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Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome

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Objective. The objective of this study was to report the benefit of a therapeutic approach consisting of intravenous (IV) continuous anakinra (recombinant human interleukin-1 receptor antagonist) infusions in treating severely ill adult patients with secondary hemophagocytic lymphohistiocytosis or macrophage activation syndrome (MAS).

Methods. A retrospective chart review of five patients treated at Regions Hospital from 2016 to 2019 was conducted. Demographic, clinical, and laboratory characteristics and outcomes were recorded.

Results. Continuous IV anakinra infusions up to 2400 mg/d resulted in rapid serologic, then clinical response in 4 of 5 severely ill patients who were refractory to all other therapies, including subcutaneous anakinra. Subsequently, 3 of 5 patients have been maintained on anakinra or canakinumab, with no recurrence of MAS.

Conclusion. Continuous infusion of IV anakinra may result in rapid serologic and subsequent clinical improvement in adult patients with MAS. This method for treating cytokine storm should be considered in the current COVID-19 pandemic in the subgroup of patients with severe disease who have a cytokine storm presentation.

INTRODUCTION

Histiocytic and other immune activation syndromes present diagnostic and therapeutic challenges because of significant overlap in their pathophysiological and clinical presentation with other inflammatory and infectious syndromes 1,2.

Hemophagocytic lymphohistiocytosis (HLH), a rare disorder more commonly reported in pediatric literature but increasingly recognized in adults, is a syndrome of immune activation and resultant inflammation 2,3. In HLH, early recognition and prompt treatment with immunomodulating therapies is almost always required to prevent progression of multisystem organ failure and death 2,3.

Although similar in their inflammatory pathophysiology, primary HLH, a familial or genetic syndrome, and secondary HLH (sHLH), usually triggered by infectious, rheumatologic, or hematologic/oncologic syndromes, are recognized as separate subsets of the disease spectrum 4-6. Macrophage activation syndrome (MAS) is a subset of HLH often associated with rheumatologic diseases. Unlike sHLH, which occurs with malignancy and infection, MAS may occur with systemic autoimmune diseases, including systemic lupus erythematosus (SLE), adult-onset Still disease (AOSD), and systemic juvenile idiopathic arthritis (sJIA) 7. MAS associated with underlying rheumatic conditions can be triggered by infections, such as Epstein-Barr virus and varicella zoster virus, in up to one-third of patients 8.

Immunologically, MAS is defined by a cytokine storm leading to an unregulated systemic hyperinflammation and rapidly progressive multisystem organ failure. The molecular mechanism for this immune system dysregulation is under active investigation. Proposed hypotheses include defects in cytolytic activity 9 leading to a system-wide pro-inflammatory cytokine environment rich in interleukin 6 (IL-6) and triggering a pro-inflammatory cytokine cascade 5,10, resulting in high levels of interleukin 1 (IL-1), IL-6, interleukin 18 (IL-18), soluble interleukin 2 receptor (sIL-2R), tumor necrosis factor (TNF), and interferon γ 11. These cytokines allow for unchecked activated macrophage entry into tissue, ultimately leading to hemophagocytosis.

The clinical presentation of MAS usually includes high, persisting, and unremitting fevers; generalized malaise; and signs and symptoms of multisystem organ dysfunction. In such patients, evaluation is usually directed at infection and malignancy. However, consideration of MAS and prompt evaluation for abnormalities associated with MAS should always be undertaken, particularly in patients who are atypical or who do not respond quickly to therapy. For example, markedly elevated transaminase, triglycerides, lactate dehydrogenase, and ferritin levels will suggest a diagnosis of MAS. The ferritin level is nearly always elevated to a significant degree, with a median value of 9094 ng/ml 4. The erythrocyte sedimentation rate (ESR) is typically low 4. The diagnosis of MAS is often delayed because of the lack of widely accepted diagnostic criteria

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specific to this disease 12. In addition, the lack of a true guideline-directed therapy for MAS results in high mortality 6. As such, early diagnosis and rapid initiation of therapies aimed at reducing systemic inflammation is critical to the management of MAS.

