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CASE BASED REVIEW

Successful treatment of adult-onset Still's disease with tocilizumab monotherapy: two case reports and literature review

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Abstract Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of unknown etiology. Recently, it has been reported that quite a few cases of refractory AOSD were successfully treated with tocilizumab (TCZ) and corticosteroids were withdrawn in some of these patients. We report two AOSD patients who were treated successfully with TCZ monotherapy; thus, avoiding corticosteroid treatment. Because both of the patients refused to take corticosteroids, we planned to treat them with 8 mg/kg of TCZ monotherapy at weeks 0, 2, 6 and subsequently every 4 weeks. The efficacy of TCZ was assessed by patients' clinical symptoms such as fever, arthralgia, skin eruptions, and laboratory markers such as serum levels of CRP, ferritin, and IL-6. We also reviewed 14 previous case reports including 30 cases who had been treated with TCZ for AOSD. Our patients responded rapidly and have been maintained in clinical remission without corticosteroid treatment. In the literature review, concomitant corticosteroid treatment described in 13 cases was successfully tapered in 7 and discontinued in 6 cases. TCZ monotherapy can be a candidate for the first-line therapy for some AOSD patients.

Keywords Adult-onset Still's disease · Interleukin-6 · Monotherapy · Tocilizumab

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Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of unknown etiology and is characterized by remittent fever, evanescent salmon pink rash, and polyarthralgia frequently accompanied by neutrophilic leukocytosis [1, 2]. AOSD treatment comprises non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressive drugs such as methotrexate (MTX) [3]. Corticosteroids, in particular, still provide mainstay AOSD therapy despite various adverse effects [3].

Recently, numerous studies have revealed that proinflammatory cytokines such as IL-1, IL-6, IL-18, tumor necrosis factor (TNF), and interferon-gamma are involved in AOSD's pathogenesis [4, 5]. In fact, AOSD patients have been successfully treated with anti-cytokine therapies such as with TNF-α blocking agents [6, 7], an IL-1 receptor antagonist (anakinra) [8, 9], and an anti-IL-6 receptor monoclonal antibody (tocilizumab, TCZ) [10–23]. Most of the cases are refractory to conventional therapies including high-dose corticosteroids and immunosuppressive drugs (cyclosporin and methotrexate, etc.) [11, 14, 16–18, 20, 22]. Among these case reports, TCZ seems to be highly

effective for treating patients refractory to TNF antagonists [16, 17, 20] and anakinra [11, 14, 18, 22].

Here, we describe two patients with AOSD who were treated with TCZ monotherapy without corticosteroids. Table 1 summarizes the patients' characteristics.

Case reports

Case 1

A 32-year-old woman was admitted to our hospital in January 2009 with fever, polyarthralgia, sore throat, and skin eruptions. Two years earlier, she experienced self-limiting high fever and cervical lymphadenopathy. Eight months prior to admission, she developed eruptions on her back, both arms and legs, which were improved by olopatadine hydrochloride and clobetasol propionate ointment treatment. Two weeks prior to admission, she developed a sore throat followed by skin eruptions, fever and polyarthralgia, which did not respond to cefcapene pivoxil hydrochloride hydrate and NSAIDs.

Laboratory test results on admission were as follows: leukocyte count 13,000/μl (neutrophils, 10,900/μl), hemoglobin 13.4 g/dl, platelet count 198,000/μl, erythrocyte sedimentation rate (ESR) 110 mm/hr, C-reactive protein (CRP) 33.8 mg/dl, aspartate aminotransferase (AST) 29 IU/l, alanine aminotransferase (ALT) 22 IU/l, lactate dehydrogenase (LDH) 285 IU/l, creatinine 0.55 mg/dl, ferritin 1,679 ng/ml, and normal urine values. Serological tests were negative for rheumatoid factor (RF) and antinuclear antibodies (ANA). The serum IL-6, TNF-α and soluble IL-2 receptor levels were 398 pg/ml (normal range <4.0 pg/ml), 3.2 pg/ml (normal range 0.6–2.8 pg/ml) and 1,090 U/ml (normal range 220–530 U/ml), respectively. Computed tomography revealed cervical lymphadenopathy and mild splenomegaly. Laboratory evaluations ruled out infections and malignancies, and she was therefore given a diagnosis of AOSD based on Yamaguchi's classification criteria [2].

Because the patient refused to take corticosteroids, we tried etanercept (50 mg/week) first, since there are some case reports on anti-TNF agents' efficacy for treating AOSD [6, 7]. However, there was no improvement in patient's clinical symptoms (Fig. 1).

