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**EDITORIAL**

# Ruxolitinib for myelofibrosis therapy: current context, pros and cons

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## CONTEXT

Ruxolitinib (*Jakafi*, Incyte Corp., Wilmington, DE, USA), a small-molecule JAK-1/2 inhibitor, was approved by the US Food and Drug Administration (FDA) on 16 November 2011 as the first ever drug therapy for myelofibrosis. The drug was approved under the FDA's priority review program for orphan diseases on the basis of two randomized controlled trials in patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Study 1 (Controlled Myelofibrosis Study with Oral Janus-Associated Kinase (JAK) Inhibitor treatment-I; COMFORT-I) compared ruxolitinib with placebo,[1] while study 2 (COMFORT-II) compared ruxolitinib with the best available therapy.[2] This development represents an important milestone in myelofibrosis treatment given that current drug therapy is neither curative nor adequately palliative. It raises important questions, however, regarding the precise niche for ruxolitinib in myelofibrosis treatment based on a thorough consideration of risks and benefits, which is discussed below in a question-and-answer format. This perspective is not meant to be a comprehensive review of myelofibrosis or a discussion of the treatment alternatives to ruxolitinib.

**Question:** Can you describe the clinical trial data that supported drug approval?

**Answer:** The data are currently available in abstract form only.

(i) COMFORT-I was a randomized (1:1), double-blind study comparing ruxolitinib dosed at 15 or 20 mg twice daily (depending on a baseline platelet count of $100-200\times10^9$/l or $>200\times10^9$/l, respectively) with placebo.[1] The dose was adjusted for efficacy and safety during treatment; the primary end point was the proportion of patients with $\geqslant$35% reduction in spleen volume at week 24 of therapy, assessed by a blinded review of spleen magnetic resonance imaging or computerized tomography. Secondary end points were durability of spleen response, changes in symptom burden (symptom score measured daily with the myelofibrosis symptom assessment form (MFSAF) v2.0) and survival. Exclusion criteria for study eligibility included prior treatment with a JAK inhibitor and a platelet count of $<100\times10^9$/l.

Overall, 309 patients were randomized: 155 to ruxolitinib and 154 to placebo. The median age was 68 years; 50% of the patients had high-risk primary myelofibrosis, 31% post-polycythemia vera myelofibrosis and 18% post-essential thrombocythemia myelofibrosis. Twenty-one percent of the patients had red blood cell transfusions within 8 weeks of enrollment; the median hemoglobin concentration was 10.5 g/dl and the median platelet count was $251\times10^9$/l. The median palpable spleen length was 16 cm below the costal margin, with 81% having a spleen length of $\geqslant$10 cm.[3]

At week 24, the primary end point was met by 65 patients (41.9%) in the ruxolitinib arm versus 1 patient (0.7%) in the placebo arm ($P<0.0001$). The modified myelofibrosis symptom assessment form captures symptom scores (0 to 10) for abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety–with 0 representing symptoms 'absent' and 10 representing 'worst imaginable' symptoms. The scores were added to create the daily total symptom score. At week 24, 68 patients (45.9%) in the ruxolitinib arm had a minimum 50% reduction in the total symptom score versus 8 patients (5.3%) in the placebo arm ($P<0.0001$).[1,3]

The most frequent adverse reactions (overall/grade 3/4 for ruxolitinib vs placebo, respectively) were: thrombocytopenia (69.7/12.9% vs 30.5/1.3%), anemia (96.1/45.2% vs 86.8/19.2%), neutropenia (18.7/7.1% vs 4/2%), bruising (23.2/0.6% vs 14.6/0%), dizziness (18.1/0.6% vs 7.3/0%) and headache (14.8/0% vs 5.3/0%).[3]

At a median follow-up of 32.2 weeks, there was no significant difference in the number of deaths in the two study arms;[1] after a median follow-up of approximately 1 year, however, there were significantly fewer deaths on the ruxolitinib arm ($n=13$) relative to the placebo arm ($n=24$) (hazard ratio = 0.5; $P=0.04$).[4]

(ii) COMFORT-II was a randomized (2:1) open-label study comparing ruxolitinib with the best available therapy (no therapy or best available therapy was selected by the investigator on a case-by-case basis, including hydroxyurea in 46.6%, glucocorticoids in 16.4% and no therapy in 32.9%).[2,3] The primary efficacy end point was the proportion of patients achieving $\geqslant$35% reduction in spleen volume at week 48 as measured by magnetic resonance imaging or computerized tomography. The key secondary end point was the proportion achieving $\geqslant$35% reduction in spleen volume at week 24.

