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**COMMENTARY**

# Intravenous Anakinra for Macrophage Activation Syndrome May Hold Lessons for Treatment of Cytokine Storm in the Setting of Coronavirus Disease 2019

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Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are increasingly recognized as being on a continuum of cytokine storm syndromes, with different initiating pathways culminating in cytotoxic dysfunction and uncontrolled activation and proliferation of T lymphocytes and macrophages. The activated immune cells produce large amounts of proinflammatory cytokines, including interleukin 1β (IL)-1β. Management depends on the recognized diagnosis. In the setting of a cytokine storm syndrome and infection, collaborative involvement of specialists, including infectious disease and rheumatology is ideal. Anakinra, a recombinant IL-1 receptor antagonist, has been used subcutaneously and intravenously in pediatric patients and is considered a first-line treatment for MAS and secondary HLH (sHLH) among many pediatric rheumatologists. Previous reports of anakinra used in adults for treatment of MAS or sHLH are limited to subcutaneous administration. In this issue, Moneagudo et al. present a series of adult patients with sHLH treated with intravenous anakinra, including patients in whom subcutaneous anakinra was insufficient. As the authors suggest, there is a potential therapeutic use for anakinra in sHLH or the cytokine storm syndrome triggered by COVID19. Trial design will be key, with the patient subpopulation, timing of intervention, and doses tested important.

Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are increasingly recognized as being on a continuum, with different initiating pathways culminating in cytotoxic dysfunction and uncontrolled activation and proliferation of T lymphocytes and macrophages. The activated immune cells produce large amounts of proinflammatory cytokines, including interleukin 1β (IL)-1β and interleukin 6 (IL-6), creating a cytokine storm (1,2). HLH can be familial (primary) or acquired (secondary to conditions such as infection, malignancy, or active autoimmune or autoinflammatory disease). Secondary HLH (sHLH) in association with autoimmune or autoinflammatory disease is referred to as MAS. Forms of sHLH have a lower mortality rate than primary HLH (pHLH). However, without early recognition and effective intervention, sHLH is also lethal. MAS and HLH are very rare conditions, but they may be under-recognized. The HLH-2004 criteria are insensitive to sHLH in association with chronic inflammatory diseases, often identifying patients too late in the disease course (3). In effort to attain earlier diagnosis, the diagnostic criteria was broadened to capture both pHLH and sHLH (1), and new classification criteria specifically for MAS complicating systemic-onset juvenile idiopathic arthritis were developed (4). Despite these changes in the diagnostic criteria, recognition of sHLH remains challenging because clinical and laboratory features overlap with other more common syndromes of cytokine storm, including systemic-onset inflammatory response syndrome and multiorgan dysfunction syndrome. Diagnostic tests for pHLH include functional assessment of lymphocyte cytotoxicity and guided genetic testing. These may also be useful for detecting potential genetic predisposition to sHLH, but pending results must not delay the initiation of treatment (5,6).

Management of MAS/HLH depends on the recognized diagnosis. Those with pHLH have a risk of recurrence and are not likely to survive long-term without hematopoietic cell transplantation (HCT). In the setting of sHLH associated with rheumatic disease (ie, MAS), rheumatologists are on the front line. Increasingly, rheumatologists are involved in the management of sHLH without

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associated rheumatic disease because there have been good outcomes evident with immunotherapies that rheumatologists use routinely, and these therapies are less toxic than the chemotherapeutic therapies required to treat pHLH (7,8). Management of sHLH is more varied and depends on the extent of inflammation and severity, the likelihood of concomitant infection, and the trigger (when known). Particularly with sHLH, collaborative involvement of specialists, including infectious disease, rheumatology, and hematology/oncology specialists, is ideal (9). Immunotherapy to address the abnormal immune activation was first incorporated into the management of pHLH as part of the HLH-94 protocol (7). HLH-2004 added intrathecal methotrexate and corticosteroids in select patients (3). In 2018, the FDA approved the cytokine-targeting therapy emapalumab, an interferon γ–blocking antibody, for patients with refractory, recurrent, or progressive pHLH or patients with an intolerance to conventional therapy. For patients with pHLH and any patients with severe and persistent or reactivated HLH, subsequent HCT is recommended. However, HCT is rarely indicated in MAS/sHLH.

