2018

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

Ruben Mesa
University of Texas Health Science Center at San Antonio

Ralph V. Boccia
The Center for Cancer and Blood Disorders

Michael R. Grunwald
Atrium Health

Stephen T. Oh
Washington University School of Medicine in St. Louis

Philomena Colucci
Incyte Corporation

See next page for additional authors

Original Study

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

Ruben Mesa,[1] Ralph V. Boccia,[2] Michael R. Grunwald,[3] Stephen T. Oh,[4] Philomena Colucci,[5] Dilan Paranagama,[5] Shreekant Parasuraman,[5] Brady L. Stein[6]

Abstract

Data from REVEAL (Prospective Observational Study of Patients With Polycythemia Vera in US Clinical Practices; n = 2309), the first study of its kind, confirm that many patients experience quality of life and work productivity impairments that might negatively affect their lives. In the future, longitudinal data from REVEAL will be important for evaluating how such burdens change over time.

Background: Patients with polycythemia vera (PV) often experience symptoms that adversely affect their quality of life (QoL). The ongoing, prospective, observational REVEAL (Prospective Observational Study of Patients With Polycythemia Vera in US Clinical Practices) study was designed to collect contemporary data regarding burden of disease, clinical management, patient-reported outcomes (PROs), and health care resource utilization from adult patients with PV in the United States. **Patients and Methods:** Data on PROs were collected at enrollment using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS; range, 0-100); the European Organization for Research and Treatment of Cancer—Core Quality of Life Questionnaire, version 3.0 (EORTC QLQ-C30; range, 0-100); and the Work Productivity and Activity Impairment Questionnaire—Specific Health Problem (WPAI-SHP; range, 0%-100%). **Results:** Among 2309 patients, mean (SD) disease duration was 5.8 (6.1) years and Charlson Comorbidity Index was 3.4 (0.8); 54.0% (1247/2309) were male. Mean (SD) MPN-SAF TSS was 18.8 (15.5). The most common symptoms were fatigue (80.1% [1844/2302]), early satiety (60.9% [1402/2302]), and inactivity (57.6% [1324/2302]). The most common severe symptoms were fatigue (16.8% [387/2302]), itching (13.4% [308/2302]), and inactivity (11.8% [271/2302]). The mean (SD) EORTC QLQ-C30 global health status/QoL score was 73.1 (23.2): mean functional subscale scores ranged from 80.5 (23.9) for cognitive functioning to 85.7 (24.6) for social functioning. The mean WPAI-SHP activity impairment score was 19.7% (n = 2300). Employed patients had mean WPAI-SHP scores for absenteeism, presenteeism, and overall work impairment of 3.2% (n = 810), 12.1% (n = 807), and 13.4% (n = 802), respectively. **Conclusion:** These data confirm that many patients with PV experience symptoms, QoL impairments, and work productivity impairments that negatively affect their lives. Longitudinal data from REVEAL will be important for evaluating how PROs change over time in these patients.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 18, No. 9, 590-6

Keywords: Activity impairment, Myeloproliferative neoplasm, Quality of life, Symptoms, Work productivity

ClinicalTrials.gov: NCT02252159

[1]Mays Cancer Center, UT Health San Antonio Cancer Center — An NCI Designated Cancer Center, San Antonio, TX
[2]The Center for Cancer and Blood Disorders, Bethesda, MD
[3]Levine Cancer Institute, Atrium Health, Charlotte, NC
[4]Divisions of Hematology & Oncology, Washington University School of Medicine, St Louis, MO
[5]Incyte Corporation, Wilmington, DE
[6]Department of Medicine (Hematology and Oncology), Northwestern University Feinberg School of Medicine, Chicago, IL

Submitted: Mar 30, 2018; Accepted: May 21, 2018; Epub: May 28, 2018

Address for correspondence: Ruben Mesa, MD, FACP, Mays Cancer Center, UT Health San Antonio Cancer Center — An NCI Designated Cancer Center, 6th Floor Urschel Tower, 7979 Wurzbach Rd, San Antonio, TX 78229
Fax: 210-450-1100; e-mail contact: mesa.ruben@uthscsa.edu

https://doi.org/10.1016/j.clml.2018.05.020

Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) primarily characterized by erythrocytosis and activating mutations in the Janus kinase 2 gene.[1] Patients with PV have an increased risk of mortality compared with age- and sex-matched individuals in the general population[2] and experience a broad range of symptoms that negatively affect their quality of life (QoL) and productivity.[3-6] In the recent MPN Landmark survey of US patients with MPNs, fatigue was the most frequently reported symptom among patients with PV (73%), and 49% of the patients described their fatigue as "very severe."[5] Many patients also reported itching (55%), night sweats (45%), and concentration problems (36%). In addition to the various symptoms associated with PV, approximately 40% of patients experience splenomegaly that resulted in occasional discomfort and pain.[7] Findings from an international prospective study of 1334 patients with PV (mean disease duration, 6.9 years)[8] suggest that many patients experience suboptimal symptom control with traditional treatments.