Therefore, we administered 8 mg/kg of TCZ, which rapidly mitigated symptoms and lowered inflammatory marker levels. Although the third infusion was planned at week 6, CRP and leukocyte count slightly increased and her symptoms such as low grade fever and polyarthralgia appeared at week 4 (Fig. 1). Therefore, the third infusion

Table 1 Characteristics of patients

	Patient 1	Patient 2
Sex/Age (years)	Female/32	Male/18
Disease duration (months)	20	1
Yamaguchi criteria [Reference][2]		
Major criteria	Fever	Fever
	Arthralgia	Arthralgia
	Typical rash	Leukocytosis
	Leukocytosis	
Minor criteria	Sore throat	Sore throat
	Lymphadenopathy	Splenomegaly
	Splenomegaly	RF and ANA negative
	RF and ANA negative	
Laboratory data	CRP 33.8 mg/dl	CRP 25.6 mg/dl
	Ferritin 1,679 ng/ml	Ferritin 2,756 ng/ml
	IL-6 398 pg/ml	IL-6 18.8 pg/ml
Previous treatment	NSAIDs	NSAIDs
	Etanercept	
Tocilizumab dosing	8 mg/kg infusion at week 0, 2, 5, 8, 11, and subsequently every 4 weeks	8 mg/kg infusion at week 0, 3, and subsequently every 4 weeks
Outcome	Remission	Remission
Duration to fever response (<38.0°C) (days)	1	1
Duration to arthritis response (days)	3	3
Duration to CRP response (<0.5 mg/dl) (days)	7	7

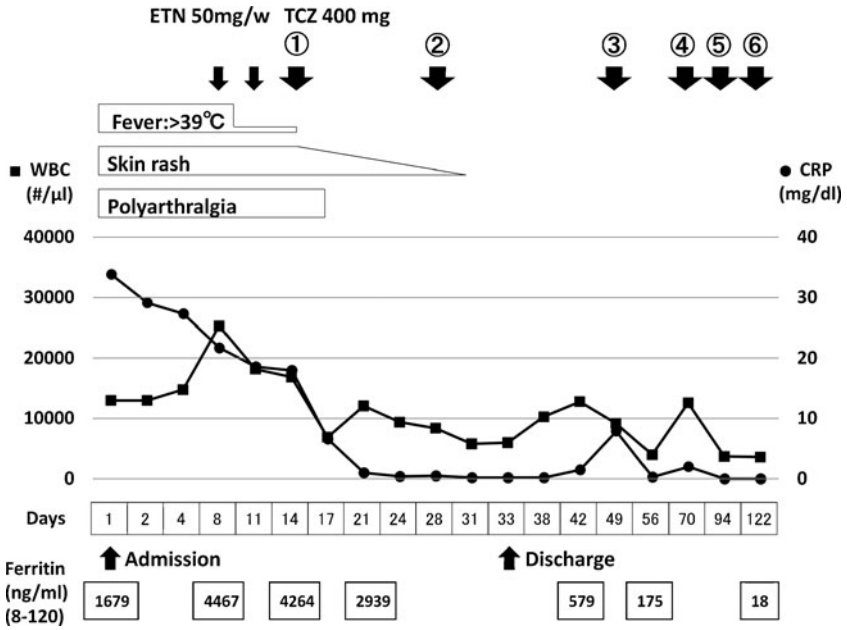

Fig. 1 Clinical course in case 1. Improvement in symptoms, WBC, CRP and ferritin levels in a patient with AOSD treated with TCZ monotherapy. Note that fever, skin rash, arthralgia and CRP levels rapidly normalized. *ETN* Etanercept

was administered at week 5 soon after. After the infusions at weeks 5, 8, and 11, all the symptoms and signs of AOSD disappeared, and the patient received TCZ subsequently every 4 weeks to remain in complete remission, which has lasted for more than 2 years. Serum IL-6 level also decreased to 5.4 pg/ml and ferritin level was normal. Corticosteroids were never administered throughout her disease course.

