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Efficacy and Safety of Ruxolitinib in Steroid-Refractory/Dependent Chronic Graft-versus-Host Disease: Real-World Data and Challenges

Sara Redondo*, Albert Esquirol, Silvana Novelli, Ana Carolina Caballero, Ana Garrido, Guadalupe Oñate, Jordi López, Carol Moreno, Silvanna-Daniela Saavedra, Miquel Granell, Javier Briones, Jorge Sierra, Rodrigo Martino, Irene García-Cadenas

Hematology Department, Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau and José Carreras Leukemia Research Institutes, Departamento de Medicina, Universidad Autónoma de Barcelona, Barcelona, Spain

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A B S T R A C T

Steroid-refractory (SR) chronic graft-versus-host disease (cGVHD) is a major obstacle in recipients of allogeneic stem cell transplantation (HCT). Ruxolitinib is the first agent to demonstrate superior efficacy to the best available therapy, but real-life data are still lacking. Here we describe the results of ruxolitinib compassionate use for the treatment of SR/steroid-dependent cGVHD in a tertiary care university hospital. In this retrospective single-center study, we evaluated the outcomes of 48 patients diagnosed with SR-cGVHD who were treated with ruxolitinib. Forty-seven (98%) had moderate-severe disease, and 27 (56%) had received ≥2 lines of prior therapy (excluding steroids). Results were analyzed using SPSS version 26.0.01 and R version 3.4.3. The overall response rate was 77% (37 of 48), with 15% (7 of 37) in complete remission. The median time to response was 2 months (range, 0.5 to 8 months). Steroid tapering was achieved in 26 patients (54%) and definitive discontinuation was achieved in 10 patients (21%) after a median of 20 months (range, 1.5 to 60 months). Toxicity was predominantly hematologic, including a 33% rate of anemia and a 17% rate of thrombocytopenia. Overall survival at 2 years was significantly higher in responders compared with nonresponders (88% [95% confidence interval (CI), 65% to 96%] versus 49% [95% CI, 12% to 78%]; $P = .01$). At last follow-up, tapering of ruxolitinib had been started in 8 of 37 responders (22%). Our experience supports the efficacy of ruxolitinib in the treatment of SR-cGVHD, along with its steroid-sparing effect and manageable toxicity. Gradual tapering of ruxolitinib seems feasible without cases of GVHD flare. More studies and longer follow-up are needed to confirm these data, as well as to identify the ideal dose adjustments in cases of toxicity.

INTRODUCTION

Chronic graft-versus-host disease GVHD (cGVHD) is the most common long-term complication after allogeneic hematopoietic stem cell transplantation (HCT) and has a substantial impact not only on survival, but also on the quality of life of HCT survivors [1]. Despite current standard prophylaxis, 25% to 80% of HCT recipients will develop cGVHD, and more than one-third of them will not to respond to first-line therapy, which still consists of systemic corticosteroids for all but those with limited skin/mucosal disease [2]. Although multiple agents had been tested in the treatment of cGVHD, none had proven efficacy in prospective randomized trials until the recent approval of ruxolitinib, which explains the lack of consensus on the optimal second-line treatment for patients who are steroid-refractory, -dependent, or -intolerant [3–5].

In 2015, a multicenter retrospective survey in various European and US transplantation centers established the potential therapeutic benefit of ruxolitinib in the treatment of steroid-refractory GVHD (SR-GVHD) [6]. Subsequently, the prospective REACH-1 phase II trial showed responses in 54.9% of patients with acute forms of SR-GVHD who received ruxolitinib [7]. Based on these results, on May 2019, the Food and Drug Administration approved the use of ruxolitinib for SR acute GVHD (aGVHD) in patients age ≥12 years. A subsequent phase 3 trial confirmed previously reported findings showing a significantly stronger and more durable response of ruxolitinib with respect to investigator-selected best available treatment (BAT) in this setting [8]. Finally, recently published results of the REACH-3 phase III trial showed that compared with BAT, ruxolitinib provides superior overall response, failure-free

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*Correspondence and reprint requests: Sara Redondo, Hospital de la Santa Creu i Sant Pau, Mas Casanovas 90, 08041, Barcelona, Spain
E-mail address: sredondov@santpau.cat (S. Redondo).

