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CASE REPORT

Benefit and a possible risk of tocilizumab therapy for adult-onset Still's disease accompanied by macrophage-activation syndrome

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Abstract We report a 57-year-old female case of intractable adult-onset Still's disease (AOSD). Initial high-dose prednisolone therapy was ineffective, and macrophage-activation syndrome (MAS) manifested after one session of additional tocilizumab therapy. After successful treatment for MAS with lipo-dexamethasone and cyclosporin, tocilizumab therapy aided in the rapid reduction of the therapeutic steroid dose. Tocilizumab may be useful for maintenance therapy for AOSD, although its efficacy is unclear for the highly active phase of the disease.

Keywords Adult-onset Still's disease · Tocilizumab · Macrophage-activation syndrome · Hemophagocytic lymphohistiocytosis

Introduction

Still's disease (SD) is a systemic inflammatory disorder of unknown etiology and has been regarded as the synonym of systemic-onset juvenile idiopathic arthritis (sJIA) [1]. An adult-onset form of the disease (adult-onset Still's disease, AOSD) has been known since the first report by Bywaters [2]. The clinical manifestations of SD and AOSD are similar [3], although fever and skin rash were reported to be more common in AOSD than SD/sJIA in 130 patients [1]. Recent studies have shown that inflammatory cytokines, including interleukin (IL)-6, IL-18, interferon-γ, and tumor necrosis factor, play pathogenic roles in the disease processes of AOSD [4, 5]. Thus, inhibiting these cytokines may be a sensible therapeutic strategy for Still's disease. On the other hand, it is unknown whether the blockade of a single cytokine pathway in the setting of a cytokine storm, if any, causes an unfavorable imbalance in the cytokine system or whether it is sufficient to suppress the inflammatory condition.

Tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, is an effective cytokine inhibitor for the treatment of rheumatoid arthritis [6]. A recent clinical trial demonstrated the therapeutic efficacy of tocilizumab for treating pediatric patients with sJIA [7–9] or rheumatoid arthritis [10–13]. Several case reports have suggested that tocilizumab therapy was also effective for intractable AOSD [14–16]. These reports on AOSD did not include cases with hemophagocytic syndrome (HPS) or macrophage-activation syndrome (MAS).

Macrophage-activation syndrome is one of the most serious complications of sJIA [17–19], and a similar clinical manifestation, HPS, has been documented in AOSD [20–22]. These hematological disorders, as described in the literature, were caused by accidental viral infections in some cases and directly by the underlying sJIA or AOSD in others [20, 23–25].

Here, we describe tocilizumab therapy in a case of AOSD that involved MAS during the induction therapy.

Case report

A 57-year-old Chinese woman was admitted to our hospital in 2009 because of fever, polyarthralgia, sore throat, and cervical lymphadenopathy. She had been well until approximately 3 weeks earlier, when lymphadenopathy

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developed on the right cervix. One week later, she developed fever and sore throat, and an evanescent skin rash on the upper limbs, lower limbs, and trunk manifested, followed by polyarthralgia. Until 1 week prior to admission, she had received antibiotics, including ceftriaxone sodium hydrate, tosufloxacin tosilate hydrate, and piperacillin sodium, but had shown no response.

Initial blood data on admission were as follows: leukocytes 20790/μL (neutrophils 18000/μL), red blood cells 421 × 10^4/μL, hemoglobin 12.8 g/dL, platelets 28.3 × 10^4/μL, erythrocyte sedimentation rate 99 mm/h, prothrombin time INR 1.50, activated partial thromboplastin time 25.5 s, fibrinogen 598 mg/dL, D-dimer 3 μg/mL, aspartate aminotransferase 40 IU/L, alanine aminotransferase 32 IU/L, blood urea nitrogen 9.5 mg/dL, creatinine 0.53 mg/dL, C-reactive protein (CRP) 26.4 mg/dL, rheumatoid factor 14.9 IU/mL, soluble interleukin-2 receptor (sIL-2R) 1640 IU/L, and ferritin 7924 ng/mL. Anti-DNA antibodies and anti-neutrophil cytoplasmic autoantibodies were negative, and anti-nuclear antibodies were positive at a dilution of 1:80. Urine β2-microglobulin was 1185 mg/dL. Serological tests for Epstein–Barr virus and anti-cytomegalovirus (CMV) IgM antibodies and a skin test for tuberculosis showed negative results.

A computed tomography (CT) scan showed mediastinal lymphadenopathy. A positron emission tomography/CT scan indicated ^{18}F-flourodeoxyglucose uptake in the bilateral knee joints, spleen, mediastinal lymph nodes, and bone marrow. Bone marrow aspiration showed no atypical cells.

