Advances in Myelofibrosis Management: New Janus Kinase Inhibitors Beyond Ruxolitinib

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Abstract

Myelofibrosis is a myeloproliferative neoplasm characterized by the buildup of fibrous scar tissue in the bone marrow occurring secondary to the secretion of inflammatory cytokines, leading to cytopenias, dysfunctional hematopoiesis, and constitutional symptoms. One of the pathologic mechanisms that underlies myelofibrosis is aberrant activation of the Janus kinase (JAK)-STAT pathway. Targeting the JAK-STAT pathway via JAK inhibition can lead to significant improvements in spleen volume reduction and symptom improvement in intermediate- and high-risk myelofibrosis. The first JAK inhibitor approved by the US Food & Drug Administration was ruxolitinib in 2011. Recently, there have been additional JAK inhibitors approved for myelofibrosis, including fedratinib, pacritinib, and momelotinib. The emergence of these new therapies offers additional treatment options for patients with myelofibrosis. This article reviews the pharmacology, efficacy, safety, dosing, administration, and implications for advanced practitioners of newer JAK inhibitors (fedratinib, pacritinib, and momelotinib) in the treatment of myelofibrosis.

Myelofibrosis is a myeloproliferative neoplasm (MPN) and clonal hematopoietic stem cell disorder characterized by the secretion of inflammatory cytokines that result in the buildup of scar tissue in the bone marrow, leading to dysfunction in the hematopoietic process and ultimately the development of cytopenias and constitutional symptoms such as fatigue, cachexia, and night sweats (Gangat & Tefferi, 2020; Reynolds & Pettit, 2022). This is a rare and often progressive disease characterized by splenomegaly, significant symptom burden, and blood count abnormalities such as leukocytosis, anemia, and thrombocytopenia. In some cases, patients may develop bone marrow failure or leukemic transformation (approximately 20% in 10 years). The

symptoms associated with myelofibrosis can significantly impact a patient's quality of life (QOL) as well as contribute to a poor prognosis (Gangat & Tefferi, 2020).

The median overall survival (OS) of patients with myelofibrosis ranges from 1.3 to 15 years and is dependent on risk status, which is determined based on several clinical, pathological, and genetic factors. The increased risk of mortality for patients with myelofibrosis is associated with leukemic transformation, a high rate of infection, and cardiovascular-related deaths (Passamonti & Mora, 2023). The discrepancy between the survival of high-risk vs. low-risk patients highlights the urgent need for effective therapeutic options in this setting. While outside the scope of this article, advanced practitioners should be familiar with standardized prognostic models for MPNs and apply these in routine practice to drive clinical decision-making.

In 2011, a breakthrough in the treatment of myelofibrosis occurred with the approval of ruxolitinib (Jakafi), the first Janus kinase (JAK) inhibitor approved by the US Food & Drug Administration (FDA) for the treatment of intermediate- or high-risk myelofibrosis. Along with the COMFORT trials, which showed benefit in patients with intermediate-2 and high-risk patients with baseline platelets at > 100 × 10^9/L, several reports and guidelines support the broader use of ruxolitinib in intermediate-1 disease, patients with lower platelet counts, and patients endorsing symptomatic disease (even in the low-risk setting; Bose & Verstovsek, 2020). Since the initial approval of ruxolitinib, other JAK inhibitors (fedratinib [Inrebic], pacritinib [Vonjo], and momelotinib [Ojjaara]) have been developed and approved for the treatment of myelofibrosis. These therapies have been shown to reduce symptoms and improve QOL in patients with myelofibrosis. Herein, we review the pharmacology, efficacy, safety, dosing, administration, and implications for advanced practitioners of recently approved alternative JAK inhibitors for the treatment of myelofibrosis.

PHARMACOLOGY AND MECHANISM OF ACTION

The JAK-STAT signal transducer and activator of transcription pathway is a universal driver of myelofibrosis as it promotes the growth and division of cells (Reynolds & Pettit, 2022). The JAK-STAT pathway transmits extracellular signals to the cell's nucleus, and its aberrant activation has been reported in a variety of disease states, including inflammatory conditions, hematologic malignancies, and solid tumors. In myelofibrosis and other MPNs, the JAK-STAT pathway is the major unifying biologic abnormality. *JAK2*, *CALR*, and *MPL* are genes involved in the pathogenesis of myelofibrosis. Their relationship to the JAK-STAT signaling pathway has been extensively studied. In myelofibrosis and other MPNs, mutations in *JAK2*, *CALR*, and *MPL* are mutually exclusive and considered drivers of JAK-STAT pathway activation and downstream transcription and gene expression. The presence of these genetic mutations carries several symptomatic, prognostic, and treatment-related implications. For example, analyses have suggested a greater efficacy in response to ruxolitinib in patients with a mutant *JAK2* allele burden of > 50%, and a lower odds of spleen response and inferior survival in those with ≥ 3 mutations in non-driver, myeloid genes (Bose & Verstovsek, 2020). *CALR* mutations are present in a significant proportion of *JAK2*-negative patients with myelofibrosis, and these mutations lead to JAK2-independent activation. Patients with *CALR* mutations have different clinical and hematologic features compared with *JAK2*-mutated patients. Overall, studies have shown that regardless of the presence of these mutations (and including in triple-negative patients), the JAK-STAT pathway is overactive in myelofibrosis, and therefore JAK inhibition can reliably be expected to elicit a response with the start of therapy.