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survival, and symptom response in patients with SR-cGVHD [9–11].

Taking into consideration that ruxolitinib is likely going to change the standard of care for SR-GVHD, real-world studies will help identify existing and potential pitfalls of this drug not identified in prospective controlled trials. In addition, the currently available data do not allow identification of optimal dosing, especially in the event of toxicity, and do not provide guidance on how should the drug be tapered in responding patients [12,13].

METHODS

Patients

This retrospective observational single-center study included 48 consecutive patients diagnosed with SR-cGVHD after allogeneic HCT who received ruxolitinib under compassionate use institutional protocol between April 2016 and March 2021 in a tertiary university hospital. The follow-up of cases from a multicentric study [12], which represent approximately 10% of the patients reported herein, was updated, and additional data were included. Informed consent was obtained from all treated patients, and the compassionate use was approved by the hospital administration. For safety and response evaluations, all data were collected from the patients' electronic medical record.

The severity of cGVHD was evaluated according to the international consensus headed by the National Institutes of Health [14]. SR-cGVHD was defined as worsening signs/symptoms while on prednisone at a dose of at least 1 mg/kg/day for 1 to 2 weeks or the requirement for prednisone at a dose of a least 0.5 mg/kg/day for at least 4 weeks. Although SR-cGVHD is classically defined as the inability to taper corticosteroids, in this study both types were classified as SR-cGVHD for simplicity.

Ruxolitinib Dosing and Response

Ruxolitinib was initiated orally at a dose of 5 mg twice daily (b.i.d.) and was increased to 10 mg b.i.d. if no response and no attributable toxicities occurred. However, the dose was lowered to 5 mg b.i.d. if ruxolitinib-attributed cytopenia occurred at the high dose, and to 5 mg once daily if it occurred at the initial dose of 5 mg b.i.d.

Patients were scored for their best response at any time after starting ruxolitinib, based on National Institutes of Health criteria [14]. Treatment responses were considered when patients achieved a complete response (CR; defined as the absence of all manifestations of cGVHD) or partial response (PR; defined as an improvement in all organ scores from baseline/laboratory clinical status). The overall response rate (ORR) was the combined CR and PR rates. Other types of responses were considered treatment failures, including of course progression of cGVHD in any organ during ruxolitinib administration. Discontinuation of ruxolitinib due to toxicity was not considered treatment failure.

Supportive Care and Anti-Infectious Prophylaxis

Antiviral prophylaxis consisted of low-dose acyclovir (400 mg b.i.d. i.v. or equivalent oral dosage). Broad-spectrum antifungal prophylaxis (other than fluconazole) was recommended in cases of prolonged high-dose steroid administration; however, the timing and duration of prophylaxis varied considerably among patients. Cotrimoxazole or pentamidine prophylaxis was administered until the CD4 T cell count exceeded 200/mm^3 for 6 consecutive months. Serial blood monitoring using quantitative PCR for cytomegalovirus (CMV) was initially done once weekly but later was performed at each follow-up visit, at varying time intervals.

Statistical Methods

Results were analyzed using SPSS version 26.0.01 (IBM, Armonk, NY). *P* values <.05 were considered statistically significant. OS was estimated and plotted using the Kaplan-Meier method. The log-rank test was applied to compare Kaplan-Meier curves. The chi-square test or Fisher's exact *t* test were used to compare the ORR by different variables analyzed. The proportional hazards method was used to estimate the cumulative incidence of relapse and nonrelapse mortality (NRM). Relapse and NRM were competing risks for each other. R version 3.4.3 (R Project for Statistical Computing, Vienna, Austria) was used for the estimation of cumulative incidences. Owing to the small sample size, no multivariate analyses were performed.

