

# Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis under Treatment with Tocilizumab

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**ABSTRACT. Objective.** To identify macrophage activation syndrome (MAS) in patients with systemic juvenile idiopathic arthritis (sJIA) undergoing tocilizumab (TCZ) treatment, and to confirm laboratory marker changes and responses to treatment in patients with MAS receiving TCZ.

**Methods.** In Japan, 394 patients with sJIA were registered in an all-patient registry surveillance of TCZ as of January 15, 2012. TCZ (8 mg/kg) was administered every 2 weeks to patients with sJIA. MAS, hemophagocytic lymphohistiocytosis, or Epstein-Barr virus-associated hemophagocytic syndrome (EB-VAHS) was reported in 23 of these patients (25 events). The Safety Evaluation Committee of Tocilizumab for JIA reviewed these cases and clinically evaluated the data and laboratory findings using their own therapeutic experience. Events were categorized into 4 groups: definitive MAS, probable MAS, EB-VAHS, and non-MAS.

**Results.** The committee's review revealed 3 events of definitive MAS in 3 patients, 12 events of probable MAS in 11 patients, 2 events of EB-VAHS in 2 patients, and 8 events of non-MAS in 8 patients. There were 2 patients who developed 2 events: 2 events in 1 patient were classified into definitive MAS and probable MAS, and 2 events in another patient were classified into probable MAS. In patients with definitive or probable MAS, common clinical manifestations and laboratory findings of MAS were observed. Changes in laboratory data observed in patients with EB-VAHS were similar to those observed in patients with MAS.

**Conclusion.** These results suggest that the clinical/laboratory features in the course of MAS appear to be similar among patients regardless of whether TCZ is administered. Similarities in the pathophysiological background of MAS and EB-VAHS were also suggested. (First Release Feb 15, 2015; J Rheumatol 2015;42:712–22; doi:10.3899/jrheum.140288)

## Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS  
TOCILIZUMAB  
INFECTIION-ASSOCIATED HEMOPHAGOCYtic SYNDROME

POSTMARKETING PRODUCT SURVEILLANCE  
MACROPHAGE ACTIVATION SYNDROME  
INTERLEUKINS

Systemic juvenile idiopathic arthritis (sJIA) is a form of chronic childhood arthritis of unknown etiology with systemic manifestations such as remittent fever, erythematous rash, and arthritis, and other symptoms including lymphadenopathy, hepatosplenomegaly, and serositis<sup>1,2</sup>. Levels of interleukin 6 (IL-6) are positively correlated with

remittent fever and inflammatory manifestations<sup>3</sup>, suggesting that IL-6 is one of the causative cytokines of this disease and also that IL-6 and IL-6 receptors could be appropriate targets for therapy<sup>4</sup>.

One of the most serious complications of sJIA is macrophage activation syndrome (MAS), in which the

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inflammation is caused by a cytokine storm<sup>5,6</sup>, a massive inflammatory cytokinemia including IL-6, IL-1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$ , and interferon (IFN)- $\gamma$ .

Tocilizumab (TCZ), a humanized anti-IL-6 receptor monoclonal antibody, was developed for rheumatoid arthritis<sup>7</sup>. Clinical trials of TCZ in sJIA were then conducted (ClinicalTrials.gov, numbers NCT00144599 and NCT00144612)<sup>8,9</sup>, and the drug was approved for the treatment of sJIA in Japan in 2008<sup>10</sup>, followed by the United States and the European Union in 2011<sup>11,12,13</sup>. After the approval, an all-patient registry surveillance of patients with sJIA receiving TCZ was started in April 2008 in Japan, and reports of MAS that occurred during TCZ treatment in patients with sJIA were accumulated as the surveillance study progressed.

Although IL-6 inhibition plays an important role in sJIA, it cannot prevent the development of MAS. Therefore, IL-6 inhibition is not thought to be the only factor that changes the pathogenesis of MAS. It is thus important to assess whether MAS even occurs with TCZ, and if so, whether IL-6 inhibition by TCZ reduces the number of MAS complications in patients with sJIA.

The objectives of our report were to identify MAS in patients with sJIA who had been treated with TCZ, and to confirm laboratory marker changes and responses to treatment in patients with MAS receiving TCZ.

## MATERIALS AND METHODS

**Patients.** All patients with sJIA in Japan who started treatment with TCZ in or after April 2008 were enrolled in a registry surveillance, which was a single-arm observational study, and monitored during the surveillance period (52 weeks). In accordance with the Japanese package insert, TCZ was administered to patients who had an inadequate response to the existing therapies for sJIA, including steroid therapy. Patient registration, which occurred before TCZ treatment started, was centrally controlled. Physicians with sufficient knowledge of TCZ and experience with the treatment of sJIA, intravenously administered TCZ (8 mg/kg) every 2 weeks to patients with sJIA. It was possible to shorten the dosing interval to a minimum of 1 week, depending on the patient's disease condition<sup>9</sup>. A total of 394 patients with sJIA were registered from April 2008 to January 2012, and the surveillance study was ongoing as of January 2012.

**MAS reports.** Among these registered patients, 23 were reported by their attending physicians to have MAS, hemophagocytic lymphohistiocytosis (HLH), or Epstein-Barr virus-associated hemophagocytic syndrome (EB-VAHS). These included all cases of spontaneously reported MAS that developed after the end of the 52-week observation period (Figure 1). The data on MAS occurring in the surveillance study observation period were collected using case report forms, and the data on MAS occurring after the completion of the observation period or discontinuation of TCZ therapy were collected using templates for adverse event data collection. The data were limited to case reports and information collected by Chugai Pharmaceutical Co. Ltd. through agreements between it and participating institutions.

