The Role of JAK1/2 Inhibitors in the Treatment of Chronic Myeloproliferative Neoplasms

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OVERVIEW

In 2005, the description of the JAK2V617F mutation for the first time provided a molecular key to enable more rapid diagnosis and target for novel therapeutics in the myeloproliferative neoplasms. In 2007, the first-in-class agent INC18424, ruxolitinib, JAKafi, or JAKAVI was first tested in patients with intermediate-risk 2 or high-risk myelofibrosis regardless of whether they possessed the JAK2V617F mutation. Patients treated with this agent had major reduction in splenomegaly as well as impressive reduction, and in some cases resolution, of symptoms. This study was followed by the two Controlled Myelofibrosis Study with Oral JAK Inhibitor Therapy (COMFORT) trials (the first-ever phase III trials in myelofibrosis), which confirmed results in these aspects were superior to either placebo or standard care, and updated results show a survival advantage with this therapy. This paper discusses these results and data from other JAK inhibitors while speculating on the future of these therapies. It also reflects on the fact that the true targets and agents' mode of action are uncertain. Unlike targeted therapy for chronic myeloid leukemia (CML), these agents do not deliver molecular remission, and it is not clear whether their predominant benefit is mediated via JAK2, JAK1, or both. Nonetheless, the advent of the JAK inhibitor is a welcome advance and has made a dramatic improvement to the therapeutic landscape of these conditions.

The chronic myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The most frequent clinical complications of ET and PV are thrombotic or hemorrhagic; however, some difficulties remain in their management: the lack of ability to predict the thrombotic or transformation events even in patients who are apparently low risk as well as a dearth of agents that reduce the risk of myelofibrotic or leukemic transformation or that effect the burden of associated chronic symptoms.[1] In contrast to ET and PV, PMF has a more severe course with a median survival of about 6 years. The most frequent manifestations of PMF are ascribed to splenomegaly and/or hepatomegaly, extramedullary hematopoiesis, thrombohemorrhagic complications, and a spectrum of debilitating symptoms, which, in aggregate, compromise the quality of life (QOL) for the majority of patients. The characteristic fibrotic changes are reactive and thought to be mediated by locally released cytokines and growth factors. With the exception of allogeneic hematopoietic stem cell transplantation, no other medical intervention has had an effect on the natural course of any MPN or improves survival.

In 2005, for the first time the description of the JAK2V617F mutation provided a molecular key to enable more rapid diagnosis and a target for novel therapeutics. Further mutations in JAK2 and other aspects of signaling and epigenetic machinery have now been well described in these disorders.[2] Clearly this is pertinent for therapeutic efficacy of JAK inhibitors; however, it has also been postulated that inflammation may be a trigger for and driver of clonal hemopoiesis and effects of these agents on inflammation may be equally important.[3,4] For example, there is now evidence that tumor necrosis factor-alpha (TNF-alpha) facilitates clonal expansion of JAK2V617F-positive cells.[5] Fleischman et al demonstrated that JAK2V617F kinase regulates TNF-alpha expression in cell lines and that colony formation by JAK2V617F-positive progenitor cells is resistant or stimulated by exposure to TNF-alpha. The study also demonstrated that the absence of TNF-alpha limits clonal expansion and attenuates disease in a murine model. Genes implicated in inflammation and immune surveillance are dysregulated in MPN (e.g., interleukin 4, which is upregulated).[6] Further support for immune dysregulation in MPN comes from reports of complete hematological and molecular remission following treatment with interferon-alpha, a potently immunosuppressive agent.[7] Epidemiologic studies have shown that inflammatory disease may precede or develop during the course of MPN, and a prior history of any autoimmune disease has been found to be associated with a significantly increased risk of MPN (p = 0.021).[7]

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CLINICAL DATA WITH JAK1/2 INHIBITORS

The development of *BCR/ABL* kinase inhibitors took decades after the description of the Philadelphia chromosome, and yet the first patients with MPN were receiving JAK inhibitors only 2 years after the identification of JAK2 V617F. Further important differences between targeted therapies in CML and in the MPNs include the following: *BCR/ABL* is a novel tumor-specific kinase; conversely, JAK2 is required for normal cellular function. Although all patients with CML have *BCR/ABL*, not all patients with MPN have JAK2 V617F, but they do have activation of both JAK1 and JAK2. A number of JAK inhibitors have been tested in patients with MPN, and current data with regard to efficacy and toxicities are provided in Figs. 1a and 1b. Although these agents provide much needed symptomatic relief and offer a sound platform for future therapeutics, there is much still to learn about their mechanism of action as well as long-term safety.

