Two Cases of Adult-onset Still’s Disease Treated with Tocilizumab that Achieved Tocilizumab-free Remission

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Abstract

There have been many previously reported cases of adult-onset Still’s disease (AOSD) which were successfully treated with tocilizumab (TCZ). However, the efficacy and safety of TCZ therapy for AOSD-associated macrophage activation syndrome (MAS), and the optimal duration of TCZ therapy, remain unclear. We herein report two cases of refractory AOSD, one of which was associated with MAS. These two patients were treated with TCZ, and the withdrawal of TCZ was planned according to the serum interleukin-6 level, which resulted in TCZ-free remission.

Key words: adult-onset Still’s disease, tocilizumab, interleukin-6, withdrawal


Introduction

Adult-onset Still’s disease (AOSD) is a multi-systemic inflammatory disease of unknown cause. It typically presents with symptoms of arthralgia, a sore throat, an elevated serum ferritin level, a “salmon-pink” rash, pyrexia, and lymphadenopathy (1, 2). Corticosteroids are the mainstay treatment, however, many patients require additional immunosuppressive agents, including methotrexate (MTX), cyclosporine A (CyA), tacrolimus or cyclophosphamide (3-6). However, a small proportion of patients show an insufficient response to combination therapy with corticosteroids and other immunosuppressive agents. Recently it has become apparent that cytokines [e.g., interleukin-1 (IL-1), IL-6, and IL-18, interferon gamma, and tumor necrosis factor-alpha (TNF-alpha)] play roles in the pathogenesis of AOSD, and the administration of biological agents to block these cytokines is effective (7-11).

Many case reports and case series have documented the dramatic effect of tocilizumab (TCZ) treatment, a humanized monoclonal anti-IL-6 receptor antibody (12-16). However, this therapy is off-label, may mask the symptoms of infection, and may lead to economic hardship on the patients. Therefore, it is important to determine the optimal duration of TCZ administration. Some authors have proposed that the decrease in the serum IL-6 level observed during TCZ therapy indicates disease remission (17) and thus may be an indicator for therapy discontinuation in the patients with rheumatoid arthritis (RA) and Castleman disease; however, there is insufficient information about this parameter in AOSD. In addition, the safety and efficacy of biologics in the cases of AOSD complicated by macrophage activation syndrome (MAS) are controversial, as these agents may exacerbate MAS (18).

We herein report two cases of AOSD. Both of the patients were successfully treated with TCZ and achieved a TCZ-free remission. One patient was complicated by MAS, and she was treated with a corticosteroid, CyA, plasma exchange, and TCZ, which did not exacerbate MAS. Although the withdrawal of TCZ was planned after the serum IL-6 level was confirmed to be decreased in both cases, one patient experienced mild recurrence. Thus, even an extremely low level of IL-6 does not ensure relapse-free remission. However, the IL-6 level may be a parameter for determining when to discontinue TCZ administration without developing serious exacerbations.

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Case Reports

Case 1
A 45-year-old Japanese woman with polyarthralgia was referred to our hospital. She additionally suffered from a sore throat and a spiking fever and had a salmon-pink rash on her arms and legs. The laboratory values were as follows: white blood cell (WBC) count 19,100/mm$^3$, aspartate aminotransferase (AST) 32 IU/L, alanine aminotransferase (ALT) 36 IU/L, lactate dehydrogenase (LDH) 286 IU/L, serum ferritin 4,007 ng/mL, and C-reactive protein (CRP) 17.0 mg/dL, with negative antinuclear antibody and rheumatoid factor. We excluded infections, malignancies, and other rheumatic diseases by radiological examinations and laboratory tests, which included repetitive cultures for microorganisms and the detection of various autoantibodies. As cervical lymph node swelling and splenomegaly were demonstrated by computed tomography (CT), the patient met the Yamaguchi criteria for AOSD (2). The administration of prednisolone (PSL) (40 mg/day, per os) was initiated, however, the fever persisted with marked leukocytosis (WBC count 30,200/mm$^3$). She was treated with three courses of methylprednisolone (mPSL) pulse therapy (500 mg/day for 3 days each, div), followed by a high dose of intravenous mPSL with MTX (8 mg/week, per os) and mizoribine (300 mg/week, per os). Although these treatments transiently suppressed the disease activity, tapering the mPSL dose to less than 120 mg/day led to a flare-up. Her general condition then deteriorated rapidly. Due to the failure of these therapies, we administered TCZ (8 mg/kg/4 weeks, div) after obtaining sufficient informed consent. This resulted in a gradual improvement of the fever and skin rash, and the serum ferritin and CRP levels normalized within 2 weeks after the first administration of TCZ. Oral PSL was gradually tapered to 5 mg/day and the dose of TCZ was tapered gradually (8 mg/kg/4 weeks for 13 times, then 8 mg/kg/6 weeks for 4 times, and then 8 mg/kg/8 weeks for 2 times). Twenty-three months after admission, the serum IL-6 level was <0.300 pg/mL with PSL (5 mg/day, per os), MTX (8 mg/week, per os), mizoribine (300 mg/week, per os), and TCZ (8 mg/kg/8 weeks, div), and we discontinued the administration of TCZ. The disease activity was completely controlled with PSL (5 mg/day, per os) and MTX (6 mg/week, per os) therapy 48 months after the admission (Fig. 1).