**Evaluation.** To evaluate the cases of MAS reported by attending physicians, 25 events in 23 patients were reviewed by the Safety Evaluation Committee of Tocilizumab for JIA (the JIA Committee). This committee was established to evaluate the safety of TCZ by reviewing information collected from the surveillance, thereby promoting proper use of TCZ in the post-marketing setting. The committee was composed of 5 members: 2

pediatric rheumatologists, 1 pediatric infection specialist, 1 pediatric cardiovascular disease specialist, and 1 adult rheumatologist. For each case, they reviewed patient data such as clinical manifestations, results of laboratory examinations, and records of patients' disease status written by their attending physicians and submitted in case report forms or templates for adverse event data collection. Because there was no control in the surveillance study, the committee reviewed these cases of MAS using their own therapeutic experience.

The JIA Committee categorized reports of MAS, HLH, or EB-VAHS into 4 groups (Table 1)<sup>14,15,16</sup>:

Group 1 (definitive MAS): MAS was confirmed on the basis of clinical manifestations and changes in laboratory findings similar to those for MAS in general patients with sJIA not given TCZ.

Group 2 (probable MAS): MAS was probable despite insufficient laboratory data. A case of HLH was classified in this category.

Group 3 (EB-VAHS): Cases confirmed as Epstein-Barr virus (EBV) infection.

Group 4 (non-MAS): Typical MAS did not occur, early treatment prevented development of MAS, or different diagnoses, such as infection or hemolytic uremic syndrome, were more appropriate.

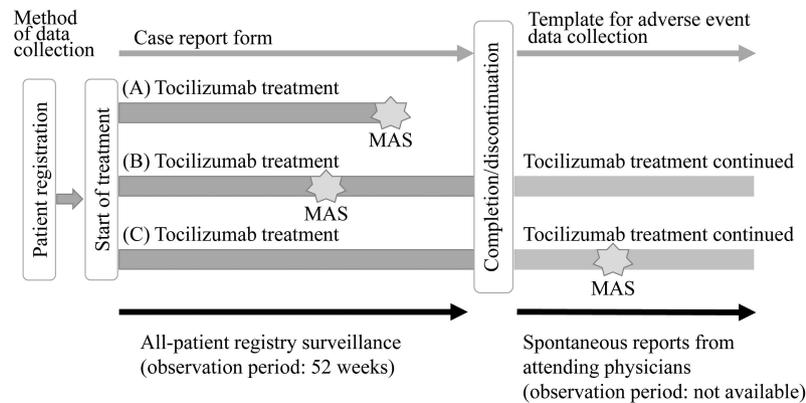
Clinical manifestations investigated were fever, arthritis, skin rash, petechiae/ecchymosis, hepatosplenomegaly, lymphadenopathy, and other symptoms and signs. The following laboratory data were examined: platelet and white blood cell (WBC) counts; levels of C-reactive protein (CRP) and/or serum amyloid A; levels of fibrin-derived proteins (FDP) and/or D-dimers; levels of urinary  $\beta_2$ -microglobulin (MG) and serum ferritin; serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and total cholesterol/triglycerides; and serum levels of creatinine and amylase.

## RESULTS

As shown in the summary of patients with reported MAS during TCZ treatment in Table 2, 25 events of MAS, HLH, or EB-VAHS were reported in 23 patients during TCZ treatment. Two patients developed MAS twice. There were 13 females and 10 males, and the mean age was 11 years (median 10 yrs, 2–28 yrs). The verbatim terms reported by physicians were MAS (20 events in 18 patients), suspected MAS (2 events in 2 patients), HLH (1 event in 1 patient), and EB-VAHS (2 events in 2 patients). The mean number of days to onset of these events after the most recent dose of TCZ was 8. Treatment for these events, such as cyclosporine or steroid pulse therapy, was rapidly initiated in most cases, and 19 patients improved or recovered. No patients were given TCZ during these events, and TCZ was resumed in 18 patients and discontinued in 5 patients after treatment of the events (Table 2).

**Patient categorization.** The JIA Committee categorized these events into 4 groups (Table 1)<sup>14,15,16</sup>: Group 1 (definitive MAS), 3 events in 3 patients; Group 2 (probable MAS), 12 events in 11 patients; Group 3 (EB-VAHS), 2 events in 2 patients; and Group 4 (non-MAS), 8 events in 8 patients. This classification included overlaps: 2 events in 1 patient were classified into Groups 1 and 2, and another 2 events in 1 patient were classified into Group 2. In 394 patients with TCZ-treated sJIA, there were 15 events of definitive or probable MAS in 14 patients (3.6%, 14/394 patients).

Although data such as CRP, transaminases, fibrinogen, and D-dimer were insufficient to fully assess the course of



**Figure 1.** Study design. All patients with sJIA in Japan who started treatment with TCZ were enrolled in an all-patient registry surveillance, which was a single-arm observational study, and monitored during the observation period (52 weeks). In our present study, events of MAS reported by attending physicians in the all-patient registry surveillance and spontaneous reports were reviewed by the JIA Committee. Example A: MAS developed during the observation period in the all-patient registry surveillance, and TCZ treatment was completed at that time. Example B: MAS developed during the observation period in the all-patient registry surveillance, and TCZ treatment was continued. Example C: MAS developed after completion/discontinuation of the all-patient registry surveillance. sJIA: systemic juvenile idiopathic arthritis; TCZ: tocilizumab; MAS: macrophage activation syndrome.

