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Does Ruxolitinib, in Comparison to Best Available Therapy (BAT), Improve Pruritis Symptoms in Patients with Polycythemia Vera?

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Abstract

Polycythemia vera manifests as a myeloproliferative neoplasm associated with diverse symptoms, including aquagenic pruritis. This systematic review addresses the pressing need to enhance the understanding of the disease's symptomatology and optimize treatment strategies for improved patient outcomes. The rarity and low prevalence of polycythemia vera underscore the importance of this investigation, as existing standard of care involves a multifaceted approach and significant healthcare costs. Despite advancement in therapeutic options, persistent symptoms and resistance to first-line treatments pose challenges. Ruxolitinib has emerged as a promising intervention, demonstrating clinically significant improvement for patients. This systematic review appraises three randomized controlled trials, shedding light on the efficacy of ruxolitinib and its potential to ameliorate pruritis symptoms in symptomatic patients.

Keywords

Polycythemia Vera, Ruxolitinib, Pruritis

1. Introduction

Polycythemia vera is a myeloproliferative neoplasm that is caused by a Janus kinase 2 (JAK2) mutation resulting in an activation of the JAK-STAT signaling pathway and unregulated hyperproliferation of myeloid cells and cytokine production [1]. Specifically, the JAK2 mutation JAK2V617F, has been identified as the responsible mutation for hematopoietic hyperproliferation. Physiologically, in patients with advanced disease progression, it is associated with leukocytosis and thrombocytopenia, differentiating it from other myeloproliferative neop-

lasms [2].

Symptoms associated with polycythemia vera are related to blood hyperviscosity. Most patients can experience a broad range of symptoms including fatigue, pruritis, muscle aches, sweating, shortness of breath, erythromelalgia, and splenomegaly [3]. This results in patients having a substantial disease burden, increased risks of thromboembolic events and shortened survival time. Moreover, recent studies have identified a "masked" presentation leading to a change to the World Health Organization's (WHO) classification system in 2016 to better capture patients with polycythemia vera [3] [4]. The current WHO-qualified diagnostic criteria for polycythemia vera requires the presence of all three major or two majors plus one minor criterion. The major criteria are hemoglobin/hematocrit above 16.5 g/dL/49% in males, hemoglobin/hematocrit above 16 g/dL/48% in females, a red cell mass >25% above mean normal predicted value, and presence of the JAK2V617F mutation, with the minor criteria having a subnormal serum erythropoietin level [5]. The inclusion of JAK2 mutation screening is favorable in the diagnostic process as the V617F mutation has been identified in 95% of patients with polycythemia vera, compared to a prevalence in the general community around 0.2% [6]. Despite recent changes to classification criteria, much remains unknown about the disease, including other possible associated symptoms, additional mutations, and mortality reduction strategies [2]. This is in part due to its relative rarity and low prevalence rates which range from 45 to 57 cases per 100,000 patients in the United States [3].

There is no specific data indicating how many annual healthcare visits patients with polycythemia vera go. However, due to significant symptom burdens and decreased quality of life, the current standard of care treatments requires a multifaceted treatment approach involving hematology, oncology, cardiology, among others, which results in increased healthcare visits each year [3] [4]. Specifically, costs related to polycythemia vera are considerably higher compared to non-cancer diseases due to inpatient and outpatient visits, alongside medication costs [2]. Several studies conducted between 2011 and 2014 found that inpatient costs and outpatient costs for patients with polycythemia vera averaged $6,806 and $4,670 compared to $2,019 and $3,863 for patients with non-cancer conditions, respectively [3]. Similarly, medication costs for polycythemia vera patients averaged $2,897 compared to $1,724 in non-cancer diseases [3]. Currently, no treatment for patients with polycythemia vera has been able to demonstrate remission, leukemia-free, or myelofibrosis-free survival. Treatment options are primarily indicated for thrombolytic prevention and symptom management. First-line treatments that have shown clinical benefits include phlebotomy, aspirin, and cytoreductive medications, such as hydroxyurea [4]. Moreover, chemotherapy options such as busulfan and immunomodulators such as interferon-alfa or ropeginterferon-alfa 2b have also shown therapeutic palliation [4]. Ruxolitinib was first approved for the treatment of patients with intermediate or high-risk myelofibrosis, but was later approved for polycythemia vera patients under priority

