

Choosing a JAK Inhibitor in Myelofibrosis: Beyond Ruxolitinib

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

Myelofibrosis (MF) presents a chronic challenge, marked by myeloproliferation, bone marrow fibrosis, and debilitating splenomegaly and constitutional symptoms. The disease's hallmark, constitutive activation of JAK-STAT signaling, has driven the development of targeted therapies. Since ruxolitinib's 2011 approval, three additional JAK inhibitors have entered the market, complicating treatment decisions for clinicians.¹ These therapies are not curative; allogeneic stem cell transplantation remains the only potentially curative option, typically reserved for higher-risk patients. JAK inhibitors serve as essential pre-transplant management, effectively reducing splenomegaly and constitutional symptoms, thereby improving the likelihood of successful transplantation.¹

KEY TAKEAWAYS

- **The Pivot:** Newer JAK inhibitors, pacritinib and momelotinib, address drug-related myelosuppression, a common challenge with earlier agents.
- **The Data:** Pacritinib is approved for patients with significant thrombocytopenia, and momelotinib for those with anemia.
- **The Action:** Tailor JAK inhibitor selection to a patient's specific cytopenic phenotype, considering thrombocytopenia for pacritinib and anemia for momelotinib.

Myelofibrosis, a chronic myeloid neoplasm, manifests through a constellation of symptoms driven by pro-inflammatory cytokine signaling. Patients often present with significant splenomegaly and constitutional symptoms, including fatigue, night sweats, and weight loss, all stemming from the underlying dysregulation of the JAK-STAT pathway. These symptoms not only diminish quality of life but also indicate disease activity that requires intervention. Early initiation of JAK inhibitor therapy is recommended for symptomatic patients to manage these manifestations effectively. Asymptomatic patients, however, may initially undergo close surveillance.¹

The initial approval of ruxolitinib in 2011 marked a significant advance in MF treatment, targeting the constitutively active JAK-STAT signaling pathway. Ruxolitinib demonstrated efficacy in reducing splenomegaly and improving constitutional symptoms. But, like many targeted therapies, it came with its own set of challenges, particularly drug-related myelosuppression. This side effect often limited its use or required dose adjustments, especially in patients already presenting with cytopenias. The subsequent development and approval of fedratinib, pacritinib, and momelotinib aimed to address these unmet needs, offering alternative options with distinct safety profiles.¹

Understanding the JAK Inhibitor Market

Ruxolitinib, as the first-in-class JAK1/JAK2 inhibitor, established the efficacy benchmark for symptom and spleen control in myelofibrosis. Its mechanism involves blocking the phosphorylation of JAK1 and JAK2, thereby disrupting the downstream signaling cascade that drives myeloproliferation and inflammation. While effective, ruxolitinib's myelosuppressive effects, particularly thrombocytopenia and anemia, posed a challenge, especially for patients with pre-existing low blood counts. This often necessitated careful monitoring and dose modifications, which could impact the overall efficacy and tolerability of the treatment.¹

Fedratinib, a selective JAK2 inhibitor, gained approval as a second-line option for patients who failed or were intolerant to ruxolitinib, or as a first-line option for those with intermediate-2 or high-risk MF. Its approval provided an important alternative for patients whose disease progressed on ruxolitinib or who could not tolerate it. Fedratinib's profile also includes myelosuppression, but its distinct selectivity offered a different therapeutic avenue. The availability of fedratinib expanded the options for managing advanced MF, particularly in the context of prior JAK inhibitor exposure.¹

Pacritinib emerged as a key option for patients with significant thrombocytopenia, a common and challenging feature of myelofibrosis. This agent is a kinase inhibitor with specificity for JAK2, FLT3, IRAK1, and CSF1R. Its approval specifically addresses the unmet need in patients with platelet counts below $50 \times 10^9/L$, a population historically difficult to treat with other JAK inhibitors due to exacerbation of thrombocytopenia. Pacritinib demonstrated efficacy in reducing spleen volume and improving symptoms in this vulnerable patient group, making it a valuable addition to the therapeutic armamentarium.¹

Momelotinib, the most recent addition, targets JAK1, JAK2, and ACVR1 (also known as ALK2). Its unique mechanism of action, particularly its inhibition of ACVR1, plays a role in reducing hepcidin production, which in turn can improve anemia. This makes momelotinib particularly suitable for patients with myelofibrosis-associated anemia, another prevalent and debilitating complication of the disease. The drug's approval provides a much-needed option for patients struggling with transfusion dependence or symptomatic anemia, offering a potential dual benefit of symptom and spleen control alongside anemia improvement.¹

