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CASE REPORT

Case report: successful use of short-term add-on tocilizumab for multirefractory systemic flare of adult-onset Still's disease

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Abstract We report on a 64-year-old woman with multirefractory flare of adult-onset Still's disease successfully treated with six-month course of add-on anti-interleukin 6 receptor antibody, tocilizumab. Before administration of tocilizumab, the combination therapy with 80 mg/day of prednisolone and cyclosporine or tacrolimus for five weeks, two courses of pulse methylprednisolone, and high-dose intravenous immunoglobulin could not control the disease. Add-on tocilizumab dramatically improved her disease state and enabled tapering of corticosteroid and tacrolimus. Furthermore remission has been maintained on low-dose corticosteroid and tacrolimus after withdrawal of tocilizumab. This case report suggests that short-term add-on tocilizumab might be a useful therapeutic option for patients with multirefractory flare of polycyclic systemic adult-onset Still's disease.

Keywords adult-onset Still's disease · interleukin 6 · interleukin 18 · tocilizumab

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease, characterized by spike fevers, evanescent rash, and polyarthritis [1]. The clinical course of AOSD may follow three distinct patterns: monocyclic systemic, polycyclic systemic, and chronic articular diseases [2].

Although systemic flares of the disease may be usually successfully treated with high-dose corticosteroids with or without immunosuppressants, refractory systemic flares of the disease may potentially cause life-threatening conditions, such as macrophage activation syndrome with hepatic failure or microangiopathies, or complicated infections related to intensive immunosuppressive treatment [1, 3]. Here, we report on a patient with AOSD with systemic flare that was refractory to the combination therapy with high-dose corticosteroids, immunosuppressants, and intravenous immunoglobulin, successfully treated by adding anti-interleukin (IL) 6 receptor antagonistic antibody, tocilizumab. Moreover, a 6-month course of tocilizumab treatment led the patient into tocilizumab-free remission.

Case report

A 62-year-old woman developed high fever and polyarthralgia in July 2007 and was diagnosed as having AOSD based on four major criteria and four minor criteria described by Yamaguchi et al. [4] as well as exclusion of other conditions. Although she had been treated with 40 mg/day of prednisolone, she developed rapidly progressive liver dysfunction and was referred to Nagoya City University Hospital. On admission, severe liver dysfunction with signs of hepatic failure (aspartate aminotransferase 4,329 U/l, alanine aminotransferase 4,806 U/l, lactate dehydrogenase 3,037 U/l, total bilirubin 3.1 mg/dl, ammo-

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nia 77 μg/dl, prothrombin time 39%), disseminated intravascular coagulation, elevated C-reactive protein (CRP, 4.19 mg/dl), and marked hyperferritinemia (179,200 ng/ml) were observed. Antinuclear antibodies and rheumatoid factor were negative. Serology for hepatitis A, B, C, and E virus and hepatitis B DNA were all negative. Epstein–Barr virus (EBV) DNA overload was not observed ($<2.0\times10^1$ copy/10^6 peripheral blood leukocytes [normal range $<2.0\times10^1$]). High-dose corticosteroid including methylprednisolone pulse therapy and cyclosporine resolved her disease into remission. Corticosteroid had been tapered and she had been well on prednisolone (3 mg/day) and cyclosporine (200 mg/day) until 1 week before the second admission at February 2009, when she developed fever, sore throat, and polyarthralgia.

On second admission, she had high fever, rheumatoid rash, and arthritis in the proximal interphalangeal joints. CRP and ferritin were 16.13 mg/dl and 7,794 ng/ml, respectively (Fig. 1). Under the diagnosis of relapse of AOSD, she received two courses of pulse methylprednisolone following prednisolone 80 mg/day combined with cyclosporine 200 mg/day (trough serum concentration 116.5–194.1 ng/ml), which did not improve her febrile state and arthritis. On day 14, cyclosporine was substituted to tacrolimus 2.5 mg twice daily (trough concentration 11.2 ng/ml). Thereafter, high fever mostly subsided, and serum levels of CRP slightly decreased, but serum ferritin level had paradoxically increased. On day 27, high-dose immunoglobulin (HD-IVIG) therapy (20 g/day for consecutive 5 days) was added, though clinical response was not observed, and serum ferritin level reached 20,720 ng/ml. She required up to 58 units of insulin per day due to steroid-induced diabetes, and mild EBV-DNA overload was observed (1.5×10^3 copy/10^6 peripheral blood leukocytes). After informed consent was obtained, biweekly infusion of 8 mg/kg of tocilizumab was added on combination therapy with prednisolone (80 mg/day) and tacrolimus (5 mg/day) on day 39. Within 1 week after the first tocilizumab infusion, CRP level was normalized and ferritin level began to decrease. Serum IL6 levels had increased after the start of tocilizumab until just before the sixth infusion, and thereafter

