ISSN: 2766-9556

Journal of Clinical Case Studies and Reviews

Review Article Open Access

Steroid-Refractory Chronic Graft-versus-Host Disease Treated with Ruxolitinib: A Narrative Review of Symptom Burden and Return to Daily Life

Jens Holm[1*], Simona Radu[2] and Petra Zupan[3]

[1]Department of Haematology and Stem Cell Transplantation, Funen Institute of Clinical Research, Odense, Denmark

[2]Department of Transplant Immunology, Moldavian University Hospital, Iasi, Romania

[3]Department of Occupational Therapy, Drava Institute of Clinical Medicine, Maribor, Slovenia

***Correspondence to:** Jens Holm, Department of Haematology and Stem Cell Transplantation, Funen Institute of Clinical Research, Odense, Denmark

Received: 4 May 2023; **Accepted:** 30 August 2023; **Published:** 4 November 2023

Copyright: © 2023 JH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Chronic graft-versus-host disease is the price a proportion of transplant survivors pay for their cure. Roughly half of those treated with glucocorticoids do not respond adequately, and until recently the second line was a list of options rather than a standard.

***Objectives:** To review the published evidence on ruxolitinib for glucocorticoid-refractory or dependent chronic graft-versus-host disease: what it achieves against the alternatives, how durable the effect is, what it costs in toxicity, and what the trial did not measure.*

***Material and Methods:** Narrative review of randomised trials, phase 2 studies, consensus criteria and outcome literature indexed in PubMed and the major haematology and transplantation journals. No new patient data were generated; every estimate quoted is one published by the original investigators.*

***Results:** In a phase 3 randomised trial of 329 patients, overall response at week 24 was 49.7 per cent with ruxolitinib against 25.6 per cent with best available therapy (odds ratio 2.99, $p < 0.001$), and best overall response to week 24 was 76.4 against 60.4 per cent. Median failure-free survival was 18.6 against 5.7 months (hazard ratio 0.37, 95% CI 0.27 to 0.51), and symptom response 24.2 against 11.0 per cent. At 36 months, 56.5 per cent against 18.2 per cent remained failure-free. Thrombocytopenia and anaemia were more common with ruxolitinib.*

***Conclusion:** Ruxolitinib is the first agent to beat a mixed comparator arm in a randomised trial in this disease, and the failure-free survival difference is the most clinically meaningful of its findings. Half of treated patients still did not respond, the comparator was heterogeneous by design, and the outcome measures capture organ scores rather than the daily function that defines the illness for the patient.*

***Abbreviations:** BAT – Best Available Therapy, cGVHD – Chronic Graft-versus-Host Disease, ECP – Extracorporeal Photopheresis, FFS – Failure-Free Survival, JAK – Janus Kinase, mSGRC – Modified Lee Symptom Scale Response, ORR – Overall Response Rate.*

Keywords: *Chronic Graft-versus-Host Disease; Ruxolitinib; JAK Inhibition; Steroid-Refractory Disease; Allogeneic Transplantation*

Introduction

Allogeneic haematopoietic cell transplantation cures malignancies that nothing else cures, and chronic graft-versus-host disease is the commonest reason its survivors do not feel cured. It affects a substantial proportion of long-term survivors, involves skin, mouth, eyes, gut, liver, lungs, joints and genitalia in varying combinations, and is the leading cause of non-relapse mortality and of impaired quality of life after transplantation [1,2,3,32].

Diagnosis and severity grading were standardised by consensus rather than derived from biology, which shapes everything downstream: the trials use response criteria built on organ scores, and those criteria were themselves revised as understanding changed [4,5,6]. Systemic glucocorticoids remain first-line treatment, and approximately half of patients become refractory to or dependent on them [7,8].

