



Cyclosporine for Adult Onset Still's Disease Flare with Hepatic Dysfunction

Song Feng Yeh¹, Deng-Ho Yang^{1,2}, Tsung-Yun Hou¹, Deh-Ming Chang¹,
San-Yuan Kuo¹, and Chen-Hung Chen^{1*}

¹*Division of Rheumatology/Immunology/Allergy, Department of Internal medicine,
Tri-Serve General Hospital, National Defense Medical Center, Taipei,*

²*Division of Rheumatology/Immunology/Allergy, Department of Internal Medicine,
Armed Forces Taichung General Hospital, Taichung,
Taiwan, Republic of China*

We report on a 27 year-old man with adult onset Still's disease (AOSD) who had a flare after two years of management with methotrexate (MTX) and prednisolone. The clinical manifestations included hepatitis, jaundice, fever and atypical skin rash. Because of hepatic dysfunction, cyclosporine was prescribed instead of MTX. After therapy with cyclosporine, the patient recovered with improved liver enzymes and clinical features.

Key words: adult onset Still's disease, methotrexate, cyclosporine, hepatic dysfunction

INTRODUCTION

AOSD is a chronic systemic inflammatory disorder of unknown etiology and pathogenesis. The diagnosis of AOSD is generally made after excluding other conditions such as systemic infection, malignancy, and systemic vasculitis^{1,2}. The typical clinical features include a recurrent spiking fever, transient maculopapular rash, arthralgia/arthritis, leukocytosis, sore throat, lymphadenopathy, splenomegaly, and abnormal liver function. Life threatening conditions such as hepatic failure, acute pericarditis, myocarditis, heart failure, disseminated intravascular coagulopathy (DIC), hemophagolytic syndrome and respiratory distress syndrome may occur in the clinical course of AOSD. Many therapeutic strategies have been reported to be effective, such as non-steroid anti-inflammatory drugs (NSAID), corticosteroids, methotrexate (MTX), interleukin (IL)-1 receptor antagonist³, and tumor necrosis factor (TNF) alpha antagonists⁴. We report a patient with an AOSD flare and hepatic dysfunction who was successfully treated with cyclosporine.

CASE REPORT

A 27-year-old man had been diagnosed with AOSD more than two years previously. Initial manifestations were high fever, skin rash, sore throat and an extremely high ferritin level with negative rheumatoid factor and anti-nuclear antibody. He had two flare-ups with a spiking fever and fatigue during the first half year after diagnosis. The disease course was stabilized during the previous two years with treatment with oral MTX 10 mg weekly and prednisolone 10 mg daily. Two weeks before admission, the patient experienced yellow urine, poor appetite and fatigue. He visited our emergency department because of a spiking fever and poor appetite. He had no other systemic diseases. He worked as a computer engineer, and had no exposure to concrete dust, chemicals or radiation. He did not smoke or drink alcohol.

He had a monogamous relationship with his girlfriend for one year. He had no recent exposure to any illnesses and had not traveled recently. Medications at the time of admission were MTX and prednisolone. He did not use Chinese herbs. On physical examination, the patient appeared uncomfortable and fatigued. The temperature was 38.2°C, pulse 70 beats per minute, blood pressure 120/74 mm Hg, and respiratory rate 12 breaths per minute. He had bilateral icteric sclerae and generalized yellowish discoloration of the skin. Some ecchymosis over the bilateral forearms were noted. No oral ulcers or mucositis was found. The remainder of the examination was normal. The hemoglobin level was 15.9 g/dL, white cell count 14,700/mL with neutrophils 80.1% and platelet count 186,000/

Received: December 24, 2008; Revised: March 30, 2009;
Accepted: April 9, 2009

*Corresponding author: Chen-Hung Chen, Division of Rheumatology/Immunology/Allergy, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec. 2, Cheng-Gong Rd, Taipei 114, Taiwan, Republic of China. Tel: +886-2-87927135; Fax: +886-2-87927136; E-mail: sfyehrolex@yahoo.com.tw

