Real-World Dosing Patterns of Ruxolitinib in Patients With Polycythemia Vera Who Are Resistant to or Intolerant of Hydroxyurea

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Abstract

Many patients with polycythemia vera switch treatment from hydroxyurea to FDA-approved ruxolitinib. This medical chart review of 249 patients investigated reasons for switching treatment and ruxolitinib treatment patterns. Most patients became resistant to hydroxyurea. Half of patients initiated ruxolitinib at the recommended dose, dose modifications were common in the first 6 months, and most patients achieved hematocrit control and continued treatment for extended time frames. Appropriate dosing of ruxolitinib early in treatment is important for effective long-term treatment.

Introduction: Approximately one-quarter of patients with polycythemia vera become resistant to and/or intolerant of hydroxyurea. This analysis characterizes reasons patients were switched from hydroxyurea to ruxolitinib and describes ruxolitinib dosing patterns and outcomes in real-world clinical practice. **Patients and Methods:** This medical chart review of United States community hematology/oncology practices in the Cardinal Health Oncology Provider Extended Network included patients with polycythemia vera who were ≥18 years old, received hydroxyurea for ≥3 months, started ruxolitinib between January 1, 2015 and December 31, 2016, and had ≥2 visits during the subsequent 6 months. Clinical data were collected at predefined intervals from diagnosis to last provider visit. **Results:** Providers identified 249 patients for inclusion. jcauses of hydroxyurea discontinuation were resistance (78%; frequently for hematocrit ≥45% [79%]) and intolerance (28%; frequently for nausea/vomiting [50%]). Initial ruxolitinib dosing was 10 mg twice daily (recommended dose) in 131 patients (53%). Among these patients, median treatment duration was 29.2 months, 35 (27%) had dose modification (increase, n = 24; decrease, n = 11) and 4 had interruptions within 6 months. The most common reason for dose increase was continued need for phlebotomy (46%); 6 patients had dose reductions owing to reduced platelets. Hematocrit control at initiation and during the first 6 months of ruxolitinib treatment was 15% and 63%, respectively. **Conclusion:** Most patients initiated ruxolitinib upon hydroxyurea resistance. Approximately half initiated ruxolitinib at the recommended dose, 27% of whom experienced dosing modifications within the first 6 months. After switching to ruxolitinib, most patients achieved hematocrit control and continued treatment for extended time frames.

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Introduction

Polycythemia vera (PV) is a Philadelphia chromosome–negative chronic myeloproliferative neoplasm affecting more than 100,000 people in the United States.[1] The disease is characterized by an abnormal increase in red cell mass and the presence of *JAK2* V617F or *JAK2* exon 12 mutations.[2] Patients with PV are at risk for thromboembolic events (TEs), premature death, and burdensome symptoms.[3-5] The goals of PV therapy are to prevent TEs and hemorrhagic complications and to manage disease-related symptoms.[6-8]

Hydroxyurea is the recommended first-line treatment for patients with high-risk PV (age ≥60 years or history of TE)[9,10]; however, about a quarter of patients become resistant to and/or intolerant of hydroxyurea.[11] Ruxolitinib, a Janus kinase 1 (JAK1)/JAK2 inhibitor, is currently the only treatment option approved by the United States Food and Drug Administration for patients with

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PV who are resistant to or intolerant of hydroxyurea.[12] Objectives of this retrospective medical chart review were to characterize the reasons patients with PV were switched from hydroxyurea to ruxolitinib and to describe dosing patterns and clinical outcomes of ruxolitinib treatment in real-world clinical practice.

Material and Methods

Study Design and Patients

This was a retrospective observational medical chart review of patients with PV treated at US community hematology/oncology practices in the Cardinal Health Oncology Provider Extended Network (OPEN). OPEN is a community of more than 7000 oncologists, hematologists, and urologists providing care to patients with cancer; providers are geographically distributed across the United States and practice in both community and academic research settings. A central Institutional Review Board approved the protocol.