**Table 1.** Evaluation and categorization of patients with reported MAS during TCZ treatment.

Group	Evaluation
Group 1	Patients in which MAS could be confirmed on the basis of changes in laboratory findings similar to those for MAS observed in general patients with sJIA who did not receive TCZ treatment. 3 events in 3 patients, definitive MAS.
Group 2	Patients in which MAS was probable despite insufficient laboratory data. 12 events in 11 patients, probable MAS.
Group 3	Patients with confirmed EB-VAHS. 2 events in 2 patients, EB-VAHS.
Group 4	Patients in which early intervention resulted in improvement or resolution, but without any confirmed typical changes in laboratory findings, or patients with other potential causes such as infections or hemolytic uremic syndrome. 8 events in 8 patients, possible MAS or non-MAS.

The JIA Committee classified the 25 events of MAS or related events into the following 4 groups for ease of understanding: Group 1, definitive MAS; Group 2, probable MAS; Group 3, EB-VAHS; Group 4, possible or non-MAS. Including overlaps, 2 events in 1 patient were classified into Groups 1 and 2, and another 2 events in 1 patient were classified into Group 2. MAS: macrophage activation syndrome; TCZ: tocilizumab; sJIA: systemic juvenile idiopathic arthritis; EB-VAHS: Epstein-Barr virus-associated hemophagocytic syndrome.

MAS, most patients had several common clinical/laboratory features that contributed to diagnosis during the course of MAS according to the laboratory findings reported from attending physicians. The earliest finding was decreased platelet count (19/25 events; Table 3A) and/or decreased WBC count, followed by elevation of urinary  $\beta_2$ -MG levels with gradual increases of FDP/D-dimers. Following the increases of serum ferritin levels (16/25 events; Table 3B), elevation in liver enzyme levels AST/LDH were detected along with coagulation/fibrinolytic abnormalities (6/25

events; Table 3C). Abnormal decreases in total cholesterol and increases in triglycerides were seen in the late stage of MAS. No deaths attributable to MAS or EB-VAHS were reported in our study.

Interestingly, the course of laboratory features for the 2 patients with EB-VAHS was similar to that seen in patients with MAS.

**Case examples.** The following case examples provide the patient profile, clinical course, and JIA Committee comments for 1 case each from Group 1, Group 2, and

Table 2. Summary of patients with reported MAS during TCZ treatment.

Characteristics	Values
Patients/events <sup>a</sup> , n	23/25
Female/male, n	13/10
Mean age, yrs (median, range)	11 (10, 2–18)
Mean days to onset after most recent dose of TCZ (median, range)	8 (8, 1–19)
Clinical symptoms at MAS onset, some overlap	
Yes	14 patients/15 events, most common clinical symptoms: fever, headache
No	7 patients/7 events
Unknown	3 patients/3 events
Bone marrow aspiration	
Yes	6 patients/6 events, including confirmed signs of hemophagocytosis: 3 patients/3 events
No	8 patients/10 events
Unknown	9 patients/9 events
Treatment for MAS, some overlap	
Yes	23 patients: Cyclosporine (IV): 16 patients/18 events Steroid pulse therapy: 14 patients/14 events Dexamethasone palmitate (IV): 14 patients/16 events Leukocyte apheresis: 2 patients/2 events Plasma replacement therapy: 3 patients/3 events
Outcome	
Recovered	17 patients
Improved	2 patients
Not recovered	2 patients
Unknown <sup>b</sup>	2 patients
Mean days from onset of MAS to outcome (median, range)	17 (14, 6–45)
Status of TCZ treatment after treatment for MAS	
Resumed	18 patients
Discontinued	5 patients

The all-patient registry surveillance revealed 25 events of MAS during TCZ treatment in 23 of 394 patients with sJIA. <sup>a</sup> These include spontaneously reported cases of MAS that developed after the end of the observation period (52 weeks) in an all-patient registry surveillance in Japan. <sup>b</sup> 1 patient being followed up and 1 patient for whom data could not be obtained. MAS: macrophage activation syndrome; TCZ: tocilizumab; IV: intravenous; sJIA: systemic juvenile idiopathic arthritis.

Group 3. The cases here were chosen because they provided a representative example of the cases in their respective groups.

*Group 1: definitive MAS.* The patient was a boy who developed sJIA at 3 years old. Previous treatment included corticosteroids, cyclosporine, and methotrexate. Treatment with TCZ was started when the patient was less than 10 years old.

*Clinical course for Group 1 (Figure 2).* sJIA was well controlled by TCZ, and the infusion schedule was changed to once every 3 weeks from the seventh TCZ infusion onward. After the patient received his 19th dose of TCZ, the primary disease became less well controlled. On Day 357, the 20th infusion was therefore administered at a shortened dosing interval of 10 days. On Day 364 (7 days after the 20th infusion), the patient developed fever and rash. Later, after reviewing the patient's subsequent course, the attending physician considered that MAS had occurred on Day 364. On Day 365, the patient developed simple febrile convulsions lasting 1 to 2 min; he recovered without sequelae. On Day 368, he was hospitalized for the treatment

of MAS, and laboratory tests showed that he was in a hypercoagulable state, with increases in various markers of organ damage, but no evidence of multiple organ failure. TCZ was discontinued, and he was treated with thrombomodulin- $\alpha$ . One day after methylprednisolone-pulse therapy was started, the patient's pyrexia resolved and laboratory data improved. Later, the route of steroid administration was changed to oral, and the doses were gradually reduced. Seven days after admission, treatment with TCZ was resumed. On Day 391, after 16 days of TCZ therapy (i.e., 23 days after hospitalization), the patient was concluded to have recovered from MAS and was discharged from hospital. With the continued biweekly administration of TCZ from that point onward, he was well controlled, without any MAS flares.