The primary benefits of ruxolitinib continue to be its effects on splenomegaly and symptom burden in patients with myelofibrosis (Bose & Verstovsek, 2020). Pooled data analysis of COMFORT-I and II showed an OS advantage at 5 years for those patients originally randomized to ruxolitinib (median OS, 5.3 vs. 3.8 years; Table 1; Verstovsek et al., 2017). Additionally, a real-world registry analysis conducted in Europe demonstrated an improvement in survival with ruxolitinib compared with hydroxyurea (Guglielmelli et al., 2022). As a class, JAK inhibitors have produced meaningful improvements in splenomegaly and

Table 1. Clinical Trial Data for JAK Inhibitors in the Treatment of Myelofibrosis

JAK inhibitor	Trial	Trial design	Study arms	*n*	Patient characteristics	Outcomes data
Ruxolitinib	COMFORT-I	Phase III RCT	15–20 mg bid vs. placebo (1:1)	309	Int-2 or high-risk disease, splenomegaly, anemia	• SVR35: 41.9% vs. 0.7% • Median duration of response: 168 weeks • Symptom improvement with worsened cytopenias and trend toward longer OS with ruxolitinib
	COMFORT-II	Phase III RCT	15-20 mg bid vs. BAT[a] (2:1)	219	Int-2 or high-risk disease, splenomegaly, symptoms	• SVR35: 28% vs. 0% • Pooled analysis showed median OS: 5.3 vs. 3.8 years
Fedratinib	JAKARTA	Phase III open-label	400 mg qd vs. 500 mg qd vs. placebo (1:1:1)	289	Int-2 or high-risk disease, splenomegaly, platelets ≥ 50 × 10^9/L	• SVR35: 37% vs. 1% (fedratinib vs. placebo) • Median duration of response: 18.2 months • Symptom improvement with fedratinib • Trial halted due to Wernicke encephalopathy concern
	JAKARTA-2	Phase II single arm	400 mg qd	97	Int-2 or high-risk disease, splenomegaly, symptoms, prior JAK inhibitor (ruxolitinib resistance/ intolerance) allowed	• SVR35: 55% • 19% discontinued due to adverse events, most commonly thrombocytopenia • No cases of Wernicke encephalopathy, but trial halted 2.5 months following accrual
Pacritinib	PERSIST-1	Phase III RCT	200 mg bid or 400 mg bid vs. BAT (2:1)	327	Int- or high-risk disease, splenomegaly, with no prior JAK inhibitor exposure	• SVR35: 19% vs. 5% • Median duration of response: 34 weeks • Symptom improvement 63%; reduction in transfusions 56% • Trial halted in 2016 due to concerns of cardiac events and bleeding, resumed 2017
	PERSIST-2	Phase III RCT	200 mg bid vs. 400 mg qd vs. BAT[b] (1:1:1)	311	Int-1/2 or high-risk disease, splenomegaly, platelets ≤ 100 × 10^9/L	• SVR35: 18% vs. 3% (pacritinib vs. BAT) • Symptom improvement by 59% with pacritinib • Reduction in transfusions 57% • Safety outcomes similar in patient subgroup < 50 × 10^9/L
	PAC203	Phase II, randomized, dose-finding study	100 mg qd or 100 mg bid or 200 mg bid	161	Int-1/2 or high-risk disease, splenomegaly, ruxolitinib intolerant or failure	• SVR35: 17% among patients with platelets < 50 × 10^9/L at 200 mg BID • Symptom response rate similar between dosing cohorts

Note. BAT = best available therapy; BID = twice daily; int = intermediate; OS = overall survival; qd = once daily; RBC = red blood cell; RCT = randomized controlled trial; SVR35 = spleen volume reduction of ≥ 35%.
[a]BAT included hydroxyurea, anagrelide, corticosteroids, exogenous epoetin, immunomodulatory drugs, interferon, or mercaptopurine at the discretion of the provider.
[b]BAT included ruxolitinib.

Table 1. Clinical Trial Data for JAK Inhibitors in the Treatment of Myelofibrosis (cont.)

