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Rate and Clinical Presentation of Macrophage Activation Syndrome in Patients With Systemic Juvenile Idiopathic Arthritis Treated With Canakinumab

Alexei A. Grom,[1] Norman T. Ilowite,[2] Virginia Pascual,[3] Hermine I. Brunner,[1] Alberto Martini,[4] Daniel Lovell,[1] Nicolino Ruperto,[5] for the Paediatric Rheumatology International Trials Organisation and the Pediatric Rheumatology Collaborative Study Group, Karolynn Leon,[6] Karine Lheritier,[7] and Ken Abrams[6]

Objective. **In pivotal trials, canakinumab has been shown to be effective in the treatment of systemic juvenile idiopathic arthritis (JIA), but reported adverse events have included macrophage activation syndrome (MAS). This study was undertaken to assess the impact of canakinumab on MAS incidence.**

Methods. **An independent MAS Adjudication Committee (MASAC), consisting of 3 of the authors, was convened, and a search of databases from clinical studies of canakinumab treatment in systemic JIA was performed using MASAC-specified adverse event terms to identify potential MAS events. These were then adjudicated as "probable MAS," "possible MAS," or "MAS unlikely," using criteria developed by the MASAC. MAS rates were expressed as numbers of cases per 100 patient-years.**

Results. **Of 72 potential MAS cases identified, 21 events (19 with canakinumab treatment; 2 with placebo treatment) in 19 patients were adjudicated as being probable MAS and 10 events in 9 patients as being possible MAS. Systemic JIA was well controlled in the majority of canakinumab-treated patients at the time of MAS. The time period between initiation of canakinumab treatment and onset of MAS ranged from 3 to 1,358 days (median 292 days). When the rates of probable MAS events were compared between canakinumab-treated patients (2.8 per 100 patient-years) and placebo-treated patients (7.7 per 100 patient-years), the difference was not significant (−4.9 [95% confidence interval −15.6, 5.9]). There were 3 deaths due to MAS-related complica-**

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[1]Alexei A. Grom, MD, Hermine I. Brunner, MD, Daniel Lovell, MD, MPH: Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [2]Norman T. Ilowite, MD: Children's Hospital at Montefiore, Bronx, New York; [3]Virginia Pascual, MD: Baylor Institute for Immunology Research, Dallas, Texas; [4]Alberto Martini, MD: Università di Genova and Istituto Giannina Gaslini, Genoa, Italy; [5]Nicolino Ruperto, MD, MPH: Istituto Giannina Gaslini, Genoa, Italy; [6]Karolynn Leon, MA, Ken Abrams, MD: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; [7]Karine Lheritier, PhD: Novartis Pharma AG, Basel, Switzerland.

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Address correspondence to Alexei A. Grom, MD, Division of Rheumatology, ML 4010, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229. E-mail: alexei.grom@cchmc.org.

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tions (2 in patients receiving canakinumab; 1 in a patient receiving placebo); full recovery was reported in all other patients. Infections were the most common trigger of MAS, and the clinical features of MAS were not modified by canakinumab.

Conclusion. **Canakinumab does not have a significant effect on MAS risk or its clinical features in patients with systemic JIA. Infections are the most common trigger, and MAS occurs even in patients whose systemic JIA is well controlled with this treatment.**

Systemic juvenile idiopathic arthritis (JIA) is a unique category of JIA characterized by arthritis, spiking fevers, a characteristic rash, hepatosplenomegaly, lymphadenopathy, and polyserositis (1,2). The triggers of the disease are unknown, although infection has been suspected. Once initiated, systemic JIA appears to be driven by the continuous activation of innate immune pathways with dysregulated production of innate proinflammatory cytokines, supporting the classification of the disease as an autoinflammatory disorder (3). Indeed, interleukin-1β (IL-1β) (4–6) and IL-6 (7) have been implicated as pivotal cytokines, although the source of excess IL-1β and IL-6 activity remains obscure.

A subset of patients with systemic JIA develop macrophage activation syndrome (MAS), a potentially fatal complication characterized by an overwhelming inflammatory reaction driven by excessive activation and expansion of T cells and hemophagocytic macrophages (8). Although the pathognomonic feature of MAS, i.e., histiocytes phagocytosing normal hematopoietic elements, is usually seen in the bone marrow, such cells can infiltrate almost any organ (9). The clinical picture in MAS is dominated by 3 cardinal features: 1) cytopenias, 2) liver dysfunction, and 3) coagulopathy resembling disseminated intravascular coagulation. Extreme hyperferritinemia is another distinctive laboratory abnormality in MAS. Despite the lack of uniformly accepted diagnostic criteria, MAS is recognized more frequently when it occurs in patients with systemic JIA, most likely due to an increasing awareness among physicians. An estimated 7–17% of patients with systemic JIA develop overt MAS (10,11), while mild "subclinical" events may be seen in as many as one-third of patients with active systemic disease (12,13).

