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Prospect of JAK2 inhibitor therapy in myeloproliferative neoplasms

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Abstract

The discovery of the Janus kinase (JAK)2 V617F mutation in patients with myeloproliferative neoplasms was a major milestone in understanding the biology of those disorders. Several groups simultaneously reported on the high incidence of this mutation in patients with myeloproliferative neoplasms: almost all patients with polycythemia vera harbor the mutation and about 50% of patients with essential thrombocythemia and primary myelofibrosis have the mutation, making the development of JAK2 tyrosine kinase inhibitors an attractive therapeutic goal. In addition, inhibition of JAK2 kinase may have a therapeutic role in other hematologic malignancies, such as chronic myeloid leukemia or lymphoma. A number of molecules that inhibit JAK2 kinase have been described in the literature, and several are being evaluated in a clinical setting. Here, we summarize current clinical experience with JAK2 inhibitors.

Keywords

essential thrombocythemia; JAK2 inhibitor; myelofibrosis; myeloproliferative neoplasm; polycythemia vera

A link between the activated intracellular Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and the pathogenesis of several hematological diseases has been previously described [1–3]. However, it was not until recently that an activating JAK2 kinase mutation was identified in patients with myeloproliferative neoplasms (MPNs) [4–8]. Several groups described almost simultaneously a novel activating somatic point mutation in the gene encoding the cytoplasmic JAK2, characterized by the substitution of valine for phenylalanine at codon 617 (JAK2 V617F). In these reports, this mutation was

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identified in approximately 50% of patients with essential thrombocytosis (ET) and primary myelofibrosis (PMF), but in polycythemia vera (PV) it is present in over 90% of patients. Since identical JAK2 mutations can be found in patients with all three diseases, it is unclear how the same molecular abnormality evolves into different phenotypes. Additional rare molecular events recently identified are mutations in c-MPL (c-MPL W515L/K), and additional mutations in exon 12 of JAK2, among patients not expressing the JAK2 V617F mutation. These discoveries are now opening an exciting new era in the development of targeted therapy for MPN. Currently, both PV and ET are treated with supportive care only, which includes aspirin, phlebotomy (for PV) and hydroxyurea (when needed, based on the thrombosis risk for a given patient) [9]. Although the survival of patients with ET and PV is largely similar to age-matched controls, these patients have increased morbidity compared with age-matched controls [10]. As for PMF, no standard therapy exists, no medication has been approved to treat this disease and attempts to help patients are palliative in nature. Among commercially available medications (off-label use), thalidomide [11,12] and its analogue lenalidomide [13] have shown some activity in improving signs and symptoms of PMF, and stem cell transplantation remains the only cure for this disease [14]. Median survival for patients with PMF is approximately 5–7 years, but varies widely according to prognostic factors, with a median survival of 27 and 135 months for patients with low- and high-risk disease, respectively [15]. Identifying the JAK2 V617F mutation in patients with MPN has led to a number of Phase I/II clinical studies focused on patients with advanced PMF or post-ET or PV MF, as they have the worst prognosis.

JAK/STAT pathway

The JAKs are cytosolic kinases that relay signal transduction between cell surface receptors and the cell nucleus. There are four mammalian JAKs: JAK1, JAK2, JAK3 and Tyk2 [16]. Several cytokines, including interleukin, interferon and granulocyte colony-stimulating factor, are JAK1-dependent for signal transduction. Other cytokines, such as erythropoietin [17], thrombopoietin [18] and granulocyte-macrophage colony-stimulating factor (GM-CSF) [19], are dependent on JAK2 for signal transduction. Of note is that the absence of JAK2 is incompatible with life, as evidenced by the embryonic lethality of JAK2-knockout mice due to defective erythropoiesis [20,21]. As for JAK3, it is essential for the signal transduction of several interleukins and plays a critical role in immune control. JAK kinases are formed of seven domains (Jhkl-7) [22]. As the JAK has two homologous kinases in tandem, it was named after Janus the Greek god who had two faces looking in opposite directions. Signal transduction occurs in the following simple steps:

- A ligand binds to its receptor
- The receptor is activated leading to recruitment and activation of the JAK2 tyrosine kinase
- This in turn leads to phosphorylation of the receptor and recruitment of the STAT proteins
- JAK phosphorylates the STAT proteins

- Phosphorylated STAT proteins dimerize and transform to the nucleus, leading to gene transcription

Patients with MPN were found to harbor a mutation in JAK2 in the Jhk2 domain. This domain is thought to have inhibitory effects on JAK2 [23]. Elimination of the inhibitory control (i.e., in the case of the mutation) leads to constitutive activation of JAK2, uncontrolled downstream signaling and cell proliferation. Therefore, inhibition of JAK2 could have therapeutic effects in patients with MPN.

Clinical experience with JAK2 inhibitors

TG101348

TG101348 is a selective and potent inhibitor of JAK2. The IC_{50} for JAK2 was 3 nM and, when profiled in 223 kinases, only FLT3 and RET had an IC_{50} of less than 50nM. It has a 35- and 334-fold selectivity for JAK2 compared with JAK3 and JAK1, respectively. In addition, it induced apoptosis in HEL and Ba/F3 cells harboring the JAK2 V617F, while much higher doses were required to induce apoptosis in fibroblasts. Finally, in a murine model of JAK2 V6l7F-induced PV, mice treated with TG101348 showed a decrease in hematocrit and spleen size and longer overall survival [24]. These preclinical data led to the evaluation of TGl01348 in a multicenter dose-escalation Phase I study. TG101348 was administered orally in 28-day cycles, with a planned dose escalation from 30 to 800 mg. Intrapatient dose escalation was permitted after completion of at least three cycles of therapy. Patients with PMF or post-PV/ET MF with high- or intermediate-risk with symptomatic splenomegaly unresponsive to available therapy were eligible. The results were updated at the American Society of Hematology (ASH) meeting in December 2008. Of the 22 patients enrolled, 19 (86%) had V617F mutation and nine (41%) were transfusion-dependent. The doses of medication ranged from 30 to 680 mg daily. Pharmacokinetic studies confirmed a half-life of 10–35 h with little intrapatient variability. With a median follow-up of 14 weeks, four patients have discontinued the drug (one no response, one patient request, one underlying cardiac condition and one unable to comply). The most-common nonhematologic grade 3 or 4 toxicities were nausea and vomiting (5%), and abdominal pain (5%). Grade 3 or 4 anemia, neutropenia and thrombocytopenia occurred in 32, 9 and 23% of patients, respectively. The maximum-tolerated dose (MTD) has not been reached. Rapid reduction of spleen size was seen in all patients receiving more than 360 mg. This confirms the dose-dependent response with TG101348 [25]. In summary, TG101348 is effective in reducing the spleen size in patients with PMF and post-PV/ET MF; however, its effect on anemia, constitutional symptoms and bone marrow fibrosis remain to be determined.

INCB018424

INCB018424 is a potent and selective JAK1 and JAK2 inhibitor. It inhibits JAK2 at less than 1 nM. In cells harvested from patients with JAK2 V617F mutation, the IC_{50} was 67 nM in clonogenic assay, while colony formation from healthy donor cells was inhibited at more than 400 nM. These encouraging preclinical data led to its evaluation in a Phase I/II trial. Following the initial dose escalation, 25 mg orally twice daily was identified as the MTD