JAK inhibitor	Trial	Trial design	Study arms	*n*	Patient characteristics	Outcomes data
Momelotinib	SIMPLIFY-1	Phase III RCT	200 mg qd or ruxolitinib	432	Int-1/2 or high-risk disease	• Noninferior SVR35: 26.5% vs. 29% (momelotinib vs. ruxolitinib) • Fewer patients with symptom response with momelotinib (28.4% vs. 42.2%) • RBC transfusion-related endpoints (rate, independence, dependence) all improved with momelotinib (nominal $p \leq .019$)
	SIMPLIFY-2	Phase III RCT	200 mg qd or BAT[b]	156	Int-1/2 or high-risk disease, ruxolitinib hematologic intolerance or suboptimal response	• SVR35: 7% vs. 6% (momelotinib vs. BAT, in which 89% of BAT was ruxolitinib) • Symptom response rate better with momelotinib (26% vs. 6%)
	MOMENTUM	Phase III RCT	200 mg qd or danazol	195	Int-1/2 or high-risk disease, symptomatic anemia	• Superior symptom response rate with momelotinib (25% vs. 9%) • SVR35: 22% vs. 3% (momelotinib vs. danazol) • Significant improvements in anemia measures with momelotinib, including rate of zero transfusions at week 24 (35% vs. 17%)

Note. BAT = best available therapy; BID = twice daily; int = intermediate; OS = overall survival; qd = once daily; RBC = red blood cell; RCT = randomized controlled trial; SVR35 = spleen volume reduction of ≥ 35%.
[a]BAT included hydroxyurea, anagrelide, corticosteroids, exogenous epoetin, immunomodulatory drugs, interferon, or mercaptopurine at the discretion of the provider.
[b]BAT included ruxolitinib.

symptom burden, yet they do not eliminate disease. Ruxolitinib revolutionized the treatment of myelofibrosis but carries on-target risks of worsening anemia and thrombocytopenia, limiting its use in cytopenic patients and often requiring additional supportive measures (Reynolds & Pettit, 2022). Cytopenias are a common rationale for ruxolitinib dose adjustments, which carries implications for patients, as higher doses have correlated with improvements in patient-reported outcomes and QOL (Mesa et al., 2013). Over time, patients are expected to lose response to ruxolitinib therapy. Fortunately, the approval of novel JAK inhibitors offers new approaches to addressing ruxolitinib failure and ineligibility.

Ruxolitinib Failure

The definition of ruxolitinib failure has been a noted debate since early in its study in myelofibrosis, with early recommendations suggesting failure at the initial signs of cytopenias. Given the benefits of ruxolitinib therapy in myelofibrosis and the significant practical insights years of experience have offered, the contemporary idea of failure allows for dose modification and therapy to the point of progression; however, there remain several limitations to its use in this setting (Bose & Verstovsek, 2020). Ruxolitinib has not been shown to have a substantial impact on the driver mutation allele burden or on the grade of bone marrow fibrosis in most patients. Anemia, a common symptom and consequence of myelofibrosis, is not improved and may be worsened by ruxolitinib; anemia is a leading cause of ruxolitinib discontinuation in practice (Bose & Verstovsek, 2020). Guidelines recommend the use of alternative dosing strategies and combinations with agents for anemia management (NCCN, 2023). Thrombocytopenia may also be worsened. There is little to no guidance available for ruxolitinib dosing in patients with platelets $< 50 \times 10^9$/L. Although clinicians have grown increasingly comfortable with low doses of ruxolitinib in this setting, these dose adjustments may be associated with a less optimal response (Bose & Verstovsek, 2020). Additionally, patients with myelofibrosis may lose the clinical benefit of ruxolitinib over time. This loss of response may be difficult to elucidate whether due to resistance or intolerance to the medication.

The idea of ruxolitinib failure may be used more inclusively to describe all situations, including intolerance and disease progression, although currently there is not a consensus definition of failure (Bose & Verstovsek, 2020). Progression is defined as worsening of or the appearance of new splenomegaly and increasing circulating and bone marrow blast counts or other signs of symptomatic disease progression (Tefferi et al., 2013). Ruxolitinib failure remains more a matter of clinical judgment and can be associated with shortened survival among patients with myelofibrosis. Reports indicate that around half of patients will discontinue ruxolitinib at around 3 years, primarily due to disease progression or treatment-related adverse events. The survival of patients following ruxolitinib discontinuation is approximately 13 months (Palandri et al., 2020; Passamonti & Mora, 2023).

Strategies to overcome ruxolitinib failure or intolerance have mainly been different approaches to continuing ruxolitinib therapy, including dose modifications and rechallenging. Given the shortened survival post-ruxolitinib discontinuation, this is an area of interest in drug development and treatment optimization (Newberry et al., 2017). Rechallenging with ruxolitinib after withdrawal has been reported to be effective in some patients with progressing disease (Bose & Verstovsek, 2020). In the setting of ruxolitinib failure, allogeneic stem cell transplantation may be considered if the patient is eligible (and especially in the setting of leukemic transformation).

With alternative JAK inhibitors now available and studies showing benefit inclusive of the second-line setting, clinicians have options to sequence JAK inhibitor therapy. Of note, given the lack of uniformity in the definition of ruxolitinib failure, clinical trials with these novel JAK inhibitors in the post-ruxolitinib setting have had varying eligibility criteria and, in some cases, leaving determination up to the treating physician's discretion (Bose & Verstovsek, 2020). With all these considerations in mind, the optimal time to switch therapy has not currently been established due to variable responses to ruxolitinib and overall patient benefit despite signs of progression (Passamonti & Mora, 2023). This should be an area of ongoing consideration and study. A common practice is to switch therapy before total ruxolitinib

exhaustion despite dose adjustments (i.e., a return to or worsening beyond baseline symptoms).