Overall, 219 patients were randomized: 146 to ruxolitinib and 73 to the best available therapy. The median age was 66 years; 53% of patients had high-risk primary myelofibrosis, 31% post-polycythemia vera myelofibrosis and 16% post-essential thrombocythemia myelofibrosis. Twenty-one percent of the patients had red blood cell transfusions within 8 weeks of enrollment; the median hemoglobin concentration was 10.4 g/dl and the median platelet count was $236\times10^9$/l. The median palpable spleen length was 15 cm below the costal margin, with 70% having a spleen length of $\geqslant$10 cm.

At week 48, the primary end point was met by 41 patients (28.5%) in the ruxolitinib arm vs 0 patients in the best available therapy arm ($P<0.0001$). At week 24, the corresponding response rates were 31.9 vs 0% ($P<0.0001$).

The most frequent hematologic adverse reactions (overall/grade 3/4 for ruxolitinib vs best available therapy, respectively) were thrombocytopenia (44.5/7.5% vs 9.6/4.1%) and anemia (40.4/11% vs 12.3/4.1%).[2] Non-hematologic adverse reactions of any grade (ruxolitinib vs best available therapy) included diarrhea (24% vs 11%) and peripheral edema (21.9% vs 26%).[2]

**Question:** Do the current trial end points capture a tangible benefit for myelofibrosis patients?

**Answer:** Yes and no.

Ruxolitinib treatment results in important symptom palliation (that is, improvement in splenomegaly and disease-related symptoms) in a significant proportion of patients, in a setting where

alternative therapies are not always available/feasible. In contrast, the primary end points for the two trials cannot be considered as appropriate surrogates for a favorable modification in the natural history of myelofibrosis.[5] There was no improvement in bone marrow osteomyelosclerosis ('complete remission' or 'partial remission' by International Working Group response criteria);[6] in general, achievement of these histologic end points is an important prerequisite for improvement in survival in hematological malignancies. Similarly, cytogenetic or molecular remissions were not observed with ruxolitinib therapy. The two studies were not adequately powered to assess for survival benefit and there was no pre-randomization risk-stratification of patients. Further, while inclusion of a placebo control arm (COMFORT-I) unambiguously isolates ruxolitinib's activity for regulatory purposes, it raises ethical concerns regarding the appropriateness of such a strategy in patients with an inexorably progressive disease. Relatively few patients in the placebo arm were eligible to cross over to receive ruxolitinib, and even in these cases disease progression may not be reversible with delayed institution of potentially active therapy. In this aspect, the study fails the 'real-world' test, in that few would consider it appropriate to observe a patient with higher-risk symptomatic disease off therapy.

So, why is the regulatory threshold set at the point that it is? In some respects, this approach is justifiable given the orphan disease status of myelofibrosis. However, clinical trial design including selection of the study end points is increasingly established as part of a negotiated agreement between regulatory officials at the FDA and regulatory employees of the pharmaceutical industry. As has been noted by others,[7] this process solicits little or no expert input from the academic physician-scientist, who arguably has the best understanding of the disease and is consequently best qualified to define what constitutes clinically meaningful benefit for patients.

**Question:** Which intermediate-2 or high-risk myelofibrosis patient stands to benefit the most (and least) with ruxolitinib treatment?

**Answer:**

(i) The median survival of intermediate-2 and high-risk myelofibrosis patients stratified by the Dynamic International Prognostic Scoring System-plus criteria is approximately 3.6 and 1.8 years, respectively.[8,9] A patient with symptomatic splenomegaly and/or significant constitutional symptoms (for example, pruritus, night sweats or bone pain) with adequate hematological reserve, and who is not a candidate for early allogeneic stem cell transplant based on the presence of very high-risk disease features,[10] is likely best suited for ruxolitinib treatment, particularly in the setting of hydroxyurea refractoriness or intolerance. However, these benefits come with important trade-offs, particularly with drug-induced anemia and thrombocytopenia that need to be factored into the decision-making process. The risk:benefit assessment is significantly more challenging for a patient who fits the aforementioned clinical profile but who has intermediate-1 risk disease (median survival approximately 7.8 years);[9] in such a patient, ruxolitinib treatment may be cautiously considered, but only after a full and transparent discussion regarding potential risks, including those pertaining to rare serious adverse events. Low-risk patients (median survival approximately 17.5 years) are likely not candidates for ruxolitinib treatment, with rare exception.[9]

(ii) The myelofibrosis patient whose primary problem is anemia (particularly with concurrent thrombocytopenia and/or leukopenia) is likely to derive the least benefit from ruxolitinib treatment. Anemia responses are relatively infrequent (up to 10–20%) and are counterbalanced by a relatively high incidence of treatment-emergent cytopenias.[11,12] In COMFORT-II, treatment-emergent anemia was 2–3-fold higher in the ruxolitinib arm relative to the best available therapy arm.[2] In COMFORT-I, 60% and 38% of ruxolitinib- and placebo-treated patients, respectively, received red blood cell transfusions during the treatment phase.[3] Treatment-related thrombocytopenia and/or neutropenia are additional risks in such patients.

