BRIEF REPORT

Serious Adverse Events During Ruxolitinib Treatment Discontinuation in Patients With Myelofibrosis

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Ruxolitinib (INCB018424) is a JAK1 and JAK2 inhibitor recently evaluated for the treatment of myelofibrosis (MF) in early- and advanced-phase clinical trials. In 2 recent communications that focused on short-term and long-term ruxolitinib treatment outcome, respectively, the drug was shown to be effective in controlling constitutional symptoms and splenomegaly but was also associated with important adverse effects, including moderate to severe thrombocytopenia and anemia. The most recent of the 2 communications focused on 51 Mayo Clinic patients who participated in the original phase 1/2 ruxolitinib clinical trial and highlighted a high treatment discontinuation rate (92% after a median time of 9.2 months), primarily for loss of treatment benefit but also because of drug-associated adverse effects. The report also discussed the occurrence of sometimes severe withdrawal symptoms during ruxolitinib treatment discontinuation. This "ruxolitinib withdrawal syndrome" was characterized by acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias, and occasional hemodynamic decompensation, including a septic shocklike syndrome. In the current sponsor-independent analysis, we describe the details of these events in 5 severely affected cases (11%) among 47 Mayo Clinic patients with MF in whom ruxolitinib therapy had been discontinued. Our experience calls for full disclosure of the ruxolitinib withdrawal syndrome to patients with MF before initiating ruxolitinib therapy, and treatment discontinuation must be done under close physician supervision and preferably in a tapering schedule.

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DLT = dose-limiting toxicity; ET = essential thrombocythemia; MF = myelofibrosis; MPN = myeloproliferative neoplasm; MTD = maximum tolerated dose; PMF = primary MF; PV = polycythemia vera

Myelofibrosis (MF) includes primary MF (PMF), post-polycythemia vera (post-PV) MF, and post-essential thrombocythemia (post-ET) MF.[1] Currently, PMF, PV, and ET are classified as myeloproliferative neoplasms (MPNs) and are characterized by stem cell–derived clonal myeloproliferation.[2] Clinical features of MF (eg, anemia, hepatosplenomegaly, leukocytosis, thrombocytosis, constitutional symptoms, and cachexia) are the result of both the underlying abnormal myeloproliferation and a reactive, cytokine-driven inflammatory state.[3,4] Current drug therapy for MF is neither curative nor adequately palliative.[5] Myelofibrosis-associated anemia is managed with transfusions or drugs such as recombinant erythropoietin, androgens, and thalidomide. Myelofibrosis-associated splenomegaly is difficult to treat with currently available drugs such as hydroxyurea, and many patients ultimately undergo splenectomy or involved field radiotherapy. Allogeneic stem cell transplantation has been used, often during advanced-stage disease, and is associated with substantial mortality and morbidity. Therefore, there is an unmet need for treatment in MF.[5]

The recent discovery of a *JAK2* mutation (*JAK2*V617F) in most patients with MF, PV, or ET has raised the prospect of molecularly targeted therapy.[6] However, unlike the case with *BCR-ABL1* and chronic myelogenous leukemia, *JAK2*V617F is not the only mutation in MF; other described mutations in MF involve *MPL, LNK, TET2, ASXL1, CBL*, *IDH1*, *IDH2*, *IKZF1, EZH2, DNMT3A*, and *TP53*.[7] At present, it is not clear if the functional consequences of these MPN-associated mutations, including *JAK2*V617F, contribute to disease initiation or disease progression. Nevertheless, because JAK-STAT–relevant mutations occur in the vast majority of MF patients,[6] result in constitutive JAK-STAT activation,[6,8] and induce MPN-like disease in mice,[6,8] it was reasonable to investigate the therapeutic potential of JAK inhibitors, such as ATP-mimetic small molecule kinase inhibitors.[9,10]