FEDRATINIB

Fedratinib is a JAK2 inhibitor indicated for the treatment of intermediate-2 and high-risk myelofibrosis. Following initial dose finding studies, fedratinib was first studied in the JAKARTA study, which included JAK inhibitor-naive patients. It compared the outcomes of three equal arms (400 mg daily, 500 mg daily, and placebo) over a 24-week period with confirmation 4 weeks later (Pardanani et al., 2015). The primary endpoint was a reduction in spleen volume by at least 35% (SVR35), with a 50% symptom burden reduction as a secondary endpoint. After the first year of the study, 289 patients were enrolled, with 36% of the 400-mg arm, 40% of the 500-mg arm, and 1% of the placebo arm achieving SVR35. Additionally, a symptom response was achieved in 36% of the 400-mg arm, 34% of the 500-mg arm, and 7% of the placebo arm. Both doses were found to be superior to placebo in JAK inhibitor-naïve patients with intermediate-2 and high-risk myelofibrosis.

In the subsequent single-arm, phase II JAKARTA-2 trial, 97 patients with intermediate- or high-risk myelofibrosis who were resistant or intolerant to prior ruxolitinib received fedratinib 400 mg once daily (Harrison et al., 2017). Dose escalation to 600 mg daily was permitted if there was a < 50% reduction in palpable spleen size by the end of cycles 2 and 4. Eligible patients were required to be ruxolitinib resistant following at least 14 days of prior therapy or ruxolitinib intolerant after any duration of treatment. Notably, ruxolitinib resistance or intolerability (i.e., failure) was not otherwise defined and left up to the individual investigator. The primary endpoint was SVR35 after six 28-day cycles. In the entire cohort, SVR35 was achieved in 31% of patients. An updated analysis of JAKARTA-2 identified 79 patients (81% of the overall cohort) who met more stringent criteria for ruxolitinib resistance or intolerance and identified that 30% of these patients met this endpoint (Harrison et al., 2020). Significant improvements were also identified across total and all individual symptoms in the treatment group. Investigators therefore determined that even those patients with advanced disease and having been heavily pretreated with ruxolitinib can expect a robust response with subsequent fedratinib (Harrison et al., 2020).

A small number of neurological events were reported in the JAKARTA trials, leading to the temporary suspension of clinical trials in 2013 (Mullally et al., 2020). Additional details are described in the following sections with other adverse event considerations, but following safety reviews and additional trials, the FDA approved fedratinib in 2019 for the treatment of myelofibrosis.

PACRITINIB

With cytopenias continuing to be a major challenge in the treatment of myelofibrosis with other JAK inhibitors, the approval of pacritinib offers a notable option for patients experiencing thrombocytopenia and even transfusion-dependent anemia (Jain & Mesa, 2016). Pacritinib inhibits several tyrosine kinases and has the highest selectively for JAK2. Pacritinib has been evaluated in several clinical trials, including two randomized, controlled phase III trials (PERSIST-1 and PERSIST-2).

The PERSIST-1 trial compared the efficacy and safety of pacritinib 400 mg daily with that of best available therapy (BAT) other than JAK inhibitors among 327 patients (Mesa et al., 2017a). The primary endpoint of this trial was SVR35 at week 24, with symptoms improvement of at least 50% as the secondary endpoint. Patients with cytopenias (including a platelet count of $< 100 \times 10^9$/L) were enrolled. Sixteen percent of these patients had a platelet count of $< 50 \times 10^9$/L. In this trial, SVR35 at week 24 was achieved in 19% of patients receiving pacritinib compared with 5% in the BAT arm in the intention-to-treat analysis. Symptoms were significantly improved with pacritinib compared with BAT. Improvements in spleen volume were also noted in patients with thrombocytopenia. In patients with platelets $< 100 \times 10^9$/L, the reduction rate was 17% with pacritinib vs. 0% in the intention-to-treat population, and 24% with pacritinib vs. 0% among evaluable patients. In patients with platelets $< 50 \times 10^9$/L, SVR35 rates were 23% with pacritinib vs. 0% in the intention-to-treat analysis, and 33% with pacritinib vs. 0% among evaluable patients. Results of this trial were encouraging and provided insight into the utility of pacritinib in patients with baseline thrombocytopenia.