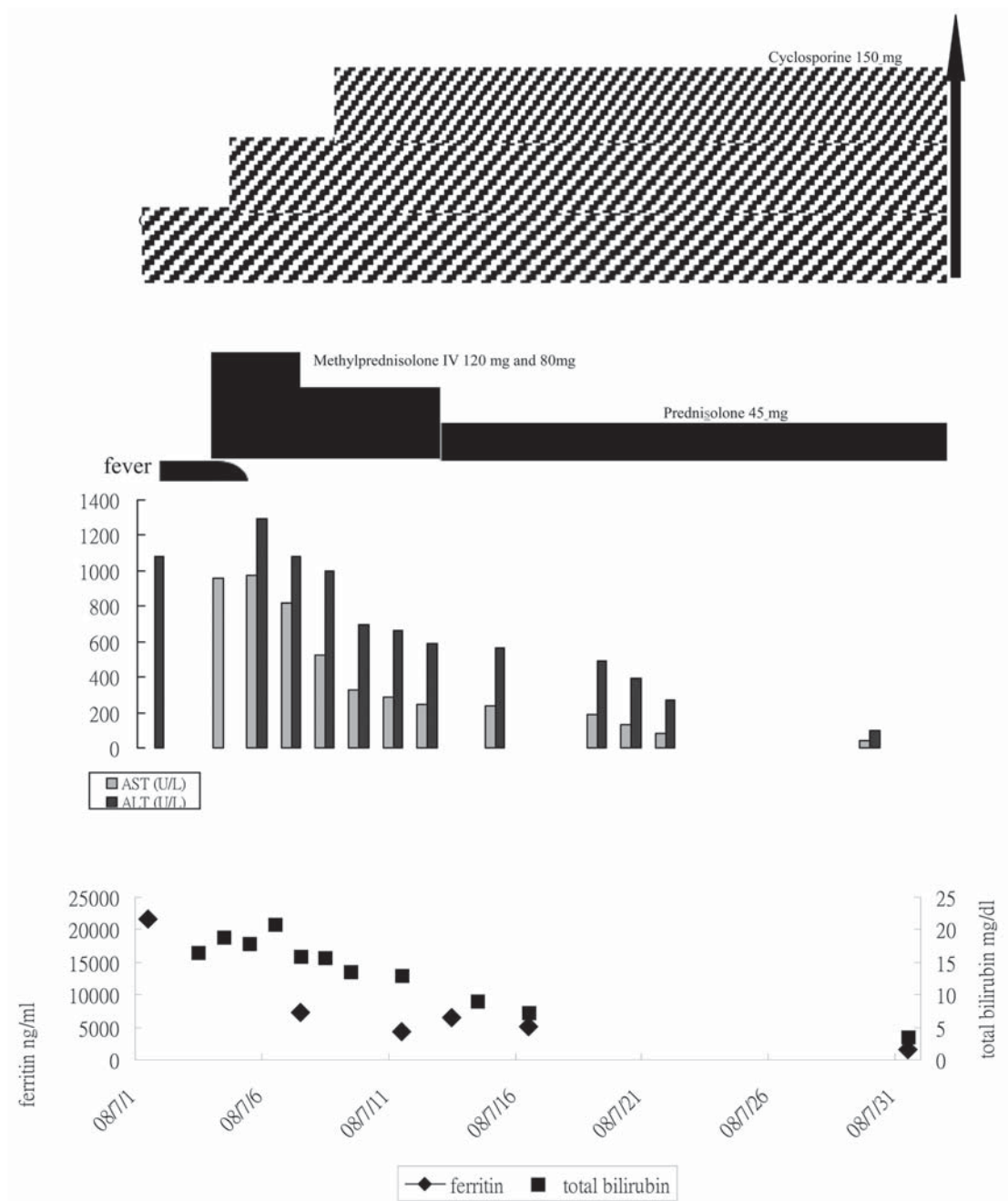


Fig 1. Clinical data Abbreviations: IV: intravenously; AST: alanine aminotransferase; AST: aspartate aminotransferase

mL. The serum total bilirubin was 16.5 mg/dL (reference value <1.0 mg/dL), aspartate aminotransferase 955 U/L, alanine aminotransferase 1,081 U/L, serum ferritin 21,643 ng/dL (reference value 22-322 ng/dL), C-reactive protein 1.94 mg/dL (reference value <0.5 mg/dL) and serum creatinine 0.9 mg/dL (reference value 0.7-1.2 mg/dL). The erythrocyte sedimentation rate was 4 mm/hr (reference

value <15 mm/hr) and prothrombin time was 14.3 seconds (reference value 0-14 seconds). Ultrasonography of the right upper quadrant showed diffuse and increased echogenicity of the liver parenchyma, and the liver and spleen were not enlarged. Chest radiography showed no abnormalities. Urinalysis showed only bilirubinuria.

