Successful treatment with tacrolimus of refractory adult-onset Still’s disease

Masashi Ohe¹, Kenji Oku², Michihito Kono², and Toshiyuki Bohgaki²

¹Department of General Medicine, Hokkaido Social Insurance Hospital, Sapporo; ²Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

To the Editor,
Adult-onset Still’s disease (AOSD) is a systemic inflammatory disorder characterized by high fever, arthralgia, transient rash, hepatosplenomegaly, lymphadenopathy, liver dysfunction and leukocytosis. The diagnosis of AOSD is conferred based on clinical findings after elimination of other causes. The mainstay of treatment is glucocorticoids and/or nonsteroidal anti-inflammatory drugs, although most cases are refractory to these conventional therapies. To treat steroid-resistant AOSD, previous reports have suggested the use of immunosuppressants such as methotrexate (MTX), cyclosporine A (Cy-A), tumor necrosis factor-alpha (TNF-α) blockers, an interleukin (IL)-1 blocker and an IL-6 receptor blocker. Recent studies suggested that higher levels of IL-18 are detected in patients with active AOSD, which correlate with disease activity and inflammatory features. In addition, AOSD with high levels of IL-18 is refractory to treatment and is often steroid-resistant. A successful outcome was reported recently in one case of refractory AOSD treated with tacrolimus (Tac), a calcineurin inhibitor similar to Cy-A [1]. Here, we report a case of AOSD with high IL-18 levels that was treated unsuccessfully with steroid in combination with Cy-A, but was subsequently treated successfully using steroid in combination with Tac.

A 58-year-old female was admitted to our hospital with a 2-week history of fever, polyarthralgia, myalgia, sore throat, and erythematous rash. Physical examination revealed the following: body temperature of 38.7°C; erythematous plaques and papules on the face, trunk, arms and extremities; enlarged cervical lymph nodes; and throat redness. Her skin rashes persisted with color tones that faded slightly with falling fever, but the rashes were not evanescent. The laboratory findings were as follows: white blood cell count (WBC), 24,520/µm³ (neutrophils, 91%; eosinophils, 3.0%; monocytes, 4.0%; lymphocytes, 2.0%); red blood cell count, 349 × 10⁴/µm³; hemoglobin, 10.3 g/dL; platelet count, 25.8 × 10⁹/mm³; aspartate aminotransferase, 88 IU/L; alanine aminotransferase, 29 IU/L; albumin, 3.8 g/dL; total protein, 5.5 g/dL; IgG, 916 mg/dL; IgM, 73 mg/dL; IgA, 159 mg/dL; IgG, 916 mg/dL; IgM, 73 mg/dL; IgA, 159 mg/dL; rheumatoid factor, < 15 IU/mL; C₃, 166 mg/dL; C₄, 32 mg/dL; and C-reactive protein (CRP), 11.80 mg/dL (normal range, < 0.3 mg/dL). Immune complexes were not detected by the C₁q-binding assay. The anti-nuclear antibody (ANA) titer was < 40×. All tests were negative for other...
autoimmune antibodies, including anti-ds-DNA, anti-SS-A, anti-SS-B, anti-DNA, anti-ribonucleic protein, anti-Smith, anti-cardiolipin, anti-centromere, anti-topoisomerase, and anti-mitochondria antibodies, and were negative for the myeloperoxidase and proteinase-3 antineutrophil cytoplasmic antibodies. Urinalysis revealed neither proteinuria nor hematuria. Computed tomography revealed bilateral axillary lymphadenopathy, slight left pleural effusion and slight splenomegaly. The diagnosis of AOSD was established based on the presence of pyrexia, sore throat, arthralgia, lymphadenopathy, leukocytosis, liver dysfunction, the lack of rheumatoid factor and the negative ANA titer. The clinical findings met three of the four major criteria and four of the four minor criteria for AOSD classification proposed by Yamaguchi et al. [2]. Treatment with prednisolone (PSL) at 50 mg/day was initiated; 2 days later, the admission levels of ferritin were reported to be 28,728 ng/mL (normal range, 5 to 157 ng/mL); therefore, PSL was exchanged for methyl-PSL at 1 g/day for 3 days (Fig. 1). Subsequently, treatment consisted of 50 mg/day PSL in combination with 200 mg/day Cy-A. Five days after the first methyl-PSL pulse therapy, the fever improved, with the WBC and CRP decreasing to 15,160/mm$^3$ and 1.47 mg/dL, respectively. However, 10 days after the initial methyl-PSL pulse therapy, the fever reappeared, with WBC and CRP increasing to 20,320/mm$^3$ and 3.54 mg/dL, respectively. Retreatment with methyl-PSL at 1 g/day for 3 days was performed, followed by administration of PSL at a maintenance dose of 50 mg/day in combination with Cy-A at 200 mg/day. At that time, the ferritin level was 1,814 ng/mL. The trough and 2-hour peak levels of Cy-A were 110 and 3,625 ng/mL, respectively; therefore, the Cy-A dosage was reduced to 150 mg/day. The fever improved immediately, with WBC and CRP levels decreasing to 12,270/mm$^3$ and 0.61 mg/dL, respectively, 6 days after the second methyl-PSL pulse therapy. However, a slight fever reappeared 2 weeks after beginning that regimen, with WBC and CRP levels increasing to 20,660/mm$^3$ and 0.75 mg/dL, respectively. Because 50 mg/day PSL was administered for ~4 weeks, the dosage could not be increased. Therefore, the third pulse therapy regimen of methyl-PSL at 1 g/day for 3 days was administered, followed by administration of PSL at a maintenance dose of 50 mg/day in combination with Cy-A at 150 mg/day. The fever improved immediately, with WBC and CRP decreasing to 10,100/mm$^3$ and 0.2 mg/dL, respectively. At this time, the ferritin level was 1,010 ng/mL. However, a slight fever reappeared 3 weeks after the third methyl-PSL pulse therapy, with WBC of 7,350/mm$^3$ and CRP increasing to 0.42 mg/dL. Because the IL-18 and IL-6 levels measured just before the second methyl-PSL pulse therapy were 89,645 pg/mL (normal range, < 260 pg/mL) and 11 pg/mL (normal range, < 4 pg/mL), respectively, and ferritin increased again to 1,793 ng/mL, Tac at 2 mg/day was initiated as an alternative to Cy-A. The trough level of Tac was 2.3 ng/mL, so the dosage was increased to 3 mg/day. The fever improved, and CRP was found to be negative. A normal body temperature and negative CRP levels continued. Ferritin decreased to normal levels (148 ng/mL) 3 weeks after initiation of Tac treatment, and the IL-18 level decreased gradually to 1,437 pg/mL after 5 months. The PSL dose was reduced gradually from 50 to 10 mg/day over a 5-month period, and the patient was discharged.

Recently, numerous studies have demonstrated that proinflammatory cytokines, such as IL-1, IL-6, IL-18, TNF-α, and interferon-gamma (INF-γ), are involved in the pathogenesis of AOSD. Regarding the cytokine

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**Figure 1.** Clinical course. Cyclosporine A (Cy-A) in combination with glucocorticoid (prednisolone [PSL] or methyl-PSL) was administered. Subsequently, Tacrolimus (Tac) (2 mg/day) was initiated, and the dose of Tac was increased to 3 mg/day. Both C-reactive protein (CRP) and ferritin levels were completely normalized by Tac even after Cy-A was discontinued. WBC, white blood cells.