Mod Rheumatol (2009) 19:69–72
DOI 10.1007/s10165-008-0116-2

CASE REPORT

A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years

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Received: 25 April 2008 / Accepted: 22 July 2008 / Published online: 2 September 2008

Abstract Interleukin-6 overproduction is pathologically involved in adult onset Still's disease (AOSD). We successfully treated a man with refractory AOSD utilizing tocilizumab. Tocilizumab was discontinued after 15 doses due to intestinal bleeding, but the efficacy was sustained over 21 months. Tocilizumab was readministered safely upon recurrence and showed similar efficacy over 6 years. Corticosteroid and NSAIDs could be discontinued and intestinal bleeding was no more observed. Tocilizumab can be a therapeutic option for AOSD.

Keywords Anti-IL-6 receptor antibody · Biologics · IL-6 · Remission · AOSD

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory rheumatic disease of unknown etiology first described in 1971 by Bywaters [1]. This disease is characterized by lasting high-spike fever, arthralgia, evanescent rash, sore throat, hepatosplenomegaly, and laboratory abnormalities including leukocytosis, abnormal liver function test and elevated acute phase proteins [1, 2]. Although non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and, if necessary, immunosuppressants are commonly used as therapeutic agents for AOSD, some patients are refractory to these conventional therapies.

Interleukin (IL) -6 has been reported to play a pathological role in AOSD [3, 4]. Overproduction of IL-6 is responsible for the manifestations of AOSD such as fever, leukocytosis, and elevated acute-phase proteins [5]. Serum IL-6 levels are elevated in AOSD patients and correlates with the disease activity of AOSD [3, 4]. These findings indicate that IL-6 can be a target molecule for the treatment of AOSD.

Tocilizumab is a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody of the IgG1 subclass, which specifically inhibits IL-6 actions by competitively blocking the binding of IL-6 to IL-6R [6]. Tocilizumab has been demonstrated, in clinical trials, to be effective for patients with systemic onset juvenile idiopathic arthritis, pathological features of which are thought to be similar to those of AOSD [7–9]. In addition, one case report described that tocilizumab therapy was effective for an AOSD patient during 17 months of treatment [10]. In this report, we describe another AOSD patient whose disease activity has been well controlled by tocilizumab over 6 years.

Case report

A 24-year-old man suffering from spiking fever, polyarthralgia, evanescent rash, sore throat, and lymphadenopathy was referred to Osaka University Hospital in March 1990.

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He had past histories of pleuritis, two instances of deep vein thrombosis (DVT), and three instances of intestinal bleeding. His blood tests revealed leukocytosis (16,730/mm^3) including 80% or more granulocytes, elevated C-reactive protein (CRP), negative rheumatoid factor, and negative antinuclear antibodies. Serum ferritin was 660 ng/ml. We excluded infections, malignancies and other rheumatic diseases by radiological examinations and laboratory tests that included repetitive culture tests for microorganisms and detection of various autoantibodies such as anti-cardiolipin antibody or lupus anticoagulant. Although he suffered from DVT and intestinal bleeding, examination of hemostatic functions such as PT and APTT ruled out hemostatic abnormalities. He was diagnosed with AOSD based on four major criteria and three minor criteria described in Yamaguchi et al. [2] as well as exclusions. He was initially treated with prednisolone (30 mg/day), but his disease activity could not be controlled at this dose. He was additionally treated with disease-modifying antirheumatic drugs (DMARDs) and/or immunosuppressants such as methotrexate (MTX) (7.5 mg/week), bucillamine (200 mg/day), gold salts (total 160 mg), sulfasalazine (1,000 mg/day), azathioprine (100 mg/day) and cyclosporin A (CyA) (150 mg/day). None of these drugs fully controlled the disease activity of AOSD. Even a combination therapy of prednisolone (15 mg/day), MTX (8 mg/week) and CyA (125 mg/day) could not improve his disease. He received bilateral total hip arthroplasty (THA) and total knee arthroplasty (TKA) due to the progression of joint destruction.