The PERSIST-2 trial provided additional insight by comparing pacritinib with BAT in patients with thrombocytopenia (≤ 100 × 10^9/L) and allowed for patients to have been previously treated with one or two other JAK inhibitors (Mascarenhas et al., 2018). Three hundred eleven patients were randomized to receive pacritinib at 400 mg daily or 200 mg twice daily, or BAT. The coprimary endpoints of this study were SVR35 and symptoms score improvement by 50% at week 24. There was also a secondary objective of comparing once- vs. twice-daily dosing of pacritinib. This trial was abruptly terminated early due to mortality and safety concerns from the FDA. However, at the time of discontinuation, the combined pacritinib arms showed an SVR35 rate of 18% vs. 3% and demonstrated a trend toward symptoms improvement. Further, the 200-mg twice-daily dosing led to significant improvement in both endpoints over BAT. Spleen volume and symptoms reduction were also seen with the twice-daily dosing regardless of prior treatment with ruxolitinib or platelets ≤ 50 × 10^9/L. When the twice-daily and once-daily dosing schemes were compared, a trend in favor of the twice-daily dosing was observed across subgroups.

PERSIST-1 and PERSIST-2 identified the efficacy of pacritinib in patients with intermediate and high-risk myelofibrosis, with a manageable side-effect profile. Despite initial concerns around safety markers and events, pacritinib was found to be safe for use, including in thrombocytopenic patients with platelets ≤ 50 × 10^9/L. This was confirmed by a pooled analysis of the PERSIST trials as well as a subsequent dose-finding study, PAC203, which identified the 200-mg twice-daily dose as the optimal dose (Gerds et al., 2020; Venugopal & Mascarenhas, 2022).

MOMELOTINIB

Momelotinib is a kinase inhibitor of JAK1, JAK2, and activin A receptor type 1 (ACVR1) that is indicated for the treatment of intermediate- or high-risk myelofibrosis in adults with anemia. ACVR1 is thought to suppress hepcidin production, which then prompts the mobilization of iron to support erythropoiesis (Reynolds & Pettit, 2022). The efficacy and safety of momelotinib has been evaluated in several phase III trials (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM).

The SIMPLIFY-1 trial was a noninferiority study that compared the efficacy and safety of momelotinib 200 mg once daily with ruxolitinib 20 mg twice daily (or dose adjusted per label) among 432 patients (Mesa et al., 2017b). The primary endpoint of this trial was SVR35 at week 24, with symptoms improvement of at least 50% and effects on red blood cell (RBC) transfusion requirements as key secondary endpoints. Patients receiving momelotinib or ruxolitinib experienced a similar rate of SVR35 achievement (26.5% vs. 29%). Symptom response was achieved in fewer patients with momelotinib (28.4%) compared with ruxolitinib (42.2%). From an anemia perspective, more patients receiving momelotinib achieved transfusion independence at week 24 than those receiving ruxolitinib (66.5% vs. 49.3%).

The SIMPLIFY-2 trial compared the efficacy and safety of momelotinib to BAT in 156 patients with myelofibrosis who had suboptimal responses to ruxolitinib or hematologic toxicity requiring RBC transfusions on ruxolitinib (Harrison et al., 2018). Ruxolitinib made up 89% of the BAT arm of the trial. The primary endpoint of SVR35 was not superior with momelotinib compared with BAT (7% vs. 6%) at 24 weeks in patients who had been previously treated with ruxolitinib. However, there was an improvement in symptom response with momelotinib compared with BAT (26% vs. 6%; $p = .0006$).

The MOMENTUM trial was a phase III trial comparing the efficacy and safety of momelotinib to danazol in patients with myelofibrosis and symptomatic anemia who were previously treated with a JAK inhibitor (Gerds et al., 2023). The primary endpoint of symptom response was superior with momelotinib compared with danazol (25% vs. 9%, $p = .0095$). More patients receiving momelotinib compared with danazol achieved SVR35 (22% vs. 3%, $p = .0011$). The rate of zero transfusions at week 24 was superior with momelotinib compared with danazol (35% vs. 17%, $p = .0012$). These findings supported the approval of momelotinib for patients with myelofibrosis and disease-related anemia.

SAFETY AND ADVERSE EVENTS

While fedratinib, pacritinib, and momelotinib have been shown to be effective in treating

myelofibrosis, they are also associated with adverse events requiring management and monitoring.

Fedratinib

The most common adverse events with fedratinib were hematologic and gastrointestinal. Anemia was the most common side effect in fedratinib clinical trials, although an initial nadir was seen that often improved. Identified hematologic side effects seen in practice may warrant dose interruption or reduction depending on the severity (Mullally et al., 2020). Thrombocytopenia was also seen less frequently. Subsequent evaluations of JAKARTA-2 looked at the disease response in patients with lower platelet counts (50–100 × 10^9/L vs. > 100 × 10^9/L), as these thrombocytopenic patients are historically difficult to treat with suboptimal ruxolitinib doses, leading to worse outcomes (Harrison et al., 2017; Mullally et al., 2020; Pardanani et al., 2015). Interestingly, better spleen responses and symptom responses were seen in patients with lower platelets, although the interpretation of this is likely that these patients may see the most benefit in switching from ruxolitinib to fedratinib (full dose) at platelets 50–100 × 10^9/L rather than dose reducing the ruxolitinib. Treatment discontinuation due to hematologic adverse events with fedratinib was uncommon, occurring in approximately 3% of cases.

