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A Real-Life Turkish Experience of Ruxolitinib in Polycythemia Vera

İstemi Serin[1], Mehmet Hilmi Doğu[2], Ömer Ekinci[3], Gülsüm Akgün Çağlıyan[4], Abdulkadir Baştürk[5], Merih Reis Aras[6], Sinan Demircioğlu[7], Burhan Turgut[8], Mustafa Merter[9], Sibel Kabukçu Hacıoğlu[4], Metin Bağcı[10], Murat Albayrak[6], Serdal Korkmaz[11], Mehmet Ali Erkurt[12], Mehmet Sinan Dal[13], Fadime Ersoy Dursun[14], Anıl Tombak[15], İsmet Aydoğdu[16], Turgay Ulaş[17], Fevzi Altuntaş[13,18]

[1]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Hematology, İstanbul, Turkey
[2]İstinye University, Liv Hospital Ulus, Clinic of Hematology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Clinic of Hematology, Diyarbakır, Turkey
[4]Pamukkale University Faculty of Medicine, Department of Hematology, Denizli, Turkey
[5]Medicana International İstanbul Hospital, İstanbul, Turkey
[6]University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Hematology, Ankara, Turkey
[7]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Hematology, Konya, Turkey
[8]Namık Kemal University Faculty of Medicine, Department of Hematology, Tekirdağ, Turkey
[9]Fırat University Faculty of Medicine, Department of Hematology, Elazığ, Turkey
[10]Selçuk University Faculty of Medicine, Department of Hematology, Konya, Turkey
[11]University of Health Sciences Turkey, Kayseri City Training and Research Hospital, Clinic of Hematology and Apheresis Unit, Kayseri, Turkey
[12]İnönü University Faculty of Medicine, Department of Hematology, Malatya, Turkey
[13]University of Health Sciences Turkey, Ankara Oncology Training and Research Hospital, Clinic of Hematology and Apheresis Unit, Ankara, Turkey
[14]İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinic of Hematology, İstanbul, Turkey
[15]Mersin University Faculty of Medicine, Department of Hematology, Mersin, Turkey
[16]Manisa Celal Bayar University Faculty of Medicine, Department of Hematology, Manisa, Turkey
[17]Near East University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Lefkoşa, Cyprus
[18]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Ankara, Turkey

ABSTRACT

Introduction: Ruxolitinib is a small -molecule inhibitor of the JAK1/2 pathway. This study aimed to reveal the results and side-effect profile of the use of ruxolitinib as a treatment option in polycythemia vera (PV).

Methods: A total of 34 patients with PV from 18 different centers were included in the study. The evaluation of the response under treatment with ruxolitinib was determined as a reduction in spleen volume (splenomegaly size: ≥35%) by imaging and control of hematocrit levels (≤45%) compared to baseline.

Results: While the number of patients in which a reduction in spleen volume and hematocrit control was achieved was 19 (55.9%) at 3 months of treatment, it was 21 (61.8%) at 6 months. Additionally, while the number of side effects was negatively correlated with the reduction in spleen volume (Spearman's rho: -0.365, p=0.034), a decrease in the hematocrit level was positively correlated (Spearman's rho: 0.75, p=0.029). Those without a reduction in spleen volume experienced more constipation (chi-square: 5.988, Fisher's exact test: p=0.033).

Conclusion: This study shed light on the use of ruxolitinib in PV and the importance of splenomegaly on studies planned with larger patient groups.

Keywords: Polycythemia vera, ruxolitinib, real-life data, response, side effect

Address for Correspondence: İstemi Serin MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Hematology, İstanbul, Turkey
Phone: +90 212 459 60 62 **E-mail:** serinistemi@hotmail.com **ORCID ID:** orcid.org/0000-0003-1855-774X

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Introduction

Polycythemia vera (PV) is a myeloproliferative disorder that is characterized by the expansion of erythroid progenitor cells, which carries the risk of developing into myelofibrosis and acute leukemia (1). It is usually diagnosed in the 6th decade or later with a high risk of thromboembolism. Ninety-five percent of patients carry the *Janus kinase 2 (JAK2)* gene V617F mutation (1).