Tailoring Treatment to Patient Phenotype

The choice among these four JAK inhibitors now hinges significantly on the patient's specific clinical phenotype, particularly their cytopenic status. For patients presenting with significant thrombocytopenia, pacritinib stands out as the preferred agent. Its approval for patients with platelet counts below $50 \times 10^9/L$ directly addresses a significant limitation of earlier JAK inhibitors. This targeted approach ensures that patients who previously had limited treatment options due to low platelet counts can now receive effective therapy for their splenomegaly and constitutional symptoms.¹

Similarly, for patients whose primary challenge is myelofibrosis-associated anemia, momelotinib offers a distinct advantage. By inhibiting ACVR1, momelotinib can mitigate the anemia often exacerbated by other JAK inhibitors. This makes it an attractive choice for patients who are transfusion-dependent or experience severe anemia, allowing for symptom management without worsening their hematological parameters. The ability to improve anemia while also controlling spleen size and constitutional symptoms represents a significant step forward in personalized MF care.¹

Ruxolitinib remains a foundational therapy for patients without significant cytopenias, particularly those with symptomatic splenomegaly and constitutional symptoms. Its long-standing use and established efficacy make it a reliable first-line choice. But, clinicians must monitor for myelosuppression and adjust dosing accordingly. For those who progress on ruxolitinib or cannot tolerate it, fedratinib offers a viable second-line option, continuing the management

of splenomegaly and symptoms. The availability of these sequential options highlights the evolving strategy in MF treatment, moving beyond a one-size-fits-all approach.¹

Allogeneic stem cell transplantation remains the only curative option for myelofibrosis. Patients deemed candidates for this procedure, typically those with higher-risk disease, should receive referral to a transplant center. JAK inhibitors play an important role in the pre-transplant setting, optimizing patient condition by reducing spleen size and improving constitutional symptoms, which can potentially improve transplant outcomes. This integrated approach, combining targeted therapy with curative intent, represents the current standard of care. For a deeper understanding of how transplant strategies are evolving in related conditions, consider our coverage on optimising transplant in haemoglobinopathies. The clinical challenge of resistance or disease progression in myelofibrosis is substantial. Progression can manifest as increasing splenomegaly, worsening constitutional symptoms, or transformation to accelerated or blast phase disease. With multiple JAK inhibitors now available, sequencing these agents offers a strategy to improve outcomes for patients experiencing progression. The specific choice of a second-line or subsequent JAK inhibitor will again depend on the patient's evolving clinical picture, including their cytopenic status and prior treatment response. The Oxford Handbook of Clinical Haematology provides a concise reference for managing such complex haematological conditions. The ongoing development of novel JAK inhibitors and JAK inhibitor-based combinations further promises to refine treatment strategies. These investigational approaches aim to overcome current limitations, such as resistance mechanisms or persistent cytopenias, and to further improve patient outcomes. The field is actively exploring combinations with other targeted agents, immunomodulators, and epigenetic modifiers to enhance efficacy and broaden the therapeutic window. This continuous innovation is vital for a disease like myelofibrosis, which remains noncurative with current pharmacological interventions. The goal is to provide more durable responses and better quality of life for patients living with this chronic condition.¹

CLINICAL IMPLICATIONS

The expanded arsenal of JAK inhibitors for myelofibrosis means clinicians must now think beyond ruxolitinib as the default. The era of one-size-fits-all is over. Patient-specific cytopenias, particularly thrombocytopenia and anemia, are no longer just side effects to manage, but rather direct determinants of which agent to prescribe. This requires a more granular understanding of each drug's unique profile.

For the pharmaceutical industry, the success of pacritinib and momelotinib in niche populations highlights the value of developing therapies that address specific unmet needs, even within an already crowded drug class. Simply being 'another JAK inhibitor' is insufficient; demonstrating efficacy in a challenging subgroup, like those with severe thrombocytopenia or anemia, is what drives adoption and improves patient care. This precision approach sets a new standard for future drug development in myelofibrosis.

Patients with myelofibrosis now have more tailored options, which translates to better symptom control and potentially improved quality of life, especially for those with debilitating cytopenias. The ability to manage anemia with momelotinib or thrombocytopenia with pacritinib means fewer transfusions and less dose reduction, allowing for more consistent disease management. This shift empowers clinicians to optimize therapy, moving beyond merely treating symptoms to actively mitigating treatment-related complications.

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