MAS is thought to be closely related to a group of histiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH) (9,14,15). The pathophysiology of MAS/HLH is poorly understood. Strikingly, in many studies high levels of both circulating cytokines and cytokine inhibitors have been observed in MAS and HLH patients (16,17). These include cytokines derived from lymphocytes, such as interferon-γ (IFNγ) and IL-2, as well as cytokines that are of monocyte and macrophage origin, including IL-1β, tumor necrosis factor (TNF), IL-6, and IL-18. Based on these observations, the rather nonspecific term "cytokine storm" has been used by many authors to characterize the immune response seen in MAS and HLH (16).

MAS is a life-threatening condition with a mortality rate of up to 20%. Therefore, early recognition and immediate therapeutic intervention are critical. In most MAS patients, treatment with corticosteroids alone or in combination with cyclosporin A (CSA) results in a satisfactory response (18,19). A proportion of these patients may require a more aggressive immunosuppressive regimen that may include etoposide (19,20) or antithymocyte globulin (21). The utility of biologic drugs in MAS treatment remains unclear. Although TNF-inhibiting agents have been reported to be effective in occasional cases of MAS, other reports describe patients who developed MAS while they were being treated with TNF inhibitors (22).

Recent clinical trials showed that biologic agents that neutralize IL-1 (23,24) or IL-6 (25,26) are very effective in the treatment of systemic JIA. Since MAS episodes are often triggered by flares of systemic JIA, one might expect that these agents would reduce MAS rates due to better control of the underlying disease. Indeed, several cases of systemic JIA–associated MAS dramatically improving with anakinra treatment after inadequate response to corticosteroids and CSA have now been reported (27,28). However, in a recent report summarizing the experience with anakinra use in systemic JIA at several pediatric rheumatology centers, it was noted that 1 of 23 patients developed MAS while being treated with anakinra (29). Moreover, in a more recent report describing 46 patients with systemic JIA treated with anakinra beginning at the time of disease onset, 5 episodes of MAS occurred in 4 children, who were receiving anakinra at 1–2 mg/kg/day (30). Nevertheless, some patients improved with anakinra at higher doses, and there was no need for permanent discontinuation of the treatment.

The effect of IL-6 blockade on rates of MAS in systemic JIA is also not clear. Blockade of IL-6 via an anti–IL-6 receptor monoclonal antibody (tocilizumab) has proven highly efficacious in treating systemic JIA (25,26). IL-6 is produced by activated macrophages in MAS (31), and the results of a study using an animal model suggest that it may amplify the response of macrophages to proinflammatory stimuli (32). However, in a phase III clinical trial in systemic JIA, MAS was observed in 3 patients receiving IL-6 blockade with tocilizumab (26).

A small phase II study (33) and 2 recent phase III clinical trials (24) demonstrated high efficacy of canakinumab, a selective human anti–IL-1β monoclonal antibody,

in systemic JIA with active systemic features. In trial 1 (double-blind portion) of the phase III study, 84 patients with systemic JIA were randomly assigned to receive a single subcutaneous dose of canakinumab or placebo. On day 15 of trial 1, 36 of 43 patients in the canakinumab group (84%) met the adapted American College of Rheumatology (ACR) Pediatric 30 criteria for improvement (34), as compared to 4 of 41 (10%) in the placebo group ($P < 0.0001$). In trial 2, after 32 weeks of open-label treatment with canakinumab, 100 patients underwent randomization in the randomized withdrawal phase. There was a significant (64%) reduced risk of systemic JIA flare among patients randomized to receive canakinumab compared to those randomized to receive placebo. Both studies included patients 2–19 years of age with active systemic JIA. Patients from both studies could be eligible to enter an open-label extension trial.

Seven MAS events were reported in the completed canakinumab systemic JIA pivotal clinical program (2 phase III trials not including the extension trial) (24). The overall clinical presentation in most of these cases (particularly in cases with fatal outcome) was complex, with a combination of clinical features characteristic of sepsis, acute respiratory distress syndrome, pulmonary hypertension, and MAS. After the second MAS event was reported, the trial sponsor convened an independent MAS Adjudication Committee (MASAC) comprising clinicians who have experience and expertise in the management of systemic JIA and MAS. The main purpose of the MASAC was to study the impact of canakinumab on the risk of developing MAS and on the clinical features and/or treatment of MAS. The summary of the analysis of the adjudication results with a data cutoff date December 10, 2014 is presented herein.

PATIENTS AND METHODS

MAS Adjudication Committee and adjudication categories. The responsibilities of the MASAC (AAG, NTI, and VP) were 1) to create a list of adverse event (AE) preferred terms and a list of laboratory criteria to identify potential MAS events from periodic searches of the safety and laboratory databases of the clinical trial program (AE term database search list available from the corresponding author upon request), 2) to develop adjudication criteria for each MAS adjudication outcome category, and 3) to define the minimal information/materials needed in order to perform complete and exhaustive case review and adjudication. The committee compiled all such information related to the reported event, as well as a complete patient profile displaying all available data in the clinical and laboratory database for that patient in the canakinumab trial. In general, the clinical data available for adjudication were sufficient as they provided information on important patient parameters relevant for MAS diagnosis according to the preliminary diagnostic criteria proposed by Ravelli et al (35) and a recent international consensus survey (36). These parameters included both clinical features (i.e., persistent continuous fever ≥38°C; neurologic dysfunction, hemorrhages) and laboratory features (i.e., a drop in platelet count, hyperferritinemia, increased liver enzyme levels, decreased leukocyte count, decreasing erythrocyte sedimentation rate, hypofibrinogenemia, and hypertriglyceridemia) (36). For the majority of the events, it was possible to assess changes in these parameters over time. In 3 cases, the original biopsy materials were made available to MASAC members, including a pathologist specializing in MAS, for review.