with thrombocytopenia as the dose-limiting toxicity. In the expansion study, more than 100 patients with PMF or post-PV/ET MF were enrolled. Several doses were explored, including 10 and 15 mg twice daily, and 25, 50, 100 and 200 mg daily. Patients were evaluated for reduction in spleen size, improvement of constitutional symptoms using the Myelofibrosis Symptom Assessment Form and improvement in overall level of daily activity. Results were updated at ASH 2008. Of the 134 patients enrolled, 108 remained on the study with a median duration of therapy of 6.8 months. Of those 134 patients, 57 patients had PMF, 97 patients harbored the JAK2 V617F mutation, median spleen size on physical exam ranged from 17 to 20 cm below left costal margin and approximately a third of patients were transfusion- dependent. The therapy did not produce significant nonhematologic toxicity. Detailed analysis was presented for the 114 patients who received 50 mg daily, or 25, 15 or 10 mg twice daily. Of those 114 patients, 19 developed grade 3/4 thrombocytopenia. Of the 75 transfusion-independent patients, 13 developed grade 3/4 anemia. The hematological toxicity was dose dependent with more patients receiving a total daily dose of 50 mg developing grade 3/4 hematological toxicity when compared with the lower doses. Three patients have achieved transfusion-independence. The great majority of patients experienced a rapid reduction in spleen size within the first month of therapy, irrespective of the JAK2 mutational status [26]. Clinically, those patients had a marked improvement in quality of life, with a mean improvement of 40–60% in night sweats, fatigue and pruritis. In addition, a marked improvement in activity limitations was also reported in those patients. The investigators also analyzed the effect on nutrition on those patients treated with INCB018424. MF is associated with hypercatabolism and weight loss. Patients receiving INCB018424 had progressive weight gain (mean increase of 0.4, 2.93 and 3.7 kg at 1, 2 and 3 months, respectively). In addition, significant improvement in the cholesterol and leptin levels were noted in those patients [27]. Interestingly, the level of inflammatory cytokines decreased after therapy with INCB018424, which correlated clinically with the improvement of symptoms seen in those patients [28]. However, none of the aforementioned clinical improvements were associated with marked reduction of the mutational (V617F: wild-type [WT] JAK2 ratio) tumor burden in those patients on therapy with INCB018424 [29].

XL019

Another potent and selective JAK2 inhibitor, XL109, is currently being evaluated in Phase I/II trials. It inhibits JAK2 kinase at concentrations of less than 2 nM, while other JAK kinases are inhibited at concentrations ranging from 134 to 344 nM. In this study, patients with PMF or post-PV/ET MF were enrolled and three regimens were explored: daily for 21 days (100–300 mg), continuously daily 25–50 mg, and 25 mg on Monday, Wednesday and Friday. Of the 30 patients enrolled, 57% had PMF, 80% had harbored the V617F or MPL W515 mutation and 37% were transfusion-dependent. The results were updated at ASH 2008. Of the 30 patients, 21 have discontinued the drug (nine due to related adverse events [AEs], three due to nerve-conduction study abnormality, six due to progressive disease, two due to unrelated severe AEs and one patient withdrew consent). XL109 was relatively well tolerated at doses ranging from 25 to 50 mg. The most common grade 1/2 AEs were formication, confusion and peripheral neuropathy. At a dose of 25 mg daily, one out of 16 patients developed grade 1 peripheral neuropathy. XL109 has a half-life of 20 h with a fivefold accumulation in the daily regimen and twofold with the Monday–Wednesday–

Friday regimen. Of the 12 patients harboring the JAK2 mutation or MPL W515F, 100% experienced a reduction in spleen size, while none of the patients with WT JAK2 experienced a response or reduction in spleen size. All patients harboring the JAK2 V617F mutation reported an improvement in generalized constitutional symptoms, including pruritis and fatigue. Interestingly, of the four patients with 10–19% blasts in the peripheral blood, three had a reduction in circulating blasts. Further studies are planned in patients with advanced JAK2-mutation-positive myeloid malignancies [30,31].