After admission, MTX were discontinued because of

severe hepatitis. Cultures of the blood, and tests for antibodies to hepatitis A, B and C viruses, Epstein—Barr virus and cytomegalovirus were all negative. On the third hospital day, oral cyclosporine 25 mg twice daily was prescribed and the dose was titrated to 150 mg daily (2.5 mg/kg/day) during hospitalization. Intravenous methylprednisolone 120 mg intravenously daily for three days was prescribed and then switched to oral prednisolone 45 mg daily. The patient's body temperature, daily activity and appetite improved. At the same time, the levels of liver enzymes, ferritin, and serum bilirubin also recovered. The patient was discharged on the 18th hospital day with prescriptions for cyclosporine and prednisolone. The drug therapy, serum ferritin, total bilirubin, aspartate aminotransferase and alanine aminotransferase levels are shown in the Figure 1. He visited our out-patient department in stable condition over the following two months.

DISCUSSION

The pathogenesis of AOSD seems to be over-activated lymphocytes with cytokine storm. These cytokines include IL-1, IL-6 and IL-18, macrophage colony-stimulating factor, interferon-gamma and TNF-alpha⁵. Disease activity is monitored by several markers, including serum ferritin, soluble IL-2 receptor, and IL-18¹. The white cell count, liver function tests, and acute phase reactants are often monitored in the disease course and treatment. Patients with self-limited or intermittent articular disease often have a benign course. However, systemic complications may be life-threatening. Acute hepatitis is a common serious complication in the disease course. However, hepatic failure is extremely rare, and most of the reported cases occurred during treatment with hepatotoxic drugs such as MTX⁶.

Common gastrointestinal side effects of MTX include dyspepsia, nausea and anorexia⁷. The most serious side effect of MTX is liver toxicity, especially in patients with chronic hepatitis B or C, alcohol consumption, diabetes and obesity⁸. Our patient had been treated with MTX long term, and there was no mucositis or cytopenia during treatment. Thus, MTX -related complications were not likely. Serial studies of infectious, infiltrative and metabolic diseases related to hepatitis were all negative in our

Table 1 Summary of adult onset Still's disease with cyclosporine therapy

Details	Case 1 ¹⁵	Case 2 ¹⁵	Case 3 ¹⁶	Our patient
Age/sex	51/female	32/female	29/female	27/male
Disease duration	3 years	Newly diagnosed	Newly diagnosed	2 years
Symptoms/signs	Fever, rash and arthralgia	Fever, rash, sorethroat and polyarthritis	Fever, rash, sorethroat and hemolytic anemia	Jaundice, fatigue and severe hepatitis
Drugs before cyclosporine	Methotrexate 6mg/week and prednisolone 5mg/day	None	None	Methotrexate 10mg/week and prednisolone 10mg/day
Cyclosporine dose	120mg/day	150mg/day	150mg/day	150mg/day
Corticosteroid dose	Intravenous dexamethasone 100mg for 3 days then oral 5mg daily	Intravenous methylprednisolone 1000mg for 3 days then oral prednisolone 50mg daily	Intravenous methylprednisolone 1000mg for 2 days then oral prednisolone 60mg daily	Intravenous methylprednisolone 120mg for 3 days then oral prednisolone 45mg daily
C-reactive protein	1.33mg/dL	0.55mg/dL	0.85mg/dL	1.94mg/dL
Ferritin level	17,700ng/dL	51,67ng/dL	36,840 ng/dL	21,643 ng/dL
AST/ALT level	1,556/2,329 U/L	344/1,260 U/L	50/33 U/L	955/1,081
Result	Improved	improved	Improved but flared after 10 months	improved

patient and the diagnosis of an AOSD flare was established clinically. MTX is contraindicated in AOSD patients with hepatic impairment. The first line therapeutic agents for AOSD are MTX and corticosteroids with NSAIDs. Therapy with biological agents including IL-1 antagonist (anakinra) and TNF-alpha inhibitors is recommended if the patient responds poorly to first line treatment⁵. Cyclosporine is recommended as a second-line treatment for AOSD. Cyclosporine inhibits calcineurin that is needed in cytokine production during T cell activation⁹. It is often used in organ transplantation and has become a therapeutic option for autoimmune diseases. Cyclosporine is effective in the treatment of rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus¹⁰⁻¹². It has been reported to be effective concomitantly with corticosteroids for some cases of severe AOSD and macrophage activation syndrome in juvenile rheumatoid arthritis¹³⁻¹⁷. A summary of the clinical uses of cyclosporine in AOSD is shown in the Table 1.