Treatment initiation for MAS generally starts with high-dose glucocorticoid monotherapy, with the subsequent use of additional immunosuppressive agents in refractory cases 6,13,14. In particularly resistant cases, the HLH-2004 protocol may be followed 14. However, it should be noted that the HLH-2004 protocol is built on the initial work of the HLH-94 study, which specifically sought to exclude cases of HLH secondary to malignancy or rheumatologic processes. This protocol uses high-dose glucocorticoids as well as both systemic (etoposide and/or cyclosporine) and intrathecal (if central nervous system involvement) therapies with a goal ultimately of hematopoietic stem cell transplant to cure familial cases in pediatric patients 15,16. Clinicians often find, however, that these therapeutic options are not adequate, and mortality in adult secondary HLH has been reported to be as high as 66% to 74% 17,18.

Over the past few years, with the advent of biologics and immunotherapies, case reports have described other therapeutic options for MAS, including intravenous immunoglobulin (IVIG) and biologics targeting different phases of the cytokine cascade 6. Anakinra, a recombinant IL-1 receptor antagonist, is currently US Food and Drug Administration (FDA) approved for the treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease. Despite its FDA designation, anakinra is used off label to treat a variety of autoinflammatory diseases. Although limited, there are now case reports and series showing both sIJA-related MAS 19-22 and other HLH secondary subtypes 22-27 responding favorably to anakinra. As such, it appears that anakinra may be viewed as an emerging and effective therapy in the treatment of MAS. The current literature regarding anakinra use in MAS, particularly as it pertains to adult cases, is limited, and further information regarding its effectiveness and potential clinical benefits and risks is needed. As such, we present a case series of our experience using an approach of continuously infused intravenous (IV) anakinra for refractory MAS in a level 1 tertiary care academic center over a 3-year period.

MATERIALS AND METHODS

This is a single-center, cross-sectional retrospective chart review using the electronic medical record at Regions Hospital, a level 1 tertiary care academic medical center in Saint Paul, MN. Five consecutive patients admitted to our hospital between 2016 and 2019 with a diagnosis of MAS were included. The diagnosis of MAS was made using the HLH-2004 criteria, which require five of the eight following findings: fever greater than or equal to 38.5°C, splenomegaly; peripheral blood cytopenias (at least two of the following: hemoglobin level less than 9 g/dl, platelet count less than 100 000 cells per µl, and absolute neutrophil count less than 1000 cells per µl); hypertriglyceridemia (fasting triglyceride level greater than 265 mg/dl) and/or hypofibrinogenemia (fibrinogen level less than 150 mg/dl); hemophagocytosis in the bone marrow, spleen, lymph node, or liver; low or absent natural killer cell activity; ferritin level greater than 500 ng/ml; and elevated soluble CD25 levels (sIL-2Rα) two SDs above age-adjusted laboratory-specific norms. Ferritin, ESR, C-reactive protein, creatinine, white blood cell count, hemoglobin, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, triglycerides, CD25, fibrinogen, soluble CD163 (when available), IL-1 (when available), and IL-6 (when available) were extracted and analyzed. The organ systems affected and the clinical course of each patient were described. Each patient's therapeutic approach was documented. Table 1 describes patient characteristics.

Patient consent rules were followed as per the instructions of the HealthPartners Institutional Review Board.

RESULTS

General characteristics. Five patients were admitted to our hospital and diagnosed with MAS between 2016 and 2019. Four were female and one was male. The mean age at the time of diagnosis was 44, with a range of 38 to 64. The initial presenting symptom of all patients was fever. Four of the five patients had an identified underlying autoimmune disease, including undifferentiated connective tissue disease (n = 1), SLE (n = 2), and AOSD (n = 1). One of the five patients did not have a history of autoimmune disease.