For those patients the second line was, until recently, a choice among options with little comparative evidence: extracorporeal photopheresis, mycophenolate mofetil, ibrutinib, rituximab, calcineurin inhibitors and others [9,10,11], with retrospective series showing how modest the success of each has been [29]. Preclinical work implicating Janus kinase signalling in the inflammation and tissue damage of graft-versus-host disease provided a rationale for testing ruxolitinib, a JAK1 and JAK2 inhibitor already licensed in myelofibrosis [12,13]. This review examines what that testing showed.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and transplantation journals were searched for studies of treatment for chronic graft-versus-host disease. Search terms combined chronic graft-versus-host disease with steroid-refractory, second-line, ruxolitinib, JAK inhibition, ibrutinib, photopheresis and failure-free survival. Reference lists of consensus documents [4,5,6] were screened by hand for primary sources.

Eligibility: Studies were included if they reported response, survival or toxicity outcomes for systemic treatment of chronic graft-versus-host disease, or defined the criteria by which those outcomes are measured. Trials in acute graft-versus-host disease are cited where they establish the mechanism or the safety profile, and are identified as such.

Data extraction and handling: Design, sample size, comparator, response definition and reported estimate were extracted as published. The composition of the comparator arm is reported alongside every comparative figure, because best available therapy is not a single treatment and the interpretation depends on what it contained. No pooling or re-analysis was performed. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The trial: REACH3 randomised 329 patients with moderate or severe chronic graft-versus-host disease that was refractory to or dependent on glucocorticoids. Median age was 49 years; 42.9 per cent had moderate and 56.5 per cent severe disease; 71.4 per cent were refractory and 28.6 per cent dependent. The comparator arm received best available therapy, most commonly extracorporeal photopheresis (34.8 per cent), mycophenolate mofetil (22.2 per cent) or ibrutinib (17.1 per cent) [14].

Response: Overall response at week 24, the primary endpoint, was 49.7 per cent with ruxolitinib against 25.6 per cent with best available therapy (odds ratio 2.99, $p < 0.001$), and the advantage held regardless of which organs were involved at baseline (Figure 1) [14]. Best overall response at any point to week 24 was 76.4 against 60.4 per cent (odds ratio 2.17, 95% CI 1.34 to 3.52), and symptom response on the modified Lee scale was 24.2 against 11.0 per cent (Figure 2) [14].

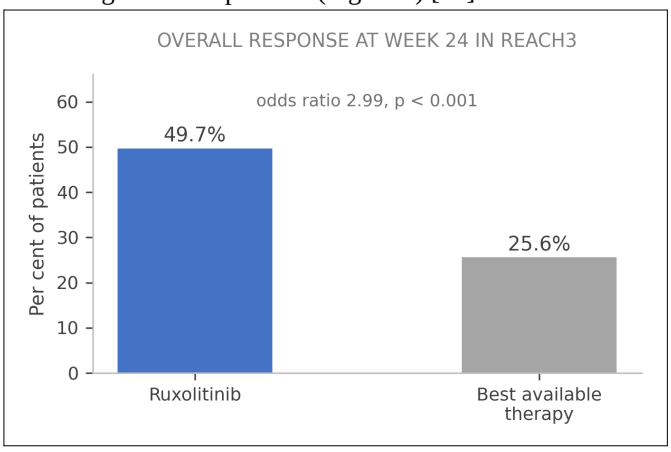

Figure 1: Overall response at week 24 in REACH3, ruxolitinib against best available therapy [14]

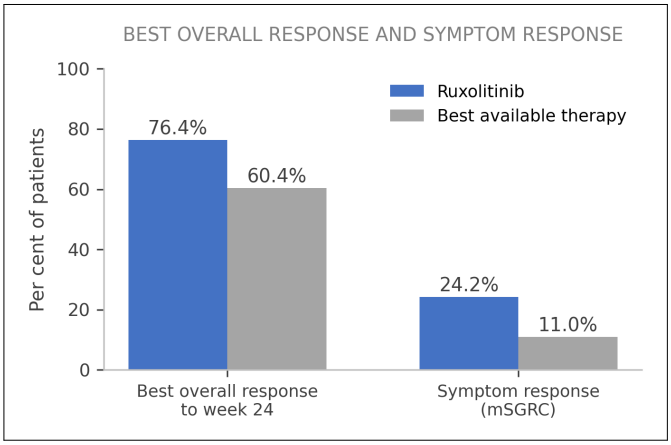

Figure 2: Best overall response to week 24 and symptom response on the modified Lee scale [14]

