

# Ruxolitinib for Refractory Macrophage Activation Syndrome Complicating Adult-Onset Still's Disease

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## Abstract

Macrophage activation syndrome is the most frequent life-threatening complication of adult-onset Still's disease. This is a nearly fatal case of a young patient, which has been refractory to corticosteroids, anakinra, tocilizumab, cyclosporine A, and etoposide, but eventually responded miraculously to salvage therapy with ruxolitinib. We review recent pertinent data related to the therapeutic value of ruxolitinib for macrophage activation syndrome triggered by adult-onset Still's disease.

**Keywords:** Adult-onset Still's disease, macrophage activation syndrome, ruxolitinib, hemophagocytic lymphohistiocytosis

## Introduction

Macrophage activation syndrome (MAS), also referred to as hemophagocytic lymphohistiocytosis (HLH) triggered by autoinflammatory/autoimmune disorders (MAS-HLH), is a life-threatening complication of rheumatologic diseases. It is mostly observed in children with systemic juvenile idiopathic arthritis (SJIA). In adults, it is rare, occurs mainly among patients with AOSD, and portends a high mortality rate.<sup>1</sup> It is also encountered in systemic lupus erythematosus, vasculitis, and other systemic autoimmune diseases.

MAS is an aberrant immune response that leads to uncontrolled expansion and activation of cytotoxic cells with hypersecretion of proinflammatory cytokines (IL-1, IL-6, IL-10, IL-2, IL-18, TNF $\alpha$ , and interferon- $\gamma$  [IFN- $\gamma$ ]). The clinical presentation of MAS is usually acute and dramatic. Fever is the main clinical manifestation. Additional clinical findings are hepatosplenomegaly, generalized lymphadenopathy, central nervous system (CNS) dysfunction, and hemorrhagic manifestations.

The management of MAS is challenging. In general, patients may be successfully treated with therapy targeted against the underlying rheumatic disease. Treatment with HLH-specific therapy is recommended if patients fail to improve after a brief trial of therapy appropriate for rheumatologic disease.<sup>2</sup> Refractory cases are candidates for allogeneic hematopoietic stem cell transplantation (alloSCT).

We describe a nearly fatal case of a young patient, which has been refractory to corticosteroids (CS), anakinra, tocilizumab, cyclosporine A (CSA), and etoposide, but eventually responded miraculously to salvage therapy with ruxolitinib. We review pertinent data related to the therapeutic value of ruxolitinib for MAS triggered by AOSD.

## Case Presentation

A 24-year-old man presented to the rheumatology clinic with a 3 months history of short episodes of arthritis and rash. The arthritis involved elbows, wrists, and knees. The rash consisted of erythematous papules and plaques on the extremities. During one episode he had fever for one day. Mild leukocytosis and elevated C-reactive protein (CRP) were documented at that time. The patient felt well between episodes. Laboratory workup revealed negative antinuclear antibody (ANA), negative rheumatoid factor, and normal complement levels. Past medical history was remarkable for obesity and fatty liver.

The patient was hospitalized after 5 days of spiking fever ( $\sim 40^\circ\text{C}$ ), evanescent rash, and joint pain. Associated symptoms included sore throat and chills. On physical examination, he appeared generally well: height 175 cm, weight 110 kg, and BMI 35.9. Pertinent findings were polycyclic urticarial rash over the trunk and extremities, and arthritis of the right knee and left elbow. Laboratory tests were remarkable for leukocytosis

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(white blood cell count 24.4 K/ $\mu$ L) and neutrophilia (absolute neutrophils count 22.6 K/ $\mu$ L), elevated levels of transaminases (ALT 64 U/L, AST 54 U/L), hypertriglyceridemia (312 mg/dL), hyperfibrinogenemia (585 mg/dL), elevated CRP (400 mg/dL), and hyperferritinemia (60 451 mg/L).

