associated with ASD.[13] Also in our case, the normalization of TNFα and IL-6 was followed by a decrease in IL-18. However, it should be noted that IL-18 returned completely to normal about 6 months after the initiation of tacrolimus in our patient. An in vitro study demonstrated that tacrolimus could inhibit IL-18 generation from human peripheral blood mononuclear cells by mixed lymphocyte reaction with lipopolysaccharide.[14] Whether tacrolimus has a direct or cytokine-mediated inhibitory effect on macrophages, which are supposed to be activated in ASD, should be elucidated in future studies.

Most patients with ASD require aggressive treatment with corticosteroids with or without immunosuppressive agents such as MTX to control the systemic manifestations.[15] Marchesoni et al. have reported the efficacy of another calcineurin inhibitor, cyclosporine, in six patients with chronic or relapsing ASD.[16] With cyclosporine, the disease activity of ASD was completely remitted (4 patients) or markedly improved (2 patients) within 6 months. Although our patient took cyclosporine for 6 months with satisfactory serum concentration, his clinical manifestations and CRP could not be controlled. The reason is unclear why the efficacy is different between both calcineurin inhibitors. Tumor necrosis factor inhibitors prior to tacrolimus might have an additional immunomodulatory effect to tacrolimus, because both serum IL-6 and IL-18 appeared to be suppressed after the initiation of etanercept in comparison with those in the acute phase (February 1, 2003). These data suggest that etanercept might have induced a partial response in our patient although acute phase reactants (e.g., erythrocyte sedimentation rate and CRP) were not changed.

We could not determine the reason why serum TNFα level after etanercept use (August and September 2005) was higher than that in the acute phase. Whereas serum TNFα may not be a more useful marker than IL-6 and IL-18,[4] the proinflammatory cytokine hierarchy including IL-1 should be elucidated.

In conclusion, we recommend the use of tacrolimus in addition to corticosteroids for patients with ASD, even if TNF inhibitors and cyclosporine are not effective. Also, multicenter studies should be conducted to clarify the efficacy and adverse reactions of tacrolimus in ASD.

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