*Comments by the JIA Committee on Group 1.* The patient developed fever and rash, the primary disease became relatively unmanageable, and the patient was diagnosed with MAS. Laboratory findings at hospitalization showed decreased platelet count and progressive anemia, with markedly elevated ferritin and soluble IL-2 receptor;

Table 3A. Laboratory findings in 23 patients with reported MAS for platelet count.

Group	Patient No.	Event No.	Baseline Value	PLT, × 10 <sup>4</sup> /μl			Outcome of MAS
				At Time of MAS Onset	Worst Value During MAS	At Time of Outcome	
1	1	1	37.3	12.7	6.2	23.8	Recovered
	2 <sup>a</sup>	2	40.6	23.1	4.1	40.6 <sup>e</sup>	Recovered
	3	3	21.6	11.9	11.9	25.1 <sup>e</sup>	Recovered
2	3	4	21.6	8.3	3.3	29.5	Recovered
	4	5	24.1	10.9	10.9	39	Recovered
	5	6	14.4	9.4	9.4	45	Recovered
		7	14.4	14.4	11.4	27.5	Recovered
	6	8	27.7	39	3	32.3	Recovered
	7	9	76.9	—	18.3	42.6 <sup>e</sup>	Recovered
	8	10	20.1	10	10	29.6	Recovered
	9 <sup>b</sup>	11	40.6	13	9.6	26.8	Recovered
	10	12	13.1	8.5	3.9	15.5	Recovered
	11	13	20.1	17.5	16	24.9	Recovered
	12	14	21.2	14.4	14.4	26.6	Recovered
	13	15	69.3	18.2	0.2	7.1	Not recovered
	3	14	16	32.2	4.6 <sup>d</sup>	4.3	25.5
15 <sup>c</sup>		17	31	14	3.7	29.1	Improved
Median			<b>24.1</b>	<b>12.9</b>	<b>9.4</b>	<b>27.5</b>	
Range			<b>13.1–76.9</b>	<b>4.6–39</b>	<b>0.2–18.3</b>	<b>7.1–45</b>	
4	16	18	31.5	7.1 <sup>d</sup>	7.1	20.7	Recovered
	17	19	37.6	26.1	24.8	36.2	Not recovered
	18	20	35.7	10.5 <sup>d</sup>	5.9	41 <sup>e</sup>	Improved
	19	21	12.7	19	13.4	15.8	Recovered
	20	22	25.1	13.9	12.7	24.2	Recovered
	21	23	74.9	14.6	1.7	—	Unknown
	22	24	25.8	—	2.7	—	Recovered
	23	25	—	—	—	—	Unknown

Baseline value: Value at start of TCZ administration in the all-patient registry surveillance. <sup>a,b,c</sup> Representative examples of Group 1 (definitive MAS), Group 2 (probable MAS), and Group 3 (EB-VAHS), respectively. <sup>d</sup> ± 1 day from onset. <sup>e</sup> ± 3 days from outcome.

elevated LDH, creatine kinase (CK), pancreatic amylase, and other liver enzymes; and elevated triglycerides. Although no increases in FDP were noted from Day 371 onward, fibrinogen levels were low. These findings were typical of MAS<sup>14,15,16</sup>. Early therapeutic interventions prevented progression of organ damage.

*Group 2: probable MAS.* The patient was a girl who developed sJIA at 3 years old. She participated in the clinical trial conducted in Japan for marketing approval. Treatment with TCZ was started when the patient was less than 10 years old.

*Clinical course for Group 2 (Figure 3).* Because the patient participated in the preapproval clinical trial, she had been treated with TCZ at the start of postmarketing surveillance. She was transferred to the reporting hospital after the eighth infusion of TCZ. On Day 335 (6 days after the 25th infusion), she developed mild fever (37.4°C) and visited the outpatient department. She presented with fever of 37.9°C, pharyngeal pain, and neck pain. Laboratory examination revealed decreased WBC and platelet counts, and mild elevation in AST, ALT, and LDH levels. Her body temperature rose to 38.6°C at noon. Over time, the platelet count further decreased, and liver enzyme levels further increased.

Elevated levels of ferritin were also noted. These findings indicated MAS, and the patient was hospitalized on Day 336. Bone marrow aspiration was not performed. On the same day, heparin, continuous intravenous (IV) infusion of cyclosporine<sup>17,18</sup>, and IV dexamethasone palmitate (5 mg/day)<sup>19</sup> were started as treatment for MAS. Laboratory findings suggested gradual improvement. On Day 340, the dexamethasone palmitate dose was reduced to 3.75 mg/day. On Day 341, the continuous IV infusion of cyclosporine was stopped.

In the evening of Day 344, the patient showed fever of 38°C again with high levels of liver enzymes and coagulation/fibrinolytic abnormalities. The dexamethasone palmitate dose was increased, and continuous IV infusion of cyclosporine was resumed. The dexamethasone palmitate dose was then gradually reduced, and cyclosporine was administered orally. On Day 357 (20 days after MAS diagnosis), the patient had recovered from MAS; treatment with TCZ was resumed. The patient was discharged 4 days later.

*Comments by the JIA Committee on Group 2.* This patient continued receiving TCZ after the clinical trial. Abnormal laboratory test results established the diagnosis of MAS.

Table 3B. Laboratory findings in 23 patients with reported MAS for serum ferritin.