A diagnosis of AOSD was made based on the above findings, including spiking fever, polyarthritis, salmon pink skin rash, leukocytosis, sore throat, lymphadenopathy, and elevated serum transaminases. The above findings met the criteria for the classification of adult Still's disease from Yamaguchi et al. [3], and steroid therapy was started at a daily dose of 80 mg (1.3 mg/kg) oral prednisolone (PSL). After a transient improvement with the initial therapy, as shown in Fig. 1, a high fever occurred on day 23, which indicated that the inflammatory condition was resistant to >1 mg/kg/day of PSL (Fig. 1). To avoid cushingoid side effects due to further increases in steroid dose, we added 480 mg of tocilizumab therapy on day 35, and the patient

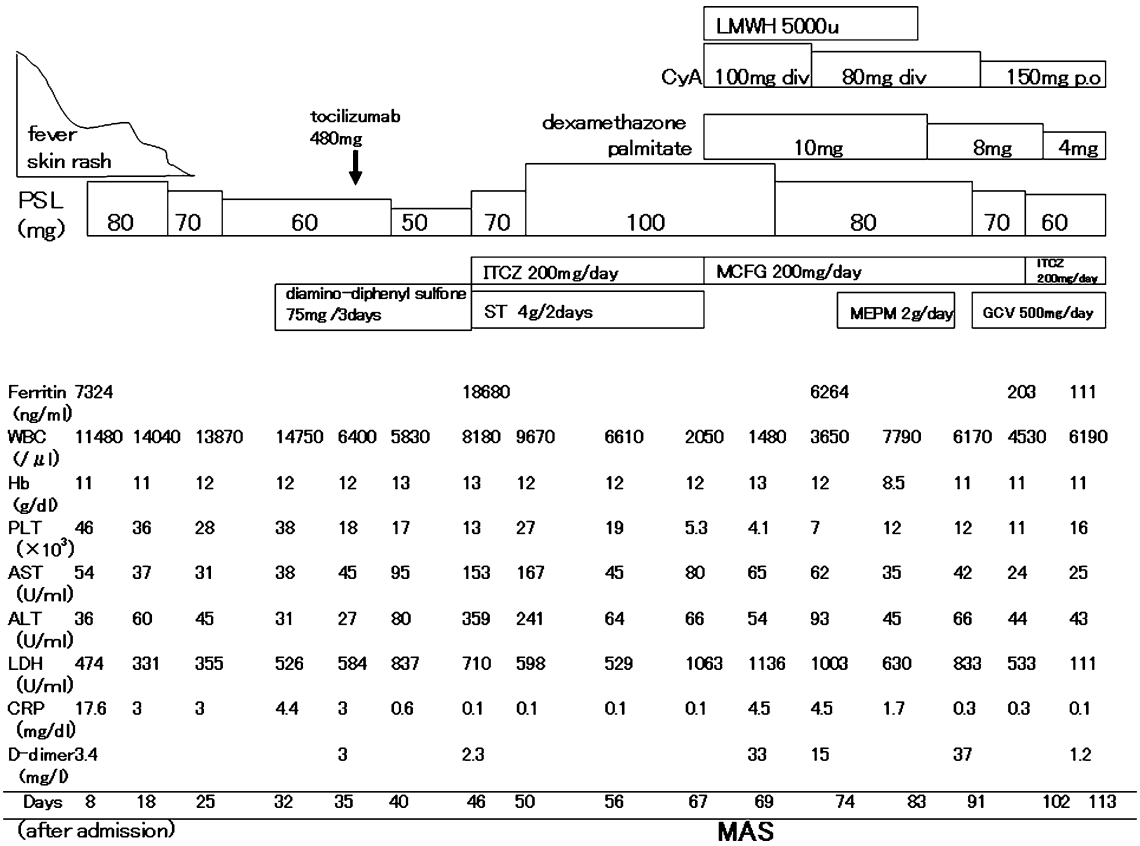

Fig. 1 The disease course during the induction therapy. The intractable disease conditions despite initial steroid therapy, macrophage-activation syndrome (MAS) after one session of tozilizumab therapy, and the successful suppression of MAS by combination therapy with high-dose steroid and cyclosporin A are shown serially. *WBC* white blood cell count; *Hb* hemoglobin; *Plt* platelet count; *ST* sulfamethoxazole/trimethoprim; *ITCZ* itraconazole; *Cy A* cyclosporin A; *LMWH* low molecular weight heparin; *MEPM* meropenem; *GCV* ganciclovir; *MCFG* micafungin

showed rapid resolution of fever and serum CRP level. After the improvement, a disease flare that included thrombocytopenia and elevated levels of serum transaminases and ferritin occurred on day 46, although serum CRP levels were still falling with tocilizumab treatment. This suggested tocilizumab-resistant Still's disease, given the negative results for infectious agents. Bone marrow aspiration revealed no hemophagocytic cells, and the dose of steroid therapy was increased (day 46). Despite the intensified therapy, fever and arthralgia recurred on day 67, and these were accompanied by neutropenia, thrombocytopenia, and re-elevation of serum transaminase and ferritin levels. No infectious etiology was detected, but bone marrow aspiration uncovered significant numbers of macrophages that had phagocytosed blood cells. These observations indicated that the patient had MAS associated with AOSD, and she was treated with intravenous dexamethasone palmitate (10 mg/day), continuous infusion of cyclosporin (100 mg/day), and low-molecular-weight heparin (5000 units/day). These therapies effectively reduced the disease activity of AOSD and MAS (Fig. 1). During the above immunosuppressive therapies, the patient suffered sequentially from *Clostridium* bacteremia and CMV viremia, which were successfully treated with specific drugs.