ITF2357

ITF2357 is a new histone deacetylase inhibitor that has interesting preclinical and clinical data in the suppression of JAK2. Preclinically, ITF2357 inhibited the clonogenic formation of HEL cells with the JAK2 V617F mutation with an IC_{50} of 0.001 μM, while the IC_{50} ranged from 100 to 500-fold for cells not harboring the JAK2 V6I7F mutation. Further analysis revealed no change in the JAK2 mRNA levels. This, however, was associated with the disappearance of phosphorylated STAT5. This suggests that ITF2357 downmodulates the mutated JAK2 V617F by post-transcriptional mechanisms [32]. In healthy volunteers, the most frequently reported drug-related AEs were diarrhea, gastric pain, headache and palpitations. This led to the Phase II trial in patients with PV, ET, MF and post-PV/ET MF. ITF2357 was administered at a daily dose of 50 mg twice daily, which could be escalated to 50 mg three-times daily in the absence of toxicity. In patients with ET/PV, seven out of 13 patients responded (two complete responses and five partial responses). Five out of the eight patients presenting with splenomegaly had a significant reduction in spleen size. In addition, ten out of the 11 patients presenting with pruritis had resolution of the pruritis. Among the 13 patients with MF, three major, one moderate and one minor response were observed. The drug was well tolerated with no reported grade 4 toxicity. The most-common reported nonhematologic toxicities were diarrhea (60%), fatigue (25%), nausea (18%) and abdominal pain (14%). Only one patient developed a grade 3 hematological toxicity in the form of neutropenia. This drug is currently being evaluated in different dosing schedules [33].

MK-0457

MK-0457 was initially developed as a small-molecule inhibitor of Aurora kinases. *In vitro,* it was recently shown to inhibit JAK2 kinase, both the WT (IC_{50} of 123 nM) and the JAK2 V617F (IC_{50} of 295 nM). MK-0457 20, 24 or 28 mg/m^2 was administered by continuous infusion for 5 days every 21 days. Almost all patients experienced a decrease in the white blood cell or platelet count. The authors reported six out of seven patients experienced a gradual steady decline in the percentage of JAK2 V617F [34]. The clinical benefit from this drug is unclear at this time.

CEP-701

CEP-701 is an oral small-molecule tyrosine kinase inhibitor of FLT3 that is being evaluated in patients with acute myeloid leukemia (AML) harboring the FLT3 mutation [35]. In a recent preclinical study, it was found to inhibit the growth of cell lines carrying both the WT and mutated JAK2. More recently, this compound was shown to inhibit the growth of cells obtained from patients with MPN harboring both the WT and mutated JAK2, which was associated with decreased expression of downstream signaling proteins, such as BclXl and

cyclin D1/D2 [36]. CEP-701 is currently being evaluated in patients with different MPN. In a multicenter trial, CEP-701 was administered in escalated doses from 80 mg twice daily to 120 mg twice daily to patients with PV and ET. Of the eight patients with splenomegaly, five have experienced a reduction in spleen size [37]. No other significant benefit has been observed and mild toxicity has been recorded, limited to gastrointestinal disturbance (nausea, vomiting and diarrhea).

Compounds with anti-JAK2 activity in preclinical models

Erlotinib is a tyrosine kinase inhibitor that is currently US FDA-approved for the therapy of patients with non-small-cell lung cancer (NSCLC). It inhibits the EGF receptor tyrosine kinase, which is mutated in 10–30% of patients with NSCLC [38,39]. A recent study compared the efficacy of imatinib, erlotinib, gefitinib, AG490 and l,2,3,4,5,6-hexabromocyclohexane in inhibiting the mutant JAK2 V617F tyrosine kinase. The investigators utilized a JAK2 kinase activity assay and a cell-based system [40]. Erlotinib was the most potent compound, with an IC_{50} of 4 μM. In addition, erlotinib inhibited the growth of PV cells harboring the JAK2 mutation, with an IC_{50} of 5 μM. Importantly, it did not affect normal cells at twice that concentration.

Atiprimod is an oral compound of the azaspirane family. Atiprimod has been previously studied in animal models and has anti-inflammatory effects [41]. Recently, it has been shown to inhibit the growth of myeloma cells through the inhibition of STAT3 [42]. In order to evaluate its mechanism of action, a recent study reported on the inhibitory effects on both AML cell lines and in cells from four patients with AML. This inhibition of colony growth was far less in marrow cells from normal volunteers. In K562 cells, the investigators reported decreased expression of both JAK2 protein and phospho-JAK2, with no effect on JAK2 RNA levels. This compound has not been evaluated in cells with mutated JAK2 [43].