Most patients with PV in the MPN Landmark cross-sectional survey reported feeling anxious or worried about their condition (78%) and that their PV symptoms reduced their QoL (66%).[5] Many patients also reported interference with family or social life (63%), daily activities (48%), and normal work hours (37%). Most of the observational studies of patients with PV have been reported out of Europe[3,6,9-11] or have been limited to single centers in the United States.[12,13] Administrative claims databases and electronic medical records can be used to characterize patterns of care in clinical practice; however, these data sources frequently lack patient-reported outcomes (PROs) and can be limited in utility because of selection bias and missing values. Cross-sectional surveys such as the Landmark survey cannot characterize how PROs change over time.

With respect to the evolution of MPN-specific PROs, the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) is a questionnaire that includes 17 MPN-related symptoms and a single question pertaining to overall QoL that was designed to assess the most impactful symptoms observed in patients with MPNs.[3,6] Subsequently, on the basis of the evaluation of the MPN-SAF in clinical practice, it was concluded that an abbreviated version was necessary.[3] Consequently, the MPN-SAF Total Symptom Score (TSS; also known as MPN10) was constructed and validated. This shorter questionnaire includes a question pertaining to the worst level of fatigue in the past 24 hours as well as the other 9 most characteristic and clinically significant MPN symptoms.[3] Both instruments remain in use. For example, in the National Comprehensive Cancer Network's clinical guidelines for MPNs, the MPN-SAF and the MPN-SAF TSS are currently recommended for the assessment of symptom burden at baseline and during the course of treatment, respectively.[14]

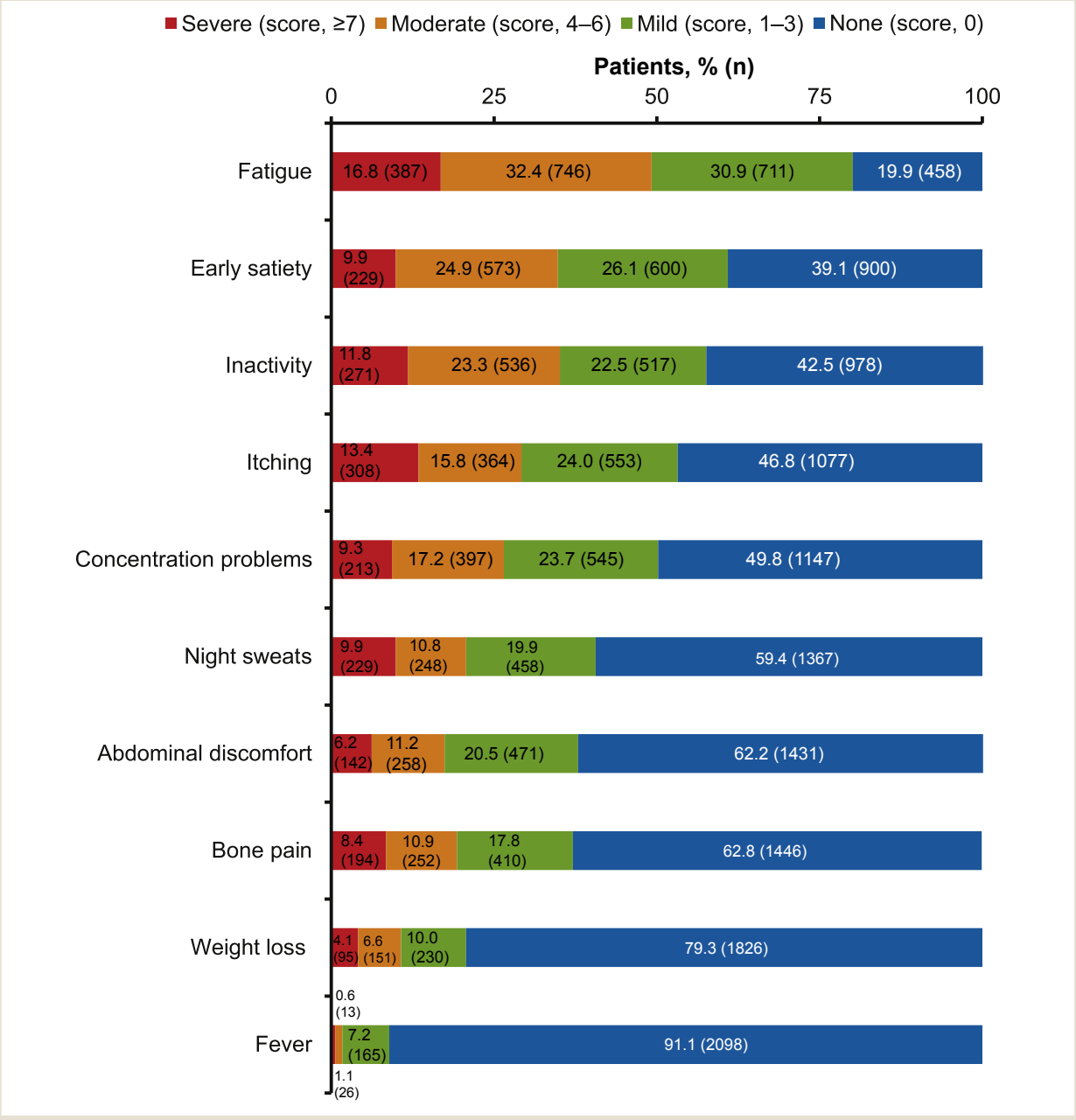
The ongoing REVEAL (Prospective Observational Study of Patients With Polycythemia Vera in US Clinical Practices; ClinicalTrials.gov: NCT02252159) was designed to collect contemporary data regarding the burden of disease, clinical management, PROs, and health care resource utilization of patients with PV in the United States. The objective of the present report was to characterize the PRO data from REVEAL at patient enrollment to assess the symptom burden, QoL impairments, and work productivity impairments associated with PV.