Group	Patient No.	Event No.	Baseline Value	Serum Ferritin, ng/ml			Outcome of MAS
				At Time of MAS Onset	Worst Value During MAS	At Time of Outcome	
1	1	1	154.6	287.5	977.6	151.6	Recovered
	2 <sup>a</sup>	2	—	1067.7	46,541	107.5 <sup>e</sup>	Recovered
	3	3	—	735.2	735.2	—	Recovered
2	3	4	—	332.1	1357.5	68.5	Recovered
	4	5	15.9	110.5	110.5	34.6	Recovered
	5	6	125	919	1103	39	Recovered
		7	125	988 <sup>d</sup>	988	63	Recovered
	6	8	5.8	34.6	241.6	27.2	Recovered
	7	9	54.5	86	131	48 <sup>e</sup>	Recovered
	8	10	2425	4146	4146	3046	Recovered
	9 <sup>b</sup>	11	10	952	1781	43	Recovered
	10	12	84.9	271.8 <sup>d</sup>	1498	126.1	Recovered
	11	13	32	51.8	137.4	137.4	Recovered
	12	14	594.2	1687	1687	212.9	Recovered
3	13	15	172.8	91.8	5423.5	5423.5 <sup>e</sup>	Not Recovered
	14	16	435	—	3306	201	Recovered
	15 <sup>c</sup>	17	764	1485	7835	173	Improved
Median			<b>125.0</b>	<b>533.7</b>	<b>1357.5</b>	<b>116.8</b>	
Range			<b>5.8–2425</b>	<b>34.6–4146</b>	<b>110.5–46,541</b>	<b>27.2–5423.5</b>	
4	16	18	21	88 <sup>d</sup>	88	43 <sup>e</sup>	Recovered
	17	19	30.7	46.2	118.7	33.4	Not recovered
	18	20	7	1974 <sup>d</sup>	1974	—	Improved
	19	21	846	114.3 <sup>d</sup>	147.2	53	Recovered
	20	22	88	136 <sup>d</sup>	143	143	Recovered
	21	23	—	138	490	—	Unknown
	22	24	74.4	—	—	—	Recovered
	23	25	—	—	—	—	Unknown

Baseline value: Value at start of TCZ administration in the all-patient registry surveillance. <sup>a, b, c</sup> Representative examples of Group 1 (definitive MAS), Group 2 (probable MAS), and Group 3 (EB-VAHS), respectively. <sup>d</sup> ± 1 day from onset. <sup>e</sup> ± 2 days from outcome.

WBC count decreased by half (4910/μl), and platelet count decreased to 96,000/μl. FDP and D-dimer levels were elevated. No data on β<sub>2</sub>-MG were available. Ferritin showed a moderate increase (1781 ng/ml). Liver function tests revealed a transition from AST predominance to ALT predominance. The overall clinical course delineated a mild form of MAS. Also in this case, early therapeutic intervention prevented a serious condition.

**Group 3: EB-VAHS.** The patient was a female who developed sJIA at 14 years old. She had been treated with etanercept followed by infliximab. TCZ was started at 20–29 years old.

**Clinical course for Group 3 (Figure 4).** Prednisolone (PSL) dose was gradually reduced from 30 mg/day after the start of TCZ. At 4 AM on Day 358 (4 days after the 25th infusion of TCZ), the patient was brought to the emergency unit for diarrhea, chills, abdominal pain, and fever of 38.1°C. Vomiting was observed despite discontinuation of oral medications. At about 8 AM, the patient was hospitalized for emergency care after examination at the outpatient department. Administration of ciprofloxacin hydrochloride gradually relieved diarrhea and chills. PSL was adminis-

tered intravenously. Decreased WBC count (2300/μl) and decreased platelet count (140,000/μl) were noted. On the day of admission, the patient was diagnosed with EB-VAHS. On Day 359, WBC count increased (14,400/μl), platelet count further decreased (80,000/μl), CRP increased (7.2 mg/dl), and skin rash developed on the face and anterior region of the neck. The PSL dose was increased.

On Day 361, further decreases were noted in platelet count (37,000/μl) and WBC count (2000/μl), and ferritin levels were increased (7656 ng/ml). Heparin sodium and gabexate mesilate were added to the treatment regimen. On Day 362, methylprednisolone-pulse therapy was started<sup>20</sup>. The patient's condition generally improved, although several abnormal laboratory values were reported. On Day 363, EBV-related laboratory data were obtained: anti-EBV-VCA-IgG 640-fold, anti-EBV-VCA-IgM > 10-fold, anti-EBV-VCA-IgA 10-fold, anti-EBV EBNA (FA) 10-fold, anti-EBNA-IgG (EIA) negative, anti-EBNA-IgM (EIA) positive, EBV DNA 121.5 ng/μl (PCR), EBV DNA copy number 44,426 copies/μg DNA.

After the completion of methylprednisolone-pulse therapy, treatment with 50 mg/day oral PSL was started. On Day 376, EB-VAHS had been resolved.

Table 3C. Laboratory findings in 23 patients with reported MAS for LDH.

Group	Patient No.	Event No.	Baseline Value	LDH, IU/l		At Time of Outcome	Outcome of MAS
				At Time of MAS Onset	Worst Value During MAS		
1	1	1	364	572	572	—	Recovered
	2 <sup>a</sup>	2	—	842	2161	339 <sup>e</sup>	Recovered
	3	3	—	—	—	—	Recovered
2	3	4	—	599	880	178	Recovered
	4	5	—	544	600	334	Recovered
	5	6	—	1149	1373	325	Recovered
		7	—	667	990	316 <sup>e</sup>	Recovered
	6	8	—	334	420	235	Recovered
	7	9	—	—	1057	623 <sup>e</sup>	Recovered
	8	10	—	808	808	520	Recovered
	9 <sup>b</sup>	11	—	395	785	298	Recovered
	10	12	222	248	950	—	Recovered
	11	13	—	516	516	—	Recovered
	12	14	384	529	529	258	Recovered
3	13	15	443	661	26,741	26,741	Not recovered
	14	16	224	1800 <sup>d</sup>	2461	499	Recovered
	15 <sup>c</sup>	17	—	565 <sup>d</sup>	1123	528	Improved
Median			<b>364.0</b>	<b>572.0</b>	<b>915.0</b>	<b>334.0</b>	
Range			<b>222–443</b>	<b>248–1800</b>	<b>420–26,741</b>	<b>178–26,741</b>	
4	16	18	—	472 <sup>d</sup>	472	368	Recovered
	17	19	—	486	588	289 <sup>e</sup>	Not recovered
	18	20	—	823 <sup>d</sup>	882	259 <sup>e</sup>	Improved
	19	21	—	147	194	130	Recovered
	20	22	—	357	386	274	Recovered
	21	23	543	1107	1206	—	Unknown
	22	24	—	—	—	—	Recovered
	23	25	—	—	—	Unknown	