Eligible patients with PV were ≥18 years old at the time of ruxolitinib initiation (baseline), were treated with hydroxyurea for ≥3 consecutive months followed by ≥3 consecutive months of treatment with ruxolitinib, started ruxolitinib therapy between January 1, 2015, and December 31, 2016 (index period), and had ≥2 follow-up visits during the 6 months after ruxolitinib initiation. Patients were excluded if they had known disease transformation at the time of ruxolitinib initiation, had been previously enrolled in a PV-related clinical trial, received hematopoietic stem cell transplant, or had received any cytoreductive treatment other than hydroxyurea (eg, interferon, anagrelide, busulfan) before, or in combination with, ruxolitinib.

Physicians extracted data for patients under their care, which were entered into an electronic case report form (eCRF). Data were collected from the last 3 clinic visits during hydroxyurea treatment, at the time of ruxolitinib initiation (baseline), at each visit during the first 6 months of ruxolitinib treatment, at the time of any dosing modification of ruxolitinib, and at discontinuation or the last provider visit while still receiving ruxolitinib. Baseline data included patient demographics, laboratory values, history of TE, hydroxyurea treatment patterns, and the reason for stopping hydroxyurea. Providers were asked to document the reason ruxolitinib was initiated, laboratory values, and initial dosing and titration at ruxolitinib initiation. Dosing patterns, frequency of phlebotomy, type and number of TEs, laboratory results (eg, platelet count, white blood cell count, hemoglobin, hematocrit), and clinical status were abstracted from all office visits during the first 6 months and at any subsequent visit in which the ruxolitinib dose was modified or the patient discontinued; for patients who did not discontinue, the most recent 2 visits were used.

Statistics

For categorical variables, descriptive statistics were reported, including frequencies and percentages. For continuous variables, mean, standard deviation (SD), median, and interquartile range (IQR) values were calculated. Change in percentage of patients undergoing phlebotomy procedures after initiation of ruxolitinib treatment was assessed with the Chi-square test.

Results

Patients

Providers (N = 43) identified for inclusion a total of 249 patients who received hydroxyurea for ≥3 months before discontinuing and initiating subsequent ruxolitinib therapy. Patients were predominantly male (57.0%), with a mean (SD) age of 65.0 (9.9) years at the time of ruxolitinib initiation (Table 1). Median (IQR) duration of PV (from diagnosis to last visit or death) was 51 (38.9-73.7) months. Eighty percent had high-risk PV (ie, age ≥60 years or history of TE). Cardiovascular disease (CVD) risk factors were observed for 77.1% of patients, with 51.4% having ≥2 CVD risk factors and 31.3% having a history of TE before ruxolitinib initiation. Of the 198 patients (79.5%) with ≥1 phlebotomy recorded at ruxolitinib initiation, approximately half (52.5%) received phlebotomy once every 4 weeks, and an additional 46 (23.2%) received phlebotomy once every 2 weeks. Median hematocrit was 51.0% at the time of ruxolitinib initiation (Table 1). Characteristics for patients initiated on 10 mg ruxolitinib twice daily (BID; US package insert [PI]–recommended starting dose for PV treatment)[12] were similar to characteristics of patients who initiated ruxolitinib at any other dose.

Hydroxyurea Treatment Patterns

At the time of hydroxyurea discontinuation, 24.9% of patients had reached a hydroxyurea dose of ≥2 g/day. The median (IQR) hydroxyurea treatment duration was 10.8 months (6.0-21.6). The most common reasons for hydroxyurea discontinuation were resistance (77.9%) and intolerance (28.1%), with 14.1% of patients having disease that was classified as both resistant and intolerant. Other reported reasons for hydroxyurea discontinuation included patient choice (22.5%); neutropenia and leukopenia (0.8% each); and leukocytoclastic vasculitis, myocardial infarction, patient request for ruxolitinib, persistent symptoms, rash, recurrent deep vein thromboses, and transient ischemic attack (0.4% each). Resistance was most frequently due to hematocrit level at or above 45% (78.9%) and/or persistent PV-related symptoms (63.4%; Figure 1). Intolerance was most frequently due to nausea/vomiting (50.0%) and/or stomatitis (37.1%).

