To the Editor,

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening hematological disorder characterized by uncontrolled activation of CD8+ T cells and NK cells, cytokine storm (including overproduction of interleukine-6 (IL6)), and uncontrolled hemophagocytosis leading to severe organ dysfunction [1]. Several causes of HLH have been identified, including infection, cancer, drugs, and autoimmune diseases [1]. Diagnosis of HLH is challenging, and the H-score may help to better identify patients with reactive HLH [2].

A combination of dexamethasone, etoposide, and treatment of the underlying cause is the cornerstone of treatment for severe forms of HLH [1]. Because some patients may develop refractory or relapsing HLH, alternative treatments targeting specific immune pathways or cytokine signaling have been tested [1]. These approaches also aim to avoid long-lasting etoposide-induced neutropenia in patients with bone marrow failure or after transplantation.

Tocilizumab, a monoclonal antibody targeting the receptor of IL6, fully reverses the multi-organ failure and the cytokine profile of the CAR-T cell-induced cytokine-release syndrome [3]. This prompted some groups including ours to treat severe HLH secondary to acute autoimmune disease with tocilizumab [4]. Targeting one of the major cytokines that orchestrate the cytokine storm may be an alternative to etoposide in patients with HLH not related to hematological malignancies.

In the herein study, we reviewed the outcomes of nine critically ill patients who received tocilizumab to treat HLH (Table 1). Eight of them received at least one organ support. Median H-score was 208 (probability of HLH according to the score, 92.5%), and all patients had at least 4 to 7 criteria of the modified 2009 HLH criteria (genetic testing and NK cell activity were not available; sCD25 was tested in one patient). Causes of HLH were multiples: autoimmune diseases in four, infection (bacterial or viral) in three, and idiopathic in two. In addition to tocilizumab (8 mg/kg once, intravenously), five patients received concomitant treatment with dexamethasone (n = 4), cyclophosphamide (n = 2), or intravenous immunoglobulins (n = 1). Remission was observed in 8/9 patients after tocilizumab (88.9%) whereas one developed refractory HLH, also unresponsive to rescue therapy with etoposide. Ferritin progressively decreased over the first 2 weeks (Fig. 1). One patient relapsed during the hospitalization and successfully received etoposide, but she ultimately died from unrelated gut ischemia. No patient developed profound neutropenia (< 500 cells/mm3), except one who had also received cyclophosphamide. During the hospitalization, four patients died (sepsis-related multi-organ failure n = 1; refractory HLH n = 1; organ support limitation n = 2). None developed HLH relapse beyond the current hospitalization. Cytomegalovirus prophylaxis was pursued at least 3 months in transplant recipients.

In critically ill patients with severe forms of HLH, etoposide rapidly reverses cytokine storm and improves...
clinical condition [1]. HLH 94 and 2004 protocols were
developed for children with primary HLH (50% successes),
but adult patients may be more at risk to develop chemo-
therapy toxicities [1]. Alternatives should thus be dis-
cussed in adult patients with chemotherapy-induced bone
marrow failure, underlying autoimmune diseases requiring
cytotoxic agents, or with a moderate form of HLH not re-
lated to hematological malignancies. In line with this need,
the JAK1/2 inhibitor ruxolitinib was tested in a mouse
model of genetic HLH. Its benefits were confirmed in pa-
tients with reactive HLH [5], but the oral administration
may preclude its pharmacokinetic in critically ill patients
requiring mechanical ventilation. Due to its intravenous
administration, tocilizumab may thus be a valuable alter-
native after ruling out on-going bacterial or fungal sepsis.

In conclusion, IL-6-R blockade with tocilizumab may
be an alternative in critically ill patients with moderate
forms of HLH. Whether such beneficial effects may also
be observed in the subset of patients with a cytokine-
related syndrome induced by the recently emerging
SARS-CoV2 virus remains to be addressed.