Durability: The finding with the clearest clinical meaning is failure-free survival, a composite that counts relapse, non-relapse mortality and the need to start another systemic therapy. Median failure-free survival was 18.6 months with ruxolitinib against 5.7 months with best available therapy (hazard ratio 0.37, 95% CI 0.27 to 0.51) (Figure 3) [14]. Longer

follow-up confirmed the separation: at 36 months, 56.5 per cent of ruxolitinib-treated patients remained failure-free against 18.2 per cent, and 59.6 against 26.7 per cent had maintained their response (Figure 4) [15].

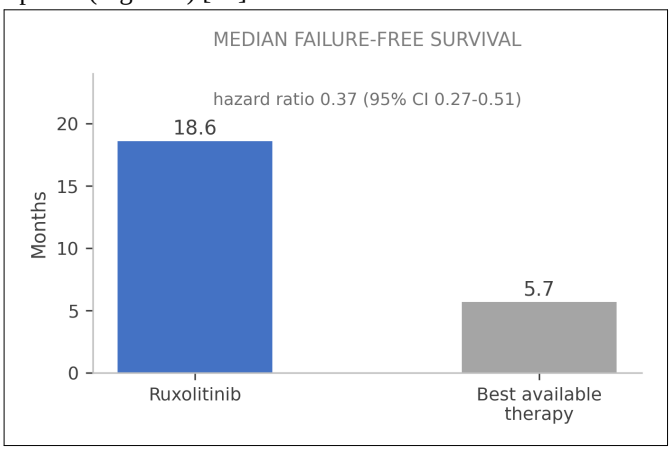

Figure 3: Median failure-free survival in REACH3 [14]

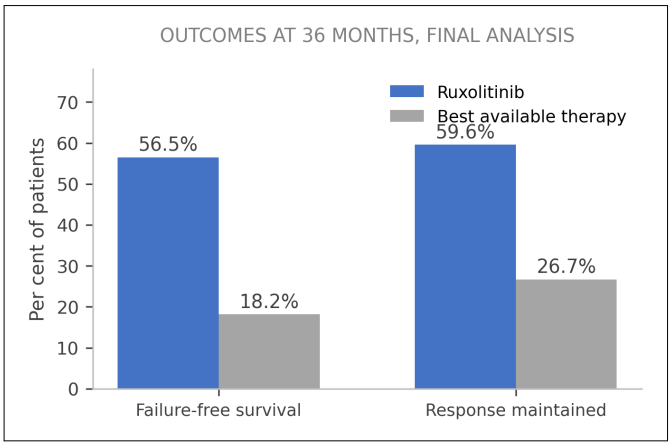

Figure 4: Failure-free survival and maintained response at 36 months in the final analysis [15]

Study	Design and cohort	Principal reported finding
Zeiser et al. 2021 [14]	Phase 3 RCT, 329 patients, chronic GVHD	ORR 49.7% vs 25.6% (OR 2.99); FFS 18.6 vs 5.7 months
Zeiser et al. 2025 [15]	REACH3 3-year final analysis	FFS at 36 months 56.5% vs 18.2%; response maintained 59.6% vs 26.7%
Zeiser et al. 2020 [16]	REACH2, phase 3 RCT, acute GVHD	Higher overall response at day 28 and durable response at day 56
Jagasia et al. 2020 [17]	REACH1, phase 2, acute GVHD	Supported activity of ruxolitinib in steroid-refractory disease
Zeiser et al. 2015 [18]	Retrospective survey, refractory GVHD	First substantial signal of activity in both acute and chronic disease
Miklos et al. 2017 [19]	Phase 2, ibrutinib in chronic GVHD	Responses in steroid-refractory disease; a comparator in REACH3
Jagasia et al. 2015 [5]	NIH consensus, response criteria	Defines the organ-score endpoints these trials report

Table 1: Principal studies reviewed, with the finding as reported by the original investigators