The MASAC functioned completely independently of the trial sponsor in its assessment, and the members had been blinded with regard to the treatment received by patients enrolled in the placebo-controlled portion of the canakinumab trial. Based on the preliminary classification criteria for MAS (35,36) and HLH diagnostic guidelines (20), the committee developed 4 adjudication categories with corresponding probability of MAS (Table 1). Protocol approval for the studies mentioned in this report was obtained from institutional review boards or ethics committees and/or regulatory authorities in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients and/or their legal guardians.

Identification of potential MAS events. To identify all potential MAS events, a broad search of the clinical and laboratory databases on patients with systemic JIA treated with canakinumab was performed using the MASAC-specified preferred AE terms plus any AE that resulted in death. Examples of screening preferred AE terms included histiocytosis hematotophagic, lymphohistiocytosis, and terms associated with sepsis, bacteremia, viremia, fungemia, liver function

Table 1. MASAC adjudication definitions and associated probability of MAS*

Adjudication	Evidence
Probable MAS	Clinically consistent with MAS with histologic confirmation, laboratory features, or meeting current formal criteria for HLH
	or
	Clinical and laboratory features consistent with MAS but without histologic confirmation or meeting current formal criteria for HLH
Possible MAS	Laboratory features consistent with MAS but without clinical features, histologic confirmation, or meeting current formal criteria for HLH
MAS unlikely	Some clinical and/or laboratory features of MAS, but with possible alternative explanation
Insufficient information	Insufficient information for adjudication

* MASAC = Macrophage Activation Syndrome Adjudication Committee; HLH = hemophagocytic lymphohistiocytosis.

abnormalities, pancytopenias, death, seizures, and disseminated intravascular coagulation.

Additionally, clinical trial laboratory databases were searched using the following MASAC-specified laboratory criteria: 1) ferritin level ≥500 μg/liter, 2) elevated transaminase level(s), and 3) leukopenia and/or thrombocytopenia. When one of these criteria was met, the case was selected for potential adjudication.

Adjudication process. All potential cases identified for adjudication were then triaged by the MASAC chairperson to either continue to full committee adjudication or not. This decision was based on review of all of the laboratory data, adverse event data, and efficacy data for the patient. For cases triaged to be adjudicated by the committee, additional information from the investigator or treating physician, including hospital summaries, diagnostic reports, and original biopsy materials, was added to the patient profile containing the study information about the patient and was made available to the MASAC members, including a pathologist specializing in MAS, for review. A list of all investigators is shown in Appendix A. Since the duration of exposure to canakinumab in the systemic JIA clinical program was known, adjudicated probable and possible MAS rates were expressed as number of each per 100 patient-years.

RESULTS

Identification of potential cases of MAS. As of December 10, 2014, the MASAC adjudication data cutoff date, a total of 631 individual AE terms and/or individual laboratory abnormalities were identified in 324 unique patients in the systemic JIA clinical program, by the initial database screening searches as described above (Figure 1). Many represented the same event and were combined during the triage review by the MASAC chairperson. In total, 72 potential cases were identified for adjudication by the full MASAC, of which 28 represented AEs reported as MAS (26 during canakinumab treatment and 2 during placebo treatment) by the investigator and 44 represented other AEs/laboratory findings not reported as MAS. Among the events that the triage review excluded from full adjudication, the main categories were "isolated headache" and "isolated mild thrombocytopenia or neutropenia."

Adjudication outcome. Twenty-one events in 19 patients were adjudicated as being "probable MAS" based on the adjudication outcome of either 1) clinically consistent with MAS due to either histologic confirmation or meeting the formal diagnostic criteria for HLH or 2) clinical and laboratory features consistent with MAS but without either histologic confirmation or meeting the formal HLH diagnostic criteria. All probable MAS cases were reported by the investigator as MAS and satisfied the preliminary diagnostic criteria for MAS (35). Nineteen of these events occurred in the canakinumab group and 2 in the placebo group (Table 2).

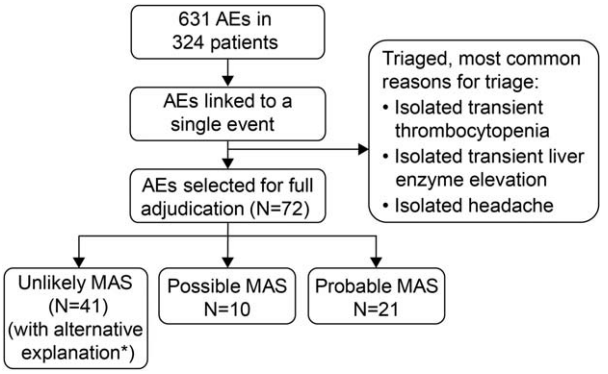

Figure 1. Flow chart of the inclusion and exclusion of patients. *Alternative explanations were as follows: flare of systemic juvenile idiopathic arthritis (n = 22), canakinumab-induced neutropenia (n = 1), isolated thrombocytopenia or neutropenia related to viral illness (n = 6), drug-induced neutropenia (n = 3), transient viral illness (n = 8), and bacterial pneumonia (n = 1). AEs = adverse events; MAS = macrophage activation syndrome.