review due to its demonstration of providing clinically significant improvement and efficacy compared to other available therapies [2]. Furthermore, many patients report persistent polycythemia vera-associated symptoms despite multiple therapies and approximately 25% of patients become resistant to, or intolerant of, first-line therapeutic options [7]. This systematic review evaluated three randomized controlled trials comparing the efficacy of the Janus kinase inhibitor ruxolitinib in the treatment of polycythemia vera and its reduction of pruritus symptoms in patients with symptomatic polycythemia vera.

2. Methods

Randomized controlled trials that investigated of the use of ruxolitinib and its efficacy in improving pruritic symptoms in patients with polycythemia vera compared with the current best available therapy were included for this systematic review. Furthermore, studies were selected based on their relevance and applicability to the clinical question and evaluation of patient-orientated outcomes. Studies were identified on PubMed and Cochrane library that were published in English and in peer-reviewed journals by using the keywords "polycythemia vera", "ruxolitinib", and "pruritis". Inclusion criteria were studies published from 2012 that were randomized controlled trials with a study population over the age of 18 years with polycythemia vera. Exclusion criteria were studies published before 2012, non-RCT primary studies, secondary studies, and patients without polycythemia vera. Reported statistics include NNT, mean change from baseline, p-values, and calculated ABI and RBI.

2.1. Study Population

In the study conducted by Mesa *et al.*, a total of 110 patients, ranging in age from 19 to 87 years, were enrolled. The inclusion criteria comprised of individuals aged 18 years or older, diagnosed with polycythemia vera, and treated with hydroxycarbamide monotherapy for at least 12 weeks prior to enrollment, exhibiting cytokine-related symptoms as defined as a score of ≥8 on the MPN-SAF. In total, 39 patients withdrew from the study. The interventions involved comparing ruxolitinib, 10 mg BID, versus hydroxycarbamide, with a crossover arm to ruxolitinib permitted after week 16.

In Kiladjian *et al.*, a total of 222 patients, aged 33 - 90 years, were enrolled. Inclusion criteria comprised of individuals aged 18 years or older with polycythemia vera who were resistant or intolerant of hydroxyurea. Exclusion criteria included patients who have received prior JAK-inhibitor therapy, ^{32}P therapy, PEG-IFN-α-2a within 5 weeks of screening, pregnant, lactating, or demonstrated inadequate liver or renal function. In total, 19 patients withdrew from the study. The interventions involved comparing ruxolitinib, 10 mg BID, versus best available therapy with crossover to ruxolitinib permitted after week 32. Additionally, Aspirin, 75 - 150 mg per day, was recommended unless medically contraindicated.

Similarly, in Passamonti *et al.*, a total of 149 patients, ranging in age from 54 to 74 years, were enrolled. The inclusion criteria comprised of individuals aged 18 years or older, diagnosed with polycythemia veraresistant or intolerant of hydroxyurea, without palpable splenomegaly, no prior JAK-inhibitor therapy, and phlebotomy dependent. Exclusion criteria were similar to the previous study. In total, 13 patients withdrew from the study. The interventions involved comparing ruxolitinib, 10 mg BID, versus best available therapy with crossover to ruxolitinib permitted after week 32. Additionally, Aspirin, 75 - 150 mg per day, was recommended unless medically contraindicated.

