A Case of Adult-Onset Still’s Disease Treated with Monitoring of Serum Tacrolimus Levels

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Abstract

Adult-onset Still’s disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology. The mainstays of treatment are glucocorticoids (GCs) and non-steroidal anti-inflammatory drugs, although most cases are refractory to these conventional therapies. Immunosuppressants, such as methotrexate (MTX), cyclosporine A, tumor necrosis factor-α blockers, an interleukin (IL)-1 blocker, and an IL-6, receptor blocker, have been suggested in previous reports for the treatment of steroid-resistant AOSD. We report herein the case of an AOSD patient who was successfully treated with tacrolimus, another immunosuppressant, in combination with GC and MTX. Blood concentrations of tacrolimus were monitored because of the narrow therapeutic window.

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 eliminating other causes. The mainstay of treatment is glucocorticoids (GCs) or non-steroidal anti-inflammatory drugs (NSAIDs), although most cases appear refractory to these conventional therapies. Immunosuppressants, such as methotrexate (MTX), cyclosporine A,\(^1,2\) tumor necrosis factor (TNF)-\(\alpha\) blockers, interleukin (IL)-1 blockers\(^3\) and IL-6 receptor blockers\(^4,7\) have been suggested in previous reports for the treatment of steroid-resistant AOSD. Recent studies suggest that higher levels of IL-18 are detected in active AOSD patients and correlate with disease activity and inflammatory features.\(^8\) In addition, AOSD with high IL-18 levels appears refractory to treatment and is often steroid-resistant.\(^9\) One case with successful treatment of refractory AOSD using tacrolimus, a calcineurin inhibitor similar to cyclosporine A, has recently been reported.\(^10\) Tacrolimus must be used with monitoring of blood concentrations because of the narrow therapeutic window. We report herein a patient with successful treatment of AOSD showing high IL-18 with tacrolimus, blood concentrations of which were monitored, in combination with GC and MTX.

Case Report

An 81-year-old woman was admitted to our hospital with a 2-week history of fever, polyarthralgia, sore throat, and erythematous rash. Physical examination revealed: body temperature, 38.9°C; erythematous rash on the face, trunk, arms and extremities; and throat redness. Laboratory findings were as follows: white blood cell count (WBC), 4,480/mm\(^3\) (neutrophils, 91%; eosinophils, 3.0%; monocytes, 4.0%; lymphocytes, 2.0%); red blood cell count (RBC), 349×10\(^4\)/mm\(^3\); hemoglobin, 8.1 g/dL; platelet count, 24.7×10\(^4\)/mm\(^3\); aspartate aminotransferase, 137 IU/L; alanine aminotransferase, 101 IU/L; total protein, 5.5 g/dL; albumin, 2.6 g/dL; immunoglobulin (Ig)G, 916 mg/dL; IgM, 73 mg/dL; IgA, 159 mg/dL; rheumatoid factor (RF), < 15 IU/mL; C\(_3\), 166 mg/dL; C\(_4\), 32 mg/dL; and C-reactive protein (CRP), 4.49 mg/dL. Immune complexes were not detected by C\(_{1q}\)-binding assay. Antinuclear antibody (ANA) titer was less than ×40. Tests for other autoimmune antibodies, including anti-ds-DNA, anti-SS-A, anti-SS-B, anti-DNA, anti-RNP, anti-Sm, anti-cardiolipin, anti-centromere, anti-topoisomerase, and anti-mitochondria antibodies, were all negative, as were those for myeloperoxidase and proteinase-3 antineutrophil cytoplasmic antibodies. Urinalysis revealed neither protein-