Toxicity: The safety profile is the predictable consequence of inhibiting JAK signalling in patients already cytopenic after transplantation. Thrombocytopenia and anaemia were more frequent with ruxolitinib, and grade 3 or worse events of both were more common than with best available therapy; no new safety signals emerged [14,15]. Infection and cytomegalovirus reactivation are the concerns that follow from any intensification of immunosuppression in this population, and earlier series reported reactivation rates comparable with other second-line agents [18,20]. Relapse of the underlying malignancy is the other theoretical hazard, since graft-versus-leukaemia activity depends on the same immune system being suppressed; the reported relapse rates have not suggested an excess [18,21].

What it displaced: Interpreting the size of the effect requires knowing what ruxolitinib was compared against. Extracorporeal photopheresis, the commonest comparator, has a substantial observational literature but limited randomised support in chronic disease [9,22]. Ibrutinib had shown responses in a phase 2 study and was subsequently tested against placebo without confirming benefit in the first-line setting [19,23]. Mycophenolate mofetil has been examined in randomised trials without demonstrating clear advantage [24]. Guidance on how to approach refractory disease reflects that uncertainty [33,34]. Best available therapy was therefore a mixture of agents of varying and mostly modest evidential standing, which is realistic clinical practice but makes the comparison one against usual care rather than against a specific alternative.

Outcome	Ruxolitinib vs best available therapy	Interpretation
Overall response, week 24	49.7% vs 25.6% (OR 2.99)	Primary endpoint; organ-score based [14]
Best overall response	76.4% vs 60.4% (OR 2.17)	Includes transient responses [14]
Median failure-free survival	18.6 vs 5.7 months (HR 0.37)	Most clinically meaningful endpoint [14]
Symptom response (mSGRC)	24.2% vs 11.0%	Patient-reported; low in both arms [14]
Failure-free survival, 36 months	56.5% vs 18.2%	Separation is durable [15]
Thrombocytopenia and anaemia	More frequent with ruxolitinib	Expected from JAK inhibition after transplant [14]

Table 2: Reported outcomes in REACH3 and what each measures

Discussion

REACH3 changed practice, and it deserved to. It is the first adequately powered randomised trial in glucocorticoid-refractory chronic graft-versus-host disease to show superiority over the alternatives clinicians were actually using, and the effect is consistent across response, durability and symptoms [14]. The failure-free survival difference, from a median of under six months to over eighteen, is the finding that matters most, because it describes how long a patient goes before someone has to try something else, which is why this composite became the standard measure of benefit in chronic

graft-versus-host disease [30,31].

Three qualifications belong alongside that. The first is arithmetic: half the patients given ruxolitinib did not respond at week 24. The trial establishes a better option, not a solution, and the group who fail it now constitute the population for whom there is again no standard; belumosudil has since been studied after two or more prior lines [28].

The second concerns the comparator. Best available therapy was chosen by the investigator from a list, and its three commonest components had between them little randomised evidence of efficacy in this setting [9,19,24]. Beating a heterogeneous arm of weakly supported treatments is a lower bar than beating a specific active comparator, and the odds ratio should be read with that in mind. This is not a criticism of the design, which reflected real practice, but it does limit what the number means.

The third concerns what was measured. Overall response is defined by organ scores and clinician assessment. Symptom response, the endpoint closest to how the patient experiences the disease, was achieved by 24.2 per cent on ruxolitinib and 11.0 per cent on best available therapy: better, but low in absolute terms, and considerably lower than the organ-based response rate [14]. The gap between those two numbers is the gap between a sclerotic skin score improving and a patient being able to grip a fork. Function, fatigue, return to work and the burden carried by families are not endpoints in any of these trials, and the rehabilitation literature that addresses them sits almost entirely apart from the drug literature [25,26,27].