RUXOLITINIB

Ruxolitinib (INCB018424) is an ATP mimetic JAK1 and JAK2 inhibitor.[9] In healthy volunteers, the drug, given in single oral 25-mg doses, was rapidly absorbed with mean time to reach maximal drug concentration of less than 1 hour and mean half-life of 2 to 6 hours.[11] The drug is metabolized by CYP3A4.[12] Ruxolitinib was the first JAK inhibitor to be evaluated in patients with MF and has already

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undergone phase 1, 2, and 3 studies. The first phase 1/2 MF study using ruxolitinib was conducted at the MD Anderson Cancer Center and Mayo Clinic.[9] A total of 153 patients, including 51 from Mayo Clinic, participated in that clinical trial. Thrombocytopenia was identified as the dose-limiting toxicity (DLT), and the maximum tolerated dose (MTD) was established at 25 mg twice daily and 100 mg once daily.

After a median follow-up of approximately 15 months, ruxolitinib treatment responses included reduction in spleen size (44% response rate), alleviation of constitutional symptoms, and reversal of cachexia.[9] These drug effects were recently confirmed in two phase 3 studies,[13,14] although objectively measured spleen response rates in 1 of the 2 studies were substantially lower (29%) and lasted for a median of approximately 11 months.[13] The presence or absence of a *JAK2* mutation did not influence response, and the drug did not affect either *JAK2* mutation burden or bone marrow fibrosis.[9] The drug was not as effective in improving anemia (14% response rate in transfusion-dependent patients), whereas modest activity was noted in controlling leukocytosis and thrombocytosis. Response in constitutional symptoms was accompanied by a drug-induced reduction in inflammatory cytokines, including interleukin 6 and tumor necrosis factor α.[9]

Reported adverse effects of ruxolitinib therapy at the recommended dosage (25 or 10 mg twice a day) for patients with MF included grade 3/4 thrombocytopenia (39% rate) and anemia in previously nontransfused patients (43% rate).[9] These observations were similar to those seen in the recently completed phase 3 randomized studies of ruxolitinib (COMFORT [Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment] trials) compared to either placebo or best supportive care[13,14]; the incidence of treatment-induced anemia with ruxolitinib was 31%/40.4% vs 13.9%/12.3% in the placebo/best supportive care groups; the corresponding figures for thrombocytopenia were 34.2%/44.5% for ruxolitinib vs 9.3%/9.6% for placebo/best supportive care.

The current report focuses on what became apparent during treatment discontinuation among the 51 patients from Mayo Clinic who participated in the first ruxolitinib clinical trial in MF.[9] The long-term ruxolitinib treatment outcome of these 51 patients has recently been communicated.[15] These patients were enrolled between October 2007 and February 2009, and their follow-up information was updated in July 2011. To date, treatment has been discontinued in 47 patients (92%). The median time that these patients received ruxolitinib treatment was 9.2 months (range, 1.3-42 months). The treatment discontinuation rates at 1, 2, and 3 years were 51%, 72%, and 89%, respectively.[15] Reasons for treatment discontinuations included loss or lack of response/disease progression (~34%), toxicity with or without lack of response/disease progression (~34%), patient/physician choice often associated with lack of response (~13%), and death during study (~4%). Most patients experienced acute relapse of their symptoms and splenomegaly during treatment discontinuation, and these events were serious enough to require hospitalization after emergency department visits in at least 5 patients (11%), as described subsequently.

Patient 1

A 59-year-old woman with a diagnosis of post-PV MF (*JAK2*V617F-positive) accompanied by severe pruritus and fatigue was enrolled in the study in February 2008 (dosage, 50 mg/d). She was red cell transfusion–independent at study entry. She experienced relief of her pruritus within 5 days of treatment. After 2 cycles of treatment (1 cycle = 4 weeks), the dosage was reduced by half because of headaches and thrombocytopenia associated with easy bruisability. Subsequently, the patient tolerated the drug reasonably well until November 2010, when she experienced progressive splenomegaly and increasing fatigue. Her symptoms worsened during the subsequent 3 months along with emergence of leukocytosis and anemia. Accordingly, she was taken off protocol treatment in February 2011 with a dose-tapering schedule to minimize the risk of developing cytokine-rebound phenomena. Prednisone was also started. Nevertheless, despite the gradual drug discontinuation process, the patient's condition acutely deteriorated and required emergency department evaluation and hospitalization because of respiratory distress, severe anemia that required red cell transfusions, and marked symptomatic splenomegaly. The acute deterioration of symptoms subsided during the subsequent few days, and the patient was able to be enrolled into another JAK inhibitor trial after 1 month of discontinuing treatment with ruxolitinib.