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uria nor hematuria. Computed tomography (CT) revealed hepatomegaly and left pleural effusion. Six days after admission, WBC and CRP levels increased rapidly to 10,080/mm\(^3\) and 6.72 mg/dL, respectively. AOSD was finally diagnosed, based on the presence of pyrexia, polyarthralgia, skin rash, sore throat, leukocytosis, liver dysfunction, lack of RF, and the negative ANA titer. The clinical course is presented in Figure 1. Treatment with prednisolone (PSL) at 50 mg/day was initiated. Two days later, ferritin levels on admission were reported as 12,944 ng/mL (normal range, 5 to 157 ng/mL). As a result, PSL was exchanged for methyl-PSL (mPSL) at 1 g/day for 3 days. Subsequent treatment consisted of 80 mg/day mPSL and 2 mg/day tacrolimus. Four days after the first mPSL pulse therapy, fever was slightly improved, but WBC and CRP had increased to 24,010/mm\(^3\) and 15.31 mg/dL, respectively. At the same time, the patient complained of dyspnea. CT revealed aggravation of left pleural effusion and appearance of right pleural effusion, and high fever reappeared. So AOSD activity was thought to grow higher. The patient was, therefore, treated with mPSL at 500 mg/day for 3 days, then with PSL at 50 mg/day, and MTX at 6 mg/week in combination with tacrolimus. At the same time, because the trough level of tacrolimus was 2.0 ng/mL, tacrolimus dosage was increased to 3 mg/day. Ten days after the second mPSL pulse therapy, bilateral pleural effusions began to improve with WBC and CRP decreasing to 14,730/mm\(^3\) and 11.29 mg/dL, respectively. The trough level of tacrolimus proved to be 2.3 ng/mL, so the dosage was increased to 4 mg/day. At the same time, PSL dosage was decreased to 40 mg/day because of hyperglycemia. Fever was maintained at the level of 37°C. However, 7 days after starting 4 mg/day tacrolimus and 40 mg/day PSL, fever reappeared at the level of 38°C, although WBC and CRP decreased to 10,640/mm\(^3\) and 3.64 mg/dL, respectively. We regarded the optimal trough level of tacrolimus as 6.0 to 8.0 ng/mL according to the tacrolimus target concentration of lupus nephritis,\(^\text{11}\) but the trough level on 4 mg/day tacrolimus was 3.9 ng/mL. However, tacrolimus dosage could not be further increased due to its high cost. At the same time, because IL-18 and IL-6 levels measured just before the first mPSL pulse therapy were reported as 384,430 pg/mL (normal range, < 260 pg/mL) and 468 pg/mL (normal range, < 15 pg/mL), we were concerned about the possibility of drug-induced lupus. Therefore, we added clarithromycin (CAM) at 900 mg/day for 1 month. Fever, white blood cell count (WBC), C-reactive protein (CRP) level, and ferritin level all showed improvement.

Figure 1 The clinical course of the patient. Tacrolimus (Tac) was administered in combination with corticosteroid, such as prednisolone (PSL) and methyl-PSL (mPSL) and methotrexate (MTX). After 1 month, clarithromycin (CAM) was added to this treatment. Fever, white blood cell count (WBC), C-reactive protein (CRP) level, and ferritin level all showed improvement.
range, < 4 pg/mL), respectively, and high fever continued, AOSD activity was considered severely high. Therefore, for the purposes of completely suppressing AOSD activity, we added clarithromycin (CAM), which is known to raise blood tacrolimus concentrations.\(^{12,13}\) Seven days after starting CAM treatment at 400 mg/day, body temperature was completely normalized. Normal body temperature has continued since then. Because the trough level of tacrolimus reached 8.8 ng/mL only 4 days after CAM treatment, tacrolimus dose was reduced from 4 mg/day to 2 mg/day to avoid risking adverse reactions, such as renal dysfunction, while PSL dosage was reduced to 30 mg/day. Ten days after reducing tacrolimus to 2 mg/day, the trough level was 4.2 ng/mL. So tacrolimus dosage was increased to 2.5 mg/day. After that, the trough level remained within the range of 6.0 to 7.5 ng/mL. After 2 weeks of CAM treatment, normal WBC and negative results for CRP were found and continued. In the course of treatment for AOSD, ferritin levels and IL-18 gradually decreased to 285.6 ng/mL and 6,627 pg/mL, respectively, by 3.5 months after initiating treatment. The PSL dose was gradually reduced from 50 mg/day to 10 mg/day over a 3-month period, and the patient was discharged.