RESULTS

Study Population

Between April 2016 and March 2021, 48 patients with SR-cGVHD were treated with ruxolitinib under a compassionate use institutional protocol. Thirty patients (63%) were male, and the median patient age was 49 years (range, 18 to 72). The most frequent underlying diseases were acute myelogenous leukemia (n = 17; 35%), myelodysplastic syndrome (n = 10; 21%), and acute lymphoblastic leukemia (n = 9; 19%). Most (67%; n = 32) had received a reduced-intensity conditioning regimen (RIC), and 27 patients (56%) had an HLA-identical sibling donor. Twenty-two patients (46%) had developed prior aGVHD grade II-IV. Patient characteristics are summarized in Table 1.

The median time from HCT to the diagnosis of cGVHD necessitating systemic treatment was 16 months (range, 4 to 33 months). Ruxolitinib was started at a median of 5 months (range, 0.6 to 21 months) after the diagnosis of cGVHD. At the time of ruxolitinib initiation, 18 patients (38%) had severe cGVHD, and 29 (60%) had moderate cGVHD. Forty-three patients (90%) had involvement of ≥2 sites or organs. The skin was the most frequently affected organ (n = 35; 73%), followed by the eyes (n = 30; 62%) and the mouth (n = 24; 50%) (Table 2). Twenty-seven patients (56%) had received ≥2 lines of prior therapy (excluding steroids). Twenty-eight patients (58%) were considered to have truly SR-cGVHD (58%), whereas the other 20 had steroid-dependent cGVHD (42%).

Response to Ruxolitinib

After a median duration of treatment of 12 months (range, 2 to 60 months), the ORR was 77% (37 of 48), including 7 patients (15%) with a CR, achieved at a median of 2 months of

Table 1
Patient Characteristics

Characteristic	Value
Patients, n	48
Age, yr, median (range)	49 (18-72)
Male sex, n (%)	30 (63)
Baseline disease, n (%)	
AML	17 (35)
MDS	10 (21)
ALL	9 (19)
Others	12 (25)
Disease status at previous HSCT, n (%)	
CR	39 (82)
PR	4 (8)
SD	4 (8)
Progression	1 (2)
Peripheral blood stem cell source, n (%)	46 (96)
HCT-CI >3, n (%)	11 (23)
EBMT risk score >4, n (%)	16 (33)
Donor type, n (%)	
Related HLA-identical	27 (56)
Unrelated identical	19 (40)
Unrelated mismatch	2 (4)
CMV serostatus, donor-/recipient-, n (%)	9 (19)
Donor-recipient sex match: female to male, n (%)	13 (27)
CD34/kg E6, median (range)	5.99 (1.60-9.87)
CD3/kg E8, median (range)	2.08 (0.87-5.46)
Conditioning regimen, n (%)	
Myeloablative	16 (33)
Reduced intensity	32 (67)
GVHD prophylaxis, n (%)	
Sirolimus-tacrolimus	19 (40)
Calcineurin inhibitor-MTX	17 (36)
PTCy	6 (12)
Other	6 (12)
Prior acute GVHD, n (%)	
Yes	34 (71)
Grade II-IV	22 (46)
SR-aGVHD	6 (13)

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; SD, stable disease; MTX, methotrexate; PTCy, post-transplantation cyclophosphamide.

Table 2
Chronic GVHD Characteristics

Characteristic	Value
National Institutes of Health score, n (%)	
Mild	1 (2)
Moderate	29 (60)
Severe	18 (38)
Organs involved, n (%)	
>1 organ involved	43 (90)
Skin	35 (73)
Ocular	30 (62)
Oral	24 (50)
Lung	12 (25)
Gut	11 (23)
Liver	9 (19)
cGVHD myofasciitis	8 (17)
Indication for ruxolitinib, n (%)	
Steroid-refractoriness	28 (58)
Steroid-dependency	20 (42)
Prior lines of therapy other than steroids, n (%)	
1	21 (44)
2	15 (31)
≥3	12 (25)
Days of prior exposure to steroids, median (range)	687 (16-6435)
Steroid dose at the start of ruxolitinib therapy, mg/kg, median (range)	0.3 (0-1.5)
Time to start of ruxolitinib therapy, mo, median (range)	21 (0.6-214)

treatment (range, 0.5 to 8 months) (Table 3). Eleven patients (23%) experienced treatment failure. The median duration of response at last follow-up was 11 months (range, 0 to 55 months). By organ involvement, the ORR was 77% (27 of 35) in patients with skin sclerotic changes, 45% (5 of 11) in those with gut involvement, and 33% (4 of 12) in those with lung disease.