Patient 2

A 69-year-old woman with a diagnosis of post-PV MF (*JAK2*V617F-positive) and stable pulmonary hypertension started receiving ruxolitinib therapy (25 mg twice daily) in March 2008, with the goal of improving her symptomatic splenomegaly, night sweats, fever, and fatigue. Medical history included transient ischemic attack and deep venous thrombosis. Constitutional symptoms improved within a few days of starting treatment with ruxolitinib. During the third week of treatment, mild anemia and renal insufficiency (creatinine value increased from 0.9-1.3 mg/dL) were noted, and the dosage of the drug was decreased by half. After 1 month of starting protocol treatment, the patient was seen in the emergency department and later admitted to the hospital because of supratherapeutic prothrombin time and back pain from compression fractures. The drug was withheld because of potential contribution to the aforementioned events.

Within 24 hours of drug discontinuation, the patient developed a septic shocklike syndrome with severe hypoxia with marked A-a gradient, hypotension, fever, and confusion. She required pressor support and intubation; broad-spectrum antibiotics were initiated empirically. A working diagnosis of systemic inflammatory response syndrome, related to cytokine rebound from ruxolitinib treatment discontinuation, was made, and permission was granted from the sponsor of the clinical trial to restart treatment with ruxolitinib along with systemic corticosteroids. The patient experienced immediate (within 24 hours) improvement and was successfully extubated shortly thereafter. In the following 2 weeks, the patient developed neutropenia and circulating lymphoma cells, and bone marrow examination revealed Burkitt-like large B cell lymphoma with complex cytogenetic abnormalities, including t(8;22)(q24.1;q11.2), t(14;18)(q32;q21), add(3)(q26), +der(1;5), del(6)(q21q25), and add(11)(q23). Of note, bone marrow biopsy performed 7 weeks earlier, at the start of protocol treatment, did not show any evidence of lymphoma, and cytogenetic studies were completely normal. Despite initial response to lymphoma treatment, the patient died in February 2009 due to her comorbidities.

Patient 3

A 44-year-old man with a diagnosis of post-PV MF (*JAK2*V617F-positive) accompanied by marked symptomatic splenomegaly, profound weight loss, intractable cough, and fatigue started receiving ruxolitinib therapy in October 2008 (15 mg twice daily). Constitutional symptoms improved markedly during the first 2 weeks of treatment. Two months after initiation of the drug, the patient experienced progressive anemia that required transfusions (patient was transfusion-independent at study entry), increasing splenomegaly, and relapse of constitutional symptoms. The dosage of the drug was increased to 20 mg twice daily; even though the patient had some initial response, his symptoms continued to persist, and he requested to be removed from the study protocol in February 2009. One day after his last tapering dose, the patient developed respiratory distress associated with pleural effusion and pericardial effusion and was hospitalized. A working diagnosis of systemic inflammatory response syndrome was made; the patient was intubated, and pressors and broad-spectrum antibiotics were initiated. Considering the possibility of cytokine-rebound phenomenon as the underlying cause of his complication, ruxolitinib was restarted at 10 mg twice daily along with systemic corticosteroids. This led to dramatic and prompt improvement and extubation in a few days. However, the patient's problem with pleural effusion and pulmonary edema persisted and led to reintubation, followed shortly thereafter with successful extubation. During this period, the patient had developed anemia that required transfusions and renal insufficiency that necessitated dialysis. In addition, his progressive underlying MF required introduction of additional cytoreductive drugs, including hydroxyurea and cladribine. Other complications during the same episode included a large hematoma. Because of recurrent pleural effusion, the patient was also treated with involved field radiation. In June 2009, a second round of carefully orchestrated tapering of ruxolitinib was carried out without incident. The patient was later enrolled in another JAK inhibitor trial.