Study limitations

The limitations belong to the underlying literature. The comparator arm was heterogeneous and its components weakly evidenced [9,19,24]. Crossover from best available therapy to ruxolitinib was permitted after week 24, which is appropriate ethically but confounds any long-term survival comparison [15]. Response criteria are consensus-derived organ scores rather than validated measures of function, and have been revised over time, so results across eras are not strictly comparable [4,5,6]; the most severe manifestations were separately characterised only recently [35]. Patients enrolled had moderate or severe disease and were fit enough for a trial, so the frailest are not represented. Follow-up of three years is short relative to a condition survivors live with for decades [15]. Toxicity in a population already cytopenic is difficult to attribute confidently to any single agent [14]. And patient-reported and caregiver outcomes are sparse throughout [25,26].

Conclusion

For chronic graft-versus-host disease that does not respond to glucocorticoids, ruxolitinib now has the best randomised evidence available: roughly double the response rate of the alternatives, and a threefold longer interval before treatment fails. That is a genuine advance in a disease where advances have been rare. It should be described precisely, though. Half of patients do not respond; the comparator was a mixture of options that had never themselves been shown to work well; and the endpoint that reflects what patients feel improved in only about a quarter. The next question is not whether ruxolitinib works but what to offer the half for whom it does not, and whether any of these treatments returns people to the lives their transplant was supposed to give back.

Acknowledgements

The authors thank the investigators whose trials and consensus work are drawn together in this article, and the patients who completed symptom scales through prolonged immunosuppressive treatment.

Funding

No dedicated funding from public, commercial or charitable sources supported the preparation of this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

1. Zeiser R, Blazar BR. "Pathophysiology of chronic graft-versus-host disease and therapeutic targets". N Engl J Med 377(2017):2565-2579.

2. Lee SJ. "Classification systems for chronic graft-versus-host disease". Blood 129(2017):30-37.

3. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, et al. "Long-term survival and late deaths after allogeneic hematopoietic cell transplantation". J Clin Oncol 29(2011):2230-2239.

4. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, 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 11(2005):945-956.

5. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. "National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report". Biol Blood Marrow Transplant 21(2015):389-401.

6. Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M, et al. "Measuring therapeutic response in chronic graft-versus-host disease: 2014 response criteria working group report". Biol Blood Marrow Transplant 21(2015):984-999.

7. Flowers MED, Martin PJ. "How we treat chronic graft-versus-host disease". Blood 125(2015):606-615.

8. Wolff D, Fatobene G, Rocha V, Kroger N, Flowers ME. "Steroid-refractory chronic graft-versus-host disease: treatment options and patient management". Bone Marrow Transplant 56(2021):2079-2087.

9. Malagola M, Cancelli V, Skert C, Leali PF, Ferrari E, Tiburzi A, et al. "Extracorporeal photopheresis for treatment of acute and chronic graft versus host disease: an Italian multicentric retrospective analysis". Transplantation 100(2016):e147-e155.

10. Martin PJ, Storer BE, Carpenter PA, Chien JW, Flowers MED, Inamoto Y, et al. "Comparison of short-term response and long-term outcomes after initial systemic treatment of chronic graft-versus-host disease". Biol Blood Marrow Transplant 17(2011):124-132.

11. Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F, et al. "Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation". Lancet Haematol 7(2020):e157-e167.

12. Spoerl S, Mathew NR, Bscheider M, Schmitt-Graeff A, Chen S, Mueller T, et al. "Activity of therapeutic JAK1/2 blockade in graft-versus-host disease". Blood 123(2014):3832-3842.

13. Choi J, Cooper ML, Alahmari B, Ritchey J, Collins L, Holt M, et al. "Pharmacologic blockade of JAK1/JAK2 reduces GvHD and preserves the graft-versus-leukemia effect". PLoS One 9(2014):e109799.

14. Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. "Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease". N Engl J Med 385(2021):228-238.

15. Zeiser R, Russo D, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. "Ruxolitinib in patients with corticosteroid-refractory or corticosteroid-dependent chronic graft-versus-host disease: 3-year final analysis of the phase III REACH3 study". J Clin Oncol 43(2025):2566-2571.

16. Zeiser R, von Bubnoff N, Butler J, Mohty M, Niederwieser D, Or R, et al. "Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease". N Engl J Med 382(2020):1800-1810.