Table 1 Demographic and Clinical Characteristics at Enrollment[a]

Characteristic	All Patients (n = 2309)
Mean (SD) Age, Years	66.1 (12.1)
Age Group, Years, n (%)	
18-34	28 (1.2)
35-59	618 (26.8)
60-74	1073 (46.5)
≥75	590 (25.6)
Sex, n (%)	
Male	1247 (54.0)
Female	1062 (46.0)
Disease Duration, Years	
Mean (SD)	5.8 (6.1)
Median (range)	4.1 (0-39.2)
Primary Employment Status at PV Diagnosis, n (%)	
Full-time	1121 (48.5)
Part-time	148 (6.4)
Retired	746 (32.3)
Homemaker	116 (5.0)
Unable to work/disabled	86 (3.7)
Other	46 (2.0)
Student	13 (0.6)
Unknown/missing	33 (1.4)
Employment Status at Enrollment, n (%)	
Full-time	669 (29.0)
Part-time	110 (4.8)
Retired	1176 (50.9)
Homemaker	80 (3.5)
Unable to work/disabled	101 (4.4)
Other	70 (3.0)
Student	6 (0.3)
Unknown/missing	97 (4.2)
PV Risk Status, n (%)	
Low	528 (22.9)
High[b]	1781 (77.1)
Mean (SD) Charlson Comorbidity Index	3.4 (0.8)
Management of PV, n (%)	
Watchful Waiting	123 (5.3)
Phlebotomy Only (With or Without Aspirin)	787 (34.1)
Hydroxyurea (With or Without Aspirin)	661 (28.6)
Hydroxyurea With Phlebotomy (With or Without Aspirin)	550 (23.8)
Other	186 (8.1)
Missing	2 (0.1)

Abbreviation: PV = polycythemia vera.
[a]All patients with age and sex information enrolled on or before May 18, 2017, and with at least 1 nonmissing patient-reported outcome at enrollment.
[b]High-risk PV defined as patients with a history of thrombotic events and/or patients 60 years of age or older.

Figure 1 Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Symptom Severity at Enrollment.[a] Weight Loss Indicates Unintentional Weight Loss in the Past 6 Months



[a] Each item was scored on a scale from 0 (absent) to 10 (worst imaginable). Only evaluable patients with MPN-SAF data (n = 2302) were included.