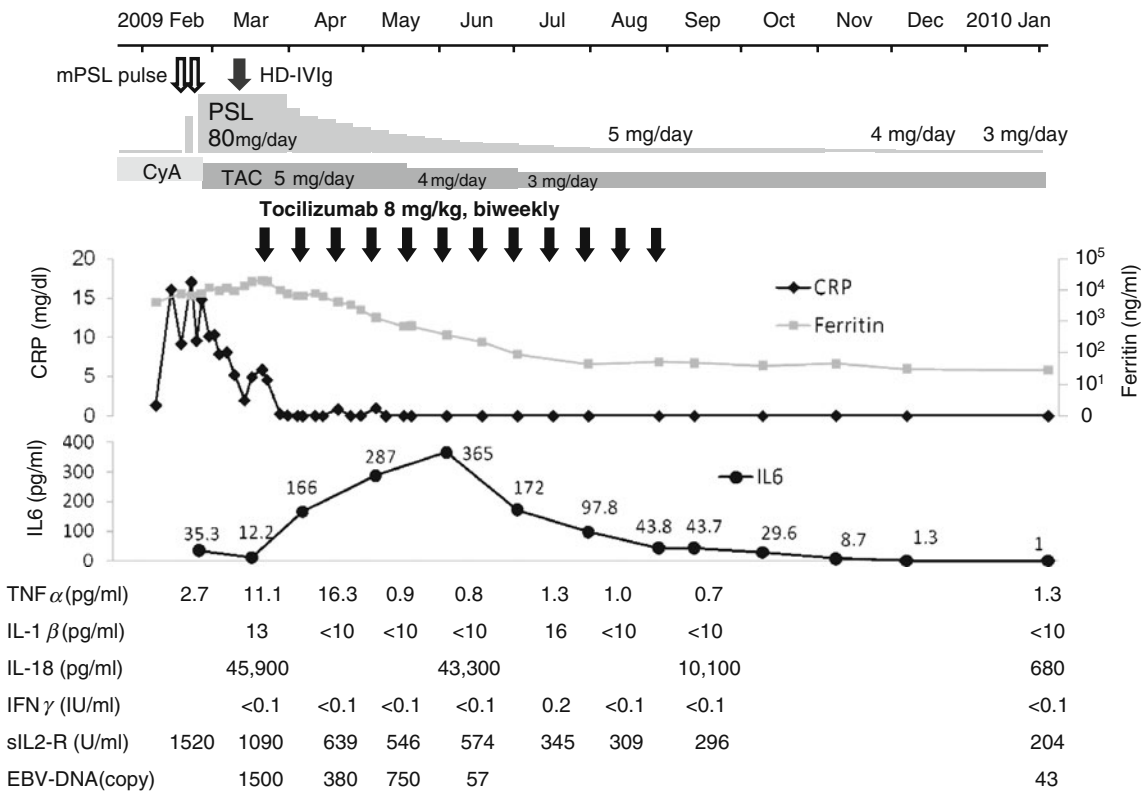

Fig. 1 Patient's treatment, inflammatory biomarkers, and EBV-DNA levels during the clinical course. *CRP* C-reactive protein, *CyA* cyclosporine, *EBV* Epstein–Barr virus, *HD-IVIg* high-dose intravenous immunoglobulin therapy, *IFN* interferon, *IL* interleukin, *mPSL* methylprednisolone, *PSL* prednisolone, *sIL2-R* soluble interleukin 2 receptor, *TAC* tacrolimus. Reference values are as follows: IFN-γ (normal <0.1 pg/ml), IL-18 (normal <259.4 pg/ml), IL-1β (normal <10 pg/ml), IL-6 (normal <4 pg/ml), TNFα (normal <2.8 pg/ml), and sIL2-R (145<normal<519 U/ml). EBV-DNA levels (normal $<2.0\times10^1$) were measured by real-time polymerase chain reaction using DNA extracted from 10^6 peripheral blood leukocytes

had decreased. Serum soluble IL2 receptor levels had decreased just after the onset of tocilizumab and normalized after the sixth infusion. On the other hand, serum IL1β and tumor necrosis factor (TNF) α levels had rapidly decreased into normal range after the first and second infusion of tocilizumab, respectively. EBV-DNA load had been decreased to 5.7×10^{1} copy/10^{6} peripheral blood leukocytes at the eighth infusion. Tocilizumab enabled tapering of prednisolone and tacrolimus to 5 and 3 mg/day, respectively, and disengagement from insulin injection. After 12 infusions of tocilizumab, an attempt to reduce the dose in August 2009 was followed by no flare of clinical manifestations and laboratory findings, thus we discontinued tocilizumab. To date, there has been no relapse of AOSD and no increase in serum inflammatory cytokine levels after withdrawal of tocilizumab.