The most common nonhematologic adverse events with fedratinib are gastrointestinal events, such as diarrhea, nausea, and vomiting, which are usually low grade, and most frequently during early treatment and decreasing over time. If a patient develops severe gastrointestinal toxicity, management may involve dose reduction or interruption, prophylaxis with antiemetics, and treatment with antidiarrheal medications (Bose & Verstovsek, 2020; Mullally et al., 2020). No unexpected safety signals have been identified with fedratinib in clinical trials in patients who have received over six cycles of treatment (Talpaz & Kiladjian, 2021).

One specific concern with fedratinib is Wernicke-Korsakoff syndrome, a potentially life-threatening neurological condition that can develop due to thiamine (vitamin B1) deficiency. This adverse event was originally identified in the JAKARTA trial among patients in the 500-mg arm (Mullally et al., 2020; Pardanani et al., 2015). There has been substantial review of the eight identified cases with debate around the etiology and actual occurrence of this adverse event (Bose & Verstovsek, 2020). Despite being a rare event and ultimately not considered to be associated with fedratinib, the prescribing information does include the black box warning of encephalopathy (Mullally et al., 2020; Talpaz & Kiladjian, 2021). Therefore, it is recommended to routinely monitor thiamine levels, replete if deficient prior to starting fedratinib, and supplement with thiamine as needed to mitigate this risk, a consideration applied to ongoing clinical trials as well (Bose & Verstovsek, 2020; Mullally et al., 2020; Talpaz & Kiladjian, 2021). Other potential side effects of fedratinib may include increased amylase levels, bone pain, pain in the arms or legs, increased serum creatinine, and muscle spasms.

Pacritinib

Common adverse events associated with pacritinib include gastrointestinal events, anemia, and thrombocytopenia (Mascarenhas, 2022). Nausea, vomiting, and diarrhea are the most common gastrointestinal adverse events, which may be managed with the use of antiemetics and antidiarrheals. Bleeding, a reported adverse event, is generally associated with thrombocytopenia rather than an associated coagulopathy or platelet activity disruption. In cases of severe bleeding, treatment with pacritinib should be held until the hemorrhage resolves, then restarted at 50% of the last given dose. If the bleeding reoccurs, it is then recommended to discontinue therapy. Dose adjustments or interruptions may also be necessary in cases of anemia and thrombocytopenia based on clinical judgement and patient response, although not with baseline thrombocytopenia. Practical experience is limited, but if patients are thrombocytopenic at baseline, clinicians may consider monitoring complete blood counts weekly to every 2 weeks for the first 2 months of therapy, and then tailored based on the platelet trend thereafter (Mascarenhas, 2022). Platelet transfusions should be considered if needed to support patients for the first 4 to 6 weeks before holding or reducing the dose is considered.

In 2016, the FDA placed a clinical hold on clinical studies being conducted for pacritinib

due to excess mortality and adverse events (Jain & Mesa, 2016). This excess mortality and increased adverse events trended after alternative therapy patients had crossed over to pacritinib, and most occurred after week 24 (with similar mortality identified during the planned initial 24-week period). Deaths in the pacritinib-treated group were associated with intracranial hemorrhage, cardiac failure, and cardiac arrest. Investigators and clinicians suggest that these could possibly be an unexpected effect of the pacritinib but could also be risks associated with a high-risk thrombocytopenic population (Jain & Mesa, 2016). A subsequent pooled analysis of the PERSIST trials reviewed the thrombocytopenic patients specifically (considered at the highest risk for severe adverse events), and despite identified grade 3/4 hematologic events, dose reductions were not warranted. Further, even in the setting of treatment-associated thrombocytopenia with pacritinib, there was no excess in hemorrhagic or cardiac events, and there was similar survival between pacritinib and comparison arms. The clinical hold was then lifted in 2017 (Venugopal & Mascarenhas, 2022). It should be noted that there is still a potential for cardiotoxicity with pacritinib, primarily in the form of QTc interval prolongation. An electrocardiogram should be evaluated prior to initiating pacritinib and periodically during therapy. Pacritinib should be avoided in patients with a baseline QTc of > 480 msec. Patients should avoid the use of concomitant drugs with QTc-prolonging potential and correct hypokalemia prior to and while receiving pacritinib.

