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Brief Article

Efficacy, Toxicity, and Infectious Complications in Ruxolitinib-Treated Patients with Corticosteroid-Refractory Graft-versus-Host Disease after Hematopoietic Cell Transplantation

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A B S T R A C T

Corticosteroid-refractory graft-versus-host disease (SR-GVHD) remains a significant source of morbidity after allogeneic hematopoietic cell transplantation. No standard therapy exists in this setting; however, recent studies have demonstrated a very promising role for ruxolitinib, an oral Janus kinase 1/2 inhibitor. With increasing evidence of efficacy for SR-GVHD, limited data exist describing complications of ruxolitinib use, specifically infectious complications during use in SR-GVHD. In this study we report outcomes and infectious complications at our institution with ruxolitinib use. Overall, 43 patients were treated with ruxolitinib for SR-GVHD, 19 for acute SR-GVHD and 24 for chronic SR-GVHD. With respect to acute SR-GVHD, 15 patients had grade III acute GVHD and 4 patients had grade IV acute GVHD. At 28 days, a response rate of 84% was detected. With respect to chronic SR-GVHD, 16 patients had moderate refractory disease and 8 had severe refractory disease. At around 28 days, a 63% response rate was detected. Overall, 42% of patients (n = 18) treated with ruxolitinib had a documented infectious event. Infectious events were significantly more common among patients treated for acute SR-GVHD ($P < .005$). Among patients treated for acute SR-GVHD, both viral (n = 11) and bacterial (n = 10) events were frequently encountered. Cytomegalovirus reactivation was detected in 4 patients without organ involvement in any patient. Bacteremia was the most common bacterial event (n = 8), and 2 patients died after development of bacteremia. Only 5 of 24 patients treated with ruxolitinib for chronic SR-GVHD developed infectious complications after initiation of therapy. Nearly an even number of viral (n = 3) and bacterial (n = 4) were detected. This study supports the use of ruxolitinib in SR-GVHD, with impressive responses observed in both acute and chronic SR-GVHD. Infectious complications were particularly frequent among patients treated for acute SR-GVHD, and nearly all these patients were concurrently on high-dose steroids while on ruxolitinib. This study suggests careful monitoring for viral reactivation is required for patients initiated on ruxolitinib, supports the role of continuing prophylactic antimicrobial measures in ruxolitinib-treated GVHD patients, and raises the question of whether bacterial prophylaxis should be considered among patients initiated on ruxolitinib for acute SR-GVHD, particularly while on high-dose steroids.

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INTRODUCTION

Corticosteroid-refractory graft-versus-host disease (SR-GVHD) remains a clinical challenge and significantly contributes to nonrelapse morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). Recently, multiple retrospective studies have reported that ruxolitinib, an oral Janus kinase (JAK) 1/2 inhibitor, appears to be safe and effective in the treatment of both steroid-refractory acute and chronic GVHD, with upward of 80% of patients responding [1-3].

Mechanistically, ruxolitinib is believed to ameliorate GVHD through inhibition of JAK1/JAK2 signaling, which results in reduction of T cell proliferation and activation and potentially inhibition of B cell expansion [4-6]. As an immunomodulatory medication, ruxolitinib may potentially increase the risk of infectious complications. Indeed, among myelofibrosis patients, where ruxolitinib has been approved for use since 2011, a

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variety of infections has been associated with ruxolitinib use, including urinary tract infections, pneumonia, hepatitis reactivation, herpes zoster infections, and tuberculosis [7-13].

Limited published data exist regarding the toxicity, incidence, and severity of infectious complications associated with ruxolitinib use in allogeneic HCT patients. Cytomegalovirus (CMV) reactivation has been described with ruxolitinib use [1]; however, the extent and severity of other infections seen post-transplant, namely bacterial infections and fungal infections, remain poorly characterized. In this retrospective study, we reviewed clinical outcomes and infection-related clinical and pathologic data for all patients treated at our institution with ruxolitinib for SR-GVHD.

METHODS

This retrospective study was performed with Medical College of Wisconsin Institutional Review Board approval. We conducted a retrospective review of adult allogeneic HCT recipients at our institution who initiated ruxolitinib for SR-GVHD between February 2016 and July 2018.

Diagnosis of SR-GVHD

Determination of acute and/or chronic GVHD was performed by the treating physicians on the basis of clinical and pathologic findings. Acute GVHD was graded following consensus criteria, and chronic GVHD was graded following National Institutes of Health consensus criteria [14,15]. Acute SR-GVHD was determined based on the following findings: progression of GVHD despite treatment with 2 mg/kg/day or more of methylprednisolone (or equivalent) for at least 72 hours, no change in visceral GVHD despite treatment with 2 mg/kg or more of methylprednisolone for at least 5 days, no change or progression in skin acute GVHD after at least 1 week of 1 mg/kg/day or more of methylprednisolone, or exacerbation of acute GVHD while tapering glucocorticoid therapy at any prednisone-equivalent dose $>$ .5 mg/kg/day. Chronic SR-GVHD was determined if patients with classic chronic GVHD demonstrated a lack of response to a minimum of .5 mg/kg/day of prednisone therapy after 4 weeks.

Treatment and GVHD Response Criteria

For acute SR-GVHD, ruxolitinib was initiated at a dose of 5 mg orally twice daily. After 3 days of therapy with 5 mg twice daily, ruxolitinib dose modifications were performed at the discretion of the treating physician to a maximum dose of 10 mg twice daily. For chronic SR-GVHD, ruxolitinib was initiated at a dose of 10 mg orally twice daily.

On initiation of ruxolitinib, steroids were tapered at the discretion of the treating physician. In general, institutional guidelines recommend tapering by .5 mg/kg/day of prednisone equivalent every 5 days for steroid doses greater than .5 mg/kg/day of prednisone, until a dose of .5 mg/kg/day is achieved. Afterward, subsequent tapers are recommended to achieve a goal dose of $<$.2 mg/kg/day of prednisone by day 56.

For patients initiated on ruxolitinib for acute GVHD, a complete response (CR) was defined as complete resolution of all signs, symptoms, and laboratory manifestations of acute GVHD and a partial response (PR) as improvement in GVHD by at least 1 stage in 1 site and stable disease in all other involved sites. Patients failing to achieve at least a PR were defined as treatment failures. Initiation of additional systemic immunosuppressive agents was also considered a treatment failure. Acute GVHD responses were assessed at day 28 after ruxolitinib initiation, as well as overall best response (to include late responders). For patients initiated on ruxolitinib for chronic GVHD, response was assessed based on 2005 National Institutes of Health consensus criteria, with a CR defined as resolution of all reversible manifestations of chronic GVHD, PR defined as at least 50% improvement in organ-specific chronic GVHD, and treatment failure defined as the addition of immunosuppression after ruxolitinib [16]. Finally, for the group, failure-free survival was assessed, which was defined as 6 months of survival free of initiation of new GVHD therapy, discontinuation due to cytopenia, relapse, or death.

Infection Prophylaxis and Determination of Infection

Per institutional standards, prophylaxis with acyclovir (800 mg twice a day), a mold-active triazole (most often voriconazole), and pneumocystis prophylaxis, most often with trimethoprim/sulfamethoxazole, was recommended in patients with acute GVHD. Acute GVHD patients did not routinely received gram-negative antibacterial prophylaxis. Prophylaxis with acyclovir, antifungal, pneumocystis, and pneumococcal prophylaxis was recommended in all patients with chronic GVHD requiring systemic therapy.

Treatment-emergent infections, defined as any infection that occurred after initiation of ruxolitinib until discontinuation of the medication or through the first 180 days after initiation, were recorded. We reviewed nucleic acid amplification testing results for CMV, Epstein-Barr virus, adenovirus, human herpesvirus-6 (HHV-6), and BK virus. Viremia or viruria was confirmed if virus was detected at any level after a previously negative study. If no prior study was performed, any level of positivity was determined to be significant. Per institutional guidelines in recipients of HLA-matched transplants not receiving in vivo or ex vivo T cell depletion, CMV nucleic acid amplification testing was performed weekly, at least through day +100. Among patients receiving T cell–depleted transplants or post-transplant cyclophosphamide, weekly CMV and every other week Epstein-Barr virus nucleic acid amplification testing was performed at least until peripheral blood CD4 count of 200/μL or higher was achieved. HHV-6, adenoviral, and BK viral testing were done based on clinical signs and symptoms. All positive blood cultures were recorded. Any clinically suspected respiratory infections with the presence of a positive bronchoalveolar lavage results or positive PCR-based respiratory viral screening results were recorded. All positive urine cultures were recorded. All positive infectious stool studies were recorded.

Statistical Studies

Descriptive statistics, univariate analysis 2-way tables with chi-square measure of association, and Kaplan-Meier estimate for failure-free survival were calculated using Stata v.12.0 (StataCorp LLC, College Station, TX).

RESULTS

Baseline Characteristics

During the study time period we identified 43 patients with SR-GVHD who were treated with ruxolitinib. Ruxolitinib was initiated for acute SR-GVHD in 19 patients, whereas 24 patients received ruxolitinib for chronic SR-GVHD. Median follow-up from the start of ruxolitinib was 163 days (range, 12 to 658). Patient characteristics are outlined in Table 1.

Efficacy

Among patients treated for acute GVHD (n = 19), 3 patients had refractory skin GVHD, 7 patients had refractory gastrointestinal GVHD, and another 9 patients had multisite refractory disease, primarily involving the skin and gastrointestinal tract. Of the 19 patients, 5 patients met criteria for acute SR-GVHD with worsening or nonimproving GVHD on 2 mg/kg corticosteroids, 10 patients met criteria for acute SR-GVHD with nonimproving GVHD on 1 mg/kg corticosteroids for 1 week, and 4 were initiated on ruxolitinib because of corticosteroid taper intolerance. A median of 2 prior therapies (range, 1 to 4), including steroid administration, were administered before ruxolitinib, and ruxolitinib was initiated a median 93 days (range, 24 to 265) post-transplant and 21 days (range, 3 to 162) after onset of acute GVHD. Table 2 summarizes pretreatment characteristics. On initiation, 3 patients had grade II GVHD, 13 patients had grade III GVHD, and 3 patients had grade IV GVHD. At day 28 after ruxolitinib initiation, 84% (16/19) of acute GVHD patients achieved a CR or PR (CR, 9 patients; PR, 7 patients). Two nonresponders had grade IV GVHD at initiation of therapy, whereas the other nonresponder had grade III GVHD at treatment initiation. The best overall response rate was 89% (17/19), with 12 CRs and 5 PRs. Ruxolitinib was well tolerated, with a median duration of therapy of 90 days (range, 11 to 630). At the end of the study, 6 patients remained on ruxolitinib and 3 were successfully tapered off therapy. Reasons for discontinuation in the remaining patients included progression requiring additional therapy for GVHD (n = 4), death (n = 3), relapse (n = 2), and persistent cytopenia requiring discontinuation (n = 1). Overall, the estimated 6-month failure-free survival was 58% (95% confidence interval, 39% to 85%).

Similar results were observed among chronic GVHD patients (n = 24) treated with ruxolitinib. Among patients treated for chronic SR-GVHD, 16 patients had moderate chronic GVHD and 8 had severe chronic GVHD. Organ involvement included skin in 16 patients, oral involvement in 9 patients, liver involvement in 4 patients, ocular involvement in

Table 1
Patient Characteristics

Ruxolitinib Indication	Acute SR-GVHD (n = 19)	Chronic SR-GVHD (n = 24)
Median age, yr (range)	59 (46-70)	59 (45-70)
Gender		
Male	15 (79)	13 (54)
Female	4 (21)	11 (46)
Primary disease AL MDS/MPN Lymphoma/MM	 8 4 7	 10 9 5
Donor type		
Matched related	6 (32)	11 (46)
Matched unrelated	10 (52)	12 (50)
Haploidentica	2 (11)	1 (4)
MMUD	1 (5)	
Graft source		
Peripheral blood	17 (89)	22 (92)
Bone marrow	2 (11)	2 (8)
Conditioning regimen		
Myeloablative	9 (47)	14 (58)
Reduced-intensity	10 (53)	10 (42)
conditioning		
CMV status, donor/recipient		
+/+	4 (20)	3 (12)
+/−	2 (11)	5 (21)
−/+	2 (11)	5 (21)
−/−	11 (58)	11 (46)
Prophylaxis regimen		
Tacrolimus/MTX	15 (79)	22 (92)
Tacrolimus/MMF		1 (4)
PT-Cy based	4 (21)	1 (4)

Values are n (%) unless otherwise defined. AL indicates acute leukemia; MDS/MPN, myelodysplastic syndrome/Myeloproliferative neoplasm; MM, multiple myeloma; MMUD, mismatched unrelated donor; MTX, methotrexate; MMF, mycophenolate mofetil; PT-Cy, post-transplant cyclophosphamide.

4 patients, lung involvement in 4 patients, gastrointestinal involvement in 3 patients, and polyneuropathy as a manifestation of chronic GVHD in 1 patient. Table 2 summarizes pretreatment characteristics. A median of 2 prior therapies (range, 1 to 5) were administered before ruxolitinib. By 28 days, 63% of patients (15/24) demonstrated evidence of response to therapy. Overall, response to ruxolitinib was observed in 83% of patients (20/24), with 3 patients experiencing a CR to therapy and 17 experiencing improvement in at least 1 organ system. Although most patients with chronic skin GVHD responded, the 4 nonresponders among our patients all had severe sclerodermatous skin GVHD. Among the 4 patients with evidence of bronchiolitis obliterans syndrome, 1 patient had stabilization of lung function and 1 patient had demonstrated improvement in pulmonary function testing values. Ruxolitinib appeared to be well tolerated, and chronic SR-GVHD patients remained on therapy for a median 166 days (range, 60 to 932). Responses appeared to be durable; among responders (n = 20), only 2 patients required additional therapy after ruxolitinib initiation. One other responding patient discontinued therapy due to persistent neutropenia. Overall, among chronic GVHD treated patients, the estimated 6- month failure-free survival was 88% (95% confidence interval, 75% to 100%).

Table 2
SR-GVHD Ruxolitinib Response

Ruxolitinib Indication	Acute SR-GVHD (n = 19)	Chronic SR-GVHD (n = 24)
Maximum grade GVHD	Grade III: 15	Moderate: 16
	Grade IV: 4	Severe: 8
Interval between HCT and ruxolitinib, days	93 (24, 265)	768 (253, 1926)
Prior GVHD therapies	2 (1-4)	2 (1-5)
No response	2 (11)	2 (8)
Stable disease		3 (13)
PR	5 (26)	16 (67)
CR	12 (63)	3 (13)

Hematologic Toxicity

We recorded cytopenias attributed to ruxolitinib that resulted in a dose modification or hold. Overall, cytopenias appeared to occur more commonly among patients treated for acute SR-GVHD compared with chronic SR-GVHD (36% versus 17% of patients). Using CTCAE v5.0 criteria, a grade 3 or greater decrease in the neutrophil count was observed in 5 patients treated for acute SR-GVHD and in 4 patients treated for chronic SR-GVHD. Thrombocytopenia occurred in 3 patients with acute SR-GVHD: 1 case was a grade 3 and 2 cases were grade 4. One case of grade 2 thrombocytopenia was seen in a patient treated for chronic SR-GVHD. Finally, 2 patients treated for acute SR-GVHD developed a grade 3 anemia, and 1 patient treated for chronic SR-GVHD developed grade 2 anemia. Overall, 2 patients permanently discontinued ruxolitinib due to recurrent anemia and thrombocytopenia on therapy.

Infectious Complications

Among all patients (n = 43), 18 patients (42%) developed at least 1 documented infection while on ruxolitinib. The incidence of infection was .41 infections per 100 days on ruxolitinib. Infections were identified a median of 34 days (range, 9 to 197) after initiation of ruxolitinib. Two patients, both treated for acute SR-GVHD, died related to infectious complications.

Among acute SR-GVHD patients treated with ruxolitinib, 68% of patients (13/19) developed at least 1 infection after ruxolitinib initiation. Five patients developed multiple infections. There was a relatively high incidence of infection in this group, at 1.1 infections per 100 days on ruxolitinib. At time of infection, 13 patients (100%) were on antiviral prophylaxis primarily with acyclovir, 9 patients (69%) were on Pneumocystis jiroveci pneumonia prophylaxis primarily with trimethoprim/sulfamethoxazole, 11 patients (84%) were on antifungal prophylaxis predominantly with micafungin, and 2 patients (15%) were receiving antibacterial prophylaxis with a cephalosporin. In terms of ruxolitinib dose, 9 patients (69%) were on ruxolitinib doses of either 5 mg daily or 5 mg twice daily. Only 4 patients (31%) were at a higher dose of ruxolitinib at 10 mg twice daily. Regarding concurrent immunosuppressive agents, 5 patients (38%) were on prednisone-equivalent doses of 30 mg or greater at time of initial infection and 10 of 13 patients remained on either sirolimus or tacrolimus.

Among infections observed in acute SR-GVHD treated patients, viral infections were the most commonly detected pathogen, with a total of 12 viral events detected. Four patients (21%) developed CMV viremia. No CMV organ involvement was seen. Two patients (11%) had HHV-6 viremia, without associated cytopenia or encephalopathy. Two patients (11%) had BK viruria, associated with trace hematuria. Severe BK-viral hemorrhagic cystitis was not seen. Finally, 4 patients (21%) developed an upper respiratory infection, detected on PCR-based respiratory viral screening. Bacterial infections were the next

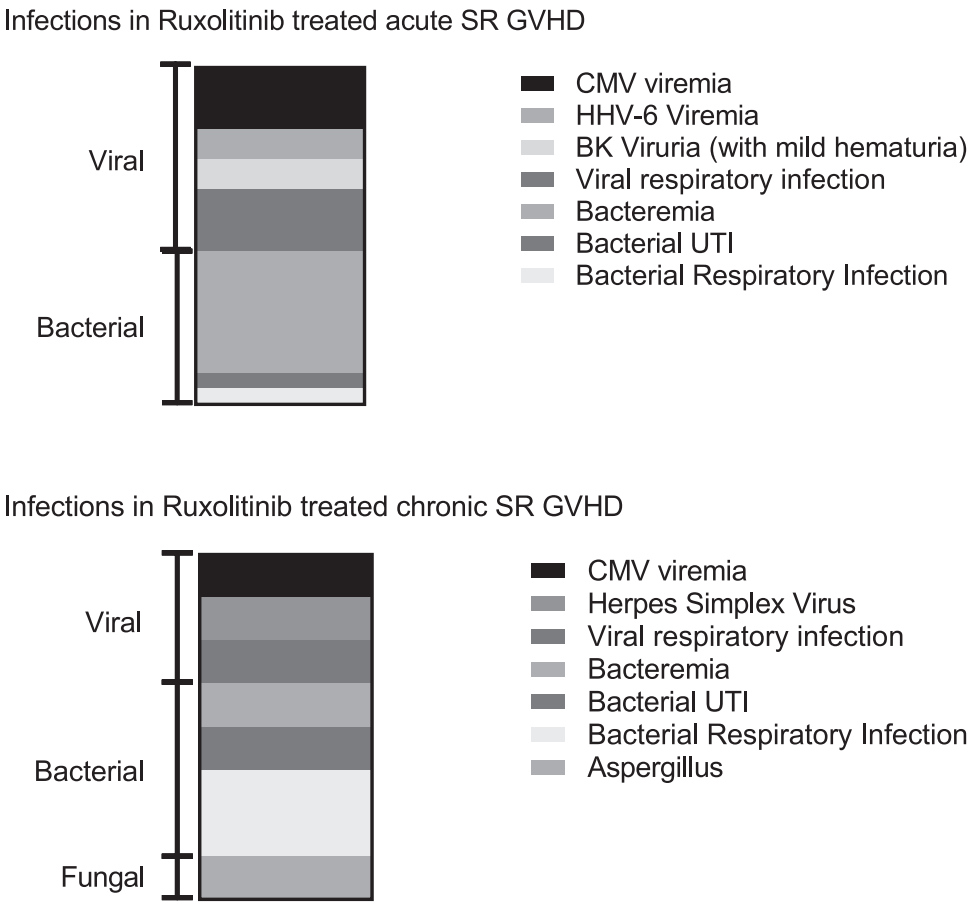

Figure 1. Infections during ruxolitinib therapy.

common infectious event, with 10 bacterial infections identified. Eight bacteremia events (42%) were recorded. *Enterococcus* was the causative bacteria in three patients, and the 2 observed deaths occurred in patients in shock with enterococcus bacteremia. *Klebsiella* (n = 1), *Escherichia coli* (n = 1), Citrobacter (n = 1), *Staphylococcus aureus* (n = 1), and *Staphylococcus epidermidis* (n = 1) were the causative bacteria for remaining bacteremia events. One patient (5%) developed an *E. coli* urinary tract infection and 1 patient (5%) a *Pseudomonas* sp. sinusitis. No fungal events were diagnosed among patients treated for acute SR-GVHD.

In patients treated for chronic SR-GVHD with ruxolitinib, infections were detected among 21% of patients (5/24). Three of these patients developed multiple infections while on ruxolitinib. A low incidence of infection was found in this group, at .15 infections per 100 days on ruxolitinib. At the time of infection, 5 patients (100%) were on antiviral prophylaxis with acyclovir, 4 patients (80%) were on P. jiroveci pneumonia prophylaxis primarily with trimethoprim/sulfamethoxazole, 2 patients (40%) were on antifungal prophylaxis with micafungin, and 1 patient (20%) was on streptococcus pneumoniae prophylaxis with penicillin VK. In terms of ruxolitinib dose, the 5 patients (100%) who developed an infection were on a ruxolitinib 10 mg twice daily dose. Finally, 4 patients (80%) were on prednisone-equivalent doses of 30 mg or greater at time of initial infection, and 2 patients (40%) were on additional immunosuppressive agents, 1 on tacrolimus and 1 on mycophenolate mofetil.

Bacterial infections represented the most common infectious event (n = 4) among chronic SR-GVHD patients treated with ruxolitinib. Two patients (8%) developed bacterial pneumonia. One patient (4%) developed *S. aureus* bacteremia. One patient (4%) developed an *E. coli* urinary tract infection. Viral events were detected in 3 patients. One patient (4%) developed CMV reactivation without organ involvement. One patient (4%) developed herpes simplex virus type 1 with oral ulcerations. One patient (4%) developed a viral upper respiratory infection. Finally, 1 patient was diagnosed with pulmonary aspergillus infection. This patient was not on any antifungal prophylaxis at time of infection. Figure 1 summarizes the infections observed on ruxolitinib therapy.

On univariate analysis, no pretransplant characteristics indicated an increased risk for infection. We did see, however, a strong correlation between development of infection and indication (acute versus chronic GVHD) for ruxolitinib use ($P < .005$). As reported earlier 13 of 19 patients treated for acute SR-GVHD developed infections compared with 5 of 24 patients treated for chronic SR-GVHD with ruxolitinib. Among patients treated for acute SR-GVHD, days post-transplant, development of neutropenia, and number of prior therapies were not associated with development of infection.

DISCUSSION

SR-GVHD remains an unmet need after allogeneic HCT; however, recent evidence suggests that inhibition of JAK-STAT signaling with ruxolitinib holds tremendous promise. Indeed, the most recent results of the REACH1 trial [17], using ruxolitinib as first therapy for acute SR-GVHD, report a best overall response rate of 73.2%. Our study also reveals, similar to other reports, that ruxolitinib appears to be an effective treatment option for SR-GVHD, both in the acute and chronic setting. Our

retrospective study demonstrates that infections represent a common complication after ruxolitinib initiation, particularly among patients treated for acute SR-GVHD.

Prior studies have mainly focused on CMV reactivation or on acute or chronic GVHD patient groups. Zeiser et al. [1] published the largest series on patients treated with ruxolitinib for SR-GVHD (n = 95). In that publication, 33% of patients treated for acute SR-GVHD and 14% of patients treated for chronic SR-GVHD developed CMV reactivation. Modi et al. [18] reported CMV reactivation in 9% of patients treated for chronic SR-GVHD. Both studies report cases of CMV with organ involvement. In contrast, we report slightly lower CMV reactivation rates at 21% and 4% in acute and chronic GVHD patients, respectively. Further, we did not observe CMV organ involvement in any of our patients. One possible reason for this difference could be absence of in vivo T cell depletion for GVHD prophylaxis among patients included in our series. There may also be unknown differences in immune-reconstitution status and number of patients at risk (based on donor–recipient CMV serostatus) across the reported studies and our data. Despite our lower rates, overall, CMV reactivation appears to be a common event and requires careful monitoring among patients treated with ruxolitinib. Currently, at our institution GVHD patients receiving ruxolitinib undergo monitoring for CMV viremia.

Unique to our review, we reviewed and recorded all viral, bacterial, and fungal events among our cohort of patients treated for both acute and chronic SR-GVHD. Overall, we found that 42% of patients developed an infection after ruxolitinib initiation and over 60% of patients treated for acute SR-GVHD developed an infection after initiation. This translated to a high incidence of infection, at 1.1 infections per 100 days on ruxolitinib among patients treated for acute SR-GVHD. The increased infection risk among acute SR-GVHD patients may be due to a couple factors. One is that nearly all patients treated for acute SR-GVHD were concurrently on other immunosuppressive agents at the time of first infection. High-dose steroids were administered in 5 of 13 patients who developed an infection, and GVHD prophylaxis continued in about 10 of 13 patients who developed an infection. This may have contributed to an additively increased risk for infection in this group. Another factor is that among patients treated for acute SR-GVHD, most had acute GVHD of the gastrointestinal tract; breakdown of the gastrointestinal mucosal barrier may have contributed to an increased susceptibility to infection. Overall, these data highlight that the addition of ruxolitinib is unlikely benign from the standpoint of infection, and similar to other GVHD treatment options, infection needs to be a careful consideration before initiation.

Through assessment for bacterial infection, we report that bacterial infections frequently occur, among both patients with acute and chronic GVHD. Nearly half of our patients treated for acute SR-GVHD developed a bacteremia, including 2 fatal bacterial sepsis events, and 4 of 24 patients treated for chronic SR-GVHD developed a bacterial infection. It should be noted that most of these patients were concurrently on high doses of steroids. In another study using ruxolitinib for acute SR-GVHD, Khandelwal et al. [2] reported the development of bacterial infections in 6 of 11 patients treated for acute SR-GVHD. Bacterial infections also appear to be a common complication among patients treated with ruxolitinib for different indications. In a cohort of 507 patients treated for myelofibrosis with ruxolitinib, it was reported that 22% of patients developed an infection, and 78% of the detected infectious events were bacterial [8]. Overall, ruxolitinib appears to result in an increased vulnerability to bacterial infections, possibly because of a number of reasons. One may be neutropenia, which develops on initiation. In our study, we did not find any correlation between neutropenia and infection; however, this may be because of the small number of patients we evaluated overall. Another mechanism may be due to reported granulocyte dysfunction that is believed to occur with ruxolitinib therapy [1,8]. Finally, a reduction in inflammation through cytokine impairment may play a role in increased vulnerability to bacterial infection. These findings may warrant consideration for antibacterial prophylaxis in patients treated for acute SR-GVHD, particularly while on high-dose steroids.

Limitations to this study include that our patients with acute GVHD were subject to increased surveillance screening studies for viral reactivation. CMV reactivation was more commonly detected in the acute SR-GVHD population. However, given the nature of their GVHD, all patients were carefully observed on ruxolitinib, and patients with findings suspicious for viral reactivation were promptly screened for this finding. Further, with prolonged ruxolitinib exposure because of a favorable response, the number of infections we captured in part could be a reflection of time on therapy. Finally, we assessed infection as a treatment-emergent complication of ruxolitinib; in other words, we reported all infections that occurred after ruxolitinib initiation. Certainly a variety of factors, including other immunosuppressive use, GVHD, and frailty, likely contributed to the development of infection, and this could not be fully teased out in this analysis.

Overall, this study affirms the role of ruxolitinib in the management of SR-GVHD but demonstrates the necessity for careful infectious monitoring for patients initiated on ruxolitinib. We report that for adults treated for acute SR-GVHD, viral reactivation and bacterial infections represent significant risks during ruxolitinib treatment. These data support the continued use of infection prophylaxis in patients receiving GVHD treatment with ruxolitinib. Ongoing data collection for ruxolitinib-treated patients are necessary; if the incidence of bacterial infections persists, careful consideration of antibacterial prophylactic measures in ruxolitinib-treated patients may be warranted.

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REFERENCES

1. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29:2062–2068.
2. Khandelwal P, Teusink-Cross A, Davies SM, et al. Ruxolitinib as salvage therapy in steroid-refractory acute graft-versus-host disease in pediatric hematopoietic stem cell transplant patients. *Biol Blood Marrow Transplant*. 2017;23:1122–1127.
3. Khoury HJ, Langston AA, Kota VK, et al. Ruxolitinib: a steroid sparing agent in chronic graft-versus-host disease. *Bone Marrow Transplant*. 2018;53:826–831.
4. Jackson SW, Jacobs HM, Arkatkar T, et al. B cell IFN-γ receptor signaling promotes autoimmune germinal centers via cell-intrinsic induction of BCL-6. *J Exp Med*. 2016;213:733–750.
5. Chen X, Das R, Komorowski R, et al. Blockade of interleukin-6 signaling augments regulatory T-cell reconstitution and attenuates the severity of graft-versus-host disease. *Blood*. 2009;114:891–900.
6. Choi J, Cooper ML, Alahmari B, et al. Pharmacologic blockade of JAK1/JAK2 reduces GvHD and preserves the graft-versus-leukemia effect. *PLoS One*. 2014;9: e109799.
7. Kusano Y, Terui Y, Ueda K, Hatake K. *Klebsiella pneumoniae* primary liver abscess associated with ruxolitinib. *Ann Hematol*. 2016;95:1561–1562.

8. Polverelli N, Breccia M, Benevolo G, et al. Risk factors for infections in myelofibrosis: role of disease status and treatment. A multicenter study of 507 patients. *Am J Hematol*. 2017;92:37–41.
9. Perricone G, Vinci M, Pungolino E. Occult hepatitis B infection reactivation after ruxolitinib therapy. *Dig Liver Dis*. 2017;49:719.
10. Liu J, Mouhayar E, Tarrand JJ, Kontoyiannis DP. Fulminant *Cryptococcus neoformans* infection with fatal pericardial tamponade in a patient with chronic myelomonocytic leukaemia who was treated with ruxolitinib: case report and review of fungal pericarditis. *Mycoses*. 2018;61:245–255.
11. Dioverti MV, Abu Saleh OM, Tande AJ. Infectious complications in patients on treatment with ruxolitinib: case report and review of the literature. *Infect Dis*. 2018;50:381–387.
12. Gill H, Leung GMK, Seto W-K, Kwong Y-L. Risk of viral reactivation in patients with occult hepatitis B virus infection during ruxolitinib treatment. *Ann Hematol*. 2019;98:215–218.
13. Dioverti MV, Abu Saleh OM, Tande AJ. Infectious complications in patients on treatment with ruxolitinib: case report and review of the literature. *Infect Dis*. 2018;50:381–387.
14. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2005;11:945–956.
15. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15:825–828.
16. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2006;12:252–266.
17. Jagasia M, Perales MA, Schroeder MA, et al. Results from REACH1, a single-arm phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute graft-vs-host disease. *Blood*. 2018;132(Suppl 1):601.
18. Modi B, Hernandez-Henderson H, Yang D, et al. Ruxolitinib as salvage therapy for chronic graft-versus-host disease. *Biol Bone Marrow Transplant*. 2019;25:265–269.