Patient 4

A 64-year-old man with PMF (*JAK2*V617F) accompanied by severe fatigue, pruritus, drenching night sweats, and symptomatic splenomegaly started receiving ruxolitinib therapy in November 2007 (25 mg twice daily). Marked improvement in his symptoms and reduction of spleen size were noted within 1 week of treatment. After 1 cycle of treatment, the patient's hemoglobin value decreased from 10.1 g/dL at baseline to 8.3 g/dL and his platelet count from 183×10^9/L to 83×10^9/L. By March 2008, his platelet count had dropped to 47×10^9/L, and the drug was withheld according to protocol requirement. Within 3 days of drug discontinuation, the patient experienced full relapse of his symptoms and developed high spiking temperatures that necessitated short-term hospitalization. He was readmitted to the hospital with similar complaints; extensive work-up did not reveal any infection, but the patient was empirically treated with broad-spectrum antibiotics and platelet transfusions for worsening thrombocytopenia. After his platelet count recovered to greater than 100×10^9/L, ruxolitinib therapy was restarted at a reduced dosage of 25 mg/d. Because of inadequate treatment response, the dose was changed to 10 mg twice daily. However, the severe pruritus persisted; by October 2009, the patient had recurrence of splenomegaly, but he continued use of the drug for an additional 3 months because of some improvement in constitutional symptoms. By January 2010, the patient experienced full relapse of his symptoms and splenomegaly and hence decided to discontinue the study drug. Despite a tapering dose schedule, the patient experienced acute deterioration of symptoms and enlargement of his spleen within 3 to 5 days of his last dose of ruxolitinib. The situation progressed to a splenic infarct and hospitalization for pain control. The patient later started receiving another JAK inhibitor with marked improvement of his symptoms and some decrease in splenomegaly.

Patient 5

A 56-year-old woman with a diagnosis of post-PV MF (*JAK2*V617F-positive) and associated symptoms of fa-

tigue and symptomatic splenomegaly started receiving ruxolitinib therapy in November 2007 (25 mg twice daily). A week later, she reported marked improvement of symptoms. By May 2008, the platelet count had dropped to 64×10^9/L, which necessitated dose reduction (10 mg twice daily). In August 2008, the patient experienced relapse of her symptoms, and the drug dosage was increased to 15 mg twice daily. In February 2010, the patient developed pneumothorax that required pleurodesis. Of note, she had had pneumothorax 4 years ago, before introduction of study medication. In May 2011, the patient experienced relapse of her symptoms and progressive splenomegaly while still taking ruxolitinib therapy, and she also developed a new extramedullary hematopoiesis tumor revealed as a posterior mediastinal and subpleural mass. The combined presence of disease relapse and persistent thrombocytopenia (platelet count, 54×10^9/L) led to the patient discontinuing the study drug under close supervision and with a tapering schedule in June 2011. Within 2 weeks of discontinuing the drug, the patient developed a "disseminated intravascular coagulation" like syndrome with digital artery thrombosis and shortly thereafter severe polyarticular arthritis. Treatment with tissue plasminogen activator infusion, splenic irradiation, and systemic corticosteroids alleviated her symptoms.

DISCUSSION

Our experience with ruxolitinib therapy for patients with MF suggests a remarkable and prompt activity in alleviating constitutional symptoms such as night sweats, pruritus, fatigue, and cachexia.[9] The effect on splenomegaly was also notable. However, these benefits come with tradeoffs, including drug-induced anemia, thrombocytopenia, and, as we have described in the current report, potentially catastrophic adverse events during drug discontinuation. We speculate that the underlying mechanism for "ruxolitinib discontinuation syndrome" involves rapid changes in inflammatory cytokine activity. