The splendor and the tyranny of JAK inhibition

Elizabeth O. Hexner

Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Correspondence: E.O. Hexner
elizabeth.hexner@pennmedicine.upenn.edu

Received: September 20, 2023.
Accepted: October 2, 2023.
Early view: October 12, 2023.

https://doi.org/10.3324/haematol.2023.283545

If you have ever treated an ill patient with myelofibrosis with a JAK inhibitor and seen them restored, Lazarus-like, to a prior version of themselves, then you know the splendor of JAK inhibitors. Picture a patient debilitated by malaise, wasting, and a massively enlarged and symptomatic spleen; within days a cytokine-mediated fog may clear, and within weeks, measurable changes in weight and spleen size are common. This is the gratifying experience of JAK inhibitors, of which there are now four FDA-approved agents for the treatment of myelofibrosis, with momelotinib as the most recently approved in the United States.[1] Each of these small molecules potently inhibits JAK2, and reduces spleen size and symptoms. They are distinguished from one another by their inhibitory activity against other kinases, and their overall safety/tolerability profile. The enthusiasm around momelotinib is related to a secondary target, ACVR1 (activin A receptor type 1). ACVR1 and its downstream pathways control iron homeostasis, including regulating hepcidin levels, which are markedly elevated in myelofibrosis and in the anemia of chronic inflammation, leading to an iron-restricted anemia. Thus, ACVR1 inhibition with momelotinib can, in some cases, improve anemia in patients with myelofibrosis or may, at a minimum, offset treatment-emergent anemia related to on target JAK2 inhibition of normal erythropoiesis.[2]

The effectiveness, the splendor, of JAK inhibitors is meaningful and may endure for years, though myelofibrosis inexorably progresses unless a patient undergoes allogeneic stem cell transplantation. Unlike small molecules that inhibit other drivers of myeloid diseases (e.g., ABL, FLT3, IDH2), available JAK inhibitors do not yet selectively target the mutant clone, regardless of driver, including *JAK2*V617F. Their benefit is largely thought to be driven by modification of the inflammatory cytokine milieu. Enter the tyranny of JAK inhibitors. The tyranny of JAK inhibitor treatment is not subtle: abrupt cessation can result in a life-threatening cytokine-driven sepsis-like syndrome, including persistent high fevers, respiratory distress, or hemodynamic instability. More commonly, even when the drug is intentionally tapered, severe pain/rapid spleen enlargement, fevers and other symptoms may ensue. Even at stable doses, over time, spleen responses may be lost. Cytopenias may worsen. The fog rolls back in. This rapid return of symptoms has posed challenges in clinical practice and clinical trials. The natural response to a patient progressing on one therapy is to change to another. But even in the setting of clear progression/loss of response, stopping a JAK inhibitor is fraught. In clinical trials, the conventional 'washout' period from a prior JAK inhibitor can render a patient so ill that they are no longer eligible for the study. Combinatorial trials of JAK inhibitors with other therapies are common now: the combinations may make biologic/translational sense, but they have the added feasibility benefit of not requiring cessation of JAK inhibitors.

But how unsafe is transitioning from one JAK inhibitor to another? In this issue,[3] Mesa *et al.* performed a post-hoc analysis of the SIMPLIFY-1 trial,[4] the trial randomizing JAK-inhibitor naïve patients to ruxolitinib *versus* momelotinib for 24 weeks followed by an open label phase where all ruxolitinib patients stopped treatment and crossed over to receive momelotinib, while momelotinib patients continued on it. This study answers an important safety question around transitioning directly and immediately from one JAK inhibitor to another. In this large study of 432 subjects, 197 subjects transitioned from ruxolitinib to momelotinib. Overall, this analysis found that there was a smooth and safe transition without "ruxolitinib discontinuation syndrome", defined as respiratory distress, shock, worsening of cytopenias or return of spleen-related symptoms. In practice, this should offer evidence and reassurance that a direct, immediate transition from ruxolitinib or other JAK inhibitor to momelotinib will be safe.

Disclosures

EOH has received research funding from Blueprint Medicines and Abbvie (for clinical trials); has sat on the Tmunity Therapeutics Advisory Board; and has had a consultancy role for the American Board of Internal Medicine, Blueprint Medicines, Pharmassentia, and Abbvie.

References

1. FDA Roundup: September 19, 2023. 2023. https://www.fda.gov/news-events/press-announcements/fda-roundup-september-19-2023.
2. Oh ST, Talpaz M, Gerds AT, et al. ACVR1/JAK1/JAK2 inhibitor momelotinib reverses transfusion dependency and suppresses hepcidin in myelofibrosis phase 2 trial. Blood Adv. 2020;4(18):4282-4291.
3. Mesa R, Verstovsek S, Platzbecker U, et al. Clinical outcomes of patients with myelofibrosis after immediate transition to momelotinib from ruxolitinib. Haematologica. 2024:109(2):676-681.
4. Mesa RA, Kiladjian JJ, Catalano JV, et al. SIMPLIFY-1: a phase III randomized trial of momelotinib versus ruxolitinib in Janus kinase inhibitor-naive patients with myelofibrosis. J Clin Oncol. 2017;35(34):3844-3850.