After the inflammatory findings had resolved completely, tocilizumab therapy was resumed in order to avoid prolonged high-dose steroid therapy, and the steroid dose was tapered rapidly, as shown in Fig. 2. Thereafter, the patient has been successfully maintained on tocilizumab every 2 weeks in combination with a maintenance dose of oral prednisolone and 75 mg/day of oral cyclosporin A.

Discussion

Still's disease (SD) responds to steroid monotherapy and shows a benign course in most cases. On the other hand, steroid-resistant and steroid-dependent forms of the disease remain challenging problems in some subsets of SD patients. Combination therapy with steroids and cyclosporin A is effective for SD [26], as observed in this patient. However, reducing the steroid dose frequently results in disease flares in patients with highly active SD, and cushingoid side effects are a serious concern in these patients, although immunosuppressants such as methotrexate may have a steroid-sparing effect [27]. In our patient, a rapid reduction in the therapeutic dose of steroids and prolonged remission on low-dose steroids were accomplished by combination therapy with tocilizumab.

Tocilizumab therapy is effective for juvenile idiopathic arthritis, including SD/sJIA, and for AOSD, as described in the "Introduction." Tumor necrosis factor blockade is also effective for treating JIA [28–31], and a case of intractable ASOD treated with infliximab has been reported [32]. There have been a number of controversial observations in the literature regarding etanercept therapy for sJIA or ASOD; MAS was induced or worsened after etanercept therapy for AOSD [33, 34], but intractable MAS in a sJIA patient was successfully treated with etanercept therapy [35]. The time profile of laboratory data in our patient (Fig. 1) suggested that MAS occurred as a consequence of highly active AOSD and that 1 mg/kg/day of PSL combined with one session of tocilizumab therapy was partially effective but insufficient for preventing MAS.

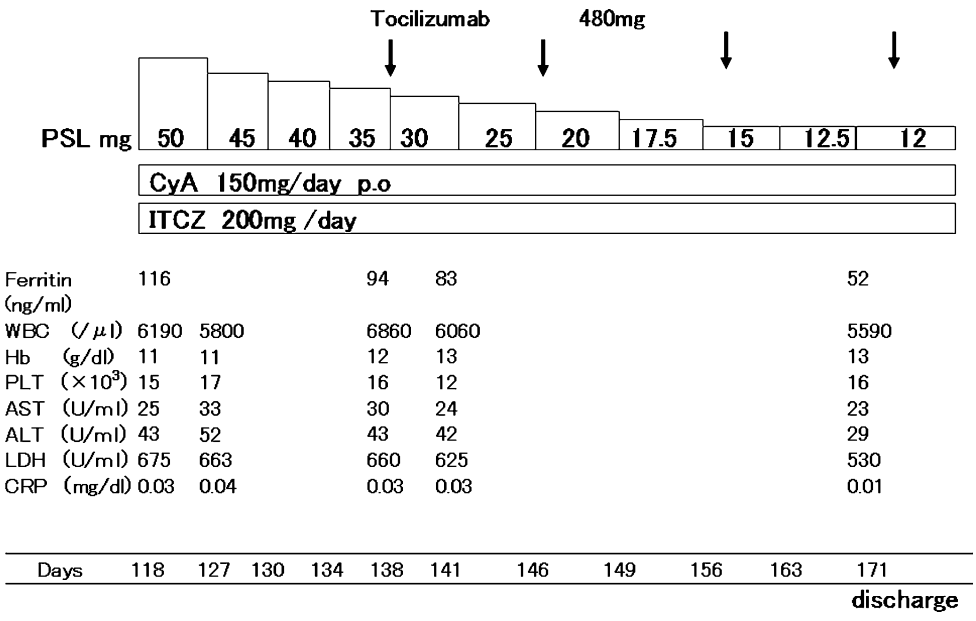

Fig. 2 Successful reduction of the therapeutic dose of steroids in combination with tocilizumab therapy

Macrophage-activation syndrome is a disorder characterized by hemophagocytosis, inappropriate systemic proliferation of benign histiocytes throughout the reticuloendothelial system, deregulation of T lymphocytes and macrophages, and subsequent overproduction of cytokines such as IL-1, IL-6, and IFN-γ [4, 5, 17, 19]. Among the rheumatic diseases, sJIA and AOSD are often associated with MAS, and one retrospective study [21] indicated a high frequency (12%) of MAS in AOSD patients. MAS of noninfectious etiology has been observed as a complication in several cases of sJIA during tocilizumab therapy [12], which was administered at various times in the course of sJIA, and the relationship between tocilizumab therapy and MAS has not been determined.

Based on the observations made in the case described here, complete suppression of AOSD activity by high-dose steroid therapy or combination therapy with cyclosporin A, followed by the rapid reduction of the therapeutic steroid dose through the application of additional tocilizumab therapy may be a reasonable strategy for treating AOSD. The efficacy of tocilizumab therapy for the active phase of AOSD is unclear, and we should be cautious of the possible induction of treatment-related MAS.

Conflict of interest None.

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