Ruxolitinib (INC424, JAKafi, JAKAVI)

Results of the phase I/II studies with ruxolitinib were unprecedented and can be divided into two main areas: splenomegaly responses and symptomatic improvements.[8,9] Specifically for splenomegaly, 50% of patients achieved a "clinical improvement," according to the International Working Group for Myelofibrosis Research and Treatment criteria, which means a 50% reduction in palpable spleen length. The investigators evaluated spleen volume by MRI and were able to demonstrate that a median reduction spleen volume of 33% corresponded to median reduction in palpable spleen length

KEY POINTS

- Before 2011, the therapeutic strategies for chronic myeloproliferative neoplasms (MPNs) were limited and did not address MPN-related symptoms or quality of life or improve overall survival.
- Activation of JAK1 and JAK2 are common to the MPN, and in 2005, a highly prevalent mutation JAK2 V617F was described, which has led to a better understanding of pathogenesis, revised diagnostic criteria, and development of targeted therapy.
- Phase III trials of first-in-class JAK1/2 inhibitor ruxolitinib demonstrated unprecedented benefits in reduction of splenomegaly and improvement of symptoms. This agent was approved by the U.S. Food and Drug Administration, by EMEA, and in Canada. Phase I and II studies with other JAK inhibitors show a similar pattern with a hint of differential benefit on allele burden, anemia, or marrow fibrosis.
- Recent updates from the COMFORT studies suggest that ruxolitinib therapy may confer a survival advantage compared with placebo or standard therapies even after patients from control arms were crossed over to receive active therapy.
- Trials are underway to explore other JAK inhibitors and how these agents can be used in earlier phase disease or in combination with other treatment strategies.
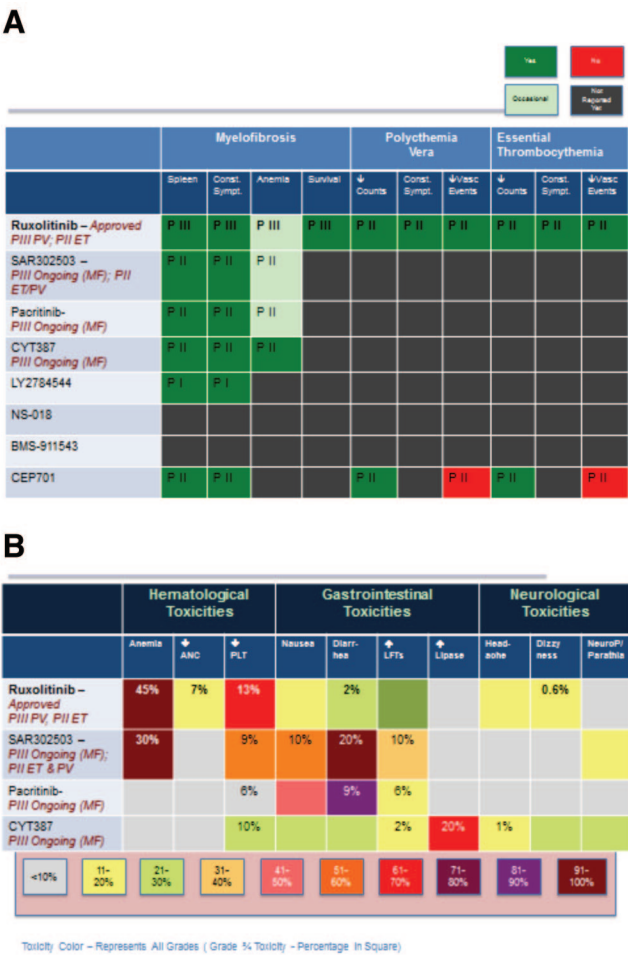

FIG 1. JAK1 and 2 inhibitors in MPNs. (A) Efficacy summary. (B) Toxicity summary.

Abbreviations: MPNs, myeloproliferative neoplasms; MF, myelofibrosis; ANC, absolute neutrophil count; PLT, platlets; LFT, liver function test.

of 52%. This facilitated the development of a standard tool for the objective and blinded assessment of response in terms of splenomegaly, and a spleen volume reduction of 35% was later adopted in the phase III studies as the primary endpoint. Interestingly, results for patients were equivalent irrespective of JAK2 mutational status or subtype of MF (i.e., primary or post-PV MF or post-ET MF). There was only a modest decrease in mutant JAK2 allele burden despite significant clinical benefit, suggesting that the mode of action may be through inhibition of JAK1 signaling, subsequent reduction in inflammatory cytokines, and aberrant JAK2 signaling rather than being ascribed to a decrease in allele burden. Toxicity and safety from the trials are discussed together below.

Ruxolitinib was subsequently evaluated in phase III trials known as the COMFORT trials. COMFORT-I was a randomized, double-blind study evaluating the efficacy and safety of ruxolitinib compared with placebo. COMFORT-II was a randomized, open-label study comparing the efficacy, safety, and tolerability of ruxolitinib with best available therapy (BAT) in patients with PMF and post-PV/post-ET

MF. The results of these trials have been published with updated data presented at the 2012 American Society of Hematology (ASH) meeting.[10-13] Ruxolitinib has been approved for the treatment of MF in the United States, Canada, and Europe.

COMFORT I included 309 patients who were randomly assigned 1:1 to ruxolitinib or placebo. The dose of ruxolitinib arm was 15 mg twice daily (patients with platelet count 100–200 x 10^9/L) or 20 mg twice daily (patients with platelet count > 200 x 10^9/L). The primary endpoint was proportion of patients with spleen volume reduction 35% or greater evaluated by MRI or CT at week 24 and was 41.9% with ruxolitinib and 0.7% with placebo (p < 0.001).[11] By week 24, 45.9% of patients receiving ruxolitinib and 5.3% of those receiving placebo (p < 0.001) experienced symptom alleviation with at least 50% reduction in their total symptom score. Mean total symptom score improved by 46.1% in the ruxolitinib arm, compared with a worsening of 41.8% in the placebo arm (p < 0.001). In contrast to the worsening of all individual symptoms observed in the placebo arm, each symptom improved with ruxolitinib treatment (abdominal discomfort, pain under left ribs, early satiety, night sweats, itching, musculoskeletal pain, and inactivity). QOL, measured by EORTC-QLQC30, improved with symptom alleviation.

COMFORT-II included 219 patients with MF randomly assigned 2:1 to ruxolitinib or BAT. Patients were dosed with ruxolitinib as per the COMFORT-I trial. The proportion of patients with spleen volume reduction 35% or greater evaluated by MRI or CT at week 48 (primary endpoint) was 28.5% with ruxolitinib and 0% with BAT (p < 0.001).[10] The proportion of patients with spleen volume reduction ≥ 35% evaluated by MRI or CT at week 24 (key secondary endpoint, and equivalent to the primary endpoint of COMFORT I) was 31.9% with ruxolitinib and 0% with BAT (p < 0.001). The median duration of response was not reached. Mean improvements from baseline in Functional Assessment of Cancer Therapy-Lymphoma System (FACT-LymS) sub-scores were greater in the ruxolitinib arm, indicating better QOL than for patients receiving BAT.[14] The EORTC-QLQ-C30 scores for symptoms relevant to patients with MF showed improvement from baseline by week 8 and continued through week 48, also indicating improvement in QOL.

Updates from the COMFORT trials at ASH 2011 suggested all MF subgroups (PMF, PET-MF, PPV-MF) benefited regardless of JAK2 V617F mutation status, gender, or International Prognostic Scoring System (IPSS) score.[15,16] Importantly the COMFORT-I trial data demonstrated a clear survival advantage with 13 patients treated with ruxolitinib and 24 patients treated with placebo dying during the study or during extended follow-up (median follow-up of 52 and 51 weeks, respectively), representing a hazard ratio (HR; 95% CI) of 0.499 (0.254, 0.98; p = 0.0395) in favor of ruxolitinib.[15] This was also shown in a comparison between the MD Anderson cohort of the 107 phase I/II patients treated

with ruxolitinib and a matched historic cohort of 310 patients with clinical characteristics that would have allowed them to participate in the phase I/II study of ruxolitinib.[17] However, an analysis of 51 phase I/II patients treated at the Mayo Clinic compared with a collection of patients with MF (all risk groups) did not show similar benefits.[18]

At ASH 2012, both COMFORT trials provided updated data; no new adverse event categories were reported with more than 2 years of follow-up. There was a lower incidence of anemia and thrombocytopenia after week 48 (anemia, 22.6%; thrombocytopenia, 25.2%), and the majority was grade 1/2 and rarely caused discontinuation. Interestingly there were no new reports of leukemic transformation in either studies, and there was no specific pattern of adverse events (AEs) or reports of a withdrawal syndrome after discontinuation of ruxolitinib. Concerning overall survival, COMFORT-I investigators report that despite the majority of patients switching to ruxolitinib treatment from placebo, earlier ruxolitinib therapy is associated with a survival advantage.[5] For COMFORT-II, an additional nine and 12 deaths were reported in the ruxolitinib and BAT arms, respectively, resulting in a total of 14% (20/146) and 22% (16/73) of patients overall; the median survival time has not yet been reached for both arms. For the first time on COMFORT-II, patients randomly assigned to ruxolitinib showed longer overall survival than those randomly assigned to BAT (HR = 0.51; 95% CI, 0.27–0.99; p = 0.041).[6] In COMFORT-II, the ruxolitinib and BAT arms may not have separated earlier because a considerable number of patients in the BAT arm were censored before 48 weeks (27.4% BAT, 14.4% ruxolitinib). This means they were considered alive (or immortalized) in the absence of any further information. This along with the 2:1 randomization may bias survival data in favor of BAT. Despite this and the crossover of most patients receiving BAT to ruxolitinib, there was an apparent survival benefit favoring ruxolitinib in this intent-to-treat analysis. Despite the limitations described above, these data may suggest that even the relatively short period of additional treatment for the patients initially randomly assigned to ruxolitinib (6 months in COMFORT-I and 1 year in COMFORT-II) may have had a marked effect on survival.

Concerning toxicity and safety, the phase I/II clinical trial reported thrombocytopenia as the dose-limiting toxicity (DLT).[3] In addition, new-onset anemia occurred in 23% and was dose dependent. Nonhematologic toxic effects were infrequent and occurred in less than 10% of patients (e.g., asthenia [2.0%], with fatigue, anxiety, fever, and insomnia [each 1.3%]). Two patients (1.3%) with a history of cardiopulmonary disease developed a clinical picture assessed by an investigator as systemic inflammatory response syndrome (SIRS) after abrupt cessation of ruxolitinib. Mayo Clinic investigators reported five cases of SIRS-like syndrome on drug withdrawal and a high rate of drug discontinuation.[18] However, a SIRS-like syndrome at the time of reporting has not been observed in the larger phase III COMFORT clinical trials.[10,11] In these trials, discontinuations because of adverse effects were 11% and 11% (ruxolitinib and placebo,

respectively) and 8.2% and 5.5% (ruxolitinib and BAT, respectively) attesting to the safety and tolerability of ruxolitinib.

SAR302503 (TG101348)

