Updates on JAK inhibitors in Myelofibrosis

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What are some interesting updates on Janus kinase (JAK) inhibitors in myelofibrosis (MF)?

Dr. Oh: JAK inhibitors represent a pivotal drug class for MF, but there are still many unanswered questions regarding their optimal use. Fortunately, recently published trials are helping to clarify their role in treating this disease.

Bone marrow fibrosis in JAK inhibitor-treated patients

For example, increasing bone marrow fibrosis (BMF) has been associated with poor prognosis in MF, and there has been some evidence linking emerging agents such as JAK inhibitors with a potential indication of disease modification as it relates to changes or improvement in BMF.[1-4] However, until recently, there has been limited data confirming this relationship.

We now have a better understanding of the impact of BMF on outcomes among JAK inhibitor-treated MF patients due to new data published by myself and my colleagues.[5] In this study, we analyzed fibrosis changes in patients from the SIMPLIFY-1 study to understand whether any changes in BMF were correlated with clinical outcomes. As a reminder, this study included over 400 JAK inhibitor-naïve patients who went on to receive treatment with either momelotinib or ruxolitinib. Fifty-eight percent of both momelotinib and ruxolitinib patients had grade 3 BMF at baseline, and in both treatment arms, approximately 21-22% of patients demonstrated at least a grade-one improvement in BMF over the course of the study. Additionally, 85% and 81.2% of the momelotinib and ruxolitinib patient populations, respectively, had stable or improved BMF over the 24-week period.

We found virtually no association between BMF change and symptom response, spleen response, or transfusion independence in either the momelotinib- or ruxolitinib-treated patients. There was also no clear association between BMF changes and overall survival (OS) in either group.

"Given the lack of association of BMF with OS, these findings indicate the need to better understand BMF changes by week 24 as a surrogate for clinical benefit and disease modification."

Effect of pacritinib on anemia and thrombocytopenia in MF

A second interesting study involved a closer look at the mechanism of action of pacritinib - specifically, its inhibition of ACVR1 – and the potential benefits conferred in terms of anemia in MF patients. Pacritinib is currently approved for patients with cytopenic myelofibrosis (platelet count <50x10^9/L). This approval was based on the PERSIST-2 trial, which determined that pacritinib was more effective than best available therapy (BAT) for 35% or more spleen volume reduction (SVR35, 18% versus 3%), 50% or more reduction in TSS (25% versus 14%).[6] The PERSIST-2 trial also indicated that pacritinib had a favorable effect on anemia. Clinical improvement in hemoglobin and reduction in transfusion requirements were more frequent in pacritinib-treated patients, particularly in the twice-daily dosing arm. Twenty-five percent of patients taking pacritinib with baseline hemoglobin <10 g/dL experienced an increase of 2 or more g/dL or achieved RBC transfusion independence for 8 or more weeks, compared to 12% in the BAT arm. While significant, this potential hemoglobin-modifying benefit has not been fully explored and the mechanism supporting anemia improvement has not been described.

To better understand the mechanism of action and effects of pacritinib on anemia in MF, my colleagues and I recently designed a study to 1) assess the *in vitro* potency of pacritinib against ACVR1 and its ability to reduce hepcidin, and 2) describe the impact of pacritinib on red blood cell (RBC) transfusion independence in the phase 3 PERSIST-2 study.[7] Utilizing *in vitro* kinase assays, pacritinib was found to be highly potent against ACVR1.

"Pacritinib was found to be four times more potent than momelotinib, which had previously been shown to have activity against ACVR1. This was a distinct difference from the other JAK inhibitors evaluated, including fedratinib, which had very weak activity against ACVR1, and ruxolitinib, which essentially had no activity against ACVR1."

Furthermore, at this concentration, pacritinib was shown to exceed ACVR1 IC_{50} (ie, half maximal inhibitory concentration) 100% of the time at all doses, while the momelotinib concentration exceeded ACVR1 IC_{50} only 55% of the time.

This analysis also confirmed the relationship between ACVR1 and hemoglobin. Pacritinib therapy was observed to decrease hepcidin expression in liver cells *in vitro* via interruption of downstream SMAD signaling. To verify the clinical effect of this mechanism of action,

researchers evaluated the transfusion status of patients in the PERSIST-2 trial at baseline and through week 24 of pacritinib treatment 200 mg BID or 400 mg QD or best available therapy (BAT). At endpoint, 37% of patients in the pacritinib 200 mg BID treatment arm converted to transfusion independence compared with 7% in the BAT arm, despite the fact that individuals in the BAT treatment arm were allowed to receive erythroid support agents. Similarly, a greater proportion of pacritinib-treated patients (49%) had at least a 50% reduction in transfusion burden compared with BAT patients (9%).