Since his disease proved refractory to DMARDs and immunosuppressants, a humanized anti-IL-6R monoclonal antibody (tocilizumab) was considered as a therapeutic option. Informed consent was obtained from the patient and his family members and the ethics committee of Osaka University Hospital approved the use of tocilizumab for this patient.

He was admitted to Osaka University Hospital to receive tocilizumab treatment at the age of 35 years in June 2001. Prior to tocilizumab administration, laboratory examination revealed leukocytosis (9,580/mm^3) and increased levels of CRP (2.3 mg/dl, normal range $<$ 0.2 mg/dl) and serum amyloid A protein (SAA) (217 μg/ml, normal range $<$ 8 μg/ml). Serum ferritin was not elevated (106 ng/ml, normal range 3–136 ng/ml) likely due to repetitive hematochezia. Serum IL-6 was 4.5 pg/ml (normal range $<$ 4 pg/ml). Concentration of serum osteocalcin and procollagen 1 carboxy-terminal propeptide (P1CP) as bone formation markers were 1.8 ng/ml (normal range 2.5–13 ng/ml) and 5.3 ng/ml (normal range 33–177 ng/ml), respectively. Concentration of urinary pyridinoline and deoxypyridinoline (Deoxy-Pyr) as bone resorption markers were 41 μmol/mol/CRE (normal range 13–36 μmol/mol/CRE) and 4 μmol/mol/CRE (normal range $<$ 6 μmol/mol/CRE), respectively.

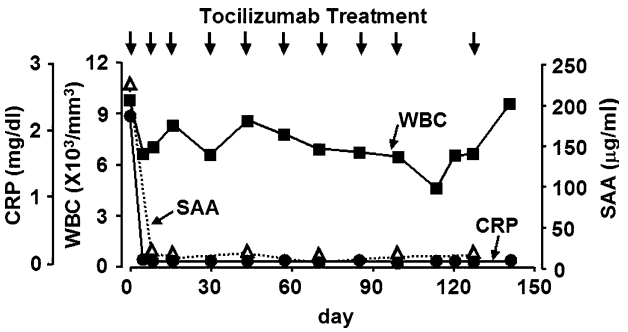

Fig. 1 Improvement in WBC and serum levels of CRP and SAA in a patient with refractory adult-onset Still's disease by tocilizumab treatment. The *arrows* show the administration of tocilizumab. Note that CRP and SAA levels were rapidly normalized

Tocilizumab monotherapy was started in July 2001 after all DMARDs and immunosuppressants were discontinued. Administration of prednisolone (15 mg/day) and diclofenac sodium (75 mg/day) was continued. Since 8 mg tocilizumab/kg body weight every 4 weeks was not an established dosing schedule at that time, treatment started with 4 mg/kg every week. The patient's CRP level decreased rapidly and was normalized ($<$0.2 mg/dl) 1 week after a single dose of 4 mg tocilizumab/kg body weight (Fig. 1). SAA levels also improved from 217.0 to 9.1 μg/ml after a week (Fig. 1). Furthermore, his arthralgia remarkably improved. The infusion schedule of tocilizumab was changed from 4 mg/kg once a week to 6 mg/kg once every 2 weeks to allow for outpatient treatment. After the 14th dose, tocilizumab dosage was increased from 6 to 8 mg/kg to extend the treatment interval up to 3 weeks. With this regimen, trough concentrations of tocilizumab in blood were maintained at approximately 20 μg/ml, a concentration sufficient to suppress the activity of AOSD. Tocilizumab increased levels of osteocalcin and P1CP (Fig. 2a), but not affect pyridinoline and Deoxy-pyr (Fig. 2b). Prednisolone dosage was not reduced and a drug to treat osteoporosis such as bisphosphonate was not added prior to and during the period shown in Fig. 2. After the 15th dose of tocilizumab, the patient suffered from DVT and massive hematochezia. Tocilizumab treatment was discontinued and he was followed with prednisolone (12.5 mg/day) treatment alone. Thereafter, the disease did not flare for 21 months (Fig. 3).