A phase I/II study with SAR302503, a more specific JAK2 inhibitor, reported good tolerability and indeed, the DLT was asymptomatic and reversible grade 3 to 4 hyperamylasaemia (± hyperlipasaemia).[19] SAR302503 significantly improved symptoms, such as anorexia and pruritus; however, in contrast to the findings with ruxolitinib, these effects occurred in the absence of a marked reduction in serum pro-inflammatory cytokine levels (e.g., IL2, IL6, IL8, TNF-alpha) and in the absence of significant JAK1 inhibition. Two unique, potentially vital aspects of response to this agent include a decrease in the JAK2V617F allele burden during therapy in the mutation-positive subjects and recently reported reduction in marrow fibrosis scores.[20] Following six cycles, 16 of 20 (80%) patients with a baseline JAK2V617F allele burden of more than 20% experienced a median reduction of 61%. These preliminary results reported with SAR302503 are promising and of great interest if confirmed in phase III studies, although the clinical significance remains to be assessed as the benefit is unlikely to equate to the reduction in the level of BCR/ABL1 burden in CML. The phase III study JAKARTA comparing 400 mg with 500 mg of SAR302503 with placebo has completed recruitment, and results are expected this year; in addition JAKARTA 2, evaluating this agent in patients resistant or refractory to ruxolitinib, is also open.

SB1518 (Pacritinib)

In the phase II study, rapid and sustained responses in the spleen have been seen for MF at the 400 mg/d dose.[21] In an update, presented at the 2011 ASH meeting, after a median time on study of 8.2 months (range, 0.5–12.1), 50% of patients had discontinued treatment, response rates were 44% on physical examination and 32% MRI (35% reduction in volume), and two patients met criteria for anemia response.[21] A phase III study with this agent is now open and will offer the opportunity to assess these results more fully.

CYT387

CYT387 is a small molecule adenosine ATP-competitive aminopyrimidine derivative with potent JAK kinase inhibitory activity. Pardanani et al recently presented data from a phase I/II multicenter study assessing 300 mg, 150 mg QD or 150 mg BID demonstrating improvements in splenomegaly and constitutional symptoms as well as in transfusion requirements.[22] Subjects have now reached a minimum of 9 months on study, and updated safety and efficacy results were presented: an impressive 166 subjects were enrolled and the median duration (range) of follow-up is 16.1 month

(0.7 to 31.0 months). Particular data of interest with this compound are transfusion independence responses, which were observed in more than half of the red blood cell transfusion–dependent subjects with a maximal transfusion-free period exceeding 2 years and ongoing. In addition, the percentage of all subjects requiring red blood cell transfusions substantially decreased over the treatment period. As has been previously reported, treatment with CYT387 resulted in rapid and sustained reductions in splenomegaly. Now with maximal response duration approaching 2 years, symptoms responses were also encouraging. Concerning safety, the most common treatment-related AEs were a first-dose effect thrombocytopenia, peripheral neuropathy, dizziness, diarrhea, nausea, and headache. Treatment-related peripheral neuropathy was reported as sensory and mainly grade 1. There were no treatment-related deaths.

USE OF JAK INHIBITORS FOR OTHER MPNs

Experience with JAK2 inhibitors in PV and ET is more limited, and few studies have been reported thus far. A phase II trial with ruxolitinib in patients with PV and ET has been completed and preliminary results reported.[23] The impressive results with ruxolitinib observed in patients with PV represented the basis for the design of RESPONSE and RELIEF, both phase III trials. An ongoing study in ET and PV (MAJIC) is also open, and SAR302503 is also being tested with patients with ET and PV in an ongoing study.

CONCLUSION

JAK inhibitors undoubtedly represent a highly important step forward in PMF and are of great potential for other MPN, whether their activity is mediated by JAK2 inhibition or whether they exert additional effects by moderating inflammation is intriguing. To date they have been assessed in patients with MF that is IPSS intermediate-risk 2 or above; a strong rationale now exists to study patients with earlier stage disease. In addition, since ruxolitinib and other JAK inhibitors are so well tolerated, testing in combination either to improve disease-related responses (e.g., example with epigenetic therapies) or to reduce complications of therapy (e.g., drug-induced anemia) is warranted. A further potential benefit would be to utilize the agent before stem cell transplantation to improve the patients' performance status and reduce massive splenomegaly, an adverse factor in transplant outcome.[24] The current role of stem cell transplantation in MF and the potential additional benefit of JAK inhibitors in normalizing inflammatory cytokine profile during and after transplantation is hypothetically attractive and has recently been reviewed.[25] These agents undoubtedly represent a major leap forward in therapeutics for MPN, both in providing new agents and in challenging conventional criteria for response in particular for patients with MF.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Relationships marked "U" are uncompensated.

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