To date, there are no completed randomized controlled trials for management of sHLH or MAS. Cytokine-directed therapies have the potential to target the effector molecules of MAS/sHLH without the myelosuppressive side effects of chemotherapeutic therapies. Interleukin 1 (IL-1) has been targeted in MAS in the setting of systemic-onset juvenile idiopathic arthritis and adult-onset Still disease. Anakinra, a recombinant IL-1 receptor antagonist, has been used both subcutaneously and intravenously in pediatric MAS/sHLH and is considered a first-line treatment for MAS/sHLH among many pediatric rheumatologists (9,10). Fewer reports of anakinra for treatment of sHLH/MAS in adults have been published, and these are limited to the use of anakinra given by subcutaneous (SQ) administration (8,11). In this issue, Monteagudo et al are the first to present a series of adult patients with sHLH/MAS treated with intravenous (IV) anakinra (12). The authors describe the clinical course and outcome of IV anakinra therapy in five adult patients with sHLH seen over a period of 3 years. Four patients who were refractory to other therapies, including SQ anakinra, showed remarkable improvement in laboratory and clinical parameters with IV anakinra doses of up to 2400 mg/d. The study has limitations typical of a single-center retrospective case review. However, the report is pivotal because it provides data to support additional prospective studies of IV anakinra for treatment of sHLH in adults.

Understandably, there is reticence to use immunomodulation in moderately or critically ill patients with possible or known infection. Among anticytokine therapies, anakinra is appealing in this situation because it has a relatively short half-life and can be discontinued quickly if an adverse effect occurs or concern for worsening infection arises. In general, withholding immunosuppressive biologics during infection is the most prudent course of action, although there is one clear exception to this approach. Continuation of IL-1 targeting therapy is favored over discontinuation in the setting of infection in patients with cryopyrin associated periodic fever syndrome (CAPS). In a study of the long-term safety of anakinra in children and adults with CAPS, continued anakinra treatment during infections prevented disease flares without complicating the course of infections (13). This exception might also apply in the setting of critical illness and cytokine storm.

The safety of SQ anakinra has already been established in children and adults (13). Safety data for IV anakinra comes from a large prospective randomized double-blind, placebo-controlled multicenter trial in adult patients with severe sepsis or septic shock (n = 696) who received standard supportive care and antimicrobial therapy for sepsis in addition to IV anakinra or placebo (14). Up to 3500 mg/d (100 mg bolus, followed by 2 mg/kg/h) IV anakinra given over 72 hours was well tolerated. Moreover, there was no increase in adverse reactions or microbial superinfections attributable to anakinra treatment (14). The ability to switch from SQ to IV administration of anakinra and to safely increase the dose to effect in patients in whom SQ therapy is insufficient is also appealing. As illustrated in the report by Monteagudo et al, the therapeutic range is broad, with some patients requiring higher doses of therapy (15). In the manufacturer's prescribing information for anakinra, the sepsis trial is mentioned, but there are no instructions regarding IV administration. Monteagudo et al discuss important details regarding IV administration of anakinra (12). To ensure safe and effective administration, when using IV anakinra, the treatment must be carried out in close consultation with pharmacy and nursing staff.

The report by Montegudo et al is timely. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID19), has tropism for the lungs, in which the cytokine storm also appears to wreak havoc. Anti-IL-1 therapy may help calm the storm and possibly prevent progression to respiratory failure. As the authors suggest, there is a potential therapeutic use for IV anakinra in sHLH triggered by COVID19. Sobi, the manufacturer of anakinra, has announced that trials of anakinra and emapalumab for use in COVID19 are in development. Trials of IL-6 targeting therapies are also underway. Although both IL-6 and IL-1β are increased in cytokine storm syndromes, in any given storm, it is unclear whether one cytokine should be targeted before another. Trial design will be key, with the patient subpopulation and timing of intervention important. For example, a prospective trial of IL-1 or IL-6 targeting therapy in patients with COVID19 who are moderately ill (hospitalized but not in respiratory failure), powered to use features of sHLH/MAS for mortality risk assessment would be ideal (16).

We are all hopeful for positive results for the trials that are in rapid development or already underway for the cytokine storm in COVID19. The first randomized placebo-controlled trial of anticytokine therapy for the treatment of MAS/sHLH in children and adults will also be completed soon (NCT02780583). Understanding genetic HLH and monogenic forms of autoinflammatory disease are informing our understanding of who may be more at risk for manifesting sHLH (17). With biosample collection as an increasingly integral part of clinical trial design and

further technological advances, we can also be hopeful that data collected in MAS/sHLH and COVID19 studies will enable the possibility of identifying individuals at higher risk for severe cytokine storm syndromes early in a course of illness.

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