All five patients fulfilled the HLH-2004 criteria, including fever with peak temperature of more than 38.5°C for more than 7 days (n = 5), cytopenia involving two cell lines (n = 5), cytopenia involving three cell lines (n = 4), hypertriglyceridemia (n = 5), decreased fibrinogen activity (n = 3), serum ferritin level greater than 500 ng/ml (n = 5), elevated sIL-2R level (n = 5), and splenomegaly (n = 1).

Patients had tissue biopsies performed. Three patients had bone marrow biopsies, two of which showed evidence of hemophagocytosis. One patient had a liver biopsy, which showed hemophagocytosis. Two patients had renal biopsies; one showed findings consistent with acute tubular necrosis, and the second showed collapsing-type focal segmental glomerulosclerosis. Two patients had lymph node biopsies performed; both were nondiagnostic. Cytomegalovirus (n = 1) and human herpesvirus 6 (n = 1) were identified as potential infectious triggers. The remaining three patients had no identifiable infection. None of the patients were found to have an underlying malignancy.

When initial therapy was ineffective, all patients (n = 5) received continuous anakinra infusion with rapid dose escalation up to a maximum of 2400 mg in total daily dose infused over 24 hours. Immunotherapies previously administered included methylprednisolone (n = 5), tocilizumab (n = 1), IVIG (n = 1), cyclophosphamide (n = 1), and cyclosporine (n = 3).

Table 1. Patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years/sex	39/male	47/female	34/female	64/female	34/female
Duration of treatment in hospital, d	34	18	50	49	48
Previous therapies	Methylprednisolone	Methylprednisolone, hydroxychloroquine, cyclosporine	Methylprednisolone, hydroxychloroquine, cyclophosphamide	Methylprednisolone, cyclosporine	Methylprednisolone, IVIG, tocilizumab, cyclosporine
Underlying autoimmune disease	None	SLE	SLE	AOSD	UCTD
Fever	Yes	Yes	Yes	Yes	Yes
Lowest Hemoglobin concentration, g/dl	5.7	6.7	6	5	6
Lowest white blood cell count, ×1000 cells per ul	0.3	1.1	2	0.3	0.6
Lowest platelet count, ×1000 cells per ul	30	16	98	16	9
Peak triglyceride concentration, mg/dl	416	391	315	429	176
Lowest fibrinogen concentration, mg/dl	80	77	290	147	90
Peak ferritin concentration, mg/dl	153 534	523 213	27 529	69 960	80 083
Peak AST, U/l	2089	686	456	1350	1506
Peak ALT, U/l	834	191	302	3048	1294
Peak soluble IL-2 receptor concentration, U/ml	8280	100 600	12 880	5070	7320

Abbreviations: ALT, alanine aminotransferase; AOSD, adult-onset still disease; AST, aspartate aminotransferase; IL-2, interleukin 2; IVIG, intravenous immunoglobulin; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease.

Anakinra dosing. Patients were started on anakinra, either continuous infusion (n = 3) or subcutaneous injection (n = 2). The starting total daily dose was 100 mg (n = 2), 300 mg (n = 1), or 400 mg (n = 2). All patients were transitioned to continuous IV infusion with worsening clinical status. The total daily dose was then increased in varying increments, between 100 mg and 800 mg daily, depending on serologies and clinical course. High total daily dose of anakinra was achieved in all patients at doses of 400 mg (0.25 mg/kg/h) (n = 1), 2400 mg (1.5-2 mg/kg/h) (n = 3), and 1200 mg (n = 1). The patient who received 1200 mg daily had renal failure; therefore, his dosage was reduced by 50% from 2400 to 1200 mg daily based on pharmacokinetics 28. Upon reaching clinical and serologic improvement on maximal dosing of anakinra, the total daily dose was cautiously decreased over a period of approximately of 3 weeks, until the disease was stable on 100 mg of subcutaneous anakinra or until the patient was transitioned to canakinumab.