Baseline value: Value at start of TCZ administration in the all-patient registry surveillance. <sup>a, b, c</sup> Representative examples of Group 1 (definitive MAS), Group 2 (probable MAS), and Group 3 (EB-VAHS), respectively. <sup>d</sup> ± 1 day from onset. <sup>e</sup> ± 3 days from outcome. Significant values for all 3 tables are in bold face. MAS: macrophage activation syndrome; PLT: platelet; TCZ: tocilizumab; EB-VAHS: Epstein-Barr virus-associated hemophagocytic syndrome; LDH: lactate dehydrogenase.

*Comments by the JIA Committee on Group 3.* The reported diagnosis of this patient was not MAS but EB-VAHS on the basis of amplified EBV DNA. The initial signs included decreased WBC and platelet counts. A marked increase in FDP and prolonged prothrombin time and activated partial thromboplastin time were observed, followed by increased levels of cellular damage markers such as CK, LDH, and AST. Cell damage led to hepatic dysfunction. Triglyceride levels were elevated. Atypical lymphocytosis was observed. However, no increases were noted in creatinine or amylase levels, suggesting that the patient did not develop multiple organ failure. The patient developed a typical course of EB-VAHS, which was confirmed by the presence of various antibodies to EBV and PCR-based detection of EBV DNA. This case suggested that EB-VAHS and MAS might share a common pathological process.

## DISCUSSION

Before the introduction of TCZ, over 50% of patients with sJIA were difficult to treat with even large amounts of corticosteroids<sup>1</sup>, and the inevitable administration of cortico-

steroids resulted in obesity, osteoporosis, growth retardation, and sometimes infectious complications. The introduction of TCZ to patients with sJIA in the United States, European Union, and Japan<sup>10,12,13</sup> has brought a new treatment option to the clinical setting of pediatric rheumatology.

The physiological effects of TCZ are the blockade of IL-6/IL-6 receptor signaling through gp130 receptors stimulated by the binding of IL-6 to both membrane-bound IL-6 receptor and soluble IL-6 receptor<sup>21,22</sup>. The clinical symptoms and signs in patients with sJIA are attributable to or closely accompanied by excessive or upregulated IL-6<sup>23,24</sup>. Our clinical trials of TCZ in these patients<sup>8,9</sup> have proved the role of IL-6 as a pathogenic and causative agent in the inflammatory disease status of sJIA.

Although only 2 patients developed MAS in the clinical trials, the all-patient registry surveillance of TCZ in patients with sJIA shown here revealed the serious adverse events of MAS, HLH, or EB-VAHS in 23 of 394 patients with sJIA treated with TCZ (25 events). The JIA Committee examined each event, using clinical course and laboratory findings for these patients reported from attending physicians.