Two patients in the canakinumab group had 2 episodes of MAS, both of which were adjudicated as probable MAS events, occurring approximately 3 months apart and 7 months apart, respectively. The majority of the patients in the canakinumab group had shown good clinical response to canakinumab before developing MAS and, for those who continued in the program, after resolution of MAS. The time period between the first injection of canakinumab and the onset of MAS ranged between 3 and 1,358 days (median 292).

In all but 1 case, MAS was reported in the setting of either an active infection or shortly after it resolved. The infectious organism was identified in only 4 cases: adenoviral gastroenteritis in 1 patient, Epstein-Barr virus in 2 patients, and cytomegalovirus in 1. In 1 additional case, MAS was associated with left lower lobe pneumonia, and in another it was reported in association with a urinary tract infection. Cutaneous impetigo was thought to be a trigger of another MAS event. In the remaining cases, the onset of MAS was preceded by acute upper respiratory infection.

Probable MAS events. All 21 reported MAS events that were adjudicated as being probable MAS, including the 2 events that occurred in patients treated with placebo, were characterized by the presence of classic features of MAS including cytopenias, extreme hyperferritinemia, liver dysfunction, coagulopathy, and increased C-reactive protein (CRP) levels. Overall, the clinical presentation of MAS did not appear to be modified by the canakinumab treatment (Table 2). Of the 19 reported MAS events in the canakinumab-treated patients, 6 events were managed with corticosteroids alone (or, in 1 case, with the addition of ganciclovir). Three MAS events were managed with the combination of

Table 2. Clinical characteristics of the patients adjudicated as having probable MAS*

Age (years)/ sex	Trial	No. of days on canakinumab; other Tx received	HSM	Cell counts, $\times 10^9$/liter	Ferritin, ng/ml	AST and ALT, units/liter	Fibrin-ogen, mg/dl	Triglyc-erides, mmoles/ liter	Other features	Tx	Outcome
5/M	Ph II	606; CS, NSAIDs	Yes	Plts 235, WBCs 5.0, ANC NA	1,900	AST 60, ALT NA	180	NA	NS	CS	Full recovery
14/M	Ph III trial 1	3; none	Yes	Plts 200, WBCs 2.2, ANC 1.0	1,300	AST 507, ALT 828	240	WNL	Pneumonia	CS, CSA	Full recovery
13/M	Ph III trial 2	64; MTX, CS, NSAIDs	NA	Plts 116, WBCs 1.0, ANC NA	>16,000	AST 53, ALT NA	274	4.0	Adenoviral acute gastroenteritis, PAH, enceph-alopathy	CS, CSA, Etop.	Death
15/F	Ph III trial 2	83; CS, NSAIDs	Yes	Plts 99, WBCs 3.2, ANC NA	>10,000	AST 436, ALT 162	NA	NA	EBV-induced, BM: HPS, encephalopathy	CS, CSA, Etop.	Full recovery
7/M	Ph III trial 2 ext.	198; CS	Yes	Plts 202, WBCs NA, ANC 4.0	1,400	AST 68, ALT NA	319	↑	LAD	CS, CSA	Full recovery
13/F	Ph III trial 2 ext.	214; CS, NSAIDs	Yes	Plts 330, WBCs 2.8, ANC 0.98	936	AST NA, ALT NA	330	WNL	LAD, Kikuchi-Fujimoto disease	CS, CSA	Full recovery
11/M	Ph III trial 2 ext.	604; CS	NA	Plts 84, WBCs 1.8, ANC NA	636	AST NA, ALT NA	206	NA	BM: HPS	CS, CSA, IVIG	Full recovery
5/M	Ph III trial 2 ext.	978; CS	NA	Plts 237, WBCs 2.39, ANC NA	5,087	AST 372, ALT 149	222	NA	BM: no apparent HPS	CS, CSA	Full recovery
16/F	Ph III trial 2 ext.	1,358; NSAIDs	Yes	Plts 46, WBCs 1.3, ANC NA	4,764	AST 626, ALT 533	150	2.7	EBV-induced, BM: histocytic expansion and mild HPS	CS, IVIG	Full recovery
2/M (2 events)	Ph III trial 2 ext.	86; none	Yes	Plts 51, WBCs 3.5, ANC NA	16,932	AST 263, ALT 575	126	1.7	Encephalopathy	CS, IVIG	Full recovery
		292; none	Yes	Plts 76, WBCs 3.58, ANC NA	952	AST NA, ALT NA	130	NA	NS	CS, IVIG	Full recovery
7/F	Ph III trial 2 ext.	134; MTX, CS, NSAIDs	Yes	Plts 59, WBCs 1.31, ANC NA	9,019	AST 175, ALT NA	115	1.81	BM: histiocytic expansion and moderate HPS	CS, CSA, IVIG	Full recovery
6/F (2 events)	Ph III trial 2 ext.	770; MTX	No	Plts 86, WBCs 1.86, ANC 0.44	1,997	AST 130, ALT 84	NA	WNL	BM: histiocytic expansion and mild HPS	CS	Full recovery
		866; MTX, CS	NA	Plts 125, WBCs 1.7, ANC 1.1	1,170	AST NA, ALT 133	NA	WNL	NS	CS	Full recovery
21/F	Ph III trial 2 ext.	1,003; CS, NSAIDs	No	Plts 160, WBCs 3.9, ANC NA	11,748	AST ↑↑, ALT NA	217	2.85	CMV-induced, BM: histiocytic expansion and rare HPS	CS, GCV	Full recovery
4/F	Ph III trial 2 ext.	18; CS	Yes	Plts 165, WBCs NA, ANC NA	5,795	AST 99, ALT 16	537	NA	NS	CS	Full recovery
17/F	Ph III trial 2 ext.	809; MTX, CS, NSAIDs	Yes	Plts 124, WBCs 4.74, ANC 1.47	3,738	AST 114, ALT NA	368	1.78	BM: histiocytic expansion and mild HPS	CS, CSA	Full recovery

