Successful treatment with tocilizumab in a patient with refractory adult-onset Still's disease (AOSD)

Sirs,

Over the past several years, there have been published reports of cases that were successfully treated with TNF blockers in AODS refractory to conventional DMARDs (1). However, some AOSD patients discontinued the treatments with anti-TNF blockers because of the inefficacy (2).

The patient was a 49-year-old woman who was diagnosed at the age 38 with AOSD. The patient presented with spiking fever, a salmon-pink rash over her entire body and arthralgia at 38 years of age. She was diagnosed as having AOSD and treated with steroid therapy. High fever and skin rash were improved by this high-dose steroid therapy. She was treated with steroids and several DMARDs (MTX, sulfasalazine, bucillamine, leflunomide) over a period of 5 years, but she continued to exhibit sustained disease with flares requiring moderate doses of steroids. At the age of 43, she was treated with infliximab (3mg/kg). However, no effect of infliximab on the arthritis was observed and the administration was discontinued. At the age of 46, etanercept (25mg sc, twice a week) was started. While improvement of the arthritis was observed, the effect of etanercept was transient. Six months after the start of entanercept, she continued to have active arthritis, therefore, the etanercept was discontinued. In June 2008, she was admitted to the Nagasaki Medical Center for tocilizumab administration; laboratory examinations revealed increased levels of CRP (2.41mg/dl, normal range <0.3mg/dl), ESR (30mm/hr, normal range <8mm/hr). Informed consent was obtained from the patient and the ethics committee of Nagasaki Medical Center approved the use of tocilizumab for the patient. Tocilizumab therapy (8mg/kg, ever 4 weeks) was started on June 27, 2008. An impressive improvement of the arthritis occurred during the first 2 weeks of treatment and the patient's CRP levels and ESR were normalised within a week. Serum levels of cytokines were measured before and after (4 weeks) tocilizumab treatments (Table I). Serum IL-6 markedly elevated after tocilizumab treatment. It is likely that free serum IL-6 increased because IL-6R-mediated consumption of IL-6 was inhibited by tocilizumab as reported previously (3). After 6 months durations of tocilizumab treatments, complete halting of the radiographic progression was observed in intercarpal and radiocarpal joints (Fig. 1A, 1B).

To protect the joint from inflammatory destruction, the use of biological-response modifiers may also be appropriate in patients with AOSD. It has been reported that some AOSD patients receiving TNF-α blockers were responsive to treatment, others have discontinued treatment and some have experienced disease flares (2). Recently, administration of tocilizumab resulted in a marked decrease of the disease activity in AOSD that was refractory to DMARDs and steroid (4-6). In this report, we demonstrated that IL-6 blockade using tocilizumab not only ameliorated the elevated levels of inflammatory arthritis signs, but also reversed the progressive joint destruction of AOSD. Tocilizumab monotherapy has been shown to reduce radiographic joint damage in RA patients (7). It has been reported that cyclosporine and plasmapheresis were effective for a case with hemophagocytic syndrome complicated with AOSD (8). More recently, Matsumoto *et al*. reported a patient with cyclosporine-resistant AOSD complicated by hemophagocytic syndrome, successfully managed with tocilizumab (9). Also, IL-1 receptor antagonist (anakinra) has been shown to be effective in AOSD patients with severe joint involvement (10. 12). However, it should be taken into account that severe systemic inflammatory response syndrome could be rarely occurred in AOSD patients receiving anakinra treatment (13).

In conclusion, we report a case of treatment-resistant AOSD, in which tocilizumab was very effective for progressive joint damage, as well as chronic inflammation. This case suggests that tocilizumab is an effective treatment in AOSD patients with progressive joint destruction.

Table I. Serum levels of cytokines during tocilzumab treatment.

Variables	Before treatment (4 weeks)	After treatment	Normal range	Unit
TNF-α	1.3	1.0	<5	pg/ml
IL-1β	ND	ND	<10	pg/ml
IL-6	36.8	81.8	<4.0	pg/ml

ND: not detected.