17. Jagasia M, Perales MA, Schroeder MA, Ali H, Shah NN, Chen YB, et al. "Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial". Blood 135(2020):1739-1749.

18. Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, et al. "Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey". Leukemia 29(2015):2062-2068.

19. Miklos D, Cutler CS, Arora M, Waller EK, Jagasia M, Pusic I, et al. "Ibrutinib for chronic graft-versus-host disease after failure of prior therapy". Blood 130(2017):2243-2250.

20. Rager A, Frey N, Goldstein SC, Reshef R, Hexner EO, Loren A, et al. "Inflammatory cytokine inhibition with combination daclizumab and infliximab for steroid-refractory acute GVHD". Bone Marrow Transplant 46(2011):430-435.

21. Modi B, Hernandez-Henderson M, Yang D, Klein J, Dadwal S, Kopp E, et al. "Ruxolitinib as salvage therapy for chronic graft-versus-host disease". Biol Blood Marrow Transplant 25(2019):265-269.

22. Flowers MED, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V, et al. "A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease". Blood 112(2008):2667-2674.

23. Miklos D, Zaid MA, Cooney JP, Albring JC, Flowers M, Skarbnik AP, et al. "Ibrutinib for first-line treatment of chronic graft-versus-host disease: results from the randomized phase III iNTEGRATE study". J Clin Oncol 41(2023):1876-1887.

24. Martin PJ, Storer BE, Rowley SD, Flowers MED, Lee SJ, Carpenter PA, et al. "Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease". Blood 113(2009):5074-5082.

25. Pidala J, Kurland B, Chai X, Majhail N, Weisdorf DJ, Pavletic S, et al. "Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium". Blood 117(2011):4651-4657.

26. Fiuza-Luces C, Simpson RJ, Ramirez M, Lucia A, Berger NA. "Physical function and quality of life in patients with chronic graft-versus-host disease: a summary of preclinical and clinical studies and a call for exercise intervention trials in patients". Bone Marrow Transplant 51(2016):13-26.

27. Carpenter PA, Kitko CL, Elad S, Flowers MED, Gea-Banacloche JC, Halter JP, et al. "National Institutes of

Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 ancillary therapy and supportive care working group report". Biol Blood Marrow Transplant 21(2015):1167-1187.

28. Cutler C, Lee SJ, Arai S, Rotta M, Zoghi B, Lazaryan A, et al. "Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar study". Blood 138(2021):2278-2289.

29. Lee SJ, Nguyen TD, Onstad L, Bar M, Krakow EF, Salit RB, et al. "Success of immunosuppressive treatments in patients with chronic graft-versus-host disease". Biol Blood Marrow Transplant 24(2018):555-562.

30. Inamoto Y, Flowers MED, Sandmaier BM, Aki SZ, Carpenter PA, Lee SJ, et al. "Failure-free survival after initial systemic treatment of chronic graft-versus-host disease". Blood 124(2014):1363-1371.

31. Palmer J, Chai X, Pidala J, Inamoto Y, Martin PJ, Storer B, et al. "Predictors of survival, nonrelapse mortality, and failure-free survival in patients treated for chronic graft-versus-host disease". Blood 127(2016):160-166.

32. Socie G, Ritz J. "Current issues in chronic graft-versus-host disease". Blood 124(2014):374-384.

33. Jamil MO, Mineishi S. "State-of-the-art acute and chronic GVHD treatment". Int J Hematol 101(2015):452-466.

34. Sarantopoulos S, Cardones AR, Sullivan KM. "How I treat refractory chronic graft-versus-host disease". Blood 133(2019):1191-1200.

35. Wolff D, Radojcic V, Lafyatis R, Cinar R, Rosenstein RK, Cowen EW, et al. "National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2020 highly morbid forms report". Transplant Cell Ther 27(2021):817-835.

Citation: Holm J, Radu S, Zupan P. "Steroid-Refractory Chronic Graft-versus-Host Disease Treated with Ruxolitinib: A Narrative Review of Symptom Burden and Return to Daily Life." J Clin Case Stud (2023): 001-006 doi: 10.5281/zenodo.22227762