Momelotinib and anaemia in myelofibrosis: a new calculus for treatment?

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

Myelofibrosis, a chronic myeloproliferative neoplasm, presents a complex clinical picture, often complicated by debilitating anaemia. This anaemia is not merely a symptom but a significant driver of morbidity, impacting quality of life and often necessitating transfusions. Existing treatments for myelofibrosis have largely focused on symptom control and spleen reduction, but their impact on anaemia has been inconsistent, sometimes even exacerbating it.

Momelotinib, a novel Janus kinase (JAK) inhibitor, has entered this therapeutic space with a differentiated profile, showing activity against both the disease's proliferative aspects and its associated anaemia. Its mechanism of action offers a potential shift in how clinicians approach patients with myelofibrosis, particularly those with moderate to severe anaemia.

KEY TAKEAWAYS

- The Pivot: Momelotinib specifically addresses anaemia in myelofibrosis, a critical unmet need often worsened by other JAK inhibitors.
- The Data: Momelotinib demonstrated improvements in transfusion independence and haemoglobin levels.
- The Action: Consider momelotinib for myelofibrosis patients with significant anaemia, especially those who are transfusion-dependent or have not responded to other JAK inhibitors.

Myelofibrosis is characterised by progressive bone marrow fibrosis, extramedullary haematopoiesis, splenomegaly, and a range of constitutional symptoms. The disease arises from clonal haematopoiesis, typically driven by mutations in JAK2, CALR, or MPL genes, leading to constitutive activation of the JAK-STAT signalling pathway. This pathway dysregulation promotes the proliferation of abnormal myeloid cells and the release of pro-inflammatory cytokines, which in turn contribute to the characteristic fibrosis and systemic symptoms. Anaemia is a near-universal feature of myelofibrosis, affecting a majority of patients at diagnosis or developing during the disease course. It is a major determinant of quality of life, often leading to fatigue, dyspnoea, and a need for regular red blood cell transfusions. Transfusion dependence itself carries risks, including iron overload, alloimmunisation, and infections, further complicating patient management. Current therapeutic strategies, including other JAK inhibitors, have shown efficacy in reducing splenomegaly and constitutional symptoms, but their effect on anaemia has been variable, with some even causing or worsening cytopenias.

The development of momelotinib represents an attempt to address this specific clinical challenge. Momelotinib is a small molecule inhibitor that targets JAK1, JAK2, and activin A receptor type 1 (ACVR1). Its inhibition of JAK1 and JAK2

contributes to the reduction of splenomegaly and constitutional symptoms, similar to other JAK inhibitors. But its unique action on ACVR1, also known as ALK2, is what differentiates it regarding anaemia. ACVR1 is a key component of the signalling pathway for hepcidin, a master regulator of iron homeostasis. By inhibiting ACVR1, momelotinib reduces hepcidin production, which in turn increases iron availability for erythropoiesis and improves red blood cell production. This dual mechanism of action, targeting both the underlying myelofibrosis pathology and the anaemia through iron regulation, positions momelotinib as a potentially valuable option for patients with myelofibrosis, particularly those struggling with anaemia.

The Patient Population and Design

Clinical trials investigating momelotinib have typically focused on patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis. These trials have enrolled patients with varying degrees of anaemia, including those who are transfusion-dependent. The inclusion of patients with significant anaemia is a deliberate design choice, reflecting the drug's proposed mechanism of action and its potential to fill an unmet need in this subgroup. Patient characteristics in these studies often reflect the real-world myelofibrosis population, including individuals with advanced disease, prior exposure to other JAK inhibitors, and a high symptom burden. The primary endpoints in these studies have generally included splenic volume reduction, total symptom score improvement, and, importantly for patient outcomes, transfusion independence rates and haemoglobin response. Safety and tolerability profiles, including haematologic and non-haematologic adverse events, are also rigorously assessed.

The Haemoglobin Story

Momelotinib has demonstrated a consistent ability to improve anaemia in patients with myelofibrosis. This is a significant finding, as anaemia is often refractory to other treatments or worsened by them. The drug's impact on transfusion independence is particularly noteworthy. Many patients with myelofibrosis require frequent red blood cell transfusions, which are burdensome and associated with complications. Momelotinib has shown the capacity to reduce or eliminate the need for transfusions in a meaningful proportion of patients. This effect is attributed to its unique mechanism of ACVR1 inhibition, which modulates hepcidin levels and improves iron utilisation for erythropoiesis. The improvements in haemoglobin levels and transfusion independence are often accompanied by a reduction in constitutional symptoms and splenic volume, indicating a broader therapeutic benefit. This dual action on both disease symptoms and anaemia sets momelotinib apart from other available therapies for myelofibrosis. For a deeper dive into how cytopenia guides treatment decisions in myelofibrosis, clinicians might find Myelofibrosis Management: Cytopenia Guides Treatment at EHA 2026 a useful resource.

Beyond Anaemia: Symptom and Spleen Response

While anaemia improvement is a key differentiator for momelotinib, the drug also demonstrates efficacy in addressing other hallmarks of myelofibrosis. Patients receiving momelotinib have shown reductions in spleen volume, a common and often painful manifestation of the disease. This reduction in splenomegaly contributes to an improved quality of life and can alleviate symptoms such as early satiety and abdominal discomfort. The drug has been associated with a decrease in total symptom scores, encompassing constitutional symptoms like fatigue, night sweats, and pruritus. These benefits are consistent with its JAK1/JAK2 inhibitory activity, aligning with the broader class of JAK inhibitors in their

ability to mitigate the inflammatory and proliferative aspects of myelofibrosis. The combined effect on anaemia, spleen size, and constitutional symptoms offers a comprehensive therapeutic profile for patients.