2.2. Outcomes Measured

The outcomes measured in this systematic EBM review include improved pruritic symptoms that was measured at varying assessment timepointsby using the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and the Pruritus Symptom Impact Scale (PSIS). The MPN-SAF comprises ten items that measures the severity of fatigue, early satiety, abdominal discomfort, inactivity, concentration, night sweats, itching, bone pain, fever, and weight loss. Each item was scored on a scale ranging from 0 (absent) to 10 (worst imaginable) [8]. If a patient assigned a score greater than zero on the MPN-SAF for pruritis, they additionally completed the Pruritus Symptom Impact Scale. The PSIS is a six-item tool that measures the severity of pruritus symptoms and how bothersome it has been for the patient during different periods of time ranging from 0 ("no itching/not bothered at all") to 10 ("bothered as bad as you can imagine/interfered as bad as you can") [8].

3. Results

Mesa *et al.*, conducted a double-blind randomized control trial comparing ruxolitinib, 10 mg BID versus hydroxycarbamide with patients in both arms also receiving low-dose aspirin unless contraindicated. Patients were randomized 1:1 during the 16-week blinded treatment phase with a crossover to the open-label ruxolitinib arm after week 16 until study termination occurred at week 48 [7]. Pruritis symptom severity was assessed once during the screening phase, and then daily at baseline, randomization, and continuation until the end of treatment. The scores at each interval were based on the MPN-SAF scaling and were averaged with the median change from baseline for pruritus symptoms (**Figure 1**).

Secondary endpointsincluded ≥50% reduction (improvement) from baseline in individual MPN-SAF symptom severity at week 16 [7]. The results demonstrated that ruxolitinib is superior at reducing pruritic symptoms compared to hydroxycarbamide, with an odds ratio of 2.51 (95% CI, 1.10-5.71; p-value = 0.027) [7]. The calculated NNT was 5 with an ABI of 0.222 and an RBI of 5.29 which together imply clinical significance alongside a large treatment effect [7].

Kiladjian *et al.*, conducted an open-label randomized control trial comparing

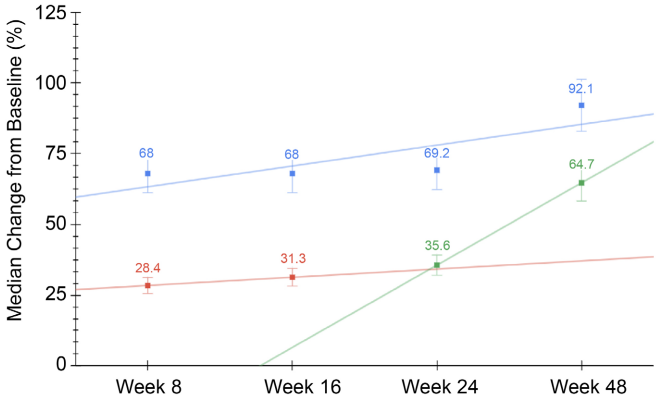

Figure 1. MPN-SAF median change from baseline for reported improvement of pruritis symptoms comparing Ruxolitinib (■), Hydroxycarbamide (■), and the Ruxolitinib crossover group (■).

ruxolitinib, 10 mg BID versus best available therapy, with patients in both arms also receiving low-dose aspirin unless contraindicated. In this study, best available therapy used were hydroxyurea, interferon, pegylated interferon, pipobroman, anagrelide, approved immunomodulators, and observation without pharmacological interventions. Patients were randomized 1:1 during the 32-week treatment phase, with a crossover to the ruxolitinib arm after week 32 until study termination at week 256 [9]. Pruritus severity was assessed during the screening phase, and again at weeks 32 and week 256 [9]. Scores at each interval were based on the Pruritis Symptom Impact Scale (PSIS) and demonstrated that ruxolitinib was far superior in self-reported improvement of pruritic symptoms compared to best available therapy. The calculated NNT was 3, with an ABI of 0.35 and RBI of 1.296, which together imply clinical significance alongside a large treatment effect.