Due to clinical suspicion of MAS in the setting of AOSD, the patient underwent a CT scan of the chest and abdomen which revealed splenomegaly. A bone marrow biopsy demonstrated reactive bone marrow, without evidence of hemophagocytosis. Additional laboratory tests revealed elevated soluble interleukin 2 receptor (CD25) at 5350 U/ml (Ref:  $\leq 2000$ ), and low natural killer cells activity at 4.2% (Ref:  $\geq 20\%$ ). An extensive infectious diseases workup was negative including whole blood PCR for Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus-6 (HHV-6) and human herpes virus-8 (HHV-8), bone marrow PCR for parvovirus B19, serologic tests for human immunodeficiency virus (HIV), hepatitis B, hepatitis C, rickettsia, chlamydia, and urine and blood cultures. Genetic testing for gene mutations associated with HLH was negative. High dose prednisone was initially implemented, but only after several days of intravenous methylprednisolone, up to 1 g/day, resolution of fever and rash was noted. Ferritin level decreased to 19 100 mg/L. Once-daily subcutaneous 100 mg anakinra was added to high dose prednisone and the patient was discharged.

Severe exacerbation occurred about 10 days after anakinra was started. The patient was

readmitted with a recurrence of persistent high fever and widespread rash. Cytopenias and significant liver impairment were remarkable; decrease in WBC count (5.6 K/ $\mu$ L), decrease in neutrophils count (4.1 K/ $\mu$ L), anemia (hemoglobin 10.1 g/dL), thrombocytopenia (94 K/ $\mu$ L), elevated ALT (600 U/L), and hyperbilirubinemia (2.5 mg/dL). Ferritin level increased to 88 000 mg/L and hypofibrinogenemia (121 mg/dL) was noted. Anakinra was switched to intravenous tocilizumab (800 mg). Pulse methylprednisolone was administered, and CSA was added. Under this treatment, fever and rash improved but neutrophils count continued to decline and severe neutropenia (100 K/ $\mu$ L) developed.

The patient was transferred to the hematology unit. Reevaluation included positron-emission tomography (PET)/computed tomography (CT), a second bone marrow biopsy and infectious diseases workup, which were negative for malignancy or infection. Dexamethasone and Etoposide were initiated based on the HLH-94 protocol, and CSA was continued. Under this treatment, neutropenia resolved and liver function improved but remission was not accomplished, according to soluble CD25 and ferritin levels. Severe glucocorticoid-induced myopathy and hyperglycemia gradually developed. A second tocilizumab infusion was added at the sixth week of the protocol. At the eighth week, the patient was transferred to ICU due to severe *E. coli* extended-spectrum beta-lactamase (ESBL) sepsis. He required mechanical ventilation, antibiotics, vasopressors, and hemodialysis to stabilize multiple organ failure. Ferritin level went up from 4300 to 56 000 mg/L, and CRP went up from 1.8 to 526 mg/dL.

After 3 months of intensive therapy, MAS was still active with all parameters persistently positive. Moreover, our patient has become severely compromised due to iatrogenic complications; immunologic (immunosuppression), hematologic (pancytopenia with zero neutrophils and 22 K/ $\mu$ L platelets), endocrine (diabetes mellitus), and musculoskeletal (proximal myopathy, central obesity, huge fat pad of neck), as well as secondary infections, and thus regarded as high risk for bone marrow transplantation.

At this point, salvage therapy with ruxolitinib was implemented in the ICU setting. Initial dosage was 5 m bid. Dose escalation was performed rapidly, according to CBC counts and renal and liver function. Favorable effects of ruxolitinib were noted in 2 weeks. Tracheostomy was required due to severe muscle weakness.

The patient was discharged to a rehabilitation facility after 5 weeks and returned home 4 months later. Under ruxolitinib, MAS remained in clinical remission, thus enabling tapering down of dexamethasone. Blood counts and CD25 level normalized (1700 U/mL), ferritin level decreased to 1600 mg/L and remained stable. The final maintenance regimen was reached in 3 months, and included ruxolitinib 30 mg/day and prednisone 5 mg/day, obviating the need for further intensive chemotherapy or alloSCT.