In conclusion, cyclosporine in combination with corticosteroid therapy may be helpful before administration of biological agents in AOSD patients who are refractory to MTX. In our patient, hepatic dysfunction improved after cyclosporine therapy, based on the recovering liver enzymes and serum bilirubin level. However, in refractory AOSD patients, the efficacy and safety of cyclosporine for long term maintenance therapy still needs further study.

REFERENCES

1. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. *Ann Rheum Dis* 2006;65:564-572.
2. Ohta A, Yamaguchi M, Tsunematsu T, Kasukawa R, Mizushima H, Kashiwagi H, Kashiwazaki S, Tanimoto K, Matsumoto Y, Akizuki M. Adult Still's disease: a multicenter survey of Japanese patients. *J Rheumatol* 1990;17:1058-1063.
3. Lequerre T, Quartier P, Rosellini D, Alaoui F, De Bandt M, Mejjad O, Kone-Paut I, Michel M, Dernis E, Khellaf M, Limal N, Job-Deslandre C, Fautrel B, Le Loët X, Sibilia J. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. *Ann Rheum Dis* 2008;67:302-308.
4. Fautrel B, Sibilia J, Mariette X, Combe B. Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. *Ann Rheum Dis* 2005;64:262-266.
5. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs* 2008;68:319-337.
6. Mylona E, Golfinopoulou S, Samarkos M, Fanourgiakis P, Papadakis V, Skoutelis A. Acute hepatitis in adult Still's disease during corticosteroid treatment successfully treated with anakinra. *Clin Rheumatol* 2008;27:659-661.
7. Schnabel A, Gross WL. Low-dose methotrexate in rheumatic diseases-efficacy, side effects, and risk factors for side effects. *Semin Arthritis Rheum* 1994;23:310-327.
8. Erickson AR, Reddy V, Vogelgesang SA, West SG. Usefulness of the American College of Rheumatology recommendations for liver biopsy in methotrexate-treated rheumatoid arthritis patients. *Arthritis Rheum* 1995;38:1115-1119.
9. Sehgal SN. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 1998;31:335-340.
10. Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G, McKendry R, Tesser J, Baker P, Wells G. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. *N Engl J Med* 1995;333:137-141.
11. Ho VC. The use of ciclosporin in psoriasis: a clinical review. *Br J Dermatol* 2004;150 Suppl 67:1-10.
12. Caccavo D, Lagana B, Mitterhofer A.P, FERRI G.M, AFELTRA A, AMOROSO A, BONOMO L. Long-term treatment of systemic lupus erythematosus with cyclosporin A. *Arthritis Rheum* 1997;40:27-35.
13. Mouy R, Stephan JL, Pillet P, Haddad E, Hubert P, Prieur AM. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases. *J Pediatr* 1996;129:750-754.
14. Omagari K, Matsunaga Y, Yamashita H, Nishiyama H, Hazama H, Oda H, Isomoto H, Mizuta Y, Murase K, Kohno S. Successful treatment with cyclosporin in adult-onset Still disease manifesting as acute hepatitis with marked hyperferritinemia. *Am J Med Sci* 2003;326:148-151.
15. Nagashima T, Aoki Y, Onishi S, Iwamoto M, Okazaki H, Minota S. Steroid-refractory severe hepatic failure in adult onset Still's disease responding to cyclosporine. *Clin Rheumatol* 2008;27:1451-1453.
16. Her MY, Kim TH, Chang HK, Lee WS, Yoo DH. Successful treatment of acquired amegakaryocytic thrombocytopenia with cyclosporine in adult onset Still's disease. *Rheumatol Int* 2007;27:295-298.
17. Hamidou M, Boutoille D, Masseau A, Garand R, Raffi F. Adult-onset Still disease with hemophagocytic syndrome treated with cyclosporine. *Presse Med* 2005;34:1634-1636.