Passamonti *et al.* conducted an open-label randomized control trial comparing ruxolitinib, 10 mg BID versus best available therapy, with patients in both arms also receiving low-dose aspirin unless contraindicated. In this study, best available therapy was hydroxyurea, interferon, pegylated interferon, pipobroman, anagrelide, lenalidomide, thalidomide, and observation without pharmacological interventions. Patients were randomized 1:1 during the 28-week treatment phase, with a crossover to the ruxolitinib arm after week 28 [8]. Pruritus severity was assessed once during the screening phase, and then every four weeks until week 28 [8]. Scores at each interval were based on the Pruritis Symptom Impact Scale (PSIS). Treatment with ruxolitinib led to a change of −1.76 from baseline and was far superior in self-reported improvement of pruritic symptoms compared to best available therapy, which showed a change from baseline of −0.23 [8]. The calculated NNT was 2, with an ABI of 0.533 and RBI of 3.55, which together imply clinical significance with a large treatment effect.

Among the three studies, there were similarities in the reported hematological and non-hematological adverse events. All adverse events were reported from grades 1 - 4 and included patients who were randomized to receive the treatment

arm at baseline and those who crossed over atweek 16 compared to the hydroxycarbamide group until the study was terminated [7].

In the study by Mesa *et al.*, headache and thrombocytopenia were clinically significant adverse events with an odds ratio of 3.53 (95% CI, 0.90 - 13.8; p-value = 0.035) and 0.28 (95% CI, 0.09 - 0.84; p-value = 0.011), respectively and are annotated in **Table 1**. The reported adverse events exhibited a wide range in the 95% confidence interval, indicating a lack of representativeness of the patient sample concerning the population mean, potentially attributed to the small patient population size.

There were two reported patient deaths during the trial that occurred after completion of the blinded treatment phase. One patient who was randomized to the hydroxycarbamide arm died from pneumonia prior to crossover, whereas the other patient who was randomized to the ruxolitinib arm, died due to progression to acute myeloid leukemia (AML). Both deaths were not considered to be related to ruxolitinib [7].

In the study by Kiladjian *et al.*, headache, pruritis, fatigue, and thrombocytopenia were clinically significant adverse events and are annotated in **Table 2**. The reported adverse events exhibited a small odds ratio, suggesting a higher likelihood of occurrence in the best available therapy group compared to the ruxolitinib arm, with the exception of anemia.

Table 1. Adverse events reported by Mesa *et al.* [7].

Adverse Events	Ruxolitinib (n = 54)	Hydroxycarbamide (n = 56)	Odds Ratio (95% CI)	*P* value
Headache	9	3	3.53 (0.90 - 13.8)	0.035
Pruritus	6	6	1.04 (0.31 - 3.45)	0.473
Fatigue	11	6	2.13 (0.73 - 6.24)	0.084
Diarrhea	5	11	0.42 (0.14 - 1.30)	0.065
Anemia	20	13	1.95 (0.85 - 4.47)	0.058
Thrombocytopenia	5	15	0.28 (0.09 - 0.84)	0.011

Abbreviations: CI, confidence interval.

Table 2. Adverse events reported by Kiladjian *et al.* [9].

Adverse Events	Ruxolitinib (n = 110)	BAT (n = 111)	Odds Ratio (95% CI)	*P* value
Headache	5.8	28.5	0.14 (0.05 - 0.38)	0.000056
Pruritus	7	32.6	0.17 (0.07 - 0.40)	0.000025
Fatigue	5.1	23.1	0.18 (0.07 - 0.50)	0.00046
Diarrhea	7	12.2	0.55 (0.21 - 1.47)	0.117653
Anemia	8.9	5.4	1.66 (0.53 - 5.26)	0.192961
Thrombocytopenia	4.4	16.3	0.22 (0.07 - 0.69)	0.004724

Abbreviations: BAT, best available therapy; CI, confidence interval.

There were four patient deaths during the trial. Two patients died of pneumonia, one of CNS hemorrhage, and the other of hypovolemic shock. None of these deaths were considered to be related to ruxolitinib [9].