In all, this study suggests that pacritinib may confer a significant anemia benefit in patients with MF through its sustained inhibition of ACVR1 activity. Given the fact that pacritinib also targets JAK2 and IRAK1, it is possible that this combination of targets may perpetuate inhibition of inflammatory cytokine production and reduction in hepcidin production, leading to amelioration of anemia in patients with MF.

To further clarify the role and impact of pacritinib in anemic and thrombocytopenic patients, an alternate study assessed the dosing and efficacy of pacritinib by degree of baseline thrombocytopenia and anemia in MF patients in the PERSIST-1 and PERSIST-2 trials.[8] In this study, patients were stratified according to baseline thrombocytopenia and anemia, and depth of spleen volume response, total symptom score, Patient Global Impression of Change (PGIC), and dose intensity were also evaluated. At endpoint, pacritinib was found to have consistent efficacy regardless of the baseline blood count, and all patients were able to continue pacritinib at 100% dose intensity throughout the evaluation period. Twenty-one percent to 28% of patients in the overall population achieved SVR35 and 84% to 93% experienced any reduction in spleen volume. In all, the vast majority (80% or more) of individuals in all cytopenia groups reported improvement in disease symptoms as assessed by total symptom score of PGIC response. These findings provide further support that pacritinib can be administered at full dose regardless of baseline anemia and thrombocytopenia.

Utility of SVR as a surrogate for disease response

One benefit of JAK inhibitors is their effect on spleen volume, which is considered a surrogate marker for disease response. In the PERSIST-2 trial, pacritinib demonstrated a SVR benefit compared with BAT; researchers have now presented a landmark analysis of the relationship between SVR and OS in the PERSIST-2 trial.[9] In this study, they determined that any SVR at 12 weeks was significantly associated with improved survival among pacritinib-treated patients. Notably, SVR 10% or higher demonstrated the greatest separation in OS curves between pacritinib-responders and non-responders. In contrast, SVR did not predict OS benefit in the BAT arm. Eleven percent of patients in the BAT treatment group who achieved SVR of 10% or more died, compared to 14% of non-responders to BAT.

"Because pacritinib can be administered at full dose regardless of platelet count, this study suggests that this therapy may offer a select survival advantage for MF patients with moderate-to-severe thrombocytopenia who achieve spleen reduction."

Comparative analyses involving momelotinib

As discussed, momelotinib inhibits both JAK1 and JAK2 as well as ACVR1 to address MF symptoms, splenomegaly, and anemia. A recent indirect treatment comparison sought to assess the safety outcomes between momelotinib and fedratinib, an alternate JAK inhibitor, in both JAK inhibitor-naïve and -experienced MF patients.[10] This study found that the risk of any Grade 3 or higher anemia, diarrhea, nausea, and serious adverse event (AE) leading to dose reduction was significantly less likely in momelotinib-treated patients compared with fedratinib patients in both naïve and experience groups. Additionally, the risk for any Grade 3 or greater thrombocytopenia was lower among momelotinib-treated patients than fedratinib-treated patients in the JAK inhibitor-naïve group only. While this study demonstrated a favorable safety profile of momelotinib over fedratinib, it is important to stress that nonrandomized groups were compared, and the results may be biased due to unmeasured or residual confounders.

There have also been some important updates to the MOMENTUM phase 3 study of momelotinib versus danazol in patients with MF previously treated with a JAK inhibitor.[11]

"The MOMENTUM study is an ongoing phase 3 study of momelotinib versus danazol in symptomatic anemia or anemic JAK-inhibitor experienced patients. Updated topline results at 24 weeks have confirmed that all key primary and secondary points have been met."

The MFSAF TSS response rate was 24.6% in the momelotinib group versus 9.2% in the danazol group, and the transfusion independence response rates were 30.8% versus 20.0%, respectively, achieving non-inferiority. Additionally, spleen volume response was 23.1% for momelotinib versus 3.1% for danazol. This efficacy was maintained in patients with thrombocytopenia, consistent with the overall intention to treat patient population. Overall favorable safety and trend towards improved overall survival were reported. Together these findings support potential future use of momelotinib as an effective agent for MF patients, in particular those with anemia.

To view the associated accredited activity please **click here**.

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