Table 1 Characteristics and outcomes of nine patients with hemophagocytic syndrome who received tocilizumab. M, male; F, female; CAPS, catastrophic antiphospholipid syndrome; TMA, thrombotic microangiopathy; PVB19, parvovirus B19; LGL, large granular
lymphocyte leukemia; HLH, hemophagocytic lymphohistiocytosis; DXM, dexamethasone; CYC, cyclophosphamide; IVIg, intravenous
immunoglobulins; AIHA, autoimmune hemolytic anemia; SCT, stem cell transplantation; MMF, mycophenolate mofetil; CsA, ciclosporin-A; CR, complete response; IS, immunosuppressive regimen; MV, mechanical ventilation; RRT, renal
replacement therapy; VD, vasopressor drugs; OSL, organ support limitations; mHLH2009, modified 2009 HLH criteria

| Age | Gender | Cause of HLH | Underlying immunodeficiency | On-going IS at the onset | H-score/mHLH2009 | Other HLH therapy | Organ supports | HLH response | Relapse | Outcomes |
|-----|--------|--------------|-----------------------------|------------------------|-----------------|-----------------|-----------------|--------------|---------|---------|
| 1   | 59     | Male         | Multiple autoimmune disorders*, TMA | Csf | 248(99.3%)/7 | DXM, CYC | MV, RRT, CR | No | Alive |
| 2   | 43     | Male         | Septicemia                 | Allogenic SCT          | Csf | 220(96.3%)/5 | No | MV, RRT, CR | No | Death (septic shock; OSL) |
| 3   | 23     | Female       | Idiopathic                 | Heart transplantation   | Tacrolimus, MMF, Csf, IVIg | 210(93%)/5 | No | RRT, CR | No | Alive |
| 4   | 60     | Male         | Infections (varicella zoster virus, parvovirus B19, HSV-2), septicemia | Heart transplantation | Tacrolimus, MMF, Csf | 188(78%)/5 | Etoposide | MV, RRT, CR | None | – | Death (septic shock, aspergillosis, refractory HLH) |
| 5   | 52     | Male         | Parvovirus B19 and CAPS    | No                      | No | 208(92.5%)/5 | IVIg, DXM | MV, RRT, CR | No | Alive |
| 6   | 53     | Male         | Idiopathic                 | Liver transplantation   | Tacrolimus, MMF, Csf | 18(79%)/5 | No | MV, RRT, CR | No | Alive |
| 7   | 66     | Female       | Overlap syndrome, TMA      | Csf | 186(75.8%)/5 | DXM | MV, RRT, CR | Yes (etoposide) | – | Death (gut ischemia; OSL) |
| 8   | 57     | Female       | Refractory AIHA            | T-LGL, B cell lymphoma | Dxm, CsA | 188(78%)/4 | CYC, DXM | MV, RRT, CR | No | Death (septic shock, refractory AIHA) |
| 9   | 25     | Female       | S. hominis bacteriemia, HSV-1 | Kidney and liver transplantation | Tacrolimus, MMF, Csf | 218(95.8%)/6 | No | – | CR | No | Alive |

*Patient 1 was described in reference [3]. He was first hospitalized for thrombotic microangiopathy associated with autoimmunity and symptoms of rheumatoid arthritis, anti-synthetase syndrome, systemic lupus erythematosus, cryoglobulinemia, and Sjogren syndrome

Fig. 1 Ferritin concentration after tocilizumab
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SF designed the study; ED collected the data; SF, NK, and ADB wrote the manuscript. All authors followed the patients. The authors read and approved the final manuscript.

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References
1. La Rosée P, Horne AC, Hines M, Greenwood TVB, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood Ame Soc Hematol. 2019;133:2465–77.
2. Fardet L, Galcier L, Lambotte O, Marzac C, Aumont G, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66:2613–20.
3. Fitzgerald JC, Weiss SL, Maude SL, Barrett DM, Lacey SF, Melenhorst JJ, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. Crit Care Med. 2017;45:e124–5.
4. Faguer S, Vergez F, Peres M, Ferrandiz I, Casemayou A, Belliere J, et al. Tocilizumab added to conventional therapy reverses both the cytokine profile and CD8+Granzyme+ T-cells/NK cells expansion in refractory hemophagocytic lymphohistiocytosis. Hematol Oncol. 2016;34(1):55–7.
5. Ahmed A, Merrill SA, Alsawah F, Bockenstedt P, Campagnaro E, Devata S, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. Lancet Haematol. 2019;6:e210–7.

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