**Discussion**

Various recent studies have demonstrated that proinflammatory cytokines, such as IL-1, IL-6, IL-18, TNF-α, and interferon (IFN)-γ, are involved in the pathogenesis of AOSD.\(^5\) Regarding the cytokine cascade, IL-18 promotes TNF-α and IL-1 production via the nuclear factor (NF)-κB pathway and induces INF-γ production by Th1 lymphocytes. TNF-α also induces IL-1, which stimulates the production of IL-6. Based on these facts, IL-18, a macrophage-derived cytokine, is thought to be an upstream cytokine in the pathogenesis of AOSD;\(^7\) on the other hand, IL-6 is thought to be a downstream cytokine. Recent studies have detected higher levels of IL-18 in patients with active AOSD, showing correlations with disease activity and inflammatory laboratory features.\(^8\) Kawaguchi and coworkers reported that levels of IL-18 were significantly higher in steroid-resistant AOSD patients than in steroid-sensitive AOSD patients.\(^9\) That report suggested that steroid monotherapy was insufficient and that additional immunosuppressive agents should be considered for the treatment of AOSD patients with high IL-18 levels.

As for refractory AOSD, Murakami and associates reported a case of AOSD with high IL-18 levels in which steroid, MTX, cyclosporin A, infliximab, and etanercept were unsuccessful, but subsequent treatment using tacrolimus in combination with steroid proved successful.\(^10\) Because tacrolimus is reported to inhibit the function of calcineurin, which activates NF-κB that up-regulates IL-18 generation from human peripheral blood mononuclear cells in vitro,\(^14\) that report and the present case of AOSD might have achieved improvement through tacrolimus inhibition of IL-18 generation. Because tacrolimus suppresses an upper cytokine, namely IL-18, tacrolimus treatment for AOSD is thought to be logical.

The present case was considered severely active because of the ferritin and IL-18 levels and was thought to be refractory; therefore, we decided to prescribe tacrolimus in combination with GC, including two courses of mPSL pulse therapy and MTX. Tacrolimus must be used with monitoring of blood concentrations because of the narrow therapeutic window. The trough level of tacrolimus was low; therefore, tacrolimus dosage was gradually increased from 2 mg/day to 4 mg/day. However, the trough level of 4 mg/day tacrolimus only increased to 3.9 ng/mL. As CRP and ferritin levels decreased, tacrolimus at 4 mg/day in combination with GC and MTX was effective to a certain extent but could not completely suppress the disease, including fever, because of the low blood tacrolimus concentration.

Tacrolimus is an immunosuppressant agent that is primarily metabolized by cytochrome P450 (CYP)3A. When tacrolimus is administered orally, blood concentrations vary widely between individuals. Levels are known to be affected by the fat content of food and genetic polymorphisms of CYP3A5.\(^15\) We administered CAM in the present case with the intention of raising blood tacrolimus concentrations. CAM is a potent CYP3A inhibitor, thus coadministration of tacrolimus and CAM leads to a pharmacokinetic interaction.\(^12,13\) As a result, CAM suppressed tacrolimus metabolism by inhibiting CYP3A, and trough levels of tacrolimus increased. This allowed disease activity to be completely controlled under optimal blood tacrolimus concentrations.

Based on these findings, in the course of treatment of AOSD with tacrolimus, CAM may provide a useful drug to raise blood tacrolimus concentrations when optimal levels are difficult to achieve. However, repeated drug monitoring of tacrolimus is required to prevent adverse reactions.

This is the first report in which CAM was used for the purpose of raising tacrolimus concentration, taking advantage of CAM inhibiting CYP3A.

Although only two such cases, including the present case, appear to have been reported, tacrolimus may be an option for the treatment of AOSD with high IL-18 levels. More research is required to substantiate the effectiveness of tacrolimus treatment before it can be recommended on a routine basis.

**Disclosure Statement**

The authors have no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

**References**