Case 2

An 18-year-old man was admitted to our hospital in August 2010 because of fever, polyarthralgia, sore throat, and myalgia. He had been well until about 3 weeks earlier. Two weeks prior to admission, he had received antibiotics, including azithromycin hydrate, levofloxacin hydrate, and panipenem/betamipron, but had shown no response. Laboratory test results on admission were as follows: leukocyte count 30,400/μl (neutrophils 25,500/μl), hemoglobin 12.5 g/dl, platelet count 521,000/μl, ESR 53 mm/h, prothrombin time INR 1.26, activated partial thromboplastin time 30.0 seconds, fibrinogen 700 mg/dl, D-dimer 1.96 μg/ml, CRP 25.6 mg/dl, AST 15 IU/l, ALT 26 IU/l, LDH 245 IU/l, serum creatinine 0.81 mg/dl, and ferritin 2,756 ng/ml. The urine values were all normal. Serological tests were negative for both RF and ANA. The serum IL-6 and soluble IL-2 receptor levels were, respectively, 18.8 pg/ml and 1,050 U/ml. Abdominal ultrasonography showed mild splenomegaly. We excluded infections, malignancies, and other rheumatic diseases by radiological examinations, gastrointestinal and colon endoscopy, and laboratory examinations that included repetitive culture for microorganisms as well as assays for various autoantibodies. The patient got a diagnosis of AOSD, but he and his family did not consent to corticosteroid therapy. We decided to administer 8 mg/kg of TCZ at weeks 0, 2, 6, and subsequently every 4 weeks. One day after the first TCZ infusion, fever and polyarthralgia abated markedly and serum CRP level returned to normal within 1 week. The second TCZ was administered at week 3 because of patient's affairs, and the patient was discharged 3 days later. TCZ has been continued every 4 weeks for 8 months and the patient is still in complete remission.

Discussion

This is the first case report, to our knowledge, demonstrating that TCZ monotherapy was effective for AOSD. Corticosteroids are usually required to improve clinical symptoms and laboratory abnormalities and are still a mainstay for inducing remission in AOSD. In fact, most (76%–95%) AOSD patients can be successfully treated with corticosteroids, and they respond dramatically [3]. However, consensus is lacking on a therapeutic corticosteroid tapering scheme after achieving clinical remission. Slow reduction is often necessary to maintain a good response and to avoid relapse. Corticosteroid dependence increases the risk for potentially serious mid- and long-term side effects caused by Cushing-like phenomena, diabetes, osteoporosis, and osteonecrosis. Anti-rheumatic drugs such as MTX are also reported to be effective [24, 25], but we are not aware of any randomized controlled trials.

Table 2 Literature review: Tocilizumab treatment for AOSD

Authors	Reference	Year	Sex	Age	Duration (years)	DMARDs before TCZ	Biologics before TCZ	Dose (Starting dose)	Outcome	Corticosteroid withdrawal
Iwamoto et al.	[10]	2002	Female	23	1.9	GST, MTX, CSA	None	4 mg/kg/2w	Good	Yes
De Bandt et al.	[11]	2009	Female	26	10	GST, MTX, LEF, thalidomide	anti-TNF (ETN, INF), ANK	8 mg/kg/2w	Good	Yes
Nakahara et al.	[12]	2009	Male	24	11.4	GST, SSZ, MTX, CSA, AZA	None	4 mg/kg/w	Good	Yes
Matsumoto et al.	[13]	2009	Female	29	0.1	CSA	None	8 mg/kg/2w	Good	Tapering
Perdan-Pirkmajer et al.	[14]	2010	Male	35	0.4	MTX	anti-TNF (ETN), ANK	8 mg/kg/4w	Good	Tapering
Naniwa et al.	[15]	2010	Female	64	1.7	CSA, tacrolimus, IvIg	None	8 mg/kg/2w	Good	Tapering
Sumida et al.	[16]	2010	Female	69	0.3	CSA, plasma exchange	anti-TNF (ETN)	8 mg/kg/4w	Good	Tapering
Yoshimura et al.	[17]	2010	Female	49	11	SSZ, bucillamine, MTX , LEF	anti-TNF (ETN, INF)	8 mg/kg/4w	Good	n.d.
Rech et al. case1	[18]	2011	Female	29	1	MTX	anti-TNF (ADA), ANK	8 mg/kg/4w	Good	Tapering
Rech et al. case2		2011	Male	73	3	MTX	anti-TNF (ADA, ETN), ANK	8 mg/kg/4w	Good	n.d.
Rech et al. case3		2011	Female	19	3	MTX	ANK	8 mg/kg/4w	Good	n.d.
Kishida et al.	[19]	2011	Male	40	22	MTX, SSZ, AZA, CY, CSA, tacrolimus	None	8 mg/kg/4w	Good	Yes
Thonhofer et al. case 1	[20]	2011	Female 1	24	1.3	MTX	anti-TNF (ADA, ETN)	8 mg/kg/4w	Good	Yes
Thonhofer et al. case 2		2011	Male 1	26	0.1	MTX	None	8 mg/kg/4w	Good	Yes
Kobayashi et al.	[21]	2011	Female	57	0.4	CSA	None	8 mg/kg/2w	Good	Tapering
Puéchal et al, 14 cases	[22]	2011	Male 5 Female 9	mean = 38.4 (23–68)	mean = 13.6 (3–27)	MTX (14), IvIg (7)	ANK (14), anti-TNF (12), abatacept (1), rituximab (1)	8 mg/kg/4w (n=9) 8 mg/kg/2w (n=4) 5 mg/kg/4w (n=1)	Good (n=11) Withdrawal (n=3; 2 AEs, 1 flare)	n.d.
Sabnis et al.	[23]	2011	Male	27	0.2	CSA	None	8 mg/kg/4w	Good	Tapering