Discussion

Aberrant production of proinflammatory cytokines such as IL1, IL6, and IL18, interferon-γ, and TNFα by uncontrollably activated and proliferated T cells and macrophages seems to play a pivotal role in the pathogenesis of AOSD [1, 5]. The biologic agents that selectively inhibit the action of proinflammatory cytokines, such as TNFα and IL1, have been successfully used for the treatment of AOSD refractory to conventional therapies that, in turn, reinforce the importance of excess of proinflammatory cytokines in the pathogenesis of AOSD [1, 5]. Selective inhibition of IL6 signal by tocilizumab has been proved to be effective for systemic-onset juvenile idiopathic arthritis [6]. In AOSD, which is an adult counterpart of systemic-onset juvenile arthritis, there have also been several case reports of AOSD regarding the therapeutic effects of tocilizumab for AOSD [7–10]. They all are single case reports that showed the remission-inducing effect of tocilizumab. The present report also reinforced the potential efficacy of tocilizumab for the treatment of AOSD and the importance of IL6 in the pathogenesis of AOSD.

Long-term tocilizumab therapy can induce remission of AOSD and decrease the dose of concomitant corticosteroids, but it remains unclear how long tocilizumab therapy should be continued for AOSD [7, 8]. In the literature, one patient had discontinued tocilizumab therapy by remission after an 18-month course of treatment and was disease-free with no medications for 7 years [7, 9], one had discontinued tocilizumab therapy by adverse events after 15th infusion without disease flare for 21 months with 12.5–15 mg of prednisolone alone, and the others were in ongoing use in the clinical course on the reports [8–10]. In the present case, 24-week course of add-on tocilizumab induced remission of the refractory disease despite combination therapy with high-dose corticosteroids, calcineurin inhibitors, and high-dose intravenous immunoglobulin, and led this case into tocilizumab free remission, which has been maintained on low-dose prednisolone and tacrolimus.

Serum IL6 levels, which have been known to correlate well with the disease activity of AOSD [11, 12], continued to increase after the onset of tocilizumab therapy until the time of the sixth infusion, and thereafter decreased and stabilized while tapering off the concomitant immunosuppressive drugs. Nishimoto et al. [13] reported that the increased level of serum IL6 during tocilizumab treatment closely reflects the actual endogenous IL6 production and true disease activity of patients with rheumatoid arthritis or Castleman's disease much better than the serum IL6 level before tocilizumab treatment. They also suggested that decrease in serum IL6 during tocilizumab treatment may indicate disease remission and may be a guide to discontinue tocilizumab treatment. These findings and the clinical course of the present case suggests that serial measurements of serum IL6 during tocilizumab therapy may also be a useful guide to estimate the true disease activity as well as the timing to consider decreasing the dose of or cessation of tocilizumab in patients with AOSD. However, the IL6 level suggesting remission of AOSD and the length of period of remission required before discontinuation of tocilizumab need to be determined in future studies, and it should be also noted that this approach might not be appropriate for the treatment of chronic articular form of AOSD.

Serum levels of other inflammatory cytokines, such as IL18, IL1β, and TNFα, also decreased after tocilizumab therapy. Serum levels of IL1β and TNFα rapidly decreased into the normal range after the second infusion of tocilizumab. On the other hand, serum levels of IL18 slowly decreased after tocilizumab was administered, but remained elevated even after reaching clinical remission and normalization of serum levels of IL1β, IL6, INFγ, and TNFα. These findings might indicate that IL18 is an upstream initiator of the inflammatory cascade including IFNγ, IL6, and TNFα [5].

We also observed that EBV overload and glucose intolerance were elicited during the treatment with high-dose corticosteroids, and immunosuppressants had been ameliorated along with the relatively rapid tapering of these drugs after the induction of tocilizumab. Immunosuppression may cause a decrease in EBV-specific immune response and an increase in the EBV viral load, which has been known to cause lymphoproliferative disorders [14]. Tocilizumab therapy strongly suppressed the disease activity and enabled tapering of corticosteroids and immunosuppressants that might restore the protective immune responses against microorganisms including EBV and, in turn, reduced EBV overload [15].

In conclusion, this report suggests that short-term add-on tocilizumab might be a useful therapeutic option for patients with refractory systemic flare of AOSD, not only controlling the disease activity and complications related to

conventional therapies, but also reducing medical costs when compared to longer-term tocilizumab therapy described in previous reports.

Disclosures None.

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