## Discussion

Macrophage activation syndrome (MAS), also referred to as hemophagocytic lymphohistiocytosis (HLH) triggered by autoinflammatory/autoimmune disorders (MAS-HLH), is a life-threatening complication of rheumatologic diseases. It is mostly observed in children with systemic juvenile idiopathic arthritis (sJIA). In adults, it is rare, occurs mainly among patients with AOSD, and portends a high mortality rate.<sup>1</sup> It is also encountered in systemic lupus erythematosus, vasculitis, and other systemic autoimmune diseases.

MAS is an aberrant immune response that leads to uncontrolled expansion and activation of cytotoxic cells with hypersecretion of proinflammatory cytokines (IL-1, IL-6, IL-10, IL-2, IL-18, TNF $\alpha$ , and interferon- $\gamma$  (IFN- $\gamma$ )). The clinical presentation of MAS is usually acute and dramatic. Fever is the main clinical manifestation. Additional clinical findings are hepatosplenomegaly, generalized lymphadenopathy, central nervous system (CNS) dysfunction, and hemorrhagic manifestations.

The management of MAS is challenging. In general, patients may be successfully treated with therapy targeted against the underlying rheumatic disease. Treatment with HLH-specific therapy is recommended if patients fail to improve after a brief trial of therapy appropriate for rheumatologic disease.<sup>2</sup> Refractory cases are candidates for alloSCT.

The main issue in this case is the management of patients with MAS triggered by AOSD. It is important to note that AOSD and MAS share several common clinical and biological features, as well as very similar pathophysiological mechanisms. In both conditions, a defect in granule-mediated cytotoxicity in the perforin and FAS systems in natural killer cells has been described. This defect results in enhanced antigen presentation and repeated IFN- $\gamma$ -dependent stimulation, leading to the exaggerated activation of cytotoxic cells. The resultant "cytokine storm"

## Main Points

- Macrophage activation syndrome (MAS) is the most frequent life-threatening complication of adult-onset Still's disease (AOSD).
- This is a case of MAS complicating AOSD, which has been refractory to corticosteroids (CS), anakinra, tocilizumab, cyclosporine A (CSA), and etoposide, but eventually responded miraculously to salvage therapy with ruxolitinib.
- Considering the pathophysiological similarities between MAS and AOSD, the broad mechanism of action of ruxolitinib, its remarkable activity in other hyperinflammatory diseases, and its effectiveness in secondary HLH of variety etiologies, it seems that ruxolitinib is especially promising for the treatment of cases of MAS complicating AOSD, particularly for resistant ones.

could be responsible for the development of the main clinical and laboratory features of both conditions. The two clinical entities could be considered to be on the same disease spectrum, with AOSD representing the milder form.<sup>3,4</sup>

The management of refractory MAS complicating AOSD lies in the interface between rheumatology (concentrating on AOSD) and hematology or immunology (concentrating on HLH). In the rheumatological literature, Mitrovic and Fautrel have recently reviewed the management of complicated AOSD; for all severe AOSD-related complications, high-dose corticosteroids and supportive measures remain the first-line treatment. In case of inadequate response, combination with IL-1 or IL-6 blockers is justified and CSA and etoposide remain of interest, especially in case of reactive lymphohistiocytosis hemophagocytic.<sup>4</sup> Other conventional drugs have a limited role in AOSD. IL-18 blockade is currently under investigation in clinical trials.<sup>5</sup> What about MAS cases refractory to all the above measures?