Table 2. *(Cont'd)*

Age (years)/ sex	Trial	No. of days on canakinumab; other Tx received	HSM	Cell counts, $\times 10^9$/liter	Ferritin, ng/ml	AST and ALT, units/liter	Fibrinogen, mg/dl	Triglycerides, mmoles/liter	Other features	Tx	Outcome
18/M	Ph III trial 2 ext.	253; none	NA	Plts 81, WBCs 16.7, ANC 2.38	6,330	AST 137, ALT 95	158	3.68	2 suspected subclinical MAS events treated with CS	CS	Full recovery
12/F	Ph III trial 2 ext.	911; none	No	Plts 14, WBCs 3.7, ANC NA	NA	AST 92, ALT NA	235	2.76	Cutaneous abscess/ impetigo, interstitial pneumonitis (TRALI)	CS, CSA, IVIG	Death

* Twenty-one episodes adjudicated as probable macrophage activation syndrome (MAS) occurred in 19 patients in the trials of canakinumab treatment for systemic juvenile idiopathic arthritis. Two of the 19 patients were being treated with placebo; data on the remaining 17 patients, treated with canakinumab, are shown here. All patients had fever and elevated C-reactive protein levels. Tx = treatment; HSM = hepatosplenomegaly; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Ph = phase; CS = corticosteroids; NSAIDs = nonsteroidal antiinflammatory drugs; Plts = platelets; WBCs = white blood cells; ANC = absolute neutrophil count; NA = not available; NS = not specified; WNL = within normal limits; CSA = cyclosporin A; MTX = methotrexate; PAH = pulmonary arterial hypertension; Etop. = etoposide; EBV = Epstein-Barr virus; BM = bone marrow; HPS = hemophagocytosis; ext. = extension; ↑ = reported as elevated; LAD = leukocyte adhesion deficiency; IVIG = intravenous immunoglobulin; ↑↑ = reported as highly elevated; CMV = cytomegalovirus; GCV = ganciclovir; TRALI = transfusion-related acute lung injury.

Table 3. Clinical characteristics of the patients adjudicated as having possible MAS*

Age (years)/ sex	Trial	No. of days on canakinumab; other Tx received	HSM	Cell counts, $\times 10^9$/liter	Ferritin, ng/ml	AST and ALT, units/liter	Fibrin-ogen, mg/dl	Triglyc-erides, mmoles/liter	Other features	Tx	Outcome
8/F	Ph III trial 2	172; CS, MTX	No	Plts 115, WBCs NA, ANC 1.29	991	AST 115, ALT NA	228	2.02	Triggered by HSV	CS	Full recovery
13/M	Ph III trial 2	4; CS	Yes	Plts 235, WBCs NA, ANC 1.86	8,382	AST 113, ALT NA	NA	3.31	NS	CS	Full recovery
5/M	Ph III trial 2 ext.	169; MTX, NSAIDs	No	Plts 59, WBCs 2.4, ANC 1.3	3,905	AST 95, ALT 44	364	1.41	NS	NS	Full recovery
9/F	Ph III trial 2 ext.	531; CS, MTX	Yes	Plts 162, WBCs NA, ANC 2.36	5,883	AST 103, ALT NA	346	3.36	NS	CS	Full recovery
18/F (2 events)†	Ph III trial 2 ext.	656; CS	No	Plts 135, WBCs NA, ANC 1.39	547	AST 32, ALT NA	221	0.86	NS	CS	Full recovery
		1,359; CS, NSAIDs	NA	Plts 108, WBCs 2.77, ANC NA	2,170	AST 94, ALT NA	NA	NA	NS	CS	Full recovery
3/F	Ph III trial 2 ext.	645; MTX	No	Plts 155, WBCs 4.31, ANC 2.18	636	AST 56, ALT NA	247	NA	NS	CS	Full recovery
7/F	Ph III trial 2 ext.	851; MTX, CS	NA	NA	>20,000	AST NA, ALT NA	331	1.1	NS	CS	Full recovery
10/M	Ph III trial 2 ext.	617; CS, MTX, NSAIDs	Yes	Plts 226, WBCs NA, ANC 2.22	533	AST 291, ALT 636	276	NA	NS	CS	Full recovery
2/F	Ph III trial 2 ext.	233; MTX, NSAIDs	NA	Plts 243, WBCs 9.08, ANC NA	254	AST 184, ALT 123	252	NA	NS	CS	Full recovery