The median dose of concomitant prednisone at the start of ruxolitinib therapy was 0.3 mg/kg (range, 0 to 1.5 mg/kg). At their last follow-up, 36 patients (75%) who were receiving a median prednisone dose of 0.13 mg/kg (range, 0 to 1.1 mg/kg) had a dose reduction, with a reduction of at least 50% of the initial dose in 24 patients (50%), and prednisone had been discontinued in 10 patients (21%).

The ORR was similar in patients with moderate cGVHD and those with severe cGVHD (74% versus 77%; $P = .60$). The ORR was not influenced by the number of involved organs (75% in patients with 1 organ versus 74% in those with >1 organ; $P = .4$) or by the number of previous lines of treatment (76% in patients with 1 line versus 73% in those with ≥2 lines; $P = .9$).

Table 3
Response To Ruxolitinib Treatment

Response	Value
Patients, n (%)	37 (77)
Overall response, n (%)	
PR	30 (62)
CR	7 (15)
None	11 (23)
Skin response, n (%)	
PR	20 (57)
CR	7 (20)
None	8 (23)
Lung response, n (%)	
PR	4 (33)
None	8 (67)
Gut response, n (%)	
PR	6 (45)
None	6 (55)
Time to response, mo, median (range)	2 (0.5-8)
Duration of response, d, median (range)	326 (0-1671)
Steroid dose modification after initiation of ruxolitinib, n (%)	
Reduction	36 (75)
No reduction	12 (25)
50% reduction	24 (50)
Cessation	10 (21)
Current status, n (%)	
Alive	40 (83)
Dead	8 (17)

Toxicity

Thirty-one patients (64%) developed at least 1 side effect attributed to ruxolitinib (Table 4). The most frequent side effect was anemia (33%; n = 16; 6% grade 3-4), followed by thrombocytopenia (17%; n = 8; 8% grade 3-4), severe infection as defined by Cordonnier et al. [15] (18%; n = 9), cytomegalovirus reactivation (8%; n = 4), moderate liver toxicity (10%; n = 5), and thromboembolic events (10%; n = 5), including 3 cases of pulmonary embolism and 2 cases of deep vein thrombosis. Four patients (8%) discontinued treatment owing to severe infection, including pneumonia without microbiological documentation in 2 patients and invasive pulmonary aspergillosis and *Pneumocystis jirovecii* pneumonia in 1 patients each. Four patients (8%) had a ruxolitinib dose reduction owing to severe cytopenia (n = 3) or moderate hepatic impairment (n = 1).

Long-Term Outcomes

At data cutoff in March 2021, the median duration of follow-up for survivors after the start of ruxolitinib therapy was 20 months (range, 1.5 to 60 months). The cumulative incidence of NRM at 2 year was 15% (95% confidence interval [CI], 6% to 31%). Causes of NRM included invasive fungal infection in 4 patients receiving low to intermediate doses of steroids without antifungal prophylaxis with a triazole, pneumonia without microbiological documentation in 2 patients, and septic shock in 1 patient. Three of these patients experienced treatment failure, and 4 of them had achieved a PR with ruxolitinib. Relapse of the underlying malignancy occurred in only 2

Table 4
Toxicities During Ruxolitinib Treatment

Toxicity	**n (%)**
Ruxolitinib-attributed side effects	31 (64)
Cytopenia any grade/grade 3/4	
Anemia	16 (33)/3 (6)
Thrombocytopenia	8 (16)/4 (8)
Leukopenia	2 (5)/1 (2.5)
Severe infections	9 (18)*
CMV reactivation	4 (8)
Thromboembolism	
Pulmonary embolism	3 (6)
Deep vein thrombosis	2 (5)
Liver function injury (mild grade)	5 (10)
Others	
Edema	4 (8)
Dizziness	3 (6)
Hypertension	2 (4)
Diarrhea	2 (4)
Abnormal creatinine	1 (2)
Action	
Dose reduction	4 (8)
Discontinuation	5 (10.5)
No actions	22 (43)

