Original Study

Effects of Ruxolitinib Treatment on Metabolic and Nutritional Parameters in Patients With Myelofibrosis From COMFORT-I

Ruben A. Mesa,[1] Srdan Verstovsek,[2] Vikas Gupta,[3] John O. Mascarenhas,[4] Ehab Atallah,[5] Timothy Burn,[6] William Sun,[6] Victor Sandor,[6] Jason Gotlib[7]

Abstract

In a phase III, double-blind, randomized study, treatment with ruxolitinib resulted in significant reductions in splenomegaly and symptom burden in patients with intermediate-2 or high-risk myelofibrosis and was associated with a survival advantage relative to placebo. In this post hoc analysis, we assessed the effect of ruxolitinib treatment on measures of metabolic and nutritional status.

Background: In the COMFORT (COntrolled MyeloFibrosis Study with ORal JAK Inhibitor Therapy)-I study, the Janus kinase (JAK)1/JAK2 inhibitor ruxolitinib provided significant reductions in splenomegaly, improvements in myelofibrosis (MF)-related symptoms, and a survival advantage relative to placebo in patients with intermediate-2 or high-risk MF. In this post hoc analysis, we assessed the effects of ruxolitinib treatment on measures of metabolic and nutritional status. **Patients and Methods:** Patients were randomized to receive ruxolitinib (n = 155; 15 or 20 mg twice a day for patients with baseline platelet counts of 100-200 $\times$ 10^9/L or $>$ 200 $\times$ 10^9/L, respectively) or placebo (n = 154). The primary end point was the proportion of patients with a $\geq$ 35% spleen volume reduction from baseline to week 24. A secondary end point was the proportion of patients with $\geq$ 50% improvement in Total Symptom Score (TSS) from baseline to week 24, measured using the modified Myelofibrosis Symptom Assessment Form version 2.0. Weight, cholesterol, and albumin were measured at specified time points throughout the study. **Results:** Compared with placebo, ruxolitinib treatment was associated with increased weight (mean change: 3.9 kg vs. −1.9 kg), total cholesterol (mean percentage change: 26.4% vs. −3.3%), and albumin levels (mean percentage change: 5.8% vs. −1.7%) at week 24; sustained improvements were observed with longer-term ruxolitinib therapy. Relative to placebo, increases in mean weight, total cholesterol, and albumin levels were observed with ruxolitinib treatment regardless of the degree of spleen volume and TSS reductions at 24 weeks. **Conclusion:** Treatment with ruxolitinib improved measures of metabolic and nutritional status of patients with intermediate-2 or high-risk MF.

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Introduction

Myelofibrosis (MF) is a chronic Philadelphia chromosome-negative myeloproliferative neoplasm that primarily affects older individuals[1,2] and is characterized by progressive bone marrow fibrosis and ineffective hematopoiesis.[3-5] Patients with MF typically experience cytopenias, splenomegaly—attributable to extramedullary hematopoiesis and splenic sequestration—and/or debilitating symptoms, which might severely diminish their quality of life.[6-8] Although some symptoms, such as early satiety, abdominal discomfort, and splenic pain, might result from splenomegaly, many symptoms experienced by patients with MF, including fatigue, night sweats, bone pain, fever, and weight

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[1]Mayo Clinic, Scottsdale, AZ
[2]The University of Texas M.D. Anderson Cancer Center, Houston, TX
[3]Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada
[4]Icahn School of Medicine at Mount Sinai, New York, NY
[5]Medical College of Wisconsin, Froedtert Hospital, Milwaukee, WI
[6]Incyte Corporation, Wilmington, DE
[7]Stanford Cancer Institute, Stanford, CA

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Address for correspondence: Ruben A. Mesa, MD, Division of Hematology and Medical Oncology, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259
Fax: 480-301 4675; e-mail contact: mesa.ruben@mayo.edu

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loss appear to be consequences of systemic inflammation and hypercatabolism driven by abnormal levels of circulating cytokines.[9,10]

Dysregulated signaling of the Janus kinase (JAK)—signal transducers and activators of transcription (STAT) pathway is central to the pathogenesis of MF.[11] Various mechanisms of this dysregulated signaling have been identified, including somatic mutations that result in neoplastic myeloproliferation and dysfunctional hematopoiesis.[11-13] In addition, aberrant JAK-STAT signaling underlies secondary effects of myeloproliferation, particularly the excess proinflammatory cytokine production responsible for MF-associated symptoms and metabolic disturbances and chronic weight loss.[9,10]