Case 2
A 61-year-old Japanese woman was admitted to a local hospital with a spiking fever, polyarthralgia, a sore throat, and an evanescent rash. Her medical history was unremarkable. The results of the laboratory tests were as follows: WBC count 14,420/mm$^3$, AST 39 IU/L, ALT 60 IU/L, and CRP 25.7 mg/dL. Antinuclear antibody and rheumatoid factor were negative, and the urinalysis was normal. The administration of oral PSL at a dose of 10 mg/day was not ef-
fective, and the patient was transferred to our hospital. Her spiking fever persisted, and the laboratory data on this admission were as follows: WBC count 20,500/mm\(^3\), red blood cell count (RBC) 4.20\times10^6/mm\(^3\), platelet count 32.5\times10^4/mm\(^3\), AST 164 IU/L, ALT 179 IU/L, LDH 1,090 IU/L, serum ferritin 72,400 ng/mL, and CRP 15.5 mg/dL. Cervical and axillary lymph node swelling and splenomegaly were demonstrated by CT. The laboratory evaluations, including several autoantibodies, serologic tests and bacterial cultures, ruled out infections and systemic or malignant diseases. According to these findings, she was diagnosed with AOSD in agreement with the Yamaguchi criteria (2).

We started the patient on PSL (40 mg/day, per os); however, this failed to control her symptoms, and the laboratory findings worsened on the 5th day: WBC 11,400/mm\(^3\), RBC 3.75\times10^6/mm\(^3\), platelet count 13.1\times10^4/mm\(^3\), fibrinogen 125 ng/dL, fibrin degradation products 67.2 μg/mL, D-dimer 332 μg/mL, AST 1,090 IU/L, ALT 1,992 IU/L, LDH 1,070 IU/L, and CRP 4.2 mg/dL. A histological examination of a bone marrow smear demonstrated hemophagocytic syndrome. The findings of a close workup indicated that bacterial infections, viral infections [such as Epstein-Barr virus (EBV) or cytomegalovirus], and malignancies (including lymphoma) were unlikely. We diagnosed the patient with MAS due to AOSD and administered mPSL pulse therapy (1 g/day for 3 days, div), performed plasma exchange, and TCZ (8 mg/kg/biweekly, div) therapy was started after obtaining sufficient informed consent. Thereafter, the fever and skin rash improved, and the serum CRP, AST, ALT and ferritin levels gradually decreased. CyA was withdrawn 6 months later, and we gradually tapered the dose of TCZ (8 mg/kg/2 weeks for 7 times, 8 mg/kg/4 weeks for 2 times, 4 mg/kg/4 weeks for 3 times, and then 2 mg/kg/4 weeks for 2 times). Because the serum IL-6 level decreased to 0.865 pg/mL with PSL (10 mg/day, per os) and TCZ (2 mg/kg/4 weeks, div), we discontinued TCZ therapy 9 months later. After 3 months, the IL-6 level was below 0.300 pg/mL, i.e., below the limit of detection. Although the disease activity had been completely controlled with PSL (10 mg/day, per os), a relapse that was potentially triggered by an upper respiratory infection, was experienced 8 months later. The CRP and ferritin levels increased to 5.0 mg/dL and 1,070 ng/mL, respectively. We increased the dose of oral PSL from 10 mg/day to 20 mg/day, and initiated MTX treatment (4 mg/week, per os). The disease activity was thereafter easily controlled, and the dose of PSL was tapered. The patient is currently receiving treatment with PSL (6 mg/day, per os) and MTX (6 mg/week, per os), and her disease activity is considered to be fully controlled (Fig. 2).