* Includes 4 cases of possible/probable invasive pulmonary aspergillosis, 2 possible *Pneumocystis jirovecci* pneumonias, 1 *Mycobacterium avium-intracellulare* complex lower respiratory tract infection, and 2 cases of pneumonia of unknown etiology.

patients (4%) who obtained a PR with ruxolitinib. The 2-year OS for all treated patients was 83% (n = 40) (95% CI, 68% to 93%) and was significantly better in ruxolitinib responders than in nonresponders (88% [95% CI, 65% to 96%] versus 49% [95% CI, 12% to 78%]; $P = .01$) (Figure 1).

Overall, 46% of the patients (n = 22) discontinued ruxolitinib owing to lack of response (n = 10; 21%), drug-related toxicity (n = 5; 10.5%), death (n = 4; 8.5%), relapse (n = 2; 4%), or prolonged CR (n = 1; 2%). At last follow-up, 12 patients (25%) had a ruxolitinib dose reduction owing to drug-related toxicity (n = 4; 8%) or prolonged response (n = 8; 17%).

DISCUSSION

Ruxolitinib is considered by many to be the new standard of care for patients with SR- cGVHD [11]. In this single-center real life study, the ORR was 77%, with PR predominating (62%). These outcomes are similar to those previously published in other retrospective studies [6,12].

Our analysis did not identify differences in terms of response between patients with moderate disease and those with severe disease (74% versus 77%; $P = .60$) or depending on the number of involved organs (75% for 1 organ versus 74% for $\geq$2 organs; $P = .4$). Remarkably, response rates were also similar regardless of the number of previous lines of treatment (76% for 1 line versus 73% for $\geq$2 lines; $P = .9$). Of note, in the REACH-2 trial, 49 patients with SR-aGVHD who failed to respond in the control/BAT group were crossed over to ruxolitinib treatment and then showed a response rate similar to that seen in the ruxolitinib arm in the primary analysis, supporting the use of ruxolitinib in patients who have failed other systemic therapies beyond steroids [16].

Responses were observed in many patients with skin involvement (77%) and gut involvement (45%) but in fewer patients with bronchiolitis obliterans (33%), highlighting that many patients with SR-cGVHD still need better treatments beyond ruxolitinib [17]. In most patients, clinical signs of cGVHD were present in several organs, whereas 4 patients (8%) had isolated skin involvement, all of whom had sclerotic manifestations. All of these patients responded to ruxolitinib, with 2 CRs and 2 PRs. In fact, in the REACH-3 trial, very low responses were observed in patients with ocular (26%), hepatic (24.4%), and especially pulmonary (8.6%) involvement [11].

In the present study, the safety profile was manageable and consistent with prior reports [11,18]. The most frequent side effects included cytopenias, and these cases improved after a ruxolitinib dose reduction and/or addition of an erythropoietin-stimulating agent (ESA) for anemia. Eight out of 16 patients (50%) who developed moderate to severe anemia associated with ruxolitinib received an ESA during the study period. ESA administration was associated with higher hemoglobin levels and substantial improvement of anemia-related symptoms in all cases, precluding the need for ruxolitinib dose interruptions.

The incidence of grade 3 infections was 18% (n = 9), similar to previously published data [11]. Multiple studies have shown that GVHD and its treatment put patients at risk for CMV reactivation [6,12]; however, we found a low incidence of CMV reactivation (8%), similar to the observed in the REACH-3 trial [11].

GVHD is a well-known prothrombotic state, and affected patients are at greater risk of experiencing a thromboembolic event (TEE) [19,20]. In our series, 10% of the patients (n = 5) had a TEE, including 3 cases of pulmonary embolism and 2 cases of deep vein thrombosis, albeit not necessitating ruxolitinib discontinuation. In contrast, several reports in patients treated for myelofibrosis suggest that ruxolitinib may reduce the JAK2 V617F^{+} thrombotic risk through reductions in proadhesive endothelial activation and neutrophil extracellular trap formation [21,22]. Despite our high rate of TEE, this finding is not supported by the REACH-2 or REACH-3 trial and thus could have occurred simply by chance in our population at high risk for developing TEE.