In the study by Passamonti *et al.*, pruritis and anemia were clinically significant adverse events with an odds ratio of 0.23 (95% CI, 0.07 - 0.73; p-value = 0.0062) and 5.7 (95% CI, 1.21 - 27.0; p-value = 0.0141), respectively and are annotated in Table 3. Similarly to the study by Kiladjian *et al.*, the reported adverse events exhibited a small odds ratio, suggesting a higher likelihood of occurrence in the best available therapy group compared to the ruxolitinib arm, with the exception of anemia.

There were two patient deaths during the study period. One patient not undergoing pharmacological therapy died as a result of septic shock, and the other patient died due to disease progression although he was receiving pegylated interferon therapy [8].

4. Discussion

The objective of this selective EBM review was to determine whether ruxolitinib, in comparison to best available therapy (BAT), improves pruritis symptoms in patients with polycythemia vera. All three articles demonstrated that ruxolitinib can significantly improve pruritis symptoms based on the MPN-SAF and PSIS questionnaires. In the study by Mesa *et al.*, pruritus symptom improvement had an odds ratio of 2.51 (95% CI, 1.10 - 5.71; p-value = 0.027) in the ruxolitinib group, showing an association with improved symptomatic outcomes [7]. In the study by Kiladjian *et al.*, scores from the PSIS demonstrated that ruxolitinib was far superior in self-reported improvement of pruritic symptoms, especially in the "very much improved" and "much improved" categories, when compared to best available therapy [9]. In Passamonti *et al.*'s study, scores from thePSIS demonstrated that ruxolitinib was far superior in self-reported improvement of pruritic symptoms compared to best available therapy, with a change from baseline of −1.76 compared to −0.23, respectively [8]. In all three studies, the calculated NNT, ABI, and RBI values were relatively similar, with each of them demonstrating large treatment effects and efficacy of ruxolitinib.

Table 3. Adverse events reported by Passamonti *et al.* [8].

Adverse Events	Ruxolitinib (n = 74)	BAT (n = 75)	Odds Ratio (95% CI)	*P* value
Headache	7	8	0.88 (0.30 - 2.55)	0.4033
Pruritus	4	15	0.23 (0.07 - 0.73)	0.0062
Fatigue	5	6	0.83 (0.24 - 2.86)	0.386
Diarrhea	3	6	0.49 (0.12 - 2.02)	0.1604
Anemia	10	2	5.7 (1.21 - 27.0)	0.0141
Thrombocytopenia	2	6	0.32 (0.06 - 1.64)	0.0855

Abbreviations: BAT, best available therapy; CI, confidence interval.

The studies included in this review had a few limitations. First, the analysis of improvement in polycythemia vera-associated symptoms was considered a secondary endpoint across all three studies. The primary objective of each of study was designed to compare the management of splenomegaly and hematocrit control with systemic symptom improvement. Second, patients in all three trials showed improvement with ruxolitinib, and there was also an unanticipated improvement in patients who were receiving best available therapy. This could be due to improved standards of care such as closer medical observation, follow-up, and the availability of support, which might not be available to patients not enrolled in a clinical trial. Thirdly, in all three studies all patients were eventually crossed over to receive ruxolitinib and discontinued from taking best available therapy regardless of efficacy or improvement on that specific regimen. Lastly, not all three studies reported confidence intervals or p-values for pruritus symptom improvement; therefore, complete statistical significance could not be calculated.

5. Conclusion

All three randomized controlled trials that were included in this systematic review demonstrated that ruxolitinib did improve pruritus symptoms in patients with polycythemia vera compared to best available therapy. Although not every study used confidence intervals or p-values to determine statistical significance, the self-reported Myeloproliferative Neoplasm Symptom Assessment Form and Pruritis Symptom Impact Scale showed greater favorability towards ruxolitinib than best available therapy. Thus, the results of this review are conclusive, but not statistically significant. Further studies focusing specifically on longer term evaluation of ruxolitinib compared to best available therapy, as it pertains to symptomatic improvement, are warranted to determine whether there is a true statistical significance.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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