Treatment of PV consists of intermittent phlebotomy and low-dose acetylsalicylic acid to keep the hematocrit level below 45%. In patients defined as high risk (those over 60 years of age and the presence of any thrombohemorrhagic event), cytoreductive treatment is indicated. Hydroxyurea (HU) is the first agent recommended for cytoreduction, with the most experience available for HU (1-5).

The European Leukemia Net and the International Working Group-Myeloproliferative Neoplasms Research and Treatment have defined both resistance and intolerance to HU (6). HU resistance can be defined as the presence of one of the following criteria: 1) The need for phlebotomy to maintain a hematocrit levels of <45% during treatment. 2) Uncontrolled myeloproliferation (platelet count of 400×10^9/L and white blood cell count of $>10\times10^9$/L). 3) The inability to reduce massive splenomegaly by >50%, as measured by palpation, or complete relieved symptoms related to splenomegaly. HU intolerance is defined as one of the following criteria: 1) Having an absolute neutrophil count of $<1.0\times10^9$/L or platelet count of $<100\times10^9$/L, or hemoglobin level of <10 g/dL under the lowest dose of HU was used to achieve a complete or partial hematological response. 2) The presence of mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, fever, leg ulcers, or other non-hematological toxicities related to HU at any dose of HU (7). Thus, it can be seen that different treatment options are on the agenda in these two patient groups.

Ruxolitinib is a small-molecule inhibitor of JAK1/2 that targets the Janus Kinase and signal transducer and activator of transcription pathway (8-10). Its efficacy has been proven in the Randomized study of Efficacy and Safety in PV with the JAK inhibitor ruxolitinib versus best available care (RESPONSE) 1 and RESPONSE 2 trials in the HU-intolerant or -unresponsive patient group (11,12). For post-HU patients, it appears to be a highly effective treatment option for hematocrit control, regression of the spleen size, and the elimination of PV-related symptoms. Another study, known as RELIEF (13), evaluated the efficacy and safety of ruxolitinib compared with HU in PV patients with controlled hematocrit levels, but whose symptoms did not regress. After 16 weeks, a 50% reduction in the cytokine total symptom score was reported in 43% of the ruxolitinib-treated patients and 29.6% of the HU-treated patients. Regarding pruritus and fatigue, the proportion of patients with greater than 50% reduction was 40% versus 26% in patients treated with ruxolitinib and HU, respectively (13).

This study aimed to reveal the results and side-effect profile of the use of ruxolitinib as a treatment option in PV.

Methods

A total of 34 patients with PV from 18 different centers were included in the study. In addition to the initial demographic data (age, and gender) of the patients, initial spleen and liver size, laboratory values (leukocyte, hemoglobin, platelet), starting dose of ruxolitinib, follow-up duration, and side effect profile and responses were recorded.

All the patients had received treatment with HU before being administered ruxolitinib. Ruxolitinib was discontinued due to HU intolerance, massive splenomegaly, severe and treatment-refractory constitutional symptoms, uncontrolled polycythemia, or severe pruritus. The evaluation of the response under treatment with ruxolitinib was determined as a reduction in spleen volume (splenomegaly size: ≥35%) by imaging and control of hematocrit levels (≤45%) compared to baseline. Patients with any side effects (grade 0-5) were recorded. Patients whose initial dose was increased or decreased were also recorded, and there were no patients who discontinued the treatment for any reason.

The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2904, date: 13.8.2021).

Statistical Analysis

The IBM SPSS Statistics for Windows 26.0 (IBM Corp., Armonk, NY, USA) analysis program was used for statistical analysis. Descriptive and inferential statistics were calculated, and appropriate hypothesis tests were used. The one-sample Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used for the conformity of the variables to the normal distribution. Quantitative variables were expressed as the mean ± standard deviation, minimum-maximum, median. Qualitative variables are expressed as number and percentages. The Mann-Whitney U test was used for numerical data that did not show a normal distribution, and the chi square test was used for nominal data for comparison of the groups. The Independent sample test was used for those with normal distribution. The equality of variances was tested using the Levene test for the equality of variances. The Spearman Rank correlation coefficient and logistic regression analyzes were used to correlate the data. The McNemar test was used to compare the categorical variables in the dependent groups. Statistical significance level in hypothesis tests was accepted as $p<0.05$.