**Discussion**

Although TCZ therapy may induce remission of AOSD, the duration of therapy is unclear. In the present cases, the serum IL-6 concentration on admission were 280.0 pg/mL in case 1 and 61.6 pg/mL in case 2 (normal level <4.0 pg/mL). TCZ suppressed the IL-6 and CRP levels in both cases (Fig. 1, 2). The disease activities of our patients were well-
controlled, and the treatment imposed an enormous economic hardship on them with fears of developing potential opportunistic infections. Iwamoto et al. reported the increase of the IL-6 and CRP levels to be associated with the reduction in the anti-IL-6 receptor antibody concentration when they extended the treatment infusion cycle (12), thus we first attempted a gradual dose reduction and/or the elongation of the dosing interval of TCZ rather than discontinuation of the treatment. In both of the present patients, TCZ was discontinued because the IL-6 level was very low and TCZ was considered to play a negligible role. In case 1, the serum IL-6 concentration was below 0.3 pg/mL, and the administration of TCZ was discontinued. No relapse was observed for at least 25 months. However, in case 2, the patient experienced recurrence along with an upper respiratory infection 11 months after the withdrawal of TCZ treatment, even though the IL-6 level was confirmed to be below 0.3 pg/mL. The escalation of the PSL dose from 10 mg/day to 20 mg/day with additive MTX therapy easily controlled the disease activity. These results indicated that even an extremely low level of IL-6 may not offer a guarantee of permanent relapse-free remission. However, it may be a possible parameter to stop the TCZ administration without inducing severe exacerbation. Naniwa et al. reported a case in which the short-term addition of TCZ therapy successfully controlled the disease activity of a patient with AOSD (19). They administered TCZ 12 times and then discontinued its infusion when the IL-6 concentration was 43.8 pg/mL; additionally, their patient experienced no relapse of AOSD for at least 10 months. However, their case may be influenced by an EBV-specific immune response. Furthermore, the serum IL-6 concentration increased from 25.0 to 216.0 pg/mL during the treatment with TCZ in the present case 2 (Fig. 2), thus we stopped the infusion of TCZ at the lower concentration.

Regarding the natural history of AOSD, the withdrawal of TCZ is a feasible strategy. The natural history of ASOD exhibits three patterns according to the course of the disease: monocyclic AOSD, polycyclic AOSD, and chronic AOSD associated with polyarthritis (20-24). It has been previously reported that 21-39.7% of the AOSD patients have the monocyclic form and 17-44% show a polycyclic pattern. Polycyclic AOSD is characterized by multiple flare-ups separated by periods of remission lasting between a couple of weeks and a couple of years, with the flare-ups decreasing in severity over time. Nakahara et al. previously reported a patient who had been treated with TCZ and followed up without TCZ later suffered relapse after 3 years (25). Thus, in monocyclic or polycyclic AOSD, it is not possible to predict when the relapse will occur. Therefore, a strategy of discontinuing the infusion of TCZ with careful observation, instead of continuous TCZ therapy to reduce the likelihood of relapse, is worth considering.

In the present case 2, although we administered TCZ for AOSD-associated MAS, the safety and efficacy of the biologics in the cases of AOSD complicated by MAS are controversial. While some cases of MAS in AOSD patients have been successfully treated with biologics (26), the occurrence of MAS after the initiation of biologics has also been reported (18, 27-32). AOSD is characterized by the elevation of many cytokines, such as IL-6, IL-18, and TNF-alpha. However, the biologics only inhibit their target cytokines. Therefore, blocking of a single cytokine may not be sufficient for preventing the exacerbation. With respect to TCZ, Yoshida et al. previously described that IL-18, which is considered to contribute largely to the pathogenesis of MAS, was not fully inhibited by TCZ (33). Furthermore, in systemic-onset juvenile idiopathic arthritis (sJIA), which is regarded as the pediatric equivalent of AOSD, MAS has been observed in many cases during TCZ therapy (34). Thus, we must be mindful that TCZ alone may not have a sufficient effect on MAS, and in some cases TCZ may exacerbate it.

Plasma exchange has been reported to be effective for AOSD-associated MAS (35-37). Ito et al. demonstrated the prompt improvement of hypercytokinemia due to IL-6 and IL-18 using plasma exchange and a high-dose corticosteroid (37). The HLH 2004 protocol recommends the use of CyA concomitantly from an early stage in the cases of AOSD-associated MAS (38). Komiya et al. have reported a case of AOSD with MAS that was treated successfully by the combined use of TCZ with corticosteroid and plasma exchange (39). In the present case 2, we used CyA and mPSL pulse therapy, however, a high-grade fever persisted. Therefore, the administration of TCZ was initiated. To decrease the cytokine levels and prevent the exacerbation of AOSD, another course of mPSL pulse therapy with plasma exchange was combined. These treatments dramatically improve the symptoms and laboratory parameters. The concomitant use of CyA, plasma exchange and corticosteroid may have prevented the TCZ-induced exacerbation of MAS and led to a successful clinical outcome.

In summary, we herein reported two cases of refractory AOSD in which a biologics-free status was achieved after the withdrawal of TCZ. Careful monitoring of the IL-6 concentration provided the basis for the discontinuation of the TCZ administration; however, a mild flare-up was observed in case 2. These two cases are informative for determining the discontinuation of TCZ treatment for AOSD, and the second case provides valuable data when considering the use of TCZ for AOSD-associated MAS.

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References