* All patients had fever and elevated C-reactive protein levels. HSV = herpes simplex virus (see Table 2 for other definitions).
† Age at time of first event.

corticosteroids and intravenous immunoglobulin (IVIG), and 8 events responded to corticosteroids plus CSA (with addition of IVIG in 3 of them). A combination of corticosteroids, CSA, and etoposide was used to manage 2 events. One patient developed posterior reversible encephalopathy syndrome from the CSA treatment and then severe bone marrow suppression from the etoposide treatment. Canakinumab was not administered during MAS episodes in any of the patients. In the canakinumab group, full recovery was observed in 17 patients (twice in 2 patients), and 2 patients died. There was 1 death in the placebo group. The placebo-treated patient who died had received steroids and IVIG for MAS. The other placebo-retreated patient who developed probable MAS recovered completely after starting canakinumab monotherapy.

Table 4. Exposure-adjusted incidence rate of events adjudicated by the MASAC as being probable MAS in the trials of canakinumab treatment for systemic JIA*

	Canakinumab treatment	Placebo treatment
No. of events adjudicated as probable MAS	19	2
Patient-years of exposure	668.61	26
Rate of probable MAS–adjudicated events/ 100 patient-years†	2.8	7.7

* The clinical trials program included the following studies: phase II, phase III trial 1, phase III trial 2, and phase III trial 2 extension. MASAC = Macrophage Activation Syndrome Adjudication Committee; JIA = juvenile idiopathic arthritis.
† The difference of −4.9 between the canakinumab-treated and placebo-treated groups (95% confidence interval −15.6, 5.9) was not significant.

Possible MAS events. Ten MAS events occurring in 9 patients were adjudicated as being possible MAS based on the presence of laboratory features consistent with MAS, but without clinical features, histologic confirmation, or meeting current formal HLH criteria. All occurred in patients treated with canakinumab, and all were identified via MASAC screening laboratory and/or non-MAS AEs. According to the reports provided by the investigators, the events were interpreted as flares of systemic JIA triggered by intercurrent infectious events

but not reported as MAS. Indeed, these patients did not have the typical clinical features of MAS that were described in the preliminary diagnostic criteria (35), and the intermittent fever pattern in the patients was more consistent with systemic JIA flare than with MAS. The laboratory features, however, were highly suggestive of MAS, and 6 of the 10 events satisfied the preliminary diagnostic MAS criteria based on the laboratory findings alone. Canakinumab was discontinued at the time of the event in all cases, and the patients were treated with corticosteroids alone. All patients fully recovered from the adjudicated MAS episode (Table 3).

Incidence of events in the systemic JIA clinical trial program adjudicated as being probable MAS. Because the cases adjudicated by the MASAC were from the canakinumab clinical trial program, it was possible to determine the rate of MAS events in patient-years for both the canakinumab and placebo groups. As shown in Table 4, the rates of events adjudicated as being probable MAS were 2.8 per 100 patient-years in the canakinumab group versus 7.7 per 100 patient-years in the placebo group, and the between-group difference of −4.9 (95% confidence interval −15.6, 5.9) was not statistically significant.

DISCUSSION

The exact role of IL-1 in the development of MAS remains unclear. Since MAS episodes are often triggered by a systemic JIA flare, it is reasonable to expect that the frequency of MAS in patients with systemic JIA would be at least somewhat reduced by treatment with IL-1 inhibitors. Indeed, there are several reports describing a marked improvement in systemic JIA–associated MAS in response to treatment with anakinra after an inadequate response to corticosteroids and cyclosporine (27,28), and treatment with anakinra was endorsed in the ACR systemic JIA treatment guidelines (37,38). In contrast, based on 2 reports summarizing experience with the use of anakinra in systemic JIA in several pediatric rheumatology centers, anakinra was a suspected MAS trigger in several children at dosages of 1–2 mg/kg/day (29,30). However, the exact cause and effect were difficult to establish in these patients, and permanent discontinuation of anakinra was unnecessary for any of them. In fact, in some of these patients, MAS features improved with higher doses of anakinra.

The phase III canakinumab trial program provided strong evidence that this treatment is highly effective for systemic JIA (24,33). Of 323 patients with systemic JIA enrolled in the trials, 19 probable MAS events were diagnosed in 17 patients (5.3%) while receiving canakinumab, resulting in an overall incidence rate of 2.8 events per 100 patient-years. Two of the canakinumab-treated patients experienced 1 repeat episode of MAS. Based on epidemiologic data reported in the literature, 7–17% of patients with systemic JIA develop clinically overt MAS (10,11), and the proportion of patients who developed probable MAS in the canakinumab trials appears to be slightly below this range. Furthermore, the incidence of MAS observed in the canakinumab trials is comparable to the incidence reported in patients with systemic JIA at a pediatric rheumatology center in Cincinnati, Ohio, i.e., 4–6 MAS events per 100 patient-years (39). Taken together, these observations support the notion that IL-1 inhibition with canakinumab does not importantly alter the risk of MAS in patients with systemic JIA, regardless of the response of systemic JIA to canakinumab treatment.