Ruxolitinib Treatment Patterns

Patients Treated With the Recommended Ruxolitinib Starting Dose. A total of 131 patients (52.6%) initiated ruxolitinib at the US PI–recommended dose of 10 mg BID (Figure 2). Among these patients, the median (IQR) ruxolitinib treatment duration was 29.2 months (11.2-37.1; Table 2). Among patients who discontinued ruxolitinib, treatment duration was 10.5 months (6.6-17.1), and among those who remained on ruxolitinib treatment, it was 35.8 months (31.4-43.8).

During the first 6 months of ruxolitinib treatment, 24 patients (18.3%) had 29 dose increases, and 11 patients (8.4%) had 13 dose decreases (no patient had both a dose increase and decrease; Table 2). Among patients with dose increases, the most common reasons for an increase were continued need for phlebotomy (45.8%) or persistent PV symptoms (37.5%); for dose decreases, low platelet counts (54.5%) and low hemoglobin (27.3%) were the most common

Table 1 Patient Demographic and Clinical Characteristics at the Time of Ruxolitinib Initiation

Characteristic	Ruxolitinib Dose at Initiation		All Patients (N = 249)
	10 mg BID[a] (n = 131)	Doses Other Than 10 mg BID (n = 118)	
Age, mean (SD), y	66.9 (9.1)	62.8 (10.4)	65.0 (9.9)
Male, n (%)	80 (61.1)	62 (52.5)	142 (57.0)
Polycythemia vera risk, n (%)			
High	115 (87.8)	85 (72.0)	200 (80.3)
Low	16 (12.2)	33 (28.0)	49 (19.7)
JAK2 V617F mutation testing, n (%)			
Positive	131 (100.0)	112 (94.9)	243 (97.6)
Negative	0	2 (1.7)	2 (0.8)
Inconclusive	0	1 (0.8)	1 (0.4)
Data not available	0	3 (2.5)	3 (1.2)
Cardiovascular risk factors, n (%)			
0	17 (13.0)	40 (33.9)	57 (22.9)
1	29 (22.1)	35 (29.7)	64 (25.7)
≥2	85 (64.9)	43 (36.4)	128 (51.4)
Patients with history of thromboembolic event before ruxolitinib, n (%)	46 (35.1)	32 (27.1)	78 (31.3)
Frequency of phlebotomy at ruxolitinib initiation, n (%)			
Once every 2 wk	20 (15.3)	26 (22.0)	46 (18.5)
Once every 4 wk	58 (44.3)	46 (39.0)	104 (41.8)
Once every 3 mo	21 (16.0)	17 (14.4)	38 (15.3)
Other	8 (6.1)	2 (1.7)	10 (4.0)
Not receiving phlebotomy	24 (18.3)	27 (22.9)	51 (20.5)
Hematologic parameters at ruxolitinib initiation, median (IQR)			
Hematocrit, %	51.0 (48.0–54.9)	51.0 (45.2–55.0)	51.0 (47.0–55.0)
Platelet count, × 10^9/L	425.0 (220.0–587.0)	479.5 (290.0–650.0)	450.0 (250.0–620.0)
Hemoglobin, g/dL	17.0 (15.7–18.0)	16.3 (14.0–17.9)	16.7 (15.0–18.0)
WBC count, × 10^9/L	11.0 (7.0–14.5)	12.0 (8.0–15.0)	12.0 (7.3–15.0)

[a] US package insert–recommended starting dose for PV treatment.
BID = twice daily; IQR = interquartile range; SD = standard deviation; WBC = white blood cell.

reasons. In addition, during the first 6 months of ruxolitinib treatment, 4 patients (3.1%) had a total of 4 dose interruptions, with adverse event (2 patients [platelet count, n = 2; complete neutrophil count, n = 1]) as the most common reason for dose interruption. There were no dose reductions after interruptions during the first 6 months of ruxolitinib treatment.

All Patients. Regardless of starting dose, patients had more dose modifications (increases or decreases) in the first 6 months of ruxolitinib treatment (all patients, 23.3%; 10 mg BID, 26.7%; Table 2) and fewer dose modifications after 6 months (all patients, 12.9%; 10 mg BID, 11.5%). Lower rates of dose interruption were observed overall with slightly fewer interruptions in the first 6 months (all patients, 2.0%; 10 mg BID, 3.1%) and more after 6 months (all patients, 2.4%; 10 mg BID, 3.8%).