SD-1008 is a polycyclic dicarboxylic acid and belongs to the tropidine class of compounds. Using ovarian and breast cancer cell lines, SD-1008 was shown to inhibit nuclear translocation and phosphorylation of STAT3. In addition, it inhibited the phosphorylation of JAK2 in those cell lines. As STAT3 overexpression has anti-apoptotic effects, the effect of SD-1008 on apoptosis was evaluated. SD-1008 was found to induce apoptosis in ovarian cancer cell lines and this effect was synergistic when combined with paclitaxel [44].

CMP6 is another pan-JAK inhibitor molecule, characterized and described in 2002. This molecule binds to the ATP-binding site of JAK kinases and it has an IC_{50} of 1 nM for JAK2 and Tyk, 5 nM for JAK3 and 15 nM for JAK1. Whether this pan-JAK activity would have more clinical efficacy with more toxicity remains to be seen [45,46].

Utilizing *in silico* molecular modeling, the compound Z3 was identified with the ability to bind to a structural pocket adjacent to the ATP-binding site of WT JAK2. This molecule was shown to inhibit the phosphorylation of both WT JAK2 and JAK2 V617F [47].

Go6976 is an indolocarbazole kinase inhibitor. In a study by Grandage *et al.,* it was found to inhibit the downstream effects of IL-6, erythropoietin, GM-CSF and IL-3 with decreased

STAT activity and phosphorylation. This was also associated with decreased JAK2 tyrosine kinase activity. It was also found to inhibit mutated JAK2 and JAK3 kinase activity [48].

Emodin is an active component of Chinese herbal medicine that was shown to inhibit JAK2 activity in multiple myeloma cells [49]. The investigators showed that emodin was capable of inducing apoptosis in multiple myeloma cells through decreased expression of Mcl-1. Mcl-1 expression is controlled by the JAK2/STAT3 pathway and the investigators showed that emodin decreased JAK2 and STAT3 phosphorylation. This inhibitory effect of emodin on the JAK2/STAT3/Mcl-1 pathway may prove beneficial in the therapy of multiple myeloma or other malignancies with STAT3 overexpression.

AG490, a tyrphostin, was found to inhibit acute lymphocytic leukemia (ALL) cells *in vitro* by Meyden *et al*. [50]. This was associated with an inhibition of JAK2 phosphorylation. To assess the efficacy of AG490 *in vivo*, the investigators inoculated severe combined immunodeficiency mice with human ALL cells. Mice that were not treated succumbed to ALL within a few weeks, while AG490 treated mice who had achieved a plasma level above 3 μM achieved complete remission (undetectable ALL). Recently, this compound has also been shown to induce apoptosis in cells from patients harboring the JAK2 mutation [51]. However, AG490 has not been utilized in human clinical trials due to its toxicity. Degrasyn (WP1130) is an analog of AG490 that was initially found to be a strong inhibitor of STAT3 with little effect on JAK2 kinase activity. Recent studies have shown a direct decrease of JAK2 protein levels (both WT and V617F) in cells after degrasyn therapy. There was no change in the RNA transcript level, suggesting a direct effect of degrasyn on the JAK2 protein [52]. WP1066, another AG490 analogue, was found to strongly inhibit the phosphorylation of JAK2 and its downstream signaling proteins (STAT3, STAT5 and ERKl/2) in cell lines harboring the JAK2 V617F. This was associated with a proapoptotic effect with activation of the caspase pathway [53]. In addition, it has shown activity in B-cell lymphoma and multiple myeloma cell lines through inhibition of STAT3 [54].

Expert commentary

Identification of the role of mutated JAK2 tyrosine kinase in the pathophysiology of MPN has led to the development of a new class of drugs, the JAK2 inhibitors (Table 1). Currently, several JAK2 inhibitors are in Phase I/II clinical trials for patients with most aggressive forms of MPN, ppMF or post-PV/ET MF (Table 2). Marked clinical improvement has been seen in patients on therapy, with significant decreases in spleen size and improved quality of life. No significant improvements in anemia in these patients have been reported so far. Despite significant clinical results, these clinical improvements were not associated with a marked reduction of the mutational tumor burden (JAK2 V617F vs WT JAK2 ratio) in patients on therapy. Although the lack of significant elimination of the disease burden may be disappointing, one should know that current medications are not specific for mutated JAK2 protein. They are more or less specific for JAK2 tyrosine kinase, therefore likely inhibiting normal JAK2 tyrosine kinase *in vivo,* which is required for normal hematopoiesis (and thus limiting the dose of the medication that can be given to the patient). Therefore, it seems that current JAK2 inhibitors at best have a potential to control the disease well (particularly the INCB018424). It remains to be seen if they will affect the natural history of