Momelotinib

Common adverse events associated with momelotinib include thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea. Further, the safety and tolerability of momelotinib was thoroughly characterized in an integrated analysis of the phase III clinical trials, which included 725 patients who received this medication for a median of 11.3 months (Verstovsek et al., 2023). Adverse events of clinical importance were identified in this analysis as all infections, malignancies, major adverse cardiovascular events, cytopenias, thromboembolism, hemorrhage, and peripheral neuropathy. Thromboembolism occurred in 8.8% patients, including 5.4% with grade ≥ 3, and the incidence rate did not increase over time. Hemorrhage occurred in 28.6%, including 6.8% with grade ≥ 3. Most patients experiencing hemorrhage had an immediate prior platelet count that was less than normal. The incidence rate was found to decrease over time. Currently, clinicians are advised to monitor for symptoms of these events, and evaluate and treat promptly. Regarding peripheral neuropathy, 14.8% of patients on momelotinib experienced this side effect, mostly peripheral sensory neuropathy as numbness and paresthesia, including 1.2% of all patients experiencing grade ≥ 3 events. The incidence decreased over time and is not considered a serious concern by authors, although it may suggest preferencing other treatment options in patients with prior neuropathy. Additionally, there is a potential for hepatoxicity with momelotinib. Transaminase elevations have a typical time of onset of approximately 2 months. Dose adjustments should be considered for patients with baseline severe hepatic dysfunction. Patients receiving momelotinib should have their liver function tests monitored at baseline, every month for 6 months during treatment, and then periodically thereafter. Transaminitis or hyperbilirubinemia may be managed with therapy interruptions and dose reductions.

Anemia management with directed therapies or transfusion support with iron chelation is a critical and common complicating factor in myelofibrosis treatment. Several JAK inhibitors may be significantly limited by this complication, and anemia often does not improve even with effective JAK inhibitor therapy. In addition to dose adjustments when anemia is identified as a side effect of therapy, patients may require additional supportive care, including transfusions, erythropoietin stimulating agents, danazol, or immunomodulatory agents. The recent approval of momelotinib for patients with myelofibrosis and anemia represents an important therapeutic option for this patient population. As previously mentioned, the mechanism behind momelotinib's ability to increase hemoglobin and improve anemia is a result of ACVR1 inhibition. Recently, the identification of ACVRI inhibition with pacritinib was reported and thought to be the underlying mechanism for

improved transfusion independence of patients treated with pacritinib vs. BAT in the PERSIST-2 trial. Therefore, it may be a consideration for therapy to address this complication (Oh et al., 2023).

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

The goal of therapy for patients with myelofibrosis continues to be aimed at improving symptoms, splenomegaly, and QOL (Reynolds & Pettit, 2022). The initial approach to the management of myelofibrosis should be individualized to account for clinical, biological, and social/patient-related factors. The COMFORT and JAKARTA trials did not offer insight into the preferred front-line option between JAK inhibitors. Given the extensive experience with ruxolitinib over the past decade, this is still recommended as first-line treatment for intermediate- and high-risk myelofibrosis patients and likely to be a preferred option among clinicians. Additionally, regarding sequencing JAK inhibitors, there are no data on ruxolitinib after alternative options vs. clinical trial data with fedratinib and pacritinib in the second-line (post-ruxolitinib) setting, making their second-line sequencing easily justifiable. In the setting of ruxolitinib failure, the selection of an alternative JAK inhibitor should be based on various factors, including the patient's individual characteristics and available options. While the strict definition of ruxolitinib failure may be debated in clinical trials, follow-up assessments reviewing responses of patients meeting current definitions of progression and failure suggest efficacy with the alternative JAK inhibitors (Maffioli et al., 2022).

As alternative therapies are considered, fedratinib and pacritinib have both been shown to be effective in patients having failed ruxolitinib. In addition to ruxolitinib failure, fedratinib may also be useful in patients unable to achieve the goal dose of ruxolitinib (20 mg twice daily) due to hematologic side effects or other reasons. Pacritinib should be considered as front-line therapy in patients with severe thrombocytopenia (platelets $\leq 50–100 \times 10^9$/L; NCCN, 2023). Once approved, momelotinib is the anticipated similarly preferred option in patients with anemia. Table 2 offers summarized insight into JAK inhibitor selection and prescribing considerations.

In addition to the reported adverse events, ruxolitinib discontinuation syndrome (RDS; sometimes referred to as a withdrawal syndrome) may occur within 21 days of stopping ruxolitinib (Palandri et al., 2021). This is especially important to keep in mind with therapy sequencing, especially from ruxolitinib to a second-line therapy. Ruxolitinib discontinuation syndrome is characterized by an acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias, and occasional hemodynamic decompensation, including acute respiratory distress and shock (Baek et al., 2022). Ruxolitinib discontinuation syndrome can occur regardless of the ruxolitinib dose and is often a diagnosis of exclusion around discontinuation.

