BRIEF REPORT

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Ruxolitinib, IV Immunoglobulin, and High-Dose Glucocorticoids for Critically Ill Adults With Secondary Hemophagocytic Lymphohistiocytosis: A Single-Center Observational Pilot Study

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OBJECTIVES: Secondary hemophagocytic lymphohistiocytosis (sHLH) is a cytokine-driven inflammatory syndrome that is associated with substantial morbidity and mortality and frequently leads to ICU admission. Overall survival in adults with sHLH remains poor, especially in those requiring intensive care. Classical chemotherapeutic treatment exhibits myelosuppression and toxicity. Recently, inhibition of Janus kinase signaling by ruxolitinib has shown efficacy in pediatric HLH. We therefore aimed to determine the activity and safety of a ruxolitinib-based regimen, in critically ill adults with sHLH.

DESIGN: Observational pilot study.

SETTING: Single-center tertiary academic ICU.

PATIENTS: Nine adults (≥ 18 yr) who fulfilled at least five of the eight HLH-2004 criteria.

INTERVENTION: Triplet regimen combining: 1) ruxolitinib, 2) polyvalent human IV immunoglobulins (IVIG) at a dose of 1 g/kg bodyweight for 5 days, and 3) high-dose corticosteroids (CSs, dexamethasone 10 mg/m² body surface area, or methylprednisolone equivalent) with subsequent tapering according to the HLH-2004 protocol.

MEASUREMENT AND MAIN RESULTS: Nine patients (median age: 42 yr [25th-75th percentile: 32–54]; male: $n = 6$ males, median H-score: 299 [255–304]) were treated with the triplet regimen. The median Sequential Organ Failure Assessment score at HLH diagnosis was 9 (median; 25th–75th percentile: 7–12), indicating multiple-organ dysfunction in all patients. Within 10 days a significant decrease of the inflammatory parameters soluble interleukin-2 receptor and ferritin as well as a stabilization of the blood count could be shown. All patients were alive at ICU discharge (100% ICU survival), 1 patient died after ICU discharge because of traumatic intracerebral hemorrhage that might be related to HLH or treatment, corresponding to an overall survival of 86% in a 6 months follow-up period.

CONCLUSION: In this small case series, a triplet regimen of ruxolitinib in combination with IVIG and CS was highly effective and save for treating critically ill adults with sHLH.

KEYWORDS: critical illness; hyperinflammation; ICU; ruxolitinib; tophemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a rare condition of hyperinflammation caused by unrestrained, prolonged activation of immune cells. First cases were described in infants presenting with unremitting fever, hepatosplenomegaly, and cytopenia (1, 2). Adults most exclusively lack a positive family history or a classical HLH mutation, but frequently

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KEY POINTS

Question: Efficacy, and tolerability of ruxolitinib in combination with polyvalent immunoglobulins and high-dose glucocorticoids in critical ill patients with secondary hemophagocytic lymphohistiocytosis (sHLH).

Finding: All nine patients survived ICU (100% ICU survival) and one subsequent death after ICU discharge (86% overall survival). No severe adverse events were recognized.

Meaning: The ruxolitinib containing triplet regimen is an effective and well-tolerated option for patients with sHLH in the ICU setting.

have an underlying medical condition (hematologic malignancy, autoimmune disease, or immunosuppression). These conditions either initiate the syndrome or predispose for HLH in response to mainly infectious triggers (secondary HLH [sHLH]) (3). Irrespective of its causative factors, the cytokine storm unleashed by HLH leads to rapid multiple-organ dysfunction and death (4). Therefore, diagnosis and treatment of HLH often take place at ICUs (5). Interestingly, a HLH-like phenotype may occur in a subset of patients with sepsis referred to as sepsis–HLH overlap (6, 7). IV immunoglobulins (IVIG) and corticosteroids (CSs) are well tolerated and are regarded beneficial for HLH treatment (5, 8). However, the use of etoposide for sHLH treatment in adults is controversial (5). Although etoposide is considered standard for primary HLH, concerns in terms of efficacy and toxicity in adult sHLH settings have led to exploration of alternative treatments with better toxicity profiles (8–10).Recently, the Janus kinase (JAK) inhibitor ruxolitinib has been used to treat sHLH in adults with encouraging results (10). However, the current data are mainly from pediatric cohorts, and data on critically ill patients in the ICU are lacking (11).

Following first reports on ruxolitinib in HLH, we started to use ruxolitinib in combination with high-dose IVIG and high-dose corticosteroids to manage a series of critically ill adult patients with sHLH. In this report, we aim to analyze biomarker dynamics outcomes and safety aspects of these patients and share our experience with this regimen.

MATERIALS AND METHODS

We performed a single-center pilot study to investigate the activity and safety of a ruxolitinib containing regimen in critically ill patients with sHLH who were treated between January 1, 2018, and March 1, 2023 at the Medical University of Graz. The study was approved by the institutional review board (study title: "Therapielandschaft und Ergebnisqualität in der Therapie der Hämophagozytischen Lymphohistiozytose"; approval date: March 29, 2023; approval number: 35-290 ex 22/23) and conducted in accordance with the Declaration of Helsinki. Nine adult patients (≥ 18 yr) who fulfilled at least five of the eight HLH-2004 criteria for HLH were included (**File S1**, **Table S2**, http://links.lww.com/CCX/B297).

All patients received ruxolitinib, IVIG, and CSs as described in File S1 and **Figure S1** (http://links.lww.com/CCX/B297). The primary endpoint was overall survival after 6 months from diagnosis of sHLH.. Secondary endpoints were dynamics of HLH-related biomarkers (blood count, soluble interleukin-2 receptor [sIL2R], and ferritin) at day 10 and safety (absence of cytopenia after 10 days, bleeding, neurologic signs [headache, vertigo], gastrointestinal complications [emesis, diarrhea] and recurrent infections).

RESULTS

We treated nine patients with the triplet regimen. Eight patients had an underlying cause for HLH (**Table S1**, http://links.lww.com/CCX/B297) and one was classified as idiopathic HLH. HLH diagnosis was established: 1) at time of ICU admission in five patients, 2) before ICU admission in three patients (median time from HLH diagnosis to ICU admission: 24 d, range: 15–68), and 3) during the ICU stay in one patient. In the overall cohort the time from hospital admission to HLH diagnosis was a median of 0 (range, 0–15) days.

The median Sequential Organ Failure Assessment score at diagnosis was 9 (median; 25th–75th percentile: 7–12), indicating multiple-organ dysfunction in all patients (Tables S1 and **S3**, http://links.lww.com/CCX/B297). More than half of our cohort (n = 5) required invasive or noninvasive ventilation, and one patient required venovenous extracorporeal membrane oxygenation. Six patients received norepinephrine, with two of them additionally renquiring vasopressin. Three patients received ruxolitinib via nasogastric tube.

Diagnosis of sHLH was based on the HLH-2004 criteria (5). One patient fulfilled eight of eight, four patients fulfilled six of eight, and four fulfilled five of eight items. The median H-score was 299 (255–304), and laboratory parameters at HLH diagnosis were consistent with severe hyperinflammation (Table S1, http://links.lww.com/CCX/B297). Hemophagocytosis was present on bone marrow specimens in all patients.

Ruxolitinib was ramped up to a dose of 20 mg bid in all patients (Fig. S1, http://links.lww.com/CCX/B297). Subsequently, the dose was modified based on inflammatory markers, blood count, and the patient's clinical status, aiming for the minimal effective dose. Ninety days after treatment initiation the median daily dose of ruxolitinib was 30 mg (range, 10–40 mg) administered as a bid results suggests divided dose.

IVIG were administered with a burst therapy of seven single doses and a dosage of 1 mg/kg of body weight. Dexamethasone was dosed according to HLH-2004.

The median follow-up time was 18.5 months (6–62) after HLH diagnosis. All patients survived until ICU discharge. The median length of the ICU stay was 7 days (range, 2–85).

We observed one death, due to traumatic intracerebral hemorrhage due to a fall in context of delirium and confusion, which occurred 14 days after ICU discharge. This corresponds to an overall survival rate of 100%, 86%, and 86% at 1, 3, and 6 months, respectively (**Fig. S3**, http://links.lww.com/CCX/B297). Except the major bleeding event in one patient, no predefined adverse events were detected.

Within 10 days of treatment, cytopenias substantially improved, all patients became transfusion independent and significant declines in ferritin and sIL2R levels were observed. (**Fig. 1**; **Fig. S2**, http://links.lww.com/CCX/B297).

During follow-up (range, 6–62 mo) two patients could discontinue treatment with ruxolitinib without any evidence of relapse after 374 and 937 days, respectively. Criteria to discontinue ruxolitinib were defined as achieving normalized levels of sIL2R and ferritin as well as the absence of HLH-associated clinical signs (File S1, http://links.lww.com/CCX/B297). Median time of ruxolitinib administration in the overall cohort was 208 days (7–374). None of the patients experienced relapse or required salvage therapy for HLH up to the last follow-up time point.

DISCUSSION

Our results suggest high-survival rates, decrease of HLH-related inflammation, and improvement of blood counts with low rates of adverse events following triplet-regimen treatment.

Treatment for HLH, based on the Histiocyte Society's clinical trials, involves etoposide and dexamethasone to suppress the cytokine storm by reducing T cell activation (9, 10). Unfortunately, these regimen are myelosuppressive/immunosuppressive and associated with a high mortality of up to 88%, whereas data varies in literature based on heterogenous populations (5).

Recently, development of more targeted, less-toxic sHLH therapy emerged as subject of interest (13). The importance of neutralizing cytokines was first noted in macrophage activation syndrome, a form of sHLH, where blockade of IL-1b with anakinra, was highly effective (14). This approach has previously been used in critically ill adults with sHLH and achieved an overall survival of 50% (15).

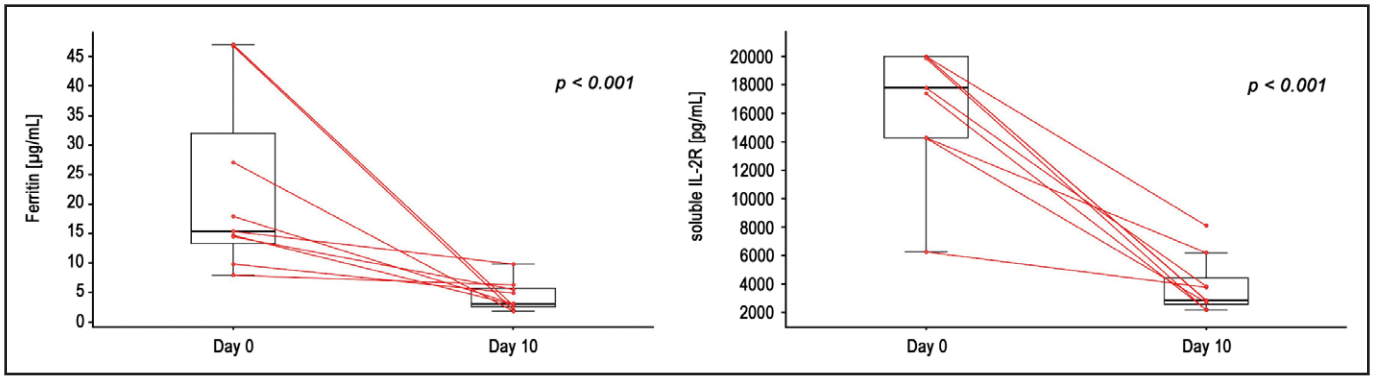

Figure 1. Treatment response at day 10 displayed by five central markers of hemophagocytic lymphohistiocytosis (HLH). The treatment response of the administered triplet regimen by response in two central biomarkers (ferritin and soluble interleukin-2 receptor [sIL-2R]) of HLH at day 10. Ferritin normal values 0.018–0.36 µg/mL, sIL-2R normal values 458–1997 pg/mL.

Ruxolitinib blocks the downstream effects of cytokine medicated JAK/signal transducer and activator of transcription pathways activation, endowing it with the ability to simultaneously inhibit the action of IFN-γ, IL-2, IL-6, and other proinflammatory cytokines. Case series of adults with refractory HLH provide evidence, that ruxolitinib can be effective as salvage therapy. However, there are few reports on the use of this medication as frontline therapy in adults or children with HLH and no reports about first-line use in critically ill patients (11, 12).

Within our approach, we modified the HLH-2004 regimen in terms of substitution of etoposide with ruxolitinib. We could thereby observe excellent ICU (100%) and overall survival rates (86%) and detected low rates of adverse effects caused by the treatment in a small case series of critically ill sHLH patients. To guarantee correct absorption of ruxolitinib when administered via nasogastric tube, we used prokinetic medication and monitored residual gastric volume (RGV). As none of the patient developed RGV of greater than or equal to 100 mL we assumed adequate absorption.

Furthermore, we believe that early diagnosis of HLH in our patients due to our ferritin screening approach of every patient entering our ICU might also have contributed to the outstanding survival rates observed. This hypothesis is supported by the fact that most patients were diagnosed at the time of ICU admission and swiftly received immunosuppression.

We cannot exclude the possibility that our patients might have eventually responded to long-term treatment with corticosteroids and/or IVIG alone. Additionally, the optimal duration of ruxolitinib therapy, and the utility of concurrent corticosteroids and IVIG, remain uncertain. During follow-up we could effectively discontinue treatment with ruxolitinib in two patients empirically under stringent controls of clinical signs and laboratory studies.

Importantly, our study included malignancy-associated sHLH patients, often excluded in trials due to poor prognosis, demonstrating our treatment's potential to overcome a phase of critical illness during malignancy-directed therapy.

Despite limitations like a small cohort size and an uncontrolled real-world setting, the nearly complete and rapid responses and the overall survival of 86% in unselected ICU patients are noteworthy.

In conclusion, our preliminary results on the activity and safety of ruxolitinib, combined with high-dose glucocorticoids and IVIG, may provide valuable insights for managing critical illness and secondary HLH. However, comparing treatment outcomes across diverse study populations mostly excluding malignancy related sHLH remains challenging, necessitating multicenter randomized trials on the activity of ruxolitinib-based triple therapy in the ICU setting for sHLH.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval of the local institutional review board: EC (35-290 ex 22/23).

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