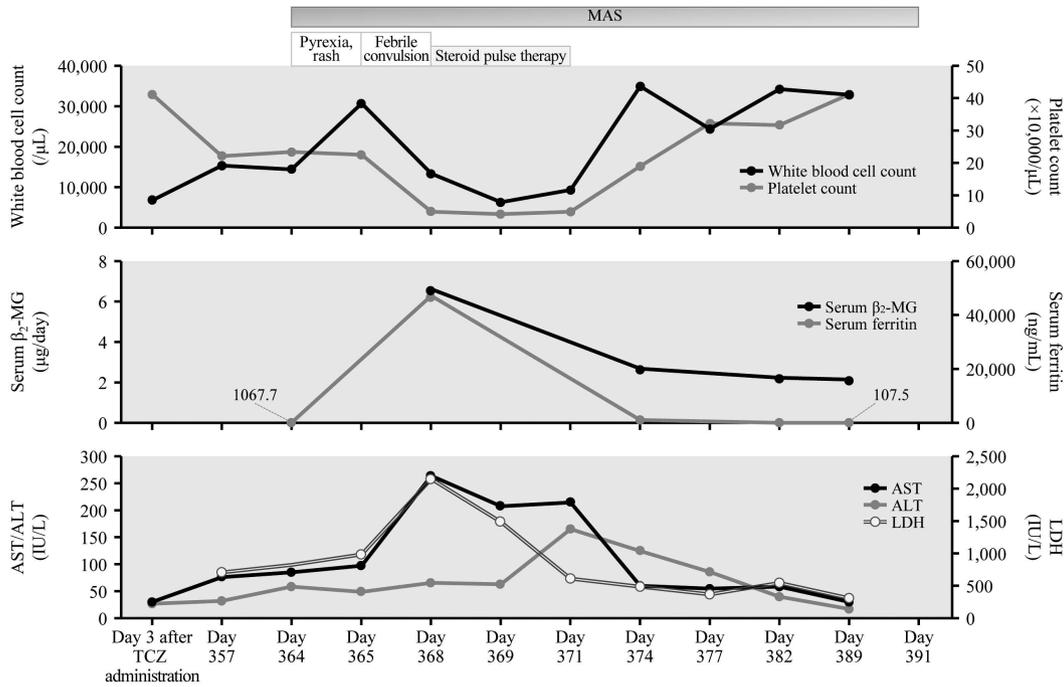


Figure 2. Clinical and laboratory findings in a patient categorized in Group 1. Patient: male. Age at onset: 3 years. TCZ start: < 10 years. The patient developed fever and rash, the primary disease became relatively unmanageable, and the patient was diagnosed with MAS. Laboratory findings at hospitalization showed decreased platelet count and progressive anemia; markedly elevated ferritin,  $\beta_2$ -MG, and soluble IL-2 receptor; elevated LDH, CK, pancreatic amylase, and other liver enzymes; and elevated triglycerides. TCZ: tocilizumab; MAS: macrophage activation syndrome; IL-2: interleukin 2; LDH: lactate dehydrogenase; CK: creatine kinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; MG: microglobulin.

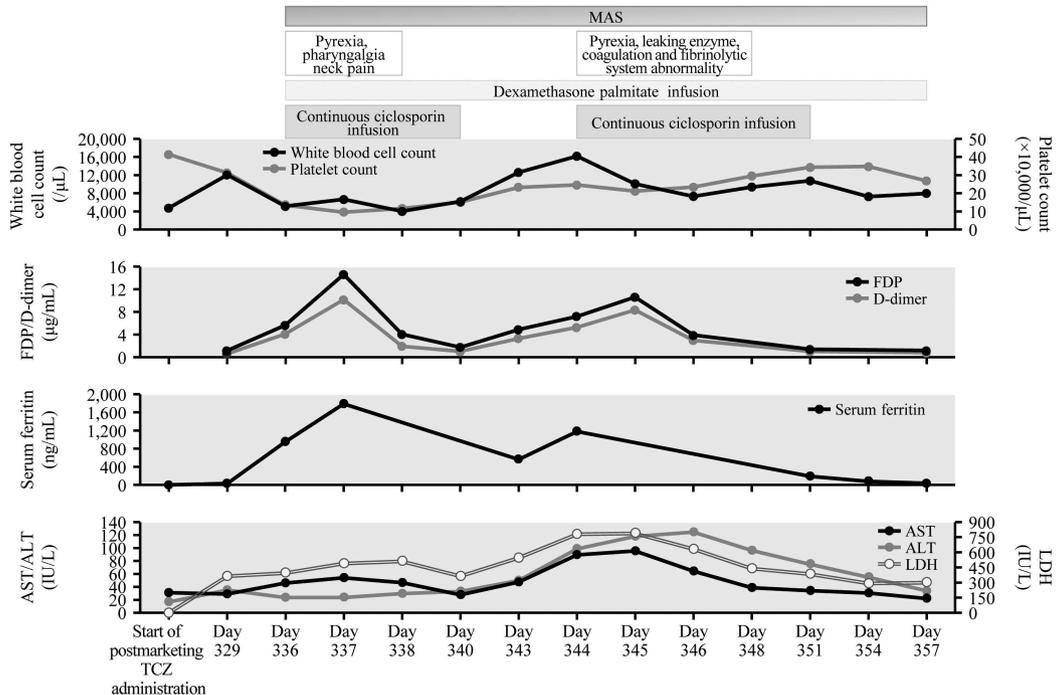
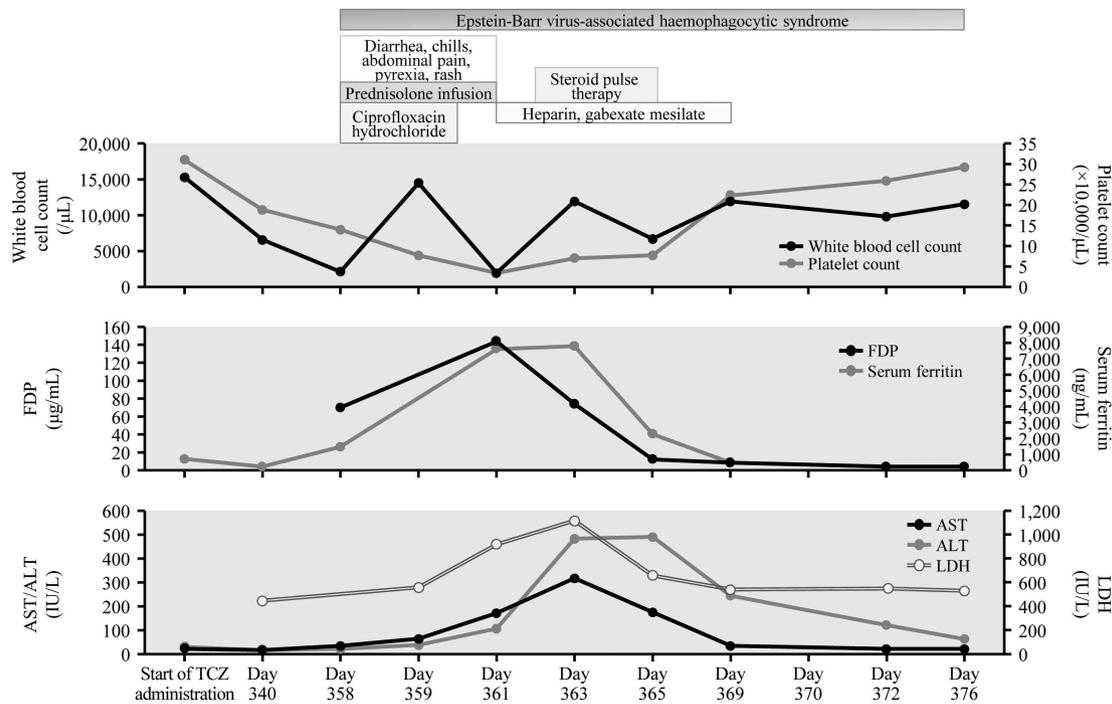


Figure 3. Clinical and laboratory findings in a patient categorized in Group 2. Patient: female. Age at onset: 3 years. TCZ start: < 10 years. This patient continued TCZ therapy after the end of the clinical trial. Abnormal laboratory results established the diagnosis of MAS. WBC and platelet counts were decreased. FDP and D-dimer levels were elevated. Ferritin showed a moderate increase. Liver function test results revealed a transition from AST predominance to ALT predominance. TCZ: tocilizumab; MAS: macrophage activation syndrome; FDP: fibrin-derived proteins; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.