Treatment remains mainly supportive in most instances, along with corticosteroids in severe cases. This syndrome may be best avoided by tapering ruxolitinib off to at least a dose of 10 mg twice daily before stopping vs. abrupt discontinuation. Various tapering strategies may be considered (Baek et al., 2022; Palandri et al., 2021). In JAKARTA-2 and PERSIST-2, ruxolitinib was tapered to 10 mg twice daily before stopping for a washout period before the subsequent JAK inhibitor was started (Harrison et al., 2017; Mascarenhas et al., 2018). To date, RDS is specific to ruxolitinib and has not been reported with other JAK inhibitors. In PERSIST-2, the investigators noted that when the clinical hold was put in place and patients abruptly stopped pacritinib, these patients experienced rapidly advancing symptoms that were difficult to control (Mascarenhas et al., 2018). The potential for withdrawal syndrome was noted; however, it was considered less of a concern given the long half-life (approximately 40 hours) of the agent. Therefore, mitigation strategies are not formally recommended but may be considered in the future or on a patient-specific basis (Mascarenhas et al., 2018; Mascarenhas, 2022). There are limited data on withdrawal symptoms with the newer JAK inhibitors, although tapering off may be considered especially in frail patients having received long-term therapy or those with a high symptom burden prior to discontinuation. One strategy to transition between JAK inhibitors is to overlap JAK inhibitor therapy; however, there are little data reported on this to date. In clinical practice,

Table 2. JAK Inhibitor Characteristics, Dosing, and Adverse Events

JAK inhibitor	Molecular targets	Dosing	Dose adjustments	Major adverse events	Clinical pearls
Ruxolitinib	JAK1, JAK2	Ranges between 5–20 mg bid, dependent on baseline platelet count	Reduce dose for thrombocytopenia or anemia; avoid in patient with severe renal or hepatic impairment	Anemia, thrombocytopenia, infections, fatigue, dizziness, nausea, diarrhea	• First JAK inhibitor approved for myelofibrosis • Starting dose is based on platelet counts and should be escalated as possible • Early anemia is common with gradual improvement; dose adjustments are not specifically indicated for early anemia • Administer with food, avoid live vaccines
Fedratinib	JAK2, JAK1, JAK3/TYK2, FLT3, BRD4 (not all inclusive)	400 mg qd (platelets > 50 × 10^9/L)	Reduce dose for thrombocytopenia or anemia; avoid in patients with severe renal or hepatic impairment	Anemia, thrombocytopenia, nausea, diarrhea, vomiting, asthenia	• Early nausea, vomiting, diarrhea common; consider administration with prophylaxis for nausea and prompt treatment for diarrhea • Food does not meaningfully alter the bioavailability of fedratinib but taking with a high-fat meal may help to reduce the incidence of nausea/vomiting • Monitor thiamine and for signs of encephalopathy along with renal and liver function • No starting dose reductions needed for moderate thrombocytopenia (50–100 × 10^9/L), but dose reductions for worsening platelets
Pacritinib	JAK2, JAK3/ TYK2, FLT3, IRAK1, ACVR1	200 mg bid	May be applied in patients with platelets < 50K with no dose adjustments; avoid in patients with severe renal or hepatic impairment	Thrombocytopenia, anemia, infections, gastrointestinal events, fatigue, dizziness	• Preferred option in patients with thrombocytopenia (cytopenic myelofibrosis), less myelosuppression seen as compared to other JAK inhibitors • Administer with food; avoid coadministration with strong CYP3A4 inhibitors • Early nausea/diarrhea are common and generally transient, improving with supportive care and mostly resolving withing 2 weeks without warranting treatment modification; 400 mg once daily studied, but associated with significant GI toxicities so consolidation of the dose is not recommended • Caution in those with cardiovascular disease or recent hemorrhage, monitor QTc (minimum baseline measure) and for bleeding (coagulation profile recommended prior to starting therapy); avoid in active bleeding and QTc > 480 ms • Before any planned surgical procedures hold pacritinib to decrease risk of bleeding
Momelotinib	JAK1, JAK2, ACVR1, ALK2	200 mg qd	Reduce starting dose in patients with severe hepatic impairment	Thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, nausea	• Preferred option in patients with anemia and presence of symptomatic splenomegaly and/or constitutional symptoms • Monitor liver function tests at baseline and periodically during treatment due to risk of hepatotoxicity • May be administered with or without food

most patients will switch directly from one JAK inhibitor to another without a washout period from the previous drug, which is likely reasonable and a patient-friendly approach in terms of adherence (Mullally et al., 2020).

CONCLUSION

The approval of ruxolitinib dramatically changed the management and outlook of myelofibrosis. However, there are notable limitations to this drug, including cytopenic effects and a predictable loss of response leading to progressive disease. The recent approvals and pipeline of novel JAK inhibitors once again represents a renaissance in the care of patients with myelofibrosis. Now, there are options for a more personalized approach to initial therapy and second-line options that continue to allow for exposure to JAK inhibition. With differing signaling pathway targets influencing potential clinical benefit, side effect profiles, and dosing strategies, prescribers can better tailor therapy to individual patients. Clinicians can also look forward to data on not only additional JAK inhibitors but also therapeutic combination regimens. Advanced practitioners should be familiar with differences between JAK inhibitor options and their roles in treating myelofibrosis to optimize patient care and outcomes. ●

Disclosure

Dr. Arnall has served on advisory boards for CTI BioPharma and HEMA Pharmaceuticals, and on the speakers bureau for NovoNordisk. Ms. Lyle has served on advisory boards for CTI BioPharma, AbbVie, and GSK, and on speakers bureaus for CTI BioPharma and Incyte. Dr. Moore has no conflicts of interest to disclose.

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