the disease and improve survival. For example, in many MPN patients who experience leukemic transformation, the JAK2 mutation is not detectable in leukemic blasts, raising the question of whether these compounds would have an effect on the rate of hematological transformation [55,56]. On the other hand, current JAK2 inhibitors do affect, in a positive way, many problems that MF patients have that contribute to their early death, such as splenomegaly and malnutrition, and may yet provide prolonged survival, as well as the markedly improved quality of life already demonstrated. Longer follow-up of patients on current studies will answer this question.

As for the utility of JAK2 inhibitors in ET and PV, one must carefully balance the possible benefit versus possible toxicity. In patients with ET and PV, thrombotic complications remain a main cause for morbidity and mortality, and there is questionable association between the JAK2-mutated allele burden, or even the presence of the JAK2 mutation and thrombosis [57]. Despite many unanswered questions, these are exciting times as we witness for the first time the evaluation of new medications targeting specific abnormalities present only in the malignant cells in MPN patients. In addition, several preclinical studies suggest that JAK2 inhibitors may play a role in the therapy of other ALLs [58], AML with t(8;21) [59–61] and chronic myeloid leukemia [62,63].

Five-year view

In the next 5 years, we expect a plethora of studies evaluating the role of the JAK2 inhibitors not only in patients with MPN, but also in other hematological disorders. The current studies have reported the benefit of these compounds (particularly INCB018424) in controlling the disease (massive reduction in organomegaly) and improving the quality of life in patients with primary or secondary MF. It is expected that at least one of the compounds will be approved as therapy for MF based on the derived clinical benefit. The next step will be to evaluate whether these compounds would actually improve survival or delay progression to acute leukemia. A randomized Phase III trial of INCB018424 versus supportive care in patients with PMF or post-ET/PV MF will open for accrual in the very near future.

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Key issues

- Several groups have identified the presence of a mutation in the janus kinase 2 (*JAK2*) gene (JAK2 V617F mutation) leading to deregulated JAK2 activity in patients with myeloproliferative neoplasms.
- Several new JAK2 inhibitors are currently being evaluated in the clinical setting in Phase I/II studies.
- These drugs have shown promise in the therapy of patients with myelofibrosis, mainly by decreasing organomegaly (spleen and liver) and improving the quality of life.
- The therapy with JAK2 inhibitors is in general well tolerated with acceptable hematological and nonhematological toxicities.
- Long-term studies are needed to assess the impact of these drugs on the natural history of the disease.

Table 1

Relative potency of the clinically evaluated JAK inhibitors.

Inhibitor	JAK1 (nM)	JAK2 (nM)	JAK3 (nM)	TYK (nM)	Ref.
INCB018424	2.7	<1	322	19	[64]
TG101348	105	3	996	405	[25]
XL019	130	2	250	340	[31]
CEP-701	NA	1	NA	3	[36]

JAK: Janus kinase; NA: Not available; TYK: Tyrosine kinase.

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Table 2

Summary of JAK2 inhibitors in clinical development.

Drug	Phase	Comments	Ref
INCB018424	Phase I/II Phase III planned	Decreased spleen size irrespective of JAK2 mutational status, improved quality of life, decreased inflammatory cytokine levels, no significant effect on JAK2 mutation allele levels	[26]
TG101348	Phase I/II	Dose-dependent reduction in spleen size	[25]
XL019	Phase I/II	Decreased spleen size only in patients with JAK2 V617F or *mpl* mutation, decreased pruritis and fatigue, reduction in circulating blasts in some patients	[31]
SB1518	Phase I	Not reported	[101]
CEP-701	Phase II	Decreased spleen size	[37]

JAK: Janus kinase.