

### EDITORIAL

#### **The paradox of macrophage activation syndrome triggered by biologic medications.**

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Macrophage activation syndrome (MAS) is a life-threatening complication of childhood rheumatic diseases, particularly systemic juvenile idiopathic arthritis (S-JIA), which is characterized by fever, hepatosplenomegaly, lymphadenopathy, profound depression of all three blood cell lines, deranged liver function, intravascular coagulation, and central nervous system dysfunction. [1] The diagnostic hallmark of the syndrome is found in the bone marrow aspiration, which reveals widespread signs of macrophage hemophagocytosis.

The clinical and pathologic manifestations of MAS are thought to result from the activation and uncontrolled proliferation of T-lymphocytes and well-differentiated macrophages, which leads to an unrestricted release of inflammatory cytokines, such as TNF- $\alpha$ , interleukin-1 and interleukin-6. The cause of the immunologic derangement in MAS is unknown. Recently, markedly decreased natural killer cell function and, in some cases, depressed perforin expression have been identified in patients with S-JIA and it has been suggested that these abnormalities may explain the distinctive susceptibility of these patients to the development of MAS. [2-3]

MAS is a serious condition that is associated with considerable morbidity and high risk of fatal outcome. Early diagnosis and immediate therapeutic intervention are, therefore, critical. The treatment of MAS has traditionally been based on the administration of high-dose corticosteroids and, more recently, cyclosporine A. [1] The demonstration that TNF- $\alpha$  may play a central role in the pathogenesis of the clinical and laboratory manifestations of the syndrome and the observation that increased serum levels of this cytokine occurs in the acute phase of MAS have provided the rationale for proposing inhibition of TNF- $\alpha$  as a way to reduce the consequences of the excessive activation of macrophages. [1] Prahalad et al reported a dramatic clinical response to etanercept in a 7-year-old boy with a S-JIA-like syndrome and MAS who responded to high-dose corticosteroid therapy, but experienced two episodes of acute clinical deterioration after the reduction of the dose of corticosteroids. [4] The favorable outcome in this patient led to suggest that TNF antagonists

represent an effective adjunctive therapeutic agent in MAS.

This important therapeutic achievement has been subsequently challenged by the description of a case of MAS apparently triggered by an anti-TNF agent. Ramanan and Schneider reported a 4.5-year-old girl with S-JIA who developed, after 4 doses of etanercept, a mildly pruritic giant urticarial rash adjacent to the injection sites and, 4 days later, a diffuse urticarial rash associated with improvement in arthritis symptoms, but laboratory evidence of MAS. [5] In the absence of a flare of systemic disease, an identifiable infection, or any other recent change in medication, etanercept was considered the most likely inciting factor.

In this issue of the Pediatric Rheumatology Online Journal, Lurati et al describe an 18-year-old girl with S-JIA who developed MAS during therapy with another biologic medication, the recombinant interleukin-1 receptor antagonist anakinra. [6] The syndrome occurred after the 10th dose of the drug and no evidence of other triggering factors, notably infection, was found. While writing this commentary, we have also admitted a 15-year-old boy with S-JIA who developed a full-blown MAS episode during treatment with anakinra.

These observations contrast with the recent anecdotal evidence regarding the excellent response of resistant S-JIA patients to anakinra therapy. [7-10] In addition, one of these resistant S-JIA patients had an episode of MAS which responded partially to corticosteroids, cyclosporine A, and VP-16. [9] This episode occurred before the start of anakinra. Interestingly, anakinra treatment appeared to lead to improvement not only in the systemic and joint symptoms of the underlying disease, but also in the residual laboratory abnormalities of MAS.

How does one explain the paradoxical occurrence of MAS during treatment with medications that are designed to antagonize the cytokines believed to be responsible for its development? Because MAS may represent the severe end of the spectrum of a very active systemic disease, one possible explanation is that the biologic agent was unable to control the disease activity and, thus, to prevent MAS. Systemic JIA is one of the more difficult forms of JIA to manage and it is known that a number of patients may not respond adequately to biologic therapies. [11] Alternatively, the syndrome might have been triggered by a drug-related toxic effect, similarly to what has been observed for other antirheumatic medications, including nonsteroidal antiinflammatory drugs, parenteral gold salts, sulfasalazine, and methotrexate. [1] A further hypothesis is that MAS was induced by an undetected infection. It is known that biologic therapies may increase the susceptibility to infection, including those that may trigger MAS. Notably, instances of MAS in patients on biologics in whom a viral infection, rather than the drug, was found to be the inciting factor have been described. [12-13]

In conclusion, the reported instances of MAS during treatment with biologic medications suggest that the administration of these agents may occasionally induce (or be associated with) this complication in patients with S-JIA. It is, however, important not to generate undue alarm about the safety of these drugs in this subset of JIA patients. The introduction of biologics holds great

promise in the management of this often aggressive and challenging form of JIA. [10,14] Simply, these observations should serve as a reminder that patients with S-JIA are uniquely susceptible to the development of this potentially serious complication and that, therefore, they deserve very careful clinical monitoring for MAS. The recently published preliminary diagnostic guidelines for the syndrome represent a valuable clinical tool to facilitate timely diagnosis and prompt therapeutic intervention. [15]

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