**Question:** Is inhibition of mutant JAK-2 the predominant mechanism for ruxolitinib's therapeutic activity in myelofibrosis?

**Answer:** While a definitive answer is currently elusive, several important points can be made:

(i) (Ruxolitinib (and other JAK inhibitors) can be considered as 'targeted therapy' for myelofibrosis only at a superficial level in this day and age. Potentially pathogenetic mutations have now been identified in many genes in *BCR-ABL1*-negative chronic myeloproliferative neoplasms.[13] It remains unclear, however, as to which mutation(s) represents the primary pathogenetic event, given that they are neither disease-specific nor mutually exclusive. Furthermore, in contrast to chronic myeloid leukemia, the clonal architecture in myeloproliferative neoplasms appears to be remarkably complex; multiple subclones are frequently identified, and dominance of a particular subclone may vary with time in a given patient.[14] Consequently, while the JAK–STAT pathway is an important therapeutic target in myelofibrosis, it is not surprising that the depth and quality of responses with JAK inhibitors do not match those seen with imatinib treatment in chronic myeloid leukemia.

(ii) Presence or absence of *JAK2*V617 does not influence the therapeutic response to ruxolitinib;[4,11] this is at least partly explained by the presence of less frequent phenocopy mutations in other genes (for example, *MPL*, *LNK* and *CBL*) that activate JAK–STAT signaling in myelofibrosis.

(iii) Ruxolitinib potently inhibits JAK-1 kinase, which likely underlies its ability to significantly downregulate pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-á in myelofibrosis patients.[11] Given the inflammatory state that accompanies clonal myeloproliferation in myelofibrosis and recent data regarding phenotypic associations of specific cytokines (for example, increased IL-6 and IL-8 levels with constitutional symptoms, increased IL-2R/IL-12 levels with red cell transfusion need and increased hepatocyte growth factor level with marked splenomegaly),[15] it is possible that cytokine down-modulation rather than direct cytotoxicity constitutes the predominant mechanism of action for ruxolitinib.

(iv) Despite its putative anti-JAK2 activity, ruxolitinib does not appear to have a major effect on circulating *JAK2*V617F allele burden; in the Phase-1/2 study, there was 13% mean maximal reduction among patients with $>75\%$ baseline mutant allele burden after 12 cycles of treatment.[11]

**Question:** Are there any unique considerations with respect to ruxolitinib treatment in myelofibrosis?

**Answer:** There are short-term and long-term considerations.

(i) Patients treated with ruxolitinib may become ineligible for protocol-based treatment with other JAK inhibitors given the design of several ongoing clinical trials.

(ii) Treatment discontinuation leads to relapse of disease-related symptoms, generally within a week. The symptoms generally revert in severity to baseline levels and sometimes exceed it.[9] On occasion, a more fulminant 'ruxolitinib withdrawal syndrome', possibly related to rapid changes in inflammatory

cytokine levels, is observed; presenting features can include accelerated splenomegaly with splenic infarction and worsening cytopenias, or hemodynamic decompensation with a septic-shock like syndrome. Patients should be closely monitored during the drug discontinuation process and follow a tapering schedule rather than abrupt cessation.

(iii) Cytopenias: In COMFORT-I and COMFORT-II, the median time to onset of grade 3/4 thrombocytopenia was 8 weeks.[3] The median time to platelet recovery $>50\times10^9$/l after dose interruption was 14 days. Similarly, the median time to onset of grade 2 or higher anemia was 6 weeks;[3] in the ruxolitinib arm, the mean hemoglobin nadir was 1.5–2.0 g/dl below baseline after 8–12 weeks of therapy. While the cytopenias are manageable over the short term, they pose a significant problem with longer follow-up. Dose reductions are necessary in some patients that lead to loss of clinical response; in others, the modest treatment benefits are deemed an inadequate justification for continued treatment in the face of a new and persistent need for red cell transfusions due to treatment-related anemia. Long-term analysis of 51 patients treated at Mayo Clinic in the Phase-1/2 study showed the ruxolitinib discontinuation rate to be 51%, 72% and 89% at 1, 2 and 3 years, respectively.[12]

**Question:** What is the projected cost of ruxolitinib treatment for myelofibrosis?

**Answer:** Current reports suggest US$7000 for a 30-day supply, equating about US$84 000 per year. Cost will obviously have a critical impact on patient access to ruxolitinib, depending upon reimbursement decisions by payers that will be forthcoming in both the United States and Europe.

## CONFLICT OF INTEREST

Dr Animesh Pardanani has served as principal investigator/co-investigator for clinical trials that received institutional support (free drug and funding) from Incyte, Sanofi-Aventis, TargeGen, YM BioSciences, Cytopia, Bristol-Myers Squibb, Celgene and Novartis. TargeGen and Cytopia have also provided support for laboratory studies relevant to clinical trials.

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