**Figure 4.** Clinical and laboratory findings in a patient categorized in Group 3. Patient: female. Age at onset: 14 years. TCZ start: 20–29 years. This patient was diagnosed not with MAS, but with EB-VAHS because of the appearance of atypical lymphocytosis (max 68%), and this diagnosis was confirmed by amplified EBV DNA. Initial signs included decreased WBC and platelet counts. A marked increase in FDP and prolonged PT and APTT were observed, followed by increased levels of cellular damage markers such as CK, LDH, and AST. Triglyceride levels were elevated. However, no increases were noted in creatinine or amylase levels. The patient developed a typical course of EB-VAHS. TCZ: tocilizumab; MAS: macrophage activation syndrome; EB-VAHS: Epstein-Barr virus-associated hemophagocytic syndrome; EBV: Epstein-Barr virus; FDP: fibrin-derived proteins; PT: prothrombin time; APTT: activated partial thromboplastin time; CK: creatine kinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; WBC: white blood cell.

In our report, definitive or probable MAS occurred in 3.6% of patients with sJIA (14/394 patients) treated with TCZ. The incidence of MAS in the sJIA population without biologic treatment has been reported as 6.8% to 13%<sup>5,14,25</sup>. The rate in the present report is therefore lower, although the methods of evaluating MAS differ between this and previous reports. Combined with previously reported findings<sup>6,14,15,16</sup>, these results suggest that the clinical/laboratory features in the course of MAS appear to be similar among patients regardless of whether TCZ is administered. Also, given that TCZ was reinitiated after improvement or resolution of MAS in 18 of 23 patients in this report (Table 2), it does not seem that TCZ induces MAS. Thus, there is no suggested association between the use of TCZ and an increased risk of developing MAS in patients with sJIA. Additionally, in patients with sJIA treated with another biologic therapy, canakinumab (anti-IL-1 $\beta$  monoclonal antibody), MAS also developed in 1 of 43 patients (2.3%) in Trial 1 and in 4 of 177 patients (2.3%) in Trial 2<sup>26</sup>. Case reports have also appeared with etanercept<sup>27,28</sup> and anakinra<sup>29,30</sup>. Thus, single cytokine inhibition by biologic agents is not sufficient to prevent the development of MAS,

suggesting that there may be a specific route or routes of inflammatory cytokine production, parts of which may be dependent on genetic differences, such as molecular polymorphism<sup>31</sup>.

It has been suggested that MAS is primarily triggered by infectious agents (EBV, varicella, parvovirus B19, salmonella, *Pneumocystis carinii*, and fungus) or addition of anti-inflammatory drugs (aspirin, nonsteroidal anti-inflammatory drugs, and methotrexate)<sup>5,14,32</sup>, and that changes of proinflammatory cytokine levels are attributable to the development of MAS as seen in the present report<sup>33</sup>. Cytopenia and hemophagocytosis, progressive apoptosis/necrosis<sup>15,16,20</sup>, elevated cytokine-induced proteins such as ferritin<sup>34</sup> and  $\beta_2$ -MG<sup>35</sup>, coagulation/fibrinolytic abnormalities<sup>36,37</sup>, and massive endothelial cell damage<sup>38</sup> are the hallmarks of MAS. Each abnormal laboratory finding could be explained as a consequence of prolonged production of cytokines and chemokines originating presumably from activated macrophages, dendritic cells, and T cells. Excessive IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IFN- $\gamma$  are likely to contribute to early persistent fevers<sup>39</sup>, production of cytokine-induced proteins<sup>34,35</sup>, bone marrow overactivation

(hemophagocytosis and cytopenia)<sup>40,41,42</sup>, endothelial cell activation and damage with expression of HLA class I molecules and adhesion molecules<sup>43</sup>, subsequent activation of coagulation/fibrinolytic system (increases in FDP and D-dimers)<sup>37</sup>, and apoptosis/necrosis attributable to mitochondrial permeability transition<sup>17</sup>. As shown in the Group 3 patient profile, the clinical/laboratory features of EBV-infected patients during the disease course were similar to those found in patients with MAS, suggesting similarities in the pathophysiological background, i.e., cytokine storm, as reported previously<sup>20,33,34</sup>.

In all patients reported to have MAS, TCZ treatment was first suspended, and patients were successfully treated with anticoagulants for coagulation/fibrinolytic abnormalities, corticosteroids for stabilizing activated inflammatory cells contributing to excess production of cytokines, and cyclosporine for inhibiting mitochondrial permeability transition<sup>32</sup>. The etiology of MAS remains elusive. However, MAS is considered to be caused by diminished natural killer cell function<sup>44</sup> and reduced perforin expression<sup>45</sup>. An association has also been demonstrated between interferon regulatory factor-5 polymorphisms and susceptibility to MAS in patients with sJIA<sup>31</sup>. Further investigations to reveal the pathophysiological etiology of MAS are needed.

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