ADA adalimumab, *AE* adverse event, *ANA* anakinra, *AZA*, azathioprine, *CSA* cyclosporine A, *CY* cyclophosphamide, *DMARDs* disease modified antirheumatic drugs, *ETN* etanercept, *GST* gold salts, *INF* infliximab, *IvIg* intravenous immunoglobulin, *LEF* leflunomide, *MTX* methotrexate, n.d. not described, *TCZ* tocilizumab, *SSZ* sulfasalazine, *TNF* tumor necrosis factor

The mechanisms underlying AOSD are not completely understood, but the role of proinflammatory cytokines may play a significant role in its pathogenesis because biological response modifiers targeted to these cytokines have been used successfully to treat AOSD. Promising results have been reported with TNF inhibitors such as etanercept and infliximab, but treatment failures and apparent loss of efficacy have also been described [6, 7]. A role for IL-1 has been also demonstrated by patient's response to anakinra [8, 9, 26].

IL-6 is also believed to play a crucial role in pathogenesis, and its serum levels correlate well with the AOSD's severity [4, 27]. There have been several other reports regarding TCZ's efficacy (Table 2) [10–23]. Fitzgerald et al. [8] proposed that TNF-α induces IL-1 production, which stimulates IL-6 expression. Therefore, Matsumoto et al. [13] stated that directly inhibiting IL-6 activity, which is the most downstream cytokine in the AOSD inflammatory cascade, may be better than blocking IL-1. In fact, AOSD patients who responded poorly to anakinra responded well to TCZ [11, 14, 18, 22]. Moreover, concomitant corticosteroid treatment described in 13 cases was successfully tapered in 7 [13–16, 18, 21, 23] and discontinued in 6 cases [10–12, 19, 20] after achieving TCZ-induced remission, suggesting that TCZ monotherapy may serve as first-line remission induction therapy.

In our present report, TCZ monotherapy rapidly improved each patient's health, and the patients have remained in complete remission. However, case 1 appeared to relapse after the second TCZ infusions. Although other cytokines such as IL-18 [4, 28, 29] might have been more important targets, TCZ may have been effective if biweekly infusion had been continued as used to treat systemic type juvenile idiopathic arthritis (classical Still's disease) [30]. Biweekly infusions of TCZ can be necessary for some AOSD patients to protect exacerbation completely.

TCZ was well tolerated by our patients. However, severe adverse events with macrophage activation syndrome (MAS) due to cytomegalovirus infection have been reported [11]. AOSD itself may cause MAS, and it may be difficult to distinguish TCZ's adverse effects from treatment insufficiency noted in the other case [21]. However, both patients were able to resume TCZ and continued after the MAS abated. Another concern is exacerbation of AOSD or MAS due to a transient increase of serum levels of target cytokine right after the cytokine blockade [31]. However, no exacerbation was seen in our cases, and was not described in all the reported cases treated with TCZ except one case [22]. We should be watchful for this kind of adverse event when we treat AOSD patients with cytokine blockade, but it seems to be rare in TCZ therapy.

In conclusion, TCZ monotherapy may be effective in some patients with AOSD.

Conflicts of interest H.K. has received honoraria from Mitsubishi-Tanabe Pharma, Pfizer, Abbott, Eisai Pharma, and Bristol-Myers KK. T.T. has received research support and consulting or lecture fees from Chugai Pharma. K.A. received research grants from Tanabe-Mitsubishi, Astellas, and Chugai pharmaceutical companies. The other authors have declared no conflicts of interest.

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