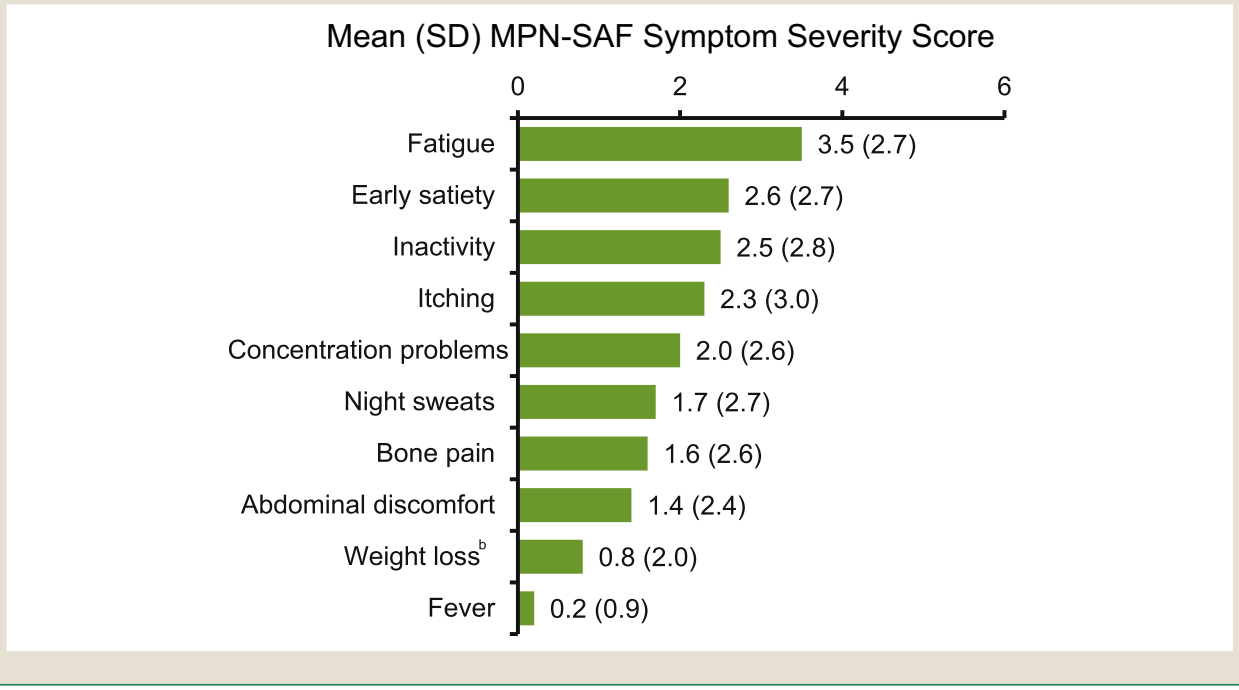
Patients and Methods

Study Design

The REVEAL study is a multicenter, noninterventional, prospective, observational study of adult patients with PV. REVEAL is being conducted in accordance with the Declaration of Helsinki; institutional review board approval of all study materials is required, and informed consent is required from all patients. Patients were recruited over a 24-month enrollment period. All treatment decisions were made by the treating physician.

Patients were eligible for inclusion if they were 18 years old or older; had a clinical diagnosis of PV; were willing and able to provide informed consent and complete patient assessments and questionnaires, either alone or with minimal assistance from a caregiver or trained site personnel; and were under physician supervision for the current management of their PV. Patients were excluded if they were participating in an active, blinded clinical trial; had a life expectancy <6 months; had a diagnosis of myelofibrosis, acute myeloid leukemia, or myelodysplastic syndrome; had a history

Figure 2 Mean (SD) Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Symptom Scores at Enrollment[a]



[a] Each item was scored on a scale from 0 (absent) to 10 (worst imaginable). Only evaluable patients with MPN-SAF data (n = 2302) were included.
[b] Unintentional weight loss in the past 6 months.

of or active plan to proceed to allogeneic hematopoietic stem cell transplantation within 3 months of enrollment; or had undergone splenectomy.

Assessments

An objective of REVEAL was to collect PRO data pertaining to health-related QoL, activity, and productivity impairment, and symptom burden in patients with PV. PRO data were collected at enrollment (baseline) and at 3-month intervals; the current analysis was conducted on PRO data collected at enrollment.

Symptom burden was assessed with the MPN-SAF TSS (also known as MPN10),[3] which consists of 10 items (fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, night sweats, itching, bone pain, fever, and unintentional weight loss) graded from 0 (absent) to 10 (worst). Severity designations for the MPN-SAF TSS were: 0, absent; 1-3, mild; 4-6, moderate; and ≥7, severe. The MPN-SAF TSS was defined as the sum of all 10 symptoms (range, 0-100). Health-related QoL was assessed with the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire, version 3.0 (EORTC QLQ-C30),[15] which is composed of 5 multi-item functional scales (physical, role, cognitive, emotional, and social), 3 multi-item symptom scales (fatigue, nausea/vomiting, and pain), and a multi-item global health status/QoL scale. It also includes 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) assessing additional symptoms. Linear transformation to 0 to 100 was applied to raw scores (averages of the items contributing to the scale or individual item values) to obtain scores for each scale or single item. Higher scores for functional scales and global health status represent higher functioning and better health status/QoL, respectively. However, higher scores for symptom scales/items represent higher symptom burden.