Recommendations for the management of HLH in adults were recently published in the hematological literature.<sup>6</sup> Recommended treatments for MAS-HLH include corticosteroids, CSA, and anakinra, and for severe refractory cases reduced dose of etoposide. These recommendations are not specific to the underlying rheumatic disease. Options for salvage therapy for refractory/relapsed HLH include anti-CD52 alemtuzumab, CHOP-like protocols plus etoposide, ruxolitinib, plasmapheresis, cytokine absorption columns, and emapalumab (anti-IFN- $\gamma$ ), which is approved as second-line therapy for primary pediatric HLH.<sup>7</sup> Which salvage therapy is most appropriate for MAS triggered by AOSD is currently unknown.

Our hematology team chose ruxolitinib for salvage therapy, which resulted in a miraculous response. This dramatic effect could have resulted from the background cumulative effects of tocilizumab, CSA, and etoposide on the immune system. Ruxolitinib is an oral JAK1 and JAK2 inhibitor that interfere with the phosphorylation of STAT1. Ruxolitinib has been found to be effective in other hyperinflammatory, cytokine-mediated diseases. It is approved for use in myelofibrosis (MF), where it reverses the hyperinflammatory state and thereby the constitutional symptoms of the disease.<sup>7</sup> It is also indicated for the treatment of corticosteroid-resistant acute graft-versus-host disease (aGVHD), which was reported to rapidly respond to ruxolitinib after the failure of standard treatment.<sup>8</sup>

Ruxolitinib has been studied in hemophagocytic lymphohistiocytosis (HLH). Two groups have shown a therapeutic effect of JAK inhibition with ruxolitinib in murine models of HLH.<sup>9,10</sup> Ruxolitinib operates in these models in an IFN- $\gamma$ -dependent manner to reduce inflammation-associated anemia and also in an IFN- $\gamma$ -independent manner to decrease numbers, activation, and migration of T cells and neutrophils.<sup>11</sup> The efficacy of ruxolitinib for the treatment of refractory/relapsed HLH was assessed in 34 patients.<sup>12</sup> The overall response rate was 73.5% (25/34 patients), with 14.7% (5/34 patients) in complete response and 58.8% (20/34 patients) in partial response. An open-label trial of ruxolitinib in seven patients with secondary HLH (including one patient with underlying AOSD), 2-month overall survival of 100% was reported, with a median follow-up of 490 days.<sup>13</sup> An additional study reported the feasibility of ruxolitinib combined with doxorubicin, etoposide, and dexamethasone for the lymphoma-associated hemophagocytic syndrome.<sup>14</sup>

This case has been refractory to both IL-1 and IL-6 inhibition but has responded miraculously to ruxolitinib. This may suggest that blocking a single cytokine pathway may be insufficient in controlling the production and activity of the other cytokines that propagate the immune-mediated damage. Therefore, JAK inhibition is an appealing target for the treatment of hypercytokinemia. JAK inhibition represents a broad mechanism of action, as JAKs are expressed on numerous immune cell lineages, including myeloid, lymphoid, dendritic, and CD561 NK cells, and mediate signaling of multiple cytokines, including IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-12, IL-10, IL-15, IL-21, granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor.<sup>15,16</sup>

Anecdotal use of JAK inhibitors in AOSD has been reported. Baricitinib, a JAK1/2 inhibitor, has been reported to be effective in a 43-year-old patient with refractory AOSD (interestingly in combination with anakinra).<sup>17</sup> Tofacitinib, a JAK 1/3 inhibitor, has been reported to contribute to disease remission/resolution allowing the reduction of corticosteroid dose in 14 patients with refractory AOSD.<sup>18</sup>

In summary, considering the pathophysiological similarities between MAS and AOSD, the broad mechanism of action of ruxolitinib, its remarkable activity in other hyperinflammatory diseases, and its effectiveness in secondary HLH of variety etiologies seems that ruxolitinib

is especially promising for the treatment of cases of MAS complicating AOSD, particularly for resistant ones. We believe that the miraculous effect of ruxolitinib, in this refractory case, strongly supports this promise. It is also encouraging to explore treatment with other JAK inhibitors, particularly selective JAK1/2, in treating AOSD.

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**Peer-review:** Externally peer-reviewed.

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