In July 2003, his arthralgia flared together with low-grade fever, leukocytosis (10,320/mm^3) and elevated levels of CRP (7.0 mg/dl) and SAA (115 μg/ml). Informed consent was obtained again and he was re-treated with tocilizumab. Readministration of tocilizumab after an interval of 21 months was well tolerated, without any signs of infusion reaction, DVT, or hematochezia. As in the first

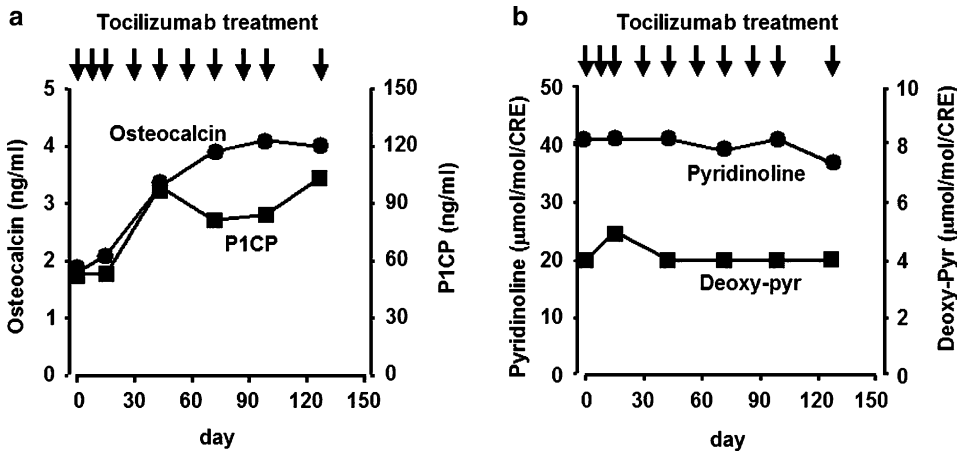

Fig. 2 Changes in bone formation markers and bone resorption markers in a patient with adult-onset Still's disease by tocilizumab treatment. The *arrows* indicate tocilizumab administration. **a** Changes in concentration of osteocalcin and procollagen 1 carboxy-terminal propeptide (P1CP). **b** Changes in concentration of urinary pyridinoline and deoxypyridinoline (Deoxy-pyr)

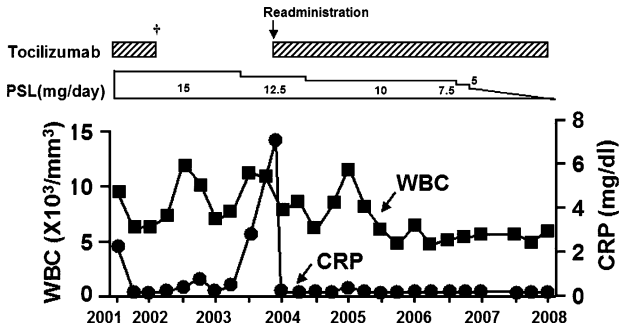

Fig. 3 Long-term treatment of a patient with refractory adult-onset Still's disease with tocilizumab monotherapy. WBC and CRP levels have been monitored since 2001. Prednisolone was successfully discontinued. *dagger* Tocilizumab treatment was discontinued due to an adverse event

tocilizumab treatment, symptoms improved 1 week after a single dose of 8 mg/kg tocilizumab, and levels of WBC and serum CRP normalized (Fig. 3). The disease was controlled and the infusion interval extended from 2 to 3 weeks after the 24th treatment. Tocilizumab treatment enabled reduction of prednisolone and nonsteroidal anti-inflammatory drug (NSAID) doses without flare. He did not suffer from DVT or hematochezia following the reduction of NSAID and prednisolone doses even while continuing tocilizumab treatment. There were no fluctuations in WBC counts after 2005 (Fig. 3) and SAA levels remained within the normal range (data not shown). Finally, prednisolone and NSAID were successfully discontinued. Tocilizumab did not induce any infusion reactions, emergence of antibodies against tocilizumab or serious infections during the long-term treatment over 6 years.

Discussion

Tocilizumab was previously reported to be effective for a 23-year-old woman with AOSD who was refractory to a combination therapy of corticosteroid, MTX, CyA, and double-filtration plasmapheresis [10]. This is the second case report that tocilizumab was therapeutically effective for an AOSD patient.