Ferritin course with response to anakinra. All five patients had elevated ferritin levels greater than 500 ng/ml. The mean peak ferritin level was 167 321 ng/ml, with a peak range of 27 529 to 523 213 ng/ml. Ferritin levels increased by at least 60% daily in the 48 hours prior to the start of anakinra infusion in four of five patients. Ferritin levels peaked and decreased within 48 hours of reaching anakinra infusion of 400 mg (n = 1), 1200 mg (n = 1), and 2400 mg (n = 2). The ferritin level continued to rise in one patient and peaked at 523 213 ng/ml on the day of death due to septic shock despite the use of 2400 mg daily of anakinra.

Hepatobiliary course with response to anakinra. Patients had AST levels at least nine times the upper limit of normal (n = 5). The mean peak AST level was 989 U/l. The peak range was between 365 and 2089 U/l. Patients had ALT levels at least three times the upper limit of normal (n = 5). The mean peak ALT level was 1123 U/l. The ALT peak range was between 139 and 3048 U/l. Three patients did not have an elevation in direct, indirect, or total bilirubin levels. Two patients had elevations in direct and total bilirubin levels. One patient had a direct bilirubin level greater than 13 mg/dl and a total bilirubin level of 27.4 mg/dl. Both the ALT and AST levels peaked and decreased within 48 hours of the start of anakinra infusion in four of five patients. Despite rapid uptitration of anakinra to 2400 mg in total daily dose, the AST, ALT, and direct bilirubin levels continued to rise in one patient on the day of death due to septic shock.

Cytopenia course with response to anakinra. Four of five patients became leukopenic (white blood cell count less than 4 × 10 g/dl). Leukopenia improved upon decrease of anakinra dosing in three of the four patients. Four of five patients became thrombocytopenic (platelet count less than 150 × 10 g/dl). Three of these four patients had an improvement in platelet count with decreasing doses of anakinra. All five patients became anemic, with hemoglobin levels less than 13.5 g/dl for men (n = 1) and 12 g/dl for women (n = 4). Hemoglobin levels improved in only one patient with decreasing doses of anakinra.

Cytokine profile. sIL-2R levels were obtained in all patients (n = 5). The mean peak sIL-2R level was 26830 pg/ml. The peak range was between 5070 and 100600 pg/ml. CD163 levels were obtained in four of five patients. The mean peak soluble CD163 level was 6566 ng/ml. The peak range was between 2831 and 16215 ng/ml. IL-1 levels were checked in two patients and were less than 5 pg/ml. IL-6 levels were checked in three of the five patients. The mean peak IL-6 level was 303 pg/ml. The peak range was less than 5 to 245 pg/ml. The IL-18 level (Cincinnati Children's Diagnostic Immunology Laboratory) was checked in one patient and was elevated at 579 pg/ml.

Renal injury with response to anakinra. None of the patients had known chronic kidney disease prior to admission for MAS. Three of the five patients developed an acute kidney injury, defined as a creatinine level increase of 0.3 mg/dl or greater from baseline. Creatinine levels continued to rise until peaking within 96 hours of the start of anakinra infusion (n = 3). Creatinine levels improved with anakinra taper (n = 3). A renal biopsy was obtained in two patients and showed acute tubular necrosis (n = 1) and collapsing-type focal segmental glomerular sclerosis (n = 1). No patients required hemodialysis.

Clinical complications and outcomes. Four of five patients had rapid serologic and clinical and serologic improvement of MAS on anakinra, and three are doing extremely well. One patient had progressive multisystem organ failure with rising ferritin and sIL-2R levels despite anakinra at 2400 mg daily. After clinical and serologic improvement, the dose of anakinra was tapered over a period of weeks in three patients, and they were able to be discharged home on either anakinra (n = 1) or canakinumab (n = 2). Anakinra was continued daily for 1 year after discharge in one patient and then discontinued. She continues to do well after 2 years. Canakinumab was continued monthly for 6 months in one of the two patients before being transitioned to once every 2 months. The third patient is 3 months from hospital discharge for MAS on monthly canakinumab. None of these patients have had a return of features of MAS to date.