Results

Of the 34 patients included in the study, 21 were female (61.8%) and 13 were male (38.2%). Initial laboratory values and liver-spleen sizes are summarized in Table 1. The median line of treatment before ruxolitinib was 1.5 (range: 1-3). The median starting dose was 30 mg (range: 20-40). The most common indication for ruxolitinib was HU intolerance (15 patients, 44.1%). The median follow-up duration was 13.5 months (range: 7-61) (Table 1).

The ruxolitinib treatment process is shown in Table 2. While the number of patients in which a reduction in spleen volume and hematocrit control was achieved was 19 (55.9%) at 3 months of treatment, it was 21 (61.8%) at 6 months. The number of patients whose initial dose was reduced for any reason was 4 (11.7%), and of these patients, 2 had anemia, 1 had thrombocytopenia, and 1 had both of them. The most common side effects were thrombocytopenia and constipation, seen in 8 patients (23.5%) (Table 2).

In the statistical analysis, which was performed for the responses and initial parameters, it was found that the group with a reduction in spleen volume at 3 months had a significantly lower number of previous treatment lines (p=0.017). No significant correlation was found between the other baseline parameters and the response criteria (Table 3).

Additionally, while the number of side effects was negatively correlated with the reduction in spleen volume (Spearman's rho -0.365, p=0.034), a decrease in the hematocrit level was positively correlated (Spearman's rho: 0.75, p=0.029) (Figure 1).

Table 1. Demographic characteristics, initial findings, and indications for ruxolitinib

		Min.-max.	Median	Mean ± SD/(n, %)
Age		47-83	65.5	65.828±9.37
Gender	Female	-	-	21 (61.8%)
	Male	-	-	13 (38.2%)
Spleen (mm)		110-400	180	196.25±61.03
Liver (mm)		120-220	165	166.91±25.45
WBC (/mm^3)		2300-28900	10000	11740.59±5884.46
Hb (gr/dL)		7.8-18.7	14.5	14.41±2.58
Platelets (/mm^3)		106000-914000	317000	374000±225421.49
Line of treatment		1-3	1.5	1.71±0.8
Ruxolitinib dosage (mg/day)		20-40	30	29.41±7.76
Indication for ruxolitinib	Massive splenomegaly	-	-	12 (35.3%)
	Uncontrolled polycythemia	-	-	5 (14.7%)
	Pruritus	-	-	1 (2.9%)
	Constitutional symptoms	-	-	1 (2.9%)
	HU intolerance	-	-	15 (44.1%)
Follow-up duration (months)		7-61	13.5	16.39±13.75

**Min.: Minimum, Max.: Maximum, SD: Standard deviation WBC: White blood cell, Hb: Hemoglobin, HU: Hydroxyurea

Table 2. Ruxolitinib results, side -effect profile

		n	%
At 3 months			
	Regression of splenomegaly	4	11.7
	Regression of polycythemia	11	32.4
	Both	19	55.9
At 6 months	Regression of splenomegaly	3	8.8
	Regression of polycythemia	10	29.4
	Both	21	61.8
Reason for dose reduction			
	Anemia	2	5.8
	Thrombocytopenia	1	2.9
	Both	1	2.9
Side effects (any of grade 0-5)			
	Weight gain	5	14.7
	Arthralgia	5	14.7
	Constipation	8	23.5
	Diarrhea	2	5.8
	Hypertension	3	8.8
	Pneumonia	6	17.6
	Anemia	7	20.6
	Thrombocytopenia	8	23.5
	Herpes zoster	1	2.9

Table 3. Statistical analysis of ruxolitinib results

			Spleen size	Liver size	Hb (gr/dL)	Leukocytes (/mm³)	Platelets (/mm³)	Follow-up duration	Age	Line of treatment
Reduction in spleen volume at 3 months	(-)	Mean	187.35	158.54	13.87	11419	389769	19	65	2.15
	(+)	Mean	201.76	172.1	14.73	11940	364238	14	66	1.43
	Mann-Whitney U	p	0.958	0.131	0.215	0.929	0.446	0.887	0.817	0.017
Decrease in hematocrit at 3 months	(-)	Mean	241.25	145	13.3	11150	258500	13	63	1.25
	(+)	Mean	190.25	169.83	14.55	11819	389400	16	66	1.77
	Mann-Whitney U	p	0.708	0.077	0.487	0.556	0.438	0.321	0.377	0.232
Reduction in spleen volume at 6 months	(-)	Mean	179.92	167.21	15.04	10814	334263	12	65	1.74
	(+)	Mean	216.93	166.53	13.61	12914	424333	21	67	1.67
	Mann-Whitney U	p	0.068	0.715	0.103	0.435	0.150	0.149	0.305	0.925
Decrease in hematocrit at 6 months	(-)	Mean	237	156	13.44	13084	304200	17	61	1.4
	(+)	Mean	189.22	168.79	14.57	11509	386034	16	67	1.76
	Mann-Whitney U	p	0.48	0.342	0.422	0.865	0.697	0.807	0.137	0.411