Work productivity and activity impairment were examined with the Work Productivity and Activity Impairment Questionnaire—Specific Health Problem (WPAI-SHP).[16] Activity impairment was assessed for all patients (7-day recall) as the percentage of impairment in daily activities. The following work-related impairments were assessed among employed patients only (7-day recall): absenteeism (percentage of work time missed because of PV), presenteeism (percentage of impairment while at work because of PV), and percentage overall work impairment due to PV. For all WPAI-SHP items, higher percentages indicate greater levels of impairment.

Morbidity was assessed using the Charlson Comorbidity Index (CCI), which is not a PRO.[17] The CCI rates International Classification of Diseases diagnosis codes on a 6-point scale, with higher scores indicating increasing severity (eg, increased risk of mortality or resource use); the sum of these scores yields a single index value for each patient (ie, there is no maximum value).

Statistics

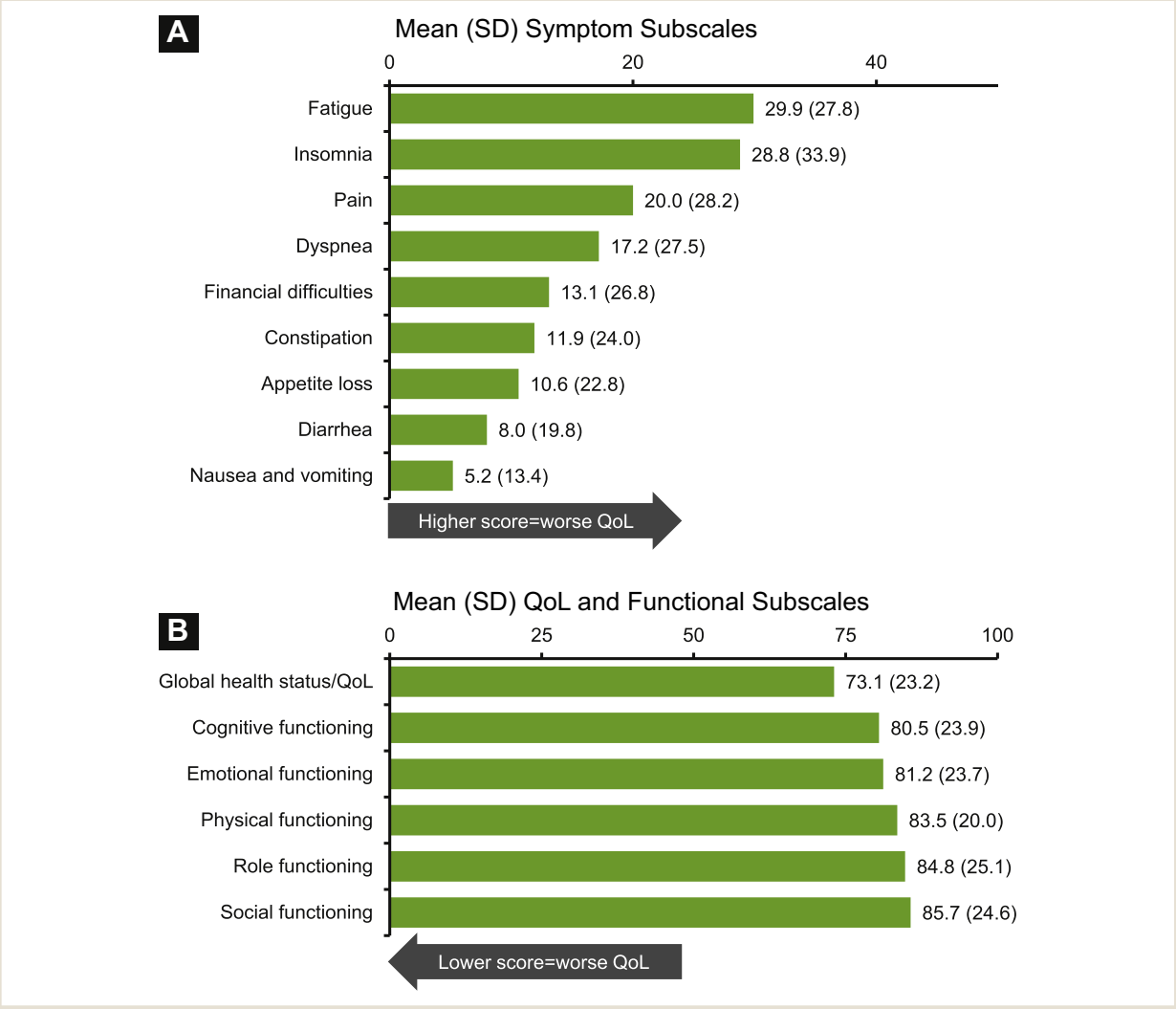
All analyses were exploratory in nature and evaluated with descriptive statistics. Statistical analysis of all data was performed using SAS statistical software (SAS Institute Inc, Cary, NC) or other commercially available standard statistical software.

