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Momelotinib, the Next JAK2 Inhibitor?

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H&O What is momelotinib and how does it work?

LM Momelotinib is a selective inhibitor of Janus kinase 1 (JAK1), JAK2, and activin A receptor type 1 (ACVR1) that has been developed for the treatment of myelofibrosis (MF). It is unique among inhibitors of the JAK/signal transducer and activator of transcription (STAT) pathway because it inhibits ACVR1 as well as JAK1/2. As an activin A receptor inhibitor, momelotinib improves iron metabolism by decreasing hepcidin, which is typically increased in patients with MF owing to chronic inflammation and other factors. Additionally, the unique ability of momelotinib to suppress hepcidin likely contributes to its ability to improve anemia, a common complication in patients with MF that is caused by bone marrow failure, inflammation, extramedullary hematopoiesis, and spleen enlargement. This sets momelotinib apart from all other JAK inhibitors because no other JAK inhibitor has been effective in addressing this problem until now, particularly not to this extent.

H&O What are the benefits of JAK inhibition for patients with MF?

LM MF is driven by a chronically hyperactivated JAK/STAT pathway, which leads to increased inflammation, significant cytokine dysregulation with pro-inflammatory and pro-cytokine states, and extramedullary hematopoiesis.

The first JAK inhibitor to be approved for use in MF was ruxolitinib (Jakafi, Incyte). This was followed by the approval of 2 other JAK inhibitors for patients with MF, fedratinib (Inrebic, Bristol Myers Squibb) and pacritinib (Vonjo, CTI BioPharma). Pilot data and early studies of ruxolitinib demonstrated how JAK inhibitors improved patient outcomes by significantly decreasing cytokines and reversing inflammation. Therefore, JAK inhibitors play a crucial role for patients with MF. They work regardless of the presence of the *JAK* V617F mutation by inhibiting hyperactivation of the JAK/STAT pathway.

H&O How does momelotinib compare with the other JAK2 inhibitors that are being evaluated for patients with MF?

LM Momelotinib is unique in that it inhibits ACVR1. It also has the ability to improve anemia, whereas ruxolitinib actually worsens anemia, especially in the first 6 months of its use. Worsening of anemia has also been shown with other JAK inhibitors, including fedratinib. Pacritinib, which has been approved for patients with severe thrombocytopenias, has been shown to improve anemia, but to a lesser degree than momelotinib.

In a presentation by Oh at the American Society of Hematology (ASH) 2022 annual meeting, pacritinib showed higher potency for ACVR1 inhibition compared with momelotinib, fedratinib, and ruxolitinib, so in theory it should better address anemia. However, we need to follow clinical data, which make it difficult to compare multiple drugs against each other given the different patient populations and eligibility criteria. But perhaps

there is a combined benefit beyond momelotinib's unique action regarding anemia. The important point here is that momelotinib is not just an anemia drug, it is also a very effective JAK inhibitor that improves patient symptoms and spleen enlargement. I see an important role for this agent in MF.

H&O Could you describe the phase 3 MOMENTUM study of momelotinib in patients with MF who were previously treated with a JAK inhibitor?

LM The phase 3 MOMENTUM study was a randomized, double-blind trial that was published in *The Lancet*. It was conducted during the COVID pandemic in patients with advanced-phase MF previously exposed to ruxolitinib who had persistent spleen enlargement, MF symptoms, and anemia. The trial was designed to compare momelotinib with danazol, an androgenic steroid that historically has been used and is endorsed by the National Comprehensive Cancer Network (NCCN) Guidelines for anemia in these patients, and it might induce an anemia response in about one-third of patients.

The study randomized 195 patients with primary MF, post–polycythemia vera, or post–essential thrombocythemia MF in a 2:1 ratio, with 130 receiving momelotinib (200 mg orally once per day) and 65 receiving danazol (300 mg orally twice per day) for 24 weeks. The median age of the patients was approximately 71 years old, and 63% were male. All patients had disease that had failed to respond to ruxolitinib, with a median duration of about 2.6 years. Approximately 5% of patients were exposed to fedratinib. More than 50% of the patients were transfusion-dependent. The major eligibility criteria required patients to have anemia with hemoglobin levels below 10 g/dL, persistent spleen enlargement, or MF symptoms measurable by standard criteria, and exposure to ruxolitinib either by 3 months, or by at least 28 days with the development of complications, such as significant transfusion dependency, anemia, other cytopenias, or hematoma. Additionally, there was a platelet count cutoff of greater than 25,000/μL. Notably, unlike other studies that previously evaluated momelotinib, the MOMENTUM study required a washout period for ruxolitinib. Patients who had been on previous ruxolitinib had to taper down the agent with 2 weeks of washout prior to enrollment.

The primary endpoint of the MOMENTUM study was an improvement in MF symptoms assessed by the standard total symptom score (TSS; Myelofibrosis Symptom Assessment Form) for MF patients, with a goal of 50% improvement at week 24. This was achieved with superiority by momelotinib. Specifically, responses were observed in 25% of patients taking momelotinib vs only 9% for danazol (P <0.05). The key secondary endpoints were improvement in spleen volume (defined as a reduction of at least 35%) and anemia responses.