Safety and Tolerability

The safety profile of momelotinib has been generally manageable. Common adverse events include gastrointestinal disturbances, such as diarrhoea and nausea, and some haematologic toxicities, though these are often less pronounced than with other JAK inhibitors, particularly regarding anaemia. Peripheral neuropathy has been observed in some patients, requiring careful monitoring. The overall tolerability allows for sustained treatment, which is essential for managing a chronic disease like myelofibrosis. Clinicians must weigh these potential side effects against the significant benefits, particularly for patients with severe anaemia who have limited treatment options. The Oxford Handbook of Clinical Haematology provides a concise reference for managing such complex haematological conditions and their associated toxicities.

Where it Falls Short

Despite its unique benefits, momelotinib is not without its limitations. The long-term impact on disease progression and overall survival remains an area of ongoing investigation. While it addresses anaemia and symptoms, its ability to modify the underlying disease biology or prevent leukaemic transformation requires further elucidation. The patient population studied, while representative of those with anaemia, may not fully capture the breadth of myelofibrosis presentations, particularly those without significant anaemia or with very early-stage disease. The comparative efficacy against other JAK inhibitors, especially in head-to-head trials, needs more data from a larger patient cohort (n=500) with a 95% confidence interval to definitively establish its place in the treatment algorithm. The cost-effectiveness of this novel therapy will be a critical consideration for healthcare systems and patients alike. The open-label design of some studies is an obvious caveat, introducing potential for bias in subjective endpoints like symptom scores. For insights into how other JAK inhibitors are being combined to improve outcomes, consider reading JAK Inhibitor Combinations Show Efficacy in Myelofibrosis at EHA 2026.

The introduction of momelotinib offers a new dimension to myelofibrosis treatment, particularly for patients whose quality of life is severely impacted by anaemia. Its distinct mechanism of action, targeting both JAK-STAT signalling and hepcidin regulation, provides a tailored approach to a challenging aspect of the disease. The drug's ability to improve transfusion independence and haemoglobin levels, alongside reductions in splenomegaly and constitutional symptoms, presents a compelling case for its use in selected patient populations. But ongoing research is essential to fully understand its long-term impact on disease modification and its optimal integration into the evolving treatment guidelines for myelofibrosis. The question remains whether its unique profile will lead to a broader shift in initial treatment strategies or if it will primarily serve as a valuable option for those failing or intolerant to existing therapies.

> **CLINICAL IMPLICATIONS**
>
> Momelotinib's arrival offers a genuine alternative for myelofibrosis patients, particularly those burdened by anaemia. For too long, clinicians have had to accept that managing splenomegaly and constitutional symptoms might come at the cost of worsening cytopenias, especially anaemia. This drug directly challenges that compromise.

> The ability to improve transfusion independence is not a minor detail; it is a profound improvement in quality of life and a reduction in the logistical and medical complexities associated with frequent transfusions. This makes momelotinib a strong contender for patients who are already transfusion-dependent or those whose anaemia is a primary driver of their symptom burden.
> But the treatment calculus does not entirely change overnight. While momelotinib offers a differentiated approach, its place relative to established JAK inhibitors in the first-line setting for patients without significant anaemia still needs to be defined. Head-to-head comparisons focusing on long-term outcomes beyond anaemia are necessary to guide broader adoption.
> The drug's unique mechanism, particularly its effect on hepcidin, provides a valuable lesson in targeting specific disease pathways. It highlights the importance of understanding the multifactorial nature of myelofibrosis and developing therapies that address distinct, often interconnected, clinical challenges.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Genthon A, Killian M, Mertz P, et al. [Myelofibrosis: A review]. Rev Med Interne. 2021;42(2):101-109. doi:10.1016/j.revmed.2020.08.018
2. 2. Wang F, Qiu T, Wang H, Yang Q. State-of-the-Art Review on Myelofibrosis Therapies. Clin Lymphoma Myeloma Leuk. 2022;22(5):e350-e362. doi:10.1016/j.clml.2021.11.007
3. 3. Vachhani P, Mesa R, Mascarenhas J, et al. JAK inhibitor selection in challenging scenarios of myelofibrosis: a review. Haematologica. 2026;111(4):1179-1197. doi:10.3324/haematol.2025.288654
4. 4. Gagelmann N, Kröger N. Allogeneic Stem Cell Transplant for Myelofibrosis and Myelodysplastic Syndromes: A Contemporary Review. Am J Hematol. 2025;100 Suppl 4(Suppl 4):16-29. doi:10.1002/ajh.27660
5. 5. Reagan WJ. A review of myelofibrosis in dogs. Toxicol Pathol. 1993;21(2):164-9. doi:10.1177/019262339302100208
6. 6. Amel Riazat-Kesh YJR, Maraveyas A, Martin L, Tremblay D. An overlooked mimic? Autoimmune myelofibrosis-A scoping review of the literature. Eur J Haematol. 2023;111(5):706-714. doi:10.1111/ejh.14064

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com