Three of five patients developed gram-negative bacteremia during their clinical course. One of these never achieved control of her MAS and died of multiorgan failure and septic shock. The second patient did achieve some control of the hyperinflammation but subsequently became septic and died. As stated, the other three patients continue to do very well. Other clinical complications included spontaneous retroperitoneal bleeding (n = 1), pulmonary embolus (n = 1), and cholecystitis (n = 1).

DISCUSSION

Patients with MAS present with a broad range of clinical features that often mimic other processes, resulting in a delay in diagnosis and treatment for this frequently life-threatening disease. Similar to cohorts noted in the literature, the five patients in our review presented with fever (n = 5) 29 and were admitted to the ICU (n = 5) 17-18,30,31. Underlying SLE and AOSD was present in three of the five patients, consistent with findings that these diseases are common among patients with MAS 32. A fourth patient had undifferentiated connective tissue disease. One patient did not have an established underlying autoimmune disease, and further workup of this patient did not identify malignancy or infection.

The hallmark of MAS is massive immune system activation and an unregulated inflammatory response. This is characterized serologically by elevated serum ferritin and cytokine levels. IL-1, IL-2, IL-6, IL-18, interleukin 33, TNF, and interferon γ have been implicated in this inflammatory cytokine cascade 10. Consistent with this, sIL-2r (n = 5) and sCD163 (n = 4) levels were elevated when checked in our study population. Levels of IL-1β and IL-6 were not checked in all patients. When obtained, they did not correlate with clinical disease activity. IL-18 was checked in one patient, and the level was elevated.

A distinguishing feature of MAS is the magnitude of the elevation of ferritin levels, with an average of 14242 µg/l in patients with MAS, compared with 2647 µg/l in patients with malignancy and iron overload syndromes 33. All five patients in this study had elevated ferritin levels consistent with MAS, with an average peak ferritin level of 167321 µg/l.

Given the underlying pathophysiology of MAS, the intent of the first phase of therapy should be to halt immune system activation and cytokine propagation as quickly as possible. However, there are no accepted guidelines for the treatment of adult HLH with anakinra. Although the HLH-2004 induction protocol can be used, patients with MAS often do not respond 34. As occasionally reported in treatment studies of pediatric patients with sJIA, anakinra may be used 35. Recent work by Eloseily et al 22 supports the use of anakinra in treating pediatric patients with non–malignancy-associated secondary HLH, particularly when given early in the disease course and when administered to patients who have underlying rheumatic disease. Treatment with anakinra was associated with improved overall survival in comparison with patients who received etoposide-based protocols. Earlier treatment with anakinra, in the first 5 days of hospitalization, was associated with a statistically significant reduction in mortality. Although promising, there is some hesitation about broad application of IL-1 blockade in cases of secondary HLH not due to underlying autoimmune disease 36 because secondary HLH remains a very heterogenous disease. As further divisions in clinical, serologic, and genetic profiles of patients with secondary HLH are established, targeted therapy algorithms for different phenotypes may be established.

Data on the use of anakinra in the treatment of adult MAS, and particularly the dosing required, are sparse. There is only one representative case report in the literature describing higher doses of 600 mg daily for the treatment of MAS presenting as fulminant liver failure in an adult 37. Experience with anakinra dosing

above this level, and particularly continuous IV infusion of anakinra to treat the cytokine storm associated with MAS, has not been previously described.

We demonstrate that rapid escalation of therapy once MAS is evident, using continuous IV anakinra infusions in higher doses, can successfully reverse the cytokine storm (n = 4) unless it has been so firmly established that even that therapy is unsuccessful (n = 1). Prior to starting anakinra, the five patients in this study received a variety of immunomodulators during the course of their disease, including methylprednisolone(n = 5), tocilizumab (n = 1), IVIG (n = 1), cyclophosphamide (n = 1), and cyclosporine (n = 3). Despite these medications, the disease progressed. Given the poor prognosis and high mortality, all five patients were started on rapidly escalating anakinra dosing up to 2400 mg of continuous infusion daily, or the equivalent in cases of renal failure, to achieve autoinflammatory cytokine storm inhibition. The dose required was usually the equivalent of 1 to 2 mg/kg/h, similar to doses used in sepsis trials 38. Clinically, as well as by laboratory studies including ferritin, cell counts, liver function tests, fibrinogen, lactate dehydrogenase, and triglycerides, four of five patients had a remarkable response. One patient did not respond.

It is important to note that anakinra has a short/unclear stability in solution, so infusion bags are made to run for 8 hours at the longest. Pharmacists are reminded to avoid making the solution too concentrated/in too small of a volume to prevent having a significant portion of the drug left in the tubing. They are also reminded to build the compound to give a rate of no less than 5 ml/h. Concentration should be from 1 to 5 mg/ml. In addition, anakinra is light sensitive. Pharmacy instructions must include the following statement: “This product needs to be protected from light, including both the final container bag and the tubing.” The infusion bag is sent in an amber bag and nurses use 2 to 3 feet of covering for the tubing. Appendix I includes the Regions Hospital pharmacy protocol for IV anakinra infusions.

Side effects, as with any immunomodulating therapy, were noted with the use of anakinra and need to be watched for diligently. Cytopenias and renal injury occurred in five of five and three of five patients, respectively. It is unclear whether this was due to the known clinical course of MAS or due to high-dose anakinra. However, in one patient, the cytopenias developed after other laboratory values were improving and persisted while anakinra was continued, even as the dose was being lowered. When the dose was reduced to 100 mg daily, all hematologic abnormalities returned to normal. Three of five patients developed gram-negative bacteremia during their clinical course. Cytokine storm was successfully inhibited with anakinra in four of five patients. One patient never achieved control, with a rising ferritin level of 523213 ng/ml on the day of death due to sepsis. One patient improved serologically and clinically but later died of sepsis.

In summary, continuous IV anakinra in a rapidly escalating dose regimen in a cohort of adult patients with MAS with unregulated immune activation was successful at reversing cytokine storm when other modalities had failed. Gram-negative bacteremia might be associated with the length of time patients were on higher doses of anakinra because, in our experience, shorter courses in other patients and/or other diseases treated did not manifest similar problems. One might, however, consider prophylactic antibiotics if prolonged therapy will be necessary. As we gained experience with this modality, we were able to decrease the anakinra dose more quickly.

We believe this approach may have relevance to the current COVID-19 pandemic. A subgroup of patients with COVID-19 with severe disease may have a cytokine storm syndrome 39, and treatment with agents used for cytokine storm may be indicated. As discussed eloquently in a recent editorial, personalized approaches to the patients with MAS and other secondary HLH syndromes are necessary. Current data do not support a carte blanche approach to hyperinflammatory syndromes using anakinra. 36. Interestingly, however, a reanalysis of data from a phase 3 randomized controlled trial of IL-1 blockade (anakinra) in sepsis showed significant survival benefit in patients with hyperinflammation, without increased adverse events. 38,39. Currently, tocilizumab is being studied as a possible therapy. The rapid serological response, followed by clinical response, in the patients described herein was striking enough to suggest that continuous IV anakinra infusions might also be considered for cytokine storm in COVID-19 infection.

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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. Gertner 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. Gertner.
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APPENDIX 1: REGIONS HOSPITAL PHARMACY PROTOCOL FOR IV ANAKINRA INFUSIONS

For anakinra continuous infusion, prepare an IV piggyback bag made to accommodate the patient-specific dosing infusion rate for a 6- to 8-hour-duration infusion per bag. This allows each piggyback bag to be completed within the 8-hour stability limit of the product. The infusion rate should be no less than 5 ml/h. Based on the dose, the infusion rate, and time limit of infusion, back calculate using 100-mg increments of anakinra in 50 to 250 ml of 0.9% sodium chloride to a final concentration within 1 to 5 mg/ml. The product is light sensitive, and both the bag and the tubing should be protected from light for the duration of the infusion.