The improvements in spleen volume reduction were also superior by momelotinib, noticed in 23% of patients with momelotinib vs 3% with danazol (P <0.05). Additional analysis focused on 25% reduction in spleen volume was also clinically significant and was achieved even more frequently with momelotinib than with danazol, at 40% vs 6%, respectively.

Regarding anemia responses, there were improvements in the momelotinib group for all anemia endpoints, including transfusion independence rate from baseline to week 24, duration of no transfusion until week 24, and increase in hemoglobin level by at least 2 g/dL for patients who were not transfusion-dependent. Specifically, transfusion independence occurred in 31% of patients on momelotinib vs 20% of those on danazol. Among patients who were transfusion–independent at baseline, 41% in the momelotinib group and 30% in the danazol group had improvements of 2 g/dL of hemoglobin or more. The rate of zero transfusions at week 24 since baseline was in 35.4% vs 16.9% of patients on momelotinib vs danazol, respectively. Overall, the MOMENTUM study results suggest that momelotinib represents a promising option for this patient population. The important thing about this agent is it can be tolerated at the recommended 200-mg daily dose, irrespective of organ function and blood counts, without the need for dose reduction, unlike ruxolitinib or other JAK inhibitors.

H&O What are the safety considerations and toxicities of momelotinib for patients with MF?

LM Momelotinib has a very favorable safety profile. Notably, concerns regarding peripheral neuropathy that were seen in previous studies with momelotinib were not reported in the MOMENTUM trial.

In terms of toxicity, the MOMENTUM study showed mostly gastrointestinal adverse events, including grade 1 or 2 nausea and diarrhea, which were noticed in up to 22% of patients. There were limited grade 3 adverse events—about 2% to 3% were related to infections—which could be also attributed to the study being conducted during the COVID pandemic. There were no reports of peripheral neuropathy. In fact, more grade 3 adverse events were observed in the danazol group, which highlights the safety of momelotinib.

H&O What other studies have looked into the use of momelotinib in MF, and what were the results?

LM Prior to the MOMENTUM study, there were several studies conducted on the development of the agent, including phase 1 and 2 dose-finding studies. There were also two randomized phase 3 studies, SIMPLIFY 1 and SIMPLIFY 2, which did not meet their endpoints and halted momelotinib's development until the MOMENTUM study was designed. However, these studies led to the understanding of this agent having the potential to enhance this field by improving transfusion independence and anemia responses.

SIMPLIFY 1 was a randomized phase 3 study that was the first head-to-head comparison between momelotinib and ruxolitinib, the only approved JAK inhibitor at the time, in 432 newly diagnosed JAK2 inhibitor–naive patients with MF and platelet counts greater than 50,000/μL. It had a noninferiority design for momelotinib, both for spleen volume reduction and TSS improvements, compared with ruxolitinib. Although momelotinib showed noninferiority to spleen volume reduction greater than or equal to 35% at week 24—26.5% and 29% for momelotinib and ruxolitinib, respectively—it did not improve symptoms. The rate of reduction in TSS of at least 50% was superior with ruxolitinib than with momelotinib, at 42.2% vs 28.4%, respectively, failing to meet the key endpoint.

The phase 3, open-label SIMPLIFY 2 study used a similar population to MOMENTUM, focusing on refractory patients who had been previously treated with ruxolitinib for at least 28 days. A total of 156 patients were randomized 2:1 to either momelotinib (n=104) or what was considered the best available therapy, which included ruxolitinib (n=52). Although the rate of spleen volume reduction of at least 35% was very low, at 7% for the momelotinib group and 6% for the best-available therapy group, it is important to note that washout was not allowed. Superiority of the agent was not shown in this trial. The TSS was also similar between the groups.

However, both SIMPLIFY studies show that transfusion independence was significantly higher with momelotinib, with more than 60% of patients experiencing it in SIMPLIFY 1 and more than 50% in SIMPLIFY 2. These results led to the continued development of momelotinib, particularly for this predefined population.

H&O Were there any other studies besides SIMPLIFY 1 and 2 that investigated momelotinib?

LM There were dose-defining phase 1 and 2 studies that helped determine the optimal dosage of 200 mg daily of momelotinib. But those aforementioned phase 3 studies were the most important for our understanding of the clinical use of the agent.

H&O Where are we going next with momelotinib?

LM I hope that it will be approved. That would be a significant milestone for us. We would also love to see the agent explored in a combination setting, given that it does not cause anemia. I think it would have a very significant and strong role for patients who experience anemia or for those who are older and have a low threshold for anemia development in the frontline setting, and who would not tolerate transfusion burden or high doses of ruxolitinib or fedratinib.

We have also seen subgroup analysis data presented by Dr Ruben Mesa and colleagues regarding patients who have thrombocytopenias and were enrolled in the MOMENTUM study. Patients with platelet counts less than 50,000/μL also had responses comparable to those that I just described for the entire MOMENTUM study. That is really exciting, as we currently have only pacritinib for patients with platelet counts less than 50,000/μL. Therefore, it is warranted to clinically explore momelotinib and its safety in this population of patients.

Additionally, combination approaches would be interesting, maybe even taking the agent into more advanced disease in combination with an effective agent, as anemia is a significant problem.

Disclosures

Dr Masarova has no relevant disclosures.

Suggested Reading

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