At the time of the last visit, 61.4% of patients were still receiving ruxolitinib (Table 2). The majority of patients (all patients, 66.7%; 10 mg BID, 58.1%) who discontinued ruxolitinib had no dose changes from the time of initiation to discontinuation.

Hematocrit Control

The percentage of patients with hematocrit control (hematocrit <45%) at the time of ruxolitinib treatment initiation was 18.9%, compared with 63.1% at any time during the first 6 months of ruxolitinib treatment and 56.2% at the time of the last visit (Table 2). In addition, patients underwent significantly fewer phlebotomy procedures during ruxolitinib treatment compared with before ruxolitinib initiation. At initiation of ruxolitinib, 79.5% (n = 198) of all patients were receiving phlebotomies; in contrast, 49.5% of patients with an office visit between 1 and 30 days after ruxolitinib treatment initiation underwent a phlebotomy procedure,

Figure 1 Rationale for treatment discontinuation among patients resistant to or intolerant of hydroxyurea. * Multiple reasons for intolerance or resistance could be reported for each patient. Hct, hematocrit; PV, polycythemia vera; WBC, white blood cell.

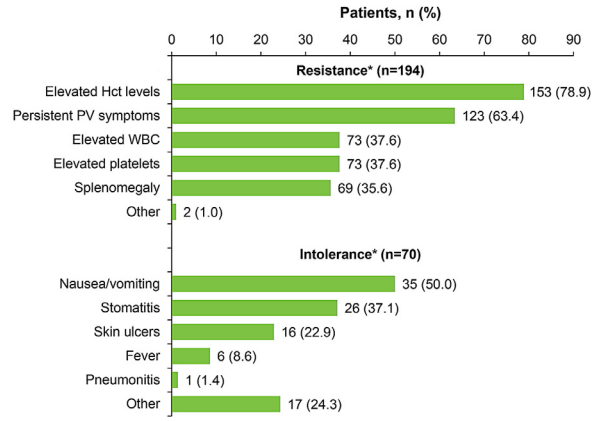
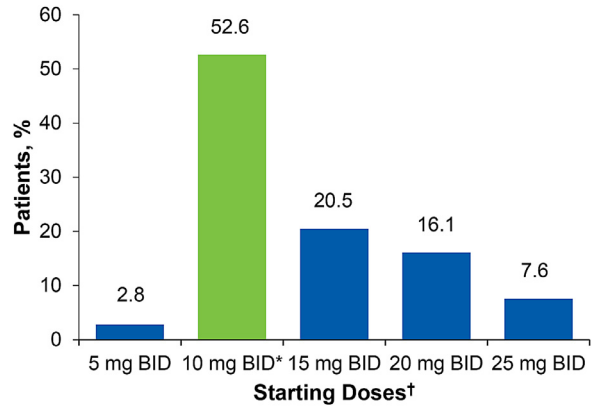


Figure 2 Ruxolitinib starting dose. * US prescribing information–recommended starting dose for polycythemia vera treatment. † One patient (0.4%) initiated ruxolitinib treatment at an unknown dose. BID, twice daily.



with phlebotomy requirement decreasing over time ($P < .0001$ vs baseline; Figure 3).

Discussion

This analysis of modern real-world practice patterns in the United States offers numerous important and practical findings concerning patients with PV who were switched from hydroxyurea to ruxolitinib. Most notably, the majority of hydroxyurea discontinuations were due to resistance, and only a quarter of the patients who discontinued hydroxyurea because of resistance received a hydroxyurea dose of ≥2 g/day. The observations are notable despite limitations inherent in retrospective chart abstraction studies, including the potential for patient selection bias, information bias (related to the availability and quality of data contained within the patient charts), and misclassification bias (related to the interpretation by the provider of the intent of the questions or data points collected through the eCRF).