Results

Demographic and Baseline Characteristics

Of the 2510 enrolled patients, 2309 had evaluable PRO data at enrollment. These patients had a mean (SD) age of 66.1 (12.1)

Figure 3 Mean European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30) Scores for (A) Symptom Subscales and (B) QoL and Functional Subscales at Enrollment[a]



Abbreviation: QoL, quality of life.
[a] All scores were standardized using linear transformation to 0 to 100. Only evaluable patients with EORTC QLQ-C30 data (n = 2298-2304 for each score) were included.

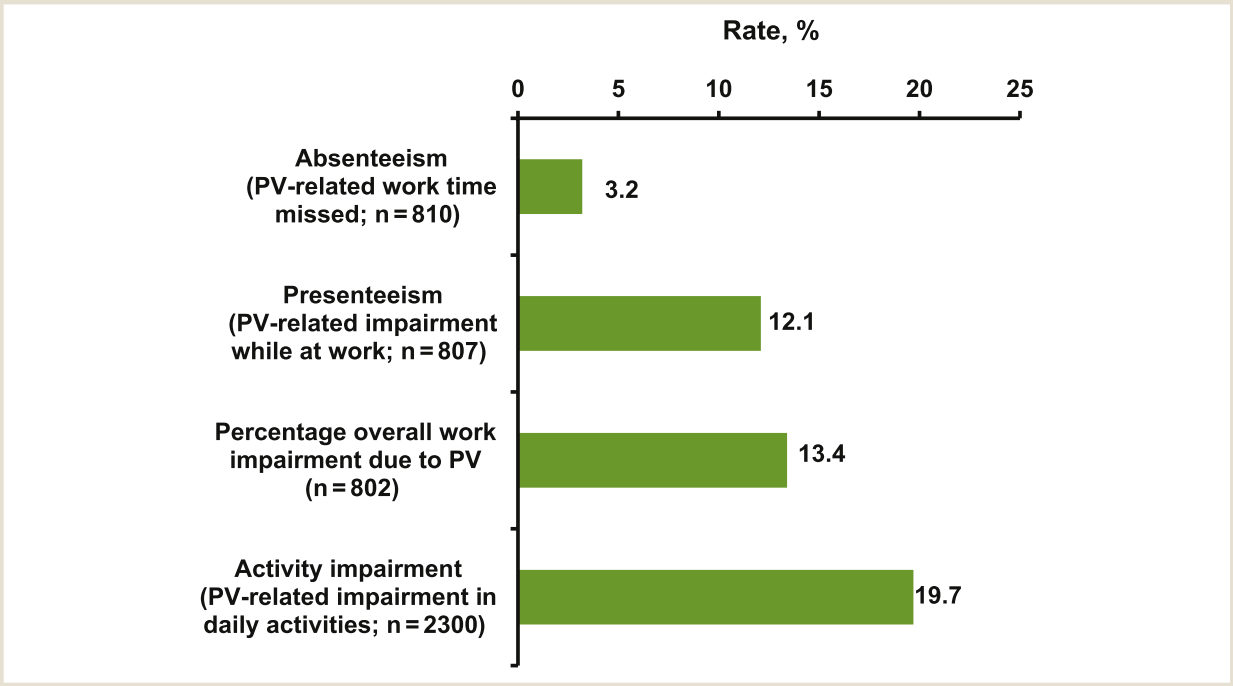
years, a median (range) disease duration of 4.1 (0-39.2) years, and a mean (SD) CCI of 3.4 (0.8). At enrollment, most patients (94.6% [2184/2309]) were managed with therapeutic interventions, the most common being hydroxyurea with or without phlebotomy and aspirin (52.4% [1211/2309]). A small proportion of patients were under watchful waiting without any therapeutic interventions (5.3% [123/2309]). More than half (55.0% [1269/2309]) of enrolled patients reported being employed full- or part-time at the time of their PV diagnosis, whereas approximately one-third (33.7% [779/2309]) were employed at enrollment (Table 1).