Since the original clinical trials were not designed to assess the effect of canakinumab on MAS rates, the results presented herein are from pooled exploratory analyses that were not adequately powered to detect potentially small protective effects of canakinumab on the development of MAS. For example, with 2 MAS events observed during treatment with placebo, 127 MAS events would have had to be observed in the canakinumab group in order to ascertain a measurable effect of canakinumab on MAS. Consequently, the pooled data do not allow for any meaningful assessment of a potential protective effect of canakinumab.

Given that infections remained the most prevalent trigger for MAS in canakinumab-treated patients with systemic JIA, increased vigilance and prompt initiation of aggressive therapy appear warranted in all suspected cases. Furthermore, the overall clinical presentation of MAS does not appear to be modified by canakinumab treatment; this is advantageous as the general approaches to MAS diagnosis can remain the same as in patients with systemic JIA who are not treated with canakinumab.

With 1 exception (AE of septic shock), all events adjudicated as being possible MAS had been initially identified because of an MASAC-defined screening laboratory criterion having been met. Surprisingly, none of these possible MAS events were recognized by the treating physicians as MAS. Based on the reports provided by the investigators, the events were interpreted as flares of systemic JIA, triggered by an infectious illness. The management of these possible MAS events was limited to a moderate increase in the dosage of corticosteroids. Since the laboratory abnormalities during these events were consistent with the early stages of MAS (or subclinical MAS), the timely increase of the corticosteroid dosage in these patients might have pre-

vented the progression to overt life-threatening MAS. One important inference from these observations is that even mild worsening of systemic JIA in a patient who is being treated with canakinumab, particularly if triggered by infection, should prompt additional laboratory evaluation to rule out the early stages of MAS.

Like IL-1β, the role of IL-6 in the pathogenesis of MAS has not been well delineated. One study in patients with MAS demonstrated the presence of IL-6–producing activated macrophages in liver biopsy specimens (31). A study of IL-6–transgenic mice showed that prolonged exposure to IL-6 in vivo leads to an exaggerated inflammatory response to Toll-like receptor ligands, with some clinical features reminiscent of MAS (32). However, MAS was observed in 5 patients with systemic JIA enrolled in a clinical trial of tocilizumab whose underlying systemic JIA responded well to IL-6 blockade. This corresponded to 1.24 MAS cases per 100 patient-years of followup (95% confidence interval 0.68, 4.00) (26,40). Another recent report from Japan described a patient with severe adult-onset Still's disease that initially responded very well to tocilizumab, but then rapidly progressed to MAS (41). Furthermore, it has been suggested that treatment with tocilizumab may mask some of the features of MAS. Shimizu and colleagues described several patients with systemic JIA who developed clinically overt MAS while being treated with tocilizumab, but with normal CRP levels and only modest increases in ferritin levels (42).

All of these observations suggest that systemic JIA therapeutic strategies aimed at the inhibition of either IL-1 or IL-6 do not provide complete protection against MAS, even if features of systemic JIA are well controlled. One conclusion is that neither IL-1 nor IL-6 is the only driver contributing to development of MAS. In hemophagocytic syndromes, the final pathophysiologic pathways lead to an escalating production of multiple cytokines, ultimately creating a "cytokine storm." Therefore, it is possible that cytokines other than IL-1 and IL-6 play a central role in MAS pathophysiology. Over the last few years, there has been increasing interest in the role of IL-18 in systemic JIA and MAS. Strikingly high serum levels of IL-18 have been observed in systemic JIA (43,44), and patients with high IL-18 concentrations have more systemic manifestations compared with those in whom arthritis is the predominant feature. High levels of IL-18 are also correlated with the development of MAS and the emergence of MAS-like features in these patients (45). Based on the general properties of IL-18, it has been assumed that it may contribute to T lymphocyte and macrophage activation in hemophagocytic syndromes (46). However, in many patients with systemic JIA, plasma IL-18 levels remain elevated even during clinical remission, suggesting that further work is needed to better characterize the role of this cytokine in systemic JIA and MAS.

The role of IFNγ in systemic JIA–associated MAS has also not been fully characterized. IFNγ mediates anemia but is dispensable for Toll-like receptor 9–induced MAS-like syndrome in mice (47). However, there have been findings in patients and animal models that support IFNγ blockade as a novel therapy for HLH (48), and a clinical trial is currently under way. Histopathologic studies of inflammatory infiltrates in the tissues affected by MAS showed numerous IFNγ-producing T cells in close proximity to activated hemophagocytic histiocytes (36,49). A recent study focusing on longitudinal cytokine changes in the serum of patients with systemic JIA showed that levels of IFNγ itself and IFNγ-induced chemokines increased markedly with the emergence of clinical features of MAS and returned to normal ranges after the resolution of this complication (50). Collectively, these observations raise the question as to whether IFNγ might be an appropriate therapeutic target in MAS as well.