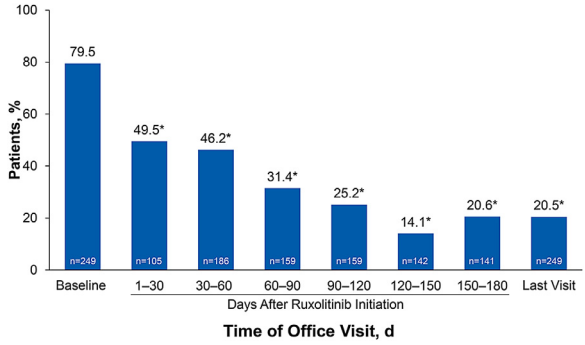
In this cohort, 78% of hydroxyurea discontinuations were due to resistance. This value is in agreement with a previous chart review on hydroxyurea treatment in patients with PV conducted in 2014, in which 229 of 1309 patients discontinued hydroxyurea. In that study, hydroxyurea resistance was also a common cause for treatment discontinuation (uncontrolled hematocrit, 23%; uncontrolled hemoglobin, 18%; uncontrolled platelet count, 11%; progression to fibrotic stage, 7%; development of thrombocytopenia, 7%); an overall discontinuation rate related to hydroxyurea resistance could not be reported because categories were not mutually exclusive.[13] Guidelines from European LeukemiaNet available at the time of the

Table 2 Ruxolitinib Dosing Patterns and Hematocrit Control

	Ruxolitinib Dose at Initiation		All Patients (N = 249)
	10 mg BID[a] (n = 131)	Doses Other Than 10 mg BID (n = 118)	
Duration of ruxolitinib treatment, median (IQR), mo	29.2 (11.2–37.1)	35.3 (19.0–42.9)	31.4 (14.5–40.4)
Patients with dosing modifications during initial 6 mo of ruxolitinib treatment, n (%)	35 (26.7)	23 (19.5)	58 (23.3)
Increase in dose[b]	24 (18.3)	3 (2.5)	27 (10.8)
Continued need for phlebotomy to maintain Hct <45%	11 (8.4)	1 (0.8)	12 (4.8)
Persistent PV symptoms	9 (6.9)	0	9 (3.6)
Persistent splenomegaly	2 (1.5)	2 (1.7)	4 (1.6)
Maintain Hct <42%	1 (0.8)	0	1 (0.4)
Leukocytosis	1 (0.8)	0	1 (0.4)
Decrease in dose[b]	11 (8.4)	20 (16.9)	31 (12.4)
Reduced platelet count	6 (4.6)	15 (12.7)	21 (8.4)
Reduced Hgb	3 (2.3)	5 (4.2)	8 (3.2)
Adverse event	0	1 (0.8)	1 (0.4)
Nausea/vomiting	1 (0.8)	0	1 (0.4)
Patient doing well but WBC count trending down	1 (0.8)	0	1 (0.4)
Patients with dose interruptions, n (%)	4 (3.1)	1 (0.8)	5 (2.0)
Adverse event	2 (1.5)	1 (0.8)	3 (1.2)
Patient request	1 (0.8)	0	1 (0.4)
Lung cancer	1 (0.8)	0	1 (0.4)
Patients with Hct control, n (%)[c]			
At ruxolitinib initiation	19 (14.5)	28 (23.7)	47 (18.9)
During first 6 mo of ruxolitinib treatment	82 (62.6)	75 (63.6)	157 (63.1)
At last visit	70 (53.4)	70 (59.3)	140 (56.2)
Remained on ruxolitinib at cutoff, n (%)	69 (52.7)	84 (71.2)	153 (61.4)
Discontinuation of ruxolitinib, n (%)	62 (47.3)	34 (28.8)	96 (38.6)
Time to ruxolitinib discontinuation, median (IQR), mo[d]	10.5 (6.6–17.1)	11.7 (6.1–18.0)	10.9 (6.3–17.4)

[a] US package insert–recommended starting dose for PV treatment.
[b] More than one reason could be cited for dose modification.
[c] Hct control is defined as Hct <45%.
[d] Values indicate numerical median among patients who discontinued ruxolitinib and do not reflect treatment duration for the entire population.
BID = twice daily; Hct = hematocrit; Hgb = hemoglobin; IQR = interquartile range; PV = polycythemia vera; WBC = white blood cell.

Figure 3 Percentage of patients undergoing phlebotomy procedures after initiation of ruxolitinib treatment. * $P < .0001$ versus baseline.



study period defined hydroxyurea resistance as a lack of response (ie, hematocrit <45%, uncontrolled myeloproliferation, or failure to reduce massive splenomegaly or relieve splenomegaly symptoms) after 3 months of hydroxyurea at a dose of ≥2 g/day.[14] In this analysis, only a quarter of the patients who discontinued hydroxyurea because of resistance received a hydroxyurea dose of ≥2 g/day, which suggests that this guideline-referenced daily dose may not be relevant in real-world clinical practice. Reasons for lack of guideline-concordant dosing cannot be determined from this chart review, but this observation is similar to findings from a prospective observational study (REVEAL), in which only 89 of 1381 patients with PV (6.4%) treated with hydroxyurea for ≥3 months received a maximum dose of 2 g/day.[15]

All patients in the current study of community hematology/oncology practices received ruxolitinib after discontinuing hydroxyurea, roughly half of whom (53%) initiated ruxolitinib at the US PI–recommended dose of 10 mg BID.[12] Although lower doses are recommended under certain circumstances (ie, for patients with renal or hepatic impairment), only 3% of patients initiated ruxolitinib at a dose lower than 10 mg BID, whereas 44% of patients received an initial ruxolitinib dose higher than 10 mg BID, which is not supported by the US PI. This is in contrast to a separate retrospective analysis by Coltoff et al. of patients with PV treated with ruxolitinib at academic centers in the United States between 2011 and 2018 (N = 126), which reported most patients initiated ruxolitinib at 10 mg BID (71%) or a lower dose (5 mg BID, 14%; 15 mg BID, 7%; 20 mg BID, 4%).[16] Among patients in the current study who initiated ruxolitinib at a dose of 10 mg BID, nearly a third (30%) underwent dose modifications (primarily dose increases) or interruptions during the initial 6 months of treatment. Notably, among patients who discontinued ruxolitinib, the majority had no dose modifications during their treatment, regardless of starting dose, suggesting a need for improved dose optimization in this population. Dose modifications were also common in the analysis by Coltoff et al., with 34% of patients receiving 10 mg BID at Week 32, 22% receiving 15 mg BID, 15% receiving 5 mg BID, and 12% receiving 20 mg BID.[16]

Ruxolitinib may be associated with disease control for some patients in real-world settings. Ruxolitinib efficacy in this study of patients in community hematology and/or oncology practices was evaluated using hematocrit control (hematocrit <45%), based on a similar measure used as part of the composite primary endpoint in the phase 3 RESPONSE trial (hematocrit control, defined as protocol-specified ineligibility for phlebotomy from Week 8 to 32 and ≤1 instance of phlebotomy eligibility between randomization and Week 8).[17] The rate of hematocrit control observed at any time during the first 24 weeks of this real-world study was similar to the 32-week efficacy reported in the RESPONSE trial (60%). The retrospective analysis in academic centers by Coltoff et al. reported a similar clinical benefit, with 56% of evaluable patients (53/94) having no phlebotomy requirement at the 32-week follow-up time point.[16] Furthermore, in both the current study and the previous retrospective study, ruxolitinib treatment duration was long (median duration, 31.4 and 22.4 months, respectively), with the majority of patients continuing ruxolitinib treatment (61% and 86%, respectively) at the end of the study observation period.

Conclusions

In conclusion, this retrospective medical chart review of real-world United States clinical practice data analyzed patients with PV who switched from hydroxyurea to ruxolitinib. Resistance to hydroxyurea was the primary reason for switching therapy to ruxolitinib. After switching to ruxolitinib, most patients achieved hematocrit control and continued treatment for extended time frames. Among those who discontinued ruxolitinib, most did so without any dose modifications. The results of this analysis further suggest that a proper starting dose and active titration during the first 6 months of ruxolitinib treatment are likely important for optimal long-term treatment.

Clinical Practice Points

Hydroxyurea is the recommended first-line treatment for patients with high-risk polycythemia vera (PV; age ≥60 years or history of thromboembolic events); however, approximately 1 in 4 patients become resistant to and/or intolerant of hydroxyurea. The Janus kinase 1 (JAK1)/JAK2 inhibitor ruxolitinib is FDA-approved for the treatment of patients with hydroxyurea-resistant/intolerant PV. This retrospective study used real-world data to characterize the reasons patients switched from hydroxyurea to ruxolitinib and describes ruxolitinib dosing patterns and limited treatment outcomes. Most patients discontinued hydroxyurea because of resistance, and did so before receiving a dose of 2 g/day, suggesting this guideline-referenced dose may not be relevant in the real world. Approximately half of the patients initiated ruxolitinib at the recommended dose (10 mg twice daily), with most dose modifications and interruptions occurring in the first 6 months. Most patients achieved hematocrit control on ruxolitinib and continued treatment for extended time frames. The majority of patients who discontinued ruxolitinib did not have dose modifications. These results suggest that the proper starting dose and active titration during the first 6 months of ruxolitinib treatment may be important to achieve optimal outcomes.

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References

1. Mehta J, Wang H, Iqbal SU, Mesa R. Epidemiology of myeloproliferative neoplasms in the United States. *Leuk Lymphoma*. 2014;55:595–600. doi:10.3109/10428194.2013.813500.
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405. doi:10.1182/blood-2016-03-643544.

3. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*. 2013;27:1874–1881. doi:10.1038/leu.2013.163.
4. Hultcrantz M, Kristinsson SY, Andersson TM, et al. Patterns of survival among patients with myeloproliferative neoplasms diagnosed in Sweden from 1973 to 2008: a population-based study. *J Clin Oncol*. 2012;30:2995–3001. doi:10.1200/JCO.2012.42.1925.
5. Mesa R, Boccia RV, Grunwald MR, et al. Patient-reported outcomes data from REVEAL at the time of enrollment (baseline): a prospective observational study of patients with polycythemia vera in the United States. *Clin Lymphoma Myeloma Leuk*. 2018;18:590–596. doi:10.1016/j.clml.2018.05.020.
6. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004;350:114–124. doi:10.1056/NEJMoa035572.
7. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368:22–33. doi:10.1056/NEJMoa1208500.
8. Grunwald MR, Burke JM, Kuter DJ, et al. Symptom burden and blood counts in patients with polycythemia vera in the United States: an analysis from the REVEAL study. *Clin Lymphoma Myeloma Leuk*. 2019;19:579–584.e1 e571. doi:10.1016/j.clml.2019.06.001.
9. Ferrari A, Carobbio A, Masciulli A, et al. Clinical outcomes under hydroxyurea treatment in polycythemia vera: a systematic review and meta-analysis. *Haematologica*. 2019;104:2391–2399. doi:10.3324/haematol.2019.221234.
10. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms, version 1.2020. *To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.* © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed June 24, 2020.. Plymouth Meeting, PA: National Comprehensive Cancer Network, Inc.; 2020.
11. Alvarez-Lárran A, Pereira A, Cervantes F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood*. 2012;119:1363–1369. doi:10.1182/blood-2011-10-387787.
12. JAKAFI®. *Full prescribing information, Incyte Corporation* Wilmington, DE; 2016:2016.
13. Parasuraman S, DiBonaventura M, Reith K, Naim A, Concialdi K, Sarlis NJ. Patterns of hydroxyurea use and clinical outcomes among patients with polycythemia vera in real-world clinical practice: a chart review. *Exp Hematol Oncol*. 2016;5:3.
14. Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*. 2011;29:761–770. doi:10.1200/JCO.2010.31.8436.
15. Grunwald MR, Kuter DJ, Altomare I, et al. Treatment patterns and blood counts in patients with polycythemia vera treated with hydroxyurea in the United States: an analysis from the REVEAL study. *Clin Lymphoma Myeloma Leuk*. 2020;20:219–225. doi:10.1016/j.clml.2019.09.601.
16. Coltoff A, Mesa R, Gotlib J, et al. Real-world outcomes of ruxolitinib treatment for polycythemia vera. *Clin Lymphoma Myeloma Leuk*. 2020;20:697–703.e1. doi:10.1016/j.clml.2020.1005.1019.
17. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372:426–435. doi:10.1056/NEJMoa1409002.