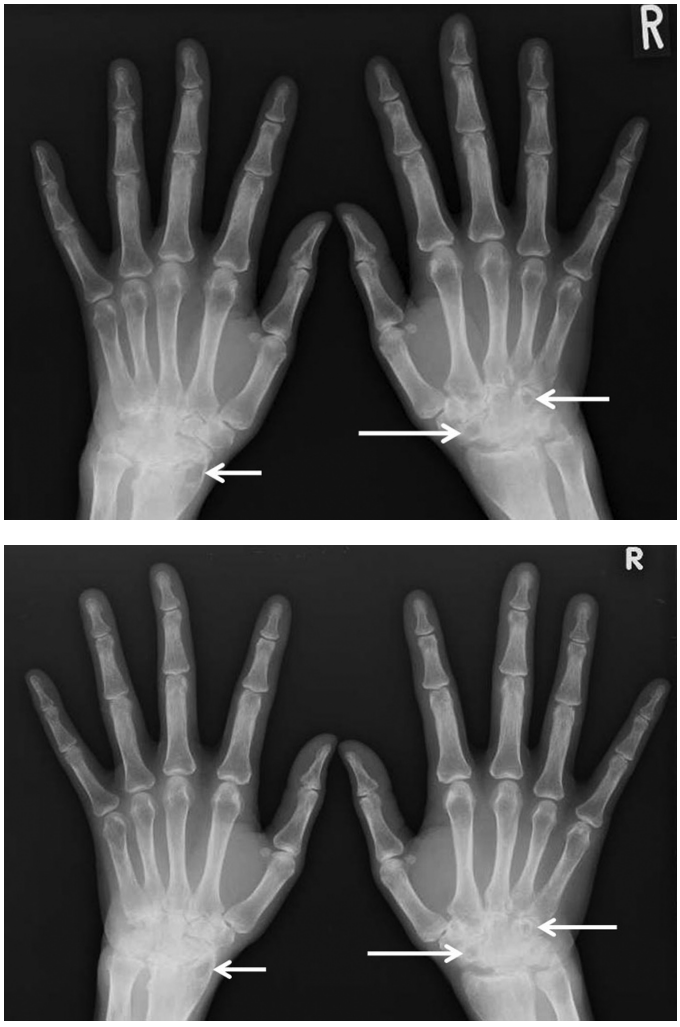

Fig. 1. There is large erosion at the distal of lt radius in addition to the ankylosis of the carpal bones. Also, cystic lesions in the rt carpal bones are noted (Fig. **1A**). The sizes of these cystic lesions (bone erosions) were decreased during 6 months of tocilizumab treatments (Fig. **1B**).

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References

1. KOKKINOS A, ILIOPOULOS A, GREKA P, EFTHYMIOU A, KATSILAMBROS N, SFIKAKIS PP: Successful treatment of refractory adult-onset Still's disease with infliximab. A prospective, non-comparative series of four patients. *Clin Rheumatol* 2004; 23: 45-9.
2. 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: 262-6.
3. NISHIMOTO N, TERAO K, MIMA T, NAKAHARA H, TAKAGI N, KAKEHI T: Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* 2008; 112: 3959-64.
4. IWAMOTO M, NARA H, HIRATA D, MINOTA S, NISHIMOTO N, YOSHIZAKI K: Humanized monoclonal anti-interleukin-6 receptor antibody for treatment of intractable adult-onset Still's disease. *Arthritis Rheum* 2002; 46: 3388-9.
5. NAKAHARA H, MIMA T, YOSHIO-HOSHINO N, MATSUSHITA M, HASHIMOTO J, NISHIMOTO N: A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. *Mod Rheumatol* 2009; 19: 69-72.
6. DE BANDT M, SAINT-MARCOUX B: Tocilizumab for multirefractory adult-onset Still's disease. *Ann Rheum Dis* 2009; 68: 153-4.
7. NISHIMOTO N, HASHIMOTO J, MIYASAKA N *et al.*: Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x-ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis* 2007; 66: 1162-7.
8. YOSHIZAKI A, KAWAKAMI A, ARAMAKI T, IDA H, EGUCHI K: Preferential recovery by an intensive initial therapy from hemophagocytic syndrome complicated with adult onset Still's disease presenting as agranulocytosis and hypercytokinemia. *Clin Exp Rheumatol* 2008; 26: 383.
9. MATSUMOTO K, NAGASHIMA T, TAKATORI S *et al.*: Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. *Clin Rheumatol* 2009; 28: 485-7.
10. FITZGERALD AA, LECLERCQ SA, YAN A, HOMIK JE, DINARELLO CA: Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum* 2005; 52: 1794-803.
11. LEQUERRÉ T, QUARTIER P, ROSELLINI D *et al.*: 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: 302-8.
12. PRIORI R, CECCARELLI F, BARONE F, IAGNOCCO A, VALESINI G: Clinical, biological and sonographic response to IL-1 blockade in adult-onset Still's disease. *Clin Exp Rheumatol* 2008; 26: 933-7.
13. GUIGNARD S, DIEN G, DOUGADOS M: Severe systemic inflammatory response syndrome in a patient with adult onset Still's disease treated with the anti-IL1 drug anakinra: a case report. *Clin Exp Rheumatol* 2007; 25: 758-9.