Data from the clinical trials of IL-6– or IL-1–inhibiting agents also suggest that the risk of MAS development has additional components that are not influenced by better control of the underlying systemic JIA with these inhibiting agents. Indeed, genetic factors might also play a role. Considering the strikingly close clinical resemblance between MAS and secondary HLH, a potential role of hypomorphic genetic variants in familial HLH–associated genes has been suggested (51–54). In this scenario, in the presence of hypomorphic variants in HLH-associated genes, an encounter with certain microbes may trigger an MAS episode in patients with systemic JIA even if the underlying disease has responded well to IL-1– or IL-6–inhibiting agents.

In conclusion, data from the canakinumab clinical trial program suggest that IL-1 inhibition has little if any effect on MAS, with regard to either the risk of developing it, the clinical presentation, or the response to treatment. Possible developing MAS should be considered and closely monitored in patients with worsening systemic JIA, and appropriate treatment adjustments made.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Grom had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ilowite, Brunner, Martini, Ruperto, Lheritier, Abrams.

Acquisition of data. Grom, Martini, Lovell, Ruperto, Leon, Lheritier, Abrams.
Analysis and interpretation of data. Grom, Ilowite, Pascual, Brunner, Martini, Lovell, Ruperto, Leon, Lheritier, Abrams.

ROLE OF THE STUDY SPONSOR

Novartis Pharma AG collaborated with Drs. Grom, Ilowite, Pascual, Brunner, Martini, Lovell, and Ruperto to design and conduct the study. All authors analyzed the data, critically reviewed the manuscript for important intellectual content, approved the final draft, and agreed to its submission. Novartis provided writing and editorial assistance (performed by Katia de Souza, PhD [Novartis Pharma, Basel, Switzerland] and Divya Chandrasekhar, PhD [Novartis Healthcare, Hyderabad, India]). Novartis Pharma did not control the analysis or interpretation of the study results. Publication of this article was not contingent upon approval by Novartis Pharma.

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APPENDIX A: STUDY INVESTIGATORS

In addition to the authors, the following investigators were involved in the study: Ruben Cuttica, MD (Argentina); Wolfgang Emminger, MD (Austria); Laurence Goffin, MD, Rik Joos, MD, Bernard Lauwerys, MD, Carine Wouters, MD (Belgium); Maria Odete Esteves Hilário, MD, Sheila Knupp Feitosa de Oliveira, MD, Claudio Len, MD, Sebastiao Radominski, MD, Flavio Roberto Sztajnbok, MD (Brazil); Elie Haddad, MD, Michael Hofer, MD, Kristin Houghton, MD, Adam Huber MD, Traudel Saurenmann, MD, Rayfel Schneider, MD, Lori Tucker, MD (Canada); Brigitte Bader-Meunier, MD, Marine Desjonqueres, MD, Michel Fischbach, MD, Isabelle Kone-Paut, MD, Isabelle Marie, MD, Agnes Mogenet, MD, Richard Mouy, MD, Pierre Quartier, MD (France); Reinhard Berner, MD, Ivan Foeldvari, MD, Dirk Foell, MD, Michael Frosch, MD, Johannes-Peter Haas, MD, Gerd Horneff, MD, Markus Hufnagel, MD, Tilmann Kallinich, MD, Jasmin Kuemmerle-Deschner, MD, Hartwig Lehmann, MD, Thomas Lutz, MD, Angelika Thon, MD, Ralf Trauzeddel, MD, Nikolay Tzaribachev, MD, Elisabeth Weibarth-Riedel, MD (Germany); Georgios Chrousos, MD; Maria Trachana, MD, Olga Vougiouka, MD (Greece); Tamas Constantin, MD (Hungary); Judith Barash, MD, Yackov Berkun, MD, Riva Brik, MD, Liora Harel, MD, Amit Nahum, MD, Shay Pade, MD, Yosef Uziel, MD (Israel); Maria Alessio, MD, Rolando Cimaz, MD, Fabrizia Corona, MD, Valeria Gerloni, MD (Italy); N. M. Wulffraat, MD (The Netherlands); Manuel Ferrandiz, MD (Peru); Lidia Rutkowska-Sak, MD (Poland); Ekaterina Alekseeva, MD, Vyacheslav Chasnyk, MD, Evgeny Nasonov, MD, Marina Stanislav, MD (Russia); Jordi Anton, MD, Inmaculada Calvo, MD, Mari Luz Gamir, MD, Juan Carlos Robledillos, MD (Spain); Bo Magnusson, MD (Sweden); Muferet Erguven, MD, Ozgur Kasapcopur, MD, Huri Ozdogan, MD, Seza Ozen, MD, Erbil Unsal, MD (Turkey); Alice Chieng, MD, Helen Foster, MD, Liza McCann, MD, Athimalaip Ramanan, MD, Taunton Southwood, MD, Nicholas Wilkinson, MD, Patricia Woo, MD (United Kingdom); Gloria Christine Higgins, MD, Daniel Kingsbury, MD, Jorge Lopez-Benitez, MD, Katherine Marzan, MD, Paula Morris, MD, Marc Natter, MD, Kenneth Noel Schikler, MD (United States).