Patient-Reported Outcomes

Symptoms and Health-Related QoL. Of the 2307 patients with MPN-SAF responses at enrollment, 93.3% (2152 of 2307) reported at least 1 PV-related symptom. The most frequently reported symptoms on the MPN-SAF TSS were fatigue (80.1% [1844/2302]), early satiety (60.9% [1402/2302]), and inactivity (57.6% [1324/2302]; Figure 1). The most frequently reported severe symptoms (MPN-SAF TSS score ≥7) were fatigue (16.8% [387/2302]), itching (13.4% [308/2302]), and inactivity (11.8% [271/2302]; Figure 1). The mean (SD) MPN-SAF TSS total score at enrollment was 18.8 (15.5). Symptoms with the highest reported mean (SD) MPN-SAF TSS severity scores were fatigue (3.5 [2.7]), early satiety (2.6 [2.7]), inactivity (2.5 [2.8]), itching (2.3 [3.0]), and concentration problems (2.0 [2.6]; Figure 2).

The most severe mean (SD) symptom scores on the EORTC QLQ-C30 at enrollment were fatigue (29.9 [27.8]), insomnia (28.8 [33.9]), pain (20.0 [28.2]), and dyspnea (17.2 [27.5]; Figure 3A). The mean (SD) EORTC QLQ-C30 global health status/QoL score at enrollment was 73.1 (23.2), with mean functional scores ranging from 80.5 (23.9) for cognitive functioning to 85.7 (24.6) for social functioning (Figure 3B).

Figure 4 Mean Work Productivity and Activity Impairment Questionnaire—Specific Health Problem Scores at Enrollment[a]



Abbreviation: PV = polycythemia vera.
[a] All items on the basis of 7-day recall (ie, regarding work/activity during the 7 days preceding the survey).

Work Productivity and Activity Impairment. Patients experienced notable work productivity and activity impairments in the 7 days preceding the assessment at enrollment (Figure 4). The mean activity impairment score at enrollment, regardless of employment status, was 19.7% (n = 2300). Among employed patients, mean WPAI-SHP scores for absenteeism, presenteeism, and overall work impairment at enrollment were 3.2% (n = 810), 12.1% (n = 807), and 13.4% (n = 802), respectively.

Discussion

The REVEAL study is the first large, prospective, observational study aimed at examining the contemporary demographic characteristics, burden of disease, clinical management, PROs, and health care resource utilization in patients with PV in the United States. Enrolled patients represent a broad, real-world segment of the PV population that is actively undergoing treatment at community or academic centers. REVEAL is unique in that it is a prospective, longitudinal study of American patients in a variety of clinical practice settings.

At the time of enrollment in the REVEAL study, most patients noted the presence of symptoms. On the MPN-SAF TSS, fatigue, early satiety, and inactivity were the most common and the most severe symptoms reported. QoL parameters assessed with the EORTC QLQ-C30 confirmed disease burden in patients with the most severe scores reported for fatigue, insomnia, and pain. Among patients who were employed at the time of enrollment, absenteeism and impairment while at work were attributed to their PV. However, in light of the median age at diagnosis (60.3 years), a decline in the proportion of patients employed at the time of diagnosis (55.0% [1269/2309]) compared with enrollment (33.7% [779/2309]) is likely attributable to age and symptom burden.

In the first publication in which the MPN-SAF TSS was used to assess symptom burden in an international cohort of patients with MPNs, there were MPN-SAF TSS data reported for 538 patients with PV.[3] The symptoms with the highest mean scores included fatigue, pruritus, concentration problems, early satiety, and inactivity. In a subsequent study, the MPN-SAF TSS was used to prospectively evaluate 1334 international patients with PV to determine how previous hydroxyurea use, phlebotomy requirements, and palpable splenomegaly contributed alone or in aggregate to PV symptom burden.[8] Among all patients, the highest mean scores included fatigue, concentration problems, pruritus, inactivity, and early satiety. When evaluating results reported from REVEAL as well as these 2 other prospective studies, fatigue was consistently the symptom with the highest mean score. Similarly, in all 3 of these prospective studies, the symptoms with the highest mean scores (fatigue, early satiety, inactivity, pruritus, and concentration problems) were consistent, although the rank order of the second through fifth highest mean scores varied.

With respect to the EORTC QLQ-C30 score results, the mean (SD) duration of PV in REVEAL patients was 5.8 (6.1) years and the mean (SD) global health status/QoL score was 73.3 (23.2). In other prospective studies[6,11] in which mean global health/QoL scores were reported for non-newly diagnosed patients (mean duration of PV not reported) and for newly diagnosed patients, the mean global health status/QoL scores were 65.7 and 69.7,

respectively. Disease duration and study location might have contributed to differences in the mean global health status/QoL scores. However, there were consistencies among the 3 studies; for example, in all 3 studies, the 4 EORTC QLQ-C30 symptoms with the highest mean scores included fatigue, insomnia, dyspnea, and pain.[6,11]

Data from the WPAI-SHP indicate that PV affects activities of daily living in all patients, and for those who are working, the overall work impairment in patients with PV is related more to impairment while at work as opposed to loss of time from work. Longitudinal analyses from REVEAL will elucidate how symptoms, QoL, and work productivity change with time and disease progression.

Limitations

Responses to PRO questionnaires were missing for some patients, which might introduce bias into the results.

Conclusion

Future results from analyses of REVEAL longitudinal data will be important for understanding the burden of PV in the United States and for promoting further research aimed at optimizing patient treatment practices and outcomes. The prospective nature of REVEAL will facilitate the understanding of how symptom burden changes with time.

Clinical Practice Points

- Previous studies in which the MPN-SAF TSS was used to assess symptom burden in patients with PV have been limited to international patients. In these previous evaluations, the symptoms with the highest severity included fatigue, pruritus, and concentration problems.
- When the MPN-SAF TSS was used to assess symptom burden in US patients with PV enrolled in REVEAL, the symptoms with the highest severity included fatigue, early satiety, and inactivity.
- In this analysis, the symptom burden associated with PV appears to have a negative effect on the QoL, daily activities, and work productivity of some patients.
- Although the primary management goal is to control blood counts to decrease the risk of a first or recurrent thrombotic event, it is also important to regularly evaluate patients for symptom burden, which might result in significant morbidity in these patients.
- The MPN-SAF TSS form offers a concise, valid, and accurate assessment of symptom burden that can be used in the clinic for all patients with MPNs, including patients with PV.

Acknowledgments

Writing assistance was provided by Tania Iqbal, PhD, at Complete Healthcare Communications, LLC (West Chester, PA), a CHC Group company, and funded by Incyte Corporation.

This work was funded by Incyte Corporation.

Disclosure

R.M. served as a consultant for Novartis and received research funding from CTI Biopharma, Genentech, Gilead, Incyte Corporation, NS Pharma, Pfizer, and Promedior. R.V.B. received honoraria from Incyte Corporation. M.R.G. has received honoraria from Alexion, Amgen, ARIAD, Cardinal Health, Celgene, Incyte Corporation, and Pfizer; served as a consultant for Incyte Corporation; received research funding from Amgen, Forma Therapeutics, Genentech, Incyte Corporation, and Janssen; and is a stockholder of Medtronic. S.T.O. served as a consultant for CTI Biopharma, Incyte Corporation, and Pfizer; and received research funding from CTI Biopharma, Gilead, Incyte Corporation, and Janssen. P.C., D.P., and S.P. are employees and stockholders of Incyte Corporation. B.L.S. served as a consultant and member of the advisory committees for Incyte Corporation.

References

1. 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; 127:2391-405.
2. 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.
3. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. *J Clin Oncol* 2012; 30:4098-103.
4. Johansson P, Mesa R, Scherber R, et al. Association between quality of life and clinical parameters in patients with myeloproliferative neoplasms. *Leuk Lymphoma* 2012; 53:441-4.
5. Mesa R, Miller CB, Thyne M, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. *BMC Cancer* 2016; 16:167.
6. Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood* 2011; 118:401-8.
7. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international internet-based survey of 1179 MPD patients. *Cancer* 2007; 109:68-76.
8. Geyer H, Scherber R, Kosiorek H, et al. Symptomatic profiles of patients with polycythemia vera: implications of inadequately controlled disease. *J Clin Oncol* 2016; 34:151-9.
9. Gruppo Italiano Studio Policitemia. Polycythemia vera: the natural history of 1213 patients followed for 20 years. Gruppo Italiano Studio Policitemia. *Ann Intern Med* 1995; 123:656-64.
10. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia* 2013; 27: 1874-81.
11. Abelsson J, Andreasson B, Samuelsson J, et al. Patients with polycythemia vera have the worst impairment of quality of life among patients with newly diagnosed myeloproliferative neoplasms. *Leuk Lymphoma* 2013; 54:2226-30.
12. Stein BL, Williams DM, Wang NY, et al. Sex differences in the JAK2 V617F allele burden in chronic myeloproliferative disorders. *Haematologica* 2010; 95:1090-7.
13. Stein BL, Saraf S, Sobol U, et al. Age-related differences in disease characteristics and clinical outcomes in polycythemia vera. *Leuk Lymphoma* 2013; 54:1989-95.
14. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Myeloproliferative neoplasms, Version 2.2018, Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed: February 14, 2018.
15. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-76.
16. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; 4:353-65.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40:373-83.