In this case, tocilizumab monotherapy improved clinical symptoms and laboratory abnormalities associated with AOSD. The findings strongly support the hypothesis that IL-6 plays an important role in the pathogenesis of AOSD. All laboratory measurements, including leukocytosis and elevated CRP levels, were normalized within a week after initiating tocilizumab treatment (Fig. 1), indicating that tocilizumab has an immediate beneficial effect. It is noteworthy that the efficacy continued for 21 months after the cessation of tocilizumab treatment. Future studies will be required to determine the mechanisms by which sustained efficacy is produced by tocilizumab. Retreatment with tocilizumab after a long-term interval of 21 months was safe and showed similar efficacy to that of the first tocilizumab treatment. This evidence provides us a choice of possible therapeutic option to use tocilizumab according to the disease activity. This case provided us with another important finding that the efficacy of tocilizumab monotherapy did not decrease at all during 6 years of continuous treatment. Consequently, NSAID and corticosteroid could be discontinued without flare.

An additional clinical benefit of tocilizumab is the improvement of bone metabolism. While reducing prednisolone dosage might contribute to this improvement, osteocalcin levels started to increase before the reduction of prednisolone dosage, indicating a tocilizumab effect. Thus, tocilizumab may be useful for osteoporosis. Although tocilizumab proved superior to conventional DMARDs in the SAMURAI clinical trial for patients with RA [11], its effectiveness in preventing joint damage progression was limited in this patient. This patient required surgical intervention due to the progression of atlantoaxial subluxation and had an advanced disease with a past history of TKA and THA prior to tocilizumab

treatment. Therefore, we need to initiate tocilizumab treatment at an early stage prior to joint destruction.

Regarding safety, this patient did not experience serious adverse events associated with tocilizumab treatment. In contrast to the frequent incidence of serious infusion reactions to infliximab after long-term intervals, no such reaction was observed even after 21 months of tocilizumab treatment [12]. No neutralizing antibodies or IgE antibodies were detected even though the patient did not use MTX. This may be an advantage of IL-6 inhibition as a B cell differentiation factor which promotes B cell differentiation into antibody-producing cells.

Deep vein thrombosis and hematochezia were initially regarded as complications of tocilizumab therapy. However, these complications were experienced in this patient prior to tocilizumab treatment. Furthermore, he had never experienced these complications after reducing NSAID and prednisolone dosage, even though he continuously received tocilizumab. This strongly suggests that the complications were likely due to NSAIDs and corticosteroid therapy rather than tocilizumab treatment.

Finally, the cytokine that should be inhibited for AOSD therapy needs to be addressed. IL-18 has been reported to be elevated in patients with AOSD [13]. In addition to inducing IL-6, IL-18 promotes TNF and IL-1 production via the nuclear factor-kB (NF-kB) pathway [14–16]. Therefore, IL-18 may be a target molecule for inhibition. However, this patient did not exhibit elevated serum IL-18 levels. IL-1 and TNF were hardly detected (<5 pg/ml) during regular monitoring every month while IL-6 was always elevated in the serum. Thus, IL-6 inhibition seemed the best candidate for anti-pro-inflammatory cytokine therapy in this patient.

Adult-onset Still's disease is sometimes complicated by macrophage activation syndrome (MAS), which is associated with abnormal laboratory findings such as pancytopenia, liver dysfunction, and increase in triglyceride and ferritin, and various inflammatory cytokines such as TNF, IFN-γ, IL-1, IL-18 and GM-CSF are markedly produced and play pathological roles. In such a condition, IL-6 inhibition alone is not sufficient to control the disease.

The success in treating this AOSD patient confirmed the pathological significance of IL-6 in this disease. Elucidating the mechanism by which IL-6 is over-produced may lead to the discovery of a new therapeutic target for AOSD. In conclusion, this case report again indicates the clinical benefit of IL-6 inhibition using tocilizumab for an AOSD patient.

Acknowledgments We thank Dr. Ichiro Kawase and Dr. Toshio Tanaka for clinical support. This work was supported by Chugai Pharmaceutical Co., Ltd. N. Nishimoto and T. Mima received a consulting fee from Chugai Pharmaceutical Co., Ltd. as medical advisors.

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