Hb: Hemoglobin

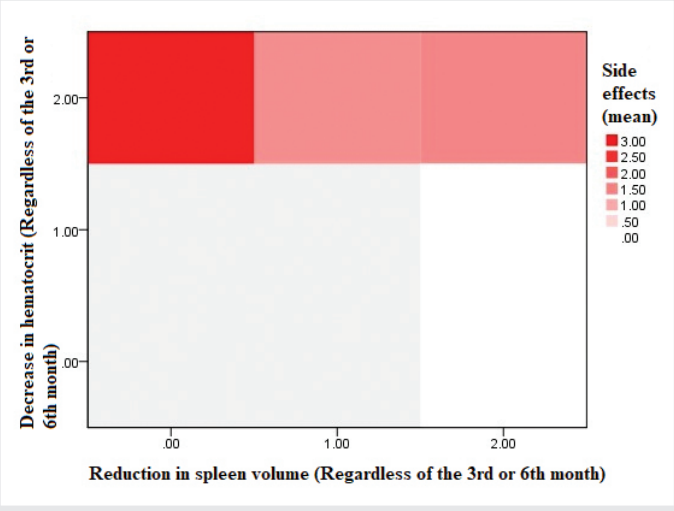

Figure 1. Responses to ruxolitinib and side -effect profile

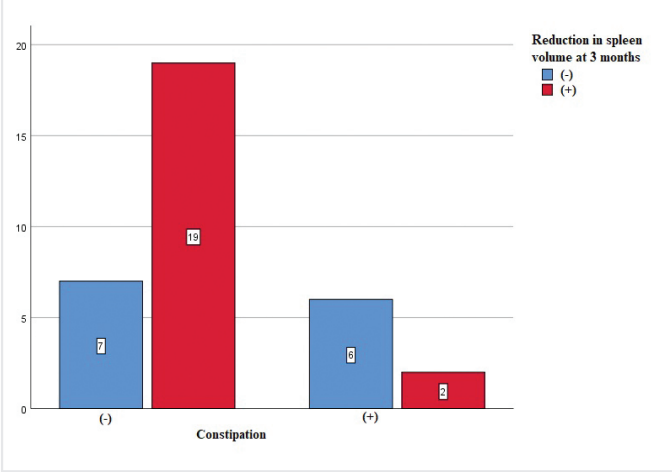

Figure 2. Reduction in spleen volume at 3 months and the presence of constipation

A positive correlation was found between the reduction in spleen volume at 3 months and constipation. In patients with a reduction in spleen volume at 3 months, the rate of constipation was also decreased. Those without a reduction in spleen volume experienced more constipation (chi-square: 5.988, Fisher' exact test: p=0.033) (Figure 2).

Discussion

This study had a multicenter patient group in which the efficacy and side -effect profile of the PV patients were demonstrated, and significant results were demonstrated. Of the patients included in the study, 44.1% switched to ruxolitinib due to HU intolerance. In the RESPONSE 1 trial, this rate was found to be 46.4% (11). In the RESPONSE 2 trial, this rate was 59% (12). The results here were similar in terms of intolerance to HU. While the median age was 65.5 years in this study, it was seen to be 62 and 63 years, respectively, in the RESPONSE 1 and 2 trials. Considering the reasons for switching to ruxolitinib, the most common reason was HU intolerance in this study, and the major reason was the same in the RESPONSE 1 and 2 trials.