In our series, infection was the most frequent cause of treatment discontinuation and NRM. Despite important advances in this area, severe infection remains the most frequent cause of morbidity and mortality in patients with GVHD even with the most optimal antimicrobial prophylaxis currently available [11]. Limited published data exist regarding the patterns of infections with ruxolitinib in stem cell transplantation recipients [23]. A detailed analysis of these complications in our patients is currently ongoing.

Tapering of prior immunosuppressive agents, especially steroids, is one of the most important endpoints in patients with SR-cGVHD. In our study, a steroid dose reduction was

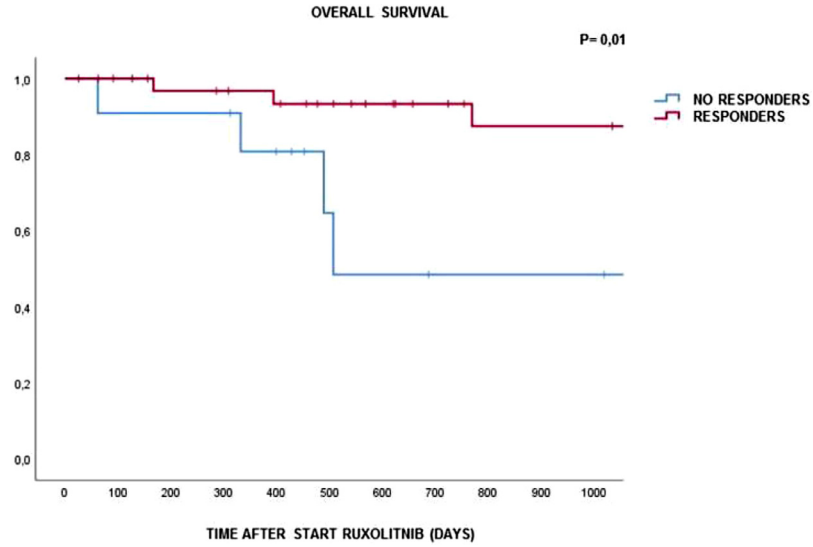

Figure 1. OS by response to ruxolitinib.

possible in 36 patients (75%), with a ≥50% reduction in 24 (50%) and discontinuation in 10 (21%) at the last follow-up. As reported previously [24,25], steroid tapering was initiated as soon as possible, approximately 2 weeks after starting ruxolitinib in responding patients, with dose reductions of at least 5 mg every 3 to 4 weeks. We did not see any cGVHD flares with this taper. Nonetheless, the optimal tapering schedule for ruxolitinib has not yet been established, explaining why many patients with PR continue treatment at the same dose for many months after achieving their best PR.

Rapid ruxolitinib tapering in patients with myelofibrosis often induces a "withdrawal syndrome" characterized by acute relapse of the disease and systemic inflammation, and many clinicians fear a high risk of GVHD flare if ruxolitinib is abruptly discontinued [26]. In our study, after withdrawal of glucocorticoids (or a >90% steroid reduction and stable daily prednisone dose <10 mg/day without GVHD flair), the ruxolitinib dose was reduced by 50%, followed by prolonged administration of low-dose ruxolitinib; 5 mg of ruxolitinib was administered for >6 months before its complete discontinuation. A ruxolitinib dose reduction was possible in 8 of 37 patients (22%) after achievement of a prolonged CR or a very good PR, without any cGVHD flares.

Some limitations of our study are intrinsic to its real-life and unicentric nature, including a potential bias in patient selection as well as a small sample size. Despite these limitations, however, this analysis demonstrates the efficacy of ruxolitinib in clinical practice to treat SR-cGVHD.

In summary, ruxolitinib treatment appears to be safe in real-life practice, with remission rates in SR-cGVHD consistent with those reported in clinical trials and in heavily pretreated patients. Gradual tapering of both steroids and ruxolitinib appears feasible in a significant number of cases. More studies and longer follow-up are needed to confirm these data, as well as to identify the ideal dose adjustments in the event of toxicity (potentially with pharmacokinetic monitoring) and the ideal tapering schedule in responding patients.

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