Cachexia is a multifactorial syndrome characterized by the loss of skeletal muscle and fat mass with detrimental consequences on quality of life, morbidity, and mortality in patients with MF.[7] The causative factors underlying cachexia in MF are complex and not well understood, but they might include reduced nutritional intake due to massive splenomegaly and metabolic disturbances caused by the systemic inflammatory state. The JAK-STAT pathway is a key regulator of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, which have been implicated in the modulation of body mass and cachexia.[14,15] In addition, C-reactive protein (CRP), a marker of systemic inflammation, is increased in patients with cancer-related cachexia.[14] Moreover, abnormal levels of proinflammatory cytokines have been identified as negative prognostic factors for overall survival in patients with primary MF, along with cachexia and constitutional symptoms.[1,9,16] In addition to weight loss, cachexia is often associated with hypoalbuminemia.[17] A chronic inflammatory and hypercatabolic state has been shown to inhibit albumin synthesis in the liver, further contributing to cachexia-induced hypoalbuminemia.[18]

Myelofibrosis is also characterized by abnormally low cholesterol levels, which has been associated with shortened survival.[7,19,20] An analysis of lipid data from 207 patients with MF treated at a single center showed that decreased levels of total or high-density lipoprotein cholesterol (HDL-C) were associated with shortened survival independent of the Dynamic International Prognostic Scoring System-Plus.[20]

Treatment with ruxolitinib, an oral JAK1/JAK2 inhibitor, resulted in significant reductions in spleen volume and improvements in symptoms and quality of life in patients with intermediate-2 or high-risk MF in 2 phase III studies, COMFORT (COntrolled MyeloFibrosis Study with ORal JAK Inhibitor Therapy)-I[21] and COMFORT-II.[22] In addition, evidence from both trials suggested that ruxolitinib was associated with a survival advantage compared with placebo[21,23] and what was previously considered best available therapy.[24] Ruxolitinib treatment has been shown to modify plasma markers associated with MF symptomatology.[21] For example, in the COMFORT-I study, ruxolitinib-treated patients had decreased plasma levels of inflammatory markers commonly upregulated in MF such as TNF-α, IL-6, and CRP.[21]

We hypothesized that the clinical benefit of ruxolitinib might be related at least in part to the alleviation of cachexia and improvement of patients' metabolic/nutritional status because ruxolitinib-treated patients in COMFORT-I generally experienced an increase in body weight whereas placebo-treated patients experienced a decrease in weight. Therefore, we conducted a post hoc analysis of long-term data from the COMFORT-I study to further investigate the effects of ruxolitinib treatment on body weight, total cholesterol, and albumin, and the association of these changes with a reduction in spleen volume and MF-related symptoms.

Patients and Methods

Patients and Study Design

Detailed methods for the COMFORT-I study have been previously reported.[21] Briefly, eligible patients from the United States, Canada, or Australia were ≥ 18 years of age with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF; disease that was classified as intermediate-2 or high-risk according to the International Prognostic Scoring System; a platelet count of ≥ 100×10^9/L; and a palpable spleen (≥ 5 cm below the left costal margin). All patients had disease requiring treatment and were refractory to or intolerant of available therapies.

Eligible patients were randomized to receive placebo (n = 154) or ruxolitinib (n = 155) at 2 different starting dosages depending on baseline platelet count. Patients with a platelet count of 100 to 200×10^9/L received a 15-mg twice-a-day (b.i.d.) starting dosage of ruxolitinib, and those with a platelet count > 200×10^9/L received a 20-mg b.i.d. starting dosage of ruxolitinib; dosages were adjusted for lack of efficacy or excess toxicity. Patients randomized to placebo crossed over to ruxolitinib or discontinued within 3 months of the primary data analysis (when all patients completed 24 weeks and half of the patients remaining in the study completed 36 weeks of treatment). The primary end point was the proportion of patients achieving ≥ 35% reduction in spleen volume (assessed using abdominal imaging) from baseline to week 24. A secondary end point was the proportion of patients who achieved ≥ 50% reduction in Total Symptom Score (TSS) from baseline to week 24 using the modified Myelofibrosis Symptom Assessment Form version 2.0.[21] The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice. The protocol was approved by the institutional review board at each participating site, and all patients provided written informed consent.

Evaluations

All patients originally randomized to ruxolitinib or placebo were included in this post hoc analysis. For patients in the placebo group who crossed over to ruxolitinib, data were only included for time points before crossover. Body weight was measured as part of the routine assessment of patients during study visits at baseline, weeks 4, 8, 12, 16, 24, 36, and every 12 weeks thereafter. The plasma lipid profile was assessed at baseline, weeks 4, 12, 24, 48, and every 24 weeks thereafter. Serum albumin levels were assessed at baseline, weeks 2, 4, 6, 8, 12, 16, 20, 24, and every 6 weeks thereafter. For patients who received placebo, these parameters were assessed up to week 48, because most patients who received placebo either discontinued participation in the study or crossed over to ruxolitinib by this time point. All patients were instructed to fast for at least 8 hours before each study visit. Lipid and albumin concentrations were assessed at a central laboratory. Spleen volume was assessed using magnetic resonance imaging or computed tomography at baseline and every 12 weeks thereafter. The TSS was assessed daily using electronic diaries through week 24.