Considering the responses observed, the number of patients in which hematocrit control was achieved at 3 months was 30 (88.3%). At 6 months, this number was 31 patients (91.2%). In the RESPONSE 1 trial (11), hematocrit control was achieved in 60% of patients at week 32, while in the RESPONSE 2 trial (12), the rate of patients in which hematocrit control was achieved at week 28 was 62%. In the RESPONSE 1 trial, the proportion of patients with a 35% spleen the volume reduction at week 32 was 38.2%. In this study, the number of patients with a reduction in spleen volume was 23 (67.6%) at 3 months and it was 24 (70.6%) at 6 months. In a retrospective analysis from 2020 (14), the initial rate of palpable splenomegaly in the patients treated with ruxolitinib was 48% compared to 20% at week 32. In this study, the group with a reduction in spleen volume at 3 months had significantly fewer previous lines of treatment (p=0.017). This was a first in terms of demonstrating the relationship between pre-ruxolitinib treatment burden and response. It can be considered that ruxolitinib is highly effective in treatment - naive patients, or patients with a low treatment burden. Here, especially with new risk scoring systems, the early use of ruxolitinib could be planned.

In this study, the most common side effect was constipation (seen in 8 patients, 23.5%). In the RESPONSE 1 trial (11), the most frequent non-hematologic adverse event was headache (16.4%, all grades). It was observed in 7 patients (9%) in the RESPONSE 2 trial and was the most common non-hematological side effect. Another common side effect in this study was thrombocytopenia (seen in 8 patients, 23.5%). This rate was 24.5% in the RESPONSE 2 trial (12). The most common hematological side effect was anemia, at 43.6%, in this study. Moreover, anemia that caused a dose reduction was seen in only 2 patients (5.8%). Cytopenia that caused ruxolitinib discontinuation was not observed.

Ruxolitinib-associated infections constitute an important side-effect profile. In the RESPONSE 1 trial (11), 7 patients experienced herpes zoster infections, the overall rate of infections observed was 41.8%, and the rate of grade-3 and -4 infections was 3.6% in the ruxolitinib arm. In the RESPONSE 2 trial (12), infections (influenza and bronchitis) were observed in 3% of ruxolitinib-treated patients. Only 1 patient experienced a herpes zoster infection in the ruxolitinib arm. In the patient group here, 6 patients had pneumonia (17.6%) and 1 patient had herpes zoster (2.9%).

In the statistical analysis, while the number of side effects was negatively correlated with the reduction in spleen volume (Spearman's rho: -0.365, p=0.034), a decrease in the hematocrit level was positively correlated (Spearman's rho: 0.375, p=0.029). The increase in the number of side effects may have been associated with the defect in the reduction in spleen volume. A positive correlation was found between the reduction in spleen volume and constipation at 3 months. These 2 results are quite significant in terms of revealing the role of PV treatment in the relationship between response and splenomegaly. In a study from 2019 (15), the effect of splenomegaly on overall survival and thrombosis in patients with PV patients was studied. A significant correlation was found with both the thrombosis and the poor overall survival rates. Considering the study results and literature data, splenomegaly in PV may be considered an important risk factor that is central to terms of ruxolitinib response and the side -effect profile.

Study Limitations

There were important limitations to this study. The limited number of patients was the most important limitation point. The fact that the statistically significant results obtained at 3 months could not be obtained at 6 months can be attributed to this reason. In terms of examining the reduction in spleen volume, a single center and uniform evaluation would provide more appropriate results, but the number of patients did not enable subcenter analysis.

Conclusion

The results of ruxolitinib in PV were revealed in this study with real-life data. The most common hematological side effect was thrombocytopenia, and the most common non-hematological side effect was constipation. The number of side effects was negatively correlated with the reduction in spleen volume, whereas it was positively correlated with hematocrit control. In patients with a reduction in spleen volume at 3 months, the rate of constipation was also decreased. This shed light on the use of ruxolitinib in PV and the importance of splenomegaly on studies planned with larger patient groups.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2904, date: 13.8.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - İ.S., M.H.D.; Design - İ.S., M.H.D.; Data Collection or Processing - İ.S., M.H.D., Ö.E., G.A.Ç., A.B., M.R.A., S.D., B.T., M.M., S.K.H., M.B., M.A., S.K., M.A.E., M.S.D., F.E.D., A.T., İ.A., T.U., F.A.; Analysis or Interpretation - İ.S.; Literature Search - İ.S.; Writing - İ.S.

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