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Ruxolitinib in adult patients with secondary hemophagocytic lymphohistiocytosis

To the Editor:

Hemophagocytic lymphohistiocytosis (HLH) is a devastating hyperinflammatory disorder in adults with protean clinical manifestations that is frequently caused by underlying autoimmune, infectious, or malignant disorders. The hyperinflammatory response ("cytokine storm"), including interferon production, instigated by these secondary disorders is the final common pathway in HLH and a therapeutic vulnerability. Therefore, antagonism of specific cytokines (eg, IL-1, IL-6, IFN-γ) is rational and well supported by pre-clinical and clinical studies. For example, a response to the anti-IFN-γ antibody emapalumab was observed in 63% of previously treated pediatric patients with primary HLH.[1] Given the pleiotropic, and in some cases partially redundant, effects of most cytokines implicated in HLH pathogenesis, inhibition of Janus family kinases (JAK), required for cytokine receptor-mediated signaling, is an alternative approach, and is well supported in pre-clinical HLH models.[2] Therefore, we launched an investigator-initiated, open-label, single-center study of ruxolitinib in adult patients with secondary HLH. A response, most of which were complete, was observed in all patients. A significant improvement in cytopenias and transfusion independence was achieved within 7 days of treatment initiation. All patients were hospitalized at the time of treatment initiation and were successfully discharged within 2 weeks. No deaths were observed, and the outcomes observed were superior to matched historic controls. Pharmacodynamic studies, including inhibition of STAT1 phosphorylation and reductions in soluble CD163, a surrogate marker for macrophage activation, further supported ruxolitinib's activity in secondary HLH. These results have been previously reported,[3] but are potentially more significant in the Covid-19 era, as severe Covid-19 is pathophysiologically related to HLH, and JAK inhibitors (including ruxolitinib) are the subject of ongoing studies in severe Covid-19 [reviewed in[4]]. Herein we report both updated outcomes, with longer follow up, and summarize our experience with ruxolitinib in HLH patients who were treated "off study".

The eligibility criteria, study design and endpoints, and statistical analysis plan have been previously reported.[4] Briefly, adult patients (≥18 years) who fulfilled five of eight HLH-2004 diagnostic criteria for HLH were eligible.[5] Patients with HLH secondary to an underlying malignancy were excluded, as were patients with known CNS involvement, or patients without adequate renal/hepatic function. This was an open label, single-center, prospective, pilot study, and was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Patients received oral ruxolitinib 15 mg twice daily on a continuous, 28-day cycle and dose reductions for renal insufficiency and toxicity were permitted. Enrollment occurred between February, 2016 and August, 2019. The primary endpoint was overall survival at 2 months, and additional secondary endpoints included response, duration of response, progression-free and overall survival. Adverse event monitoring was performed by history, physical exam, and laboratory monitoring. All quantifiable signs and laboratory abnormalities included in the diagnostic criteria for HLH were considered evaluable for response. Normalization of all signs and laboratory abnormalities was required for a complete response (CR), and at least 25% improvement in at least two signs/laboratory abnormalities was required for a partial response (PR). At least a 50% worsening in at least two signs/laboratory abnormalities defined progressive disease (PD), and failure to fulfill any of these response criteria was considered stable disease (SD). Duration of response was defined as time between first PR/CR and subsequent SD/PD. Although this pilot study was closed in January, 2020, patients without recurrent HLH were assessed as deemed clinically appropriate by the treating co-investigator after study closure. Patients with a durable PR/CR at the time of the last clinical assessment were censored.

Six patients (numbers 1–6) were enrolled in this study, and seven patients (numbers7-13) were treated off study (Table 1). One study patient (#6) enrolled after our initial report,[3] and is now included here. Patients treated off study either failed to meet eligibility criteria, were treated after study closure, or were unable to participate due to logistical considerations, and two of these patients (#7, #8) were previously reported. The secondary etiology for HLH in these patients was idiopathic (5/13), autoimmune (4/13), and/or infectious (5/13), as summarized in Table 1. Malignancy-associated HLH was underrepresented, as these patients were not eligible for this study, but a single patient with relapsed classical Hodgkin lymphoma (cHL) and EBV viremia (#11) received treatment off study. All patients satisfied diagnostic criteria for HLH (summarized in Table S1). Ruxolitinib was first-line or second-line therapy for most (9/13) patients, whereas the remaining patients had recurrent or progressive HLH despite multiple prior therapies (range: 2–5 prior lines of therapy).

An overall response rate of 77% was observed (Table 1), including five CR and five PR. As previously noted,[3] the clinical significance of the distinction between a PR and CR in these patients is doubtful, as patients achieving a PR had persistent, mild elevations in laboratory abnormalities that may have preceded their HLH diagnosis (eg, hypertriglyceridemia, mild elevations in ferritin, and anemia of chronic disease), and thus highlights the need for improved response criteria in this disease. Three patients with severe, life-threatening infections at the time of treatment failed to respond (#10, 12, 13) and died within 5–41 days of treatment initiation. No other deaths have been observed. Two patients developed recurrent HLH after achieving an initial response (#1, 11), both of which are of special interest. One patient (#1)

TABLE 1 Response to treatment

Patient no. (treated on study)	Best response	Duration of response (months)	Ruxolitinib discontinued	Last known vital status	Adverse events (Grade ≥ 2)[b]
1[a]	CR	3.5	Yes (due to recurrence)	Alive, without HLH	Febrile neutropenia (grade 4)
2[a]	CR	23.5[c]	Yes (due to toxicity)	Alive, without HLH	Pain in extremity (grade 2)
3[a]	CR	35.5[c]	No	Alive, without HLH	Pneumonitis (grade 2); fatigue (grade 3)
4[a]	CR	17[c]	Yes (treatment no longer required)	Alive, without HLH	Nausea (grade 2)
5[a]	CR	17.5[c]	Yes (treatment no longer required)	Alive, without HLH	None
6	PR	12[c]	No	Alive, without HLH	None
Patient no. (treated off study)					
7[a]	PR	41.5[c]	No	Alive, without HLH	—
8[a]	PR	34.5[c]	Yes (treatment no longer required)	Alive, without HLH	Headache (grade 2)
9	PR	16.5[c]	Yes (treatment no longer required)	Alive, without HLH	—
10	NR	N/A	N/A	Died, with HLH (and disseminated candidiasis)	—
11	PR	1.5	Yes (due to recurrence)	Alive, without HLH	—
12	NR	N/A	N/A	Died, with HLH (and septic shock, VRE bacteremia, neutropenic colitis)	—
13	NR	N/A	N/A	Died, with HLH (and invasive sinus and pulmonary aspergillosis complicated by hemorrhagic and septic shock)	—

Abbreviations: CR, complete response; PR, partial response; NR, no response; N/A, not applicable.
[a]Previously reported.[3]
[b]Unlikely, possibly, or probably related to ruxolitinib.
[c]Response ongoing at time of last follow-up.

was found to have an underlying mutation (in the *STXBP2* gene) associated with primary HLH and underwent allogeneic stem cell transplantation, as previously described.[3] The other (#11) had malignancy-associated HLH (relapsed and refractory cHL), thus highlighting the importance of incorporating malignancy-targeted therapies in these patients. Therefore, 62% of patients (8/13) achieved a durable response (duration of response, range: 12.0–41.5+ months). As the optimal duration of therapy is unknown, gradual tapering and discontinuation of ruxolitinib, at the discretion of the investigator, was allowed, although an unspecified gradual taper was recommended, given the potential for cytokine rebound with rapid discontinuation. Therefore, most patients achieving a durable response have successfully discontinued treatment without recurrent HLH (5/8), and three patients remain on treatment. As anticipated, ruxolitinib was well tolerated, with two grade ≥ 3 adverse events (febrile neutropenia and fatigue) that were possibly treatment related (Table 1). One patient discontinued treatment due to grade two extremity pain (#2).

The three deaths observed occurred in patients with challenging, difficult to treat infectious complications, thus highlighting the need for early recognition of HLH and prompt treatment initiation.[6] With the exception of a single patient with primary HLH, and multiple secondary drivers, the only patient who progressed after achieving an initial, albeit relatively transient, response (#11) had progressive cHL. A response in this patient was only achieved upon control of the underlying cHL, thus highlighting the importance of malignancy-directed therapies in similar patients. In addition, JAK inhibition may be particularly attractive in malignancies, including mature T-cell lymphomas, that are commonly associated with secondary HLH,[6] and for which ruxolitinib (or alternative JAK inhibitors) have clinical activity.

In our experience, ruxolitinib is active in secondary HLH, well tolerated, non-myelosuppressive, and manageable in the outpatient setting. Therefore, we believe these findings support ongoing efforts investigating JAK inhibitors, not only in HLH, but in other HLH-related cytokine-release syndromes, including severe Covid-19.

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AUTHOR CONTRIBUTIONS

A.A., S.A.M., and R.A.W. provided and interpreted data. P.S.B. and R.A.W. analyzed data and drafted the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

Philip S. Boonstra[1], Asra Ahmed[2], Samuel A. Merrill[3], Ryan A. Wilcox[2]

[1]*Department of Biostatistics and the Center for Cancer Biostatistics, University of Michigan, Ann Arbor, Michigan*
[2]*Division of Hematology/Medical Oncology, Department of Internal Medicine, University of Michigan Rogel Cancer Center, Ann Arbor, Michigan*
[3]*The Section of Hematology, Department of Medicine, West Virginia University, Morgantown, West Virginia*

Correspondence
Ryan A. Wilcox, University of Michigan Rogel Cancer Center, 4310 Cancer Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48130-5911.
Email: rywilcox@med.umich.edu

This trial (NCT02400463) was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was provided by clinical trial participants.

ORCID

Ryan A. Wilcox https://orcid.org/0000-0002-6420-0760

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Depression in adolescents and young adults with heavy menstrual bleeding in a referral clinic setting

To the Editor:

Heavy menstrual bleeding (HMB) is a common problem reported in up to 40% of adolescent females, with a greater frequency in adolescents with bleeding disorders (BDs).[1] Heavy menstrual bleeding is known to negatively affect health due to high rates of associated iron deficiency (ID) and iron deficiency anemia (IDA), both of which have been linked to decreased health related quality of life (HRQOL) in adults.[2] Adolescents with HMB also report decreased HRQOL compared to adolescents without HMB, and on par with or worse than adolescents with cystic fibrosis and juvenile arthritis.[3] Studies suggest that reduction in HMB, and treatment of ID leads to improvement in HRQOL.[1,2] While there is increasing evidence that HMB in adolescents impacts HRQOL negatively, the association with depression and anxiety, is unknown. We conducted a retrospective chart review at the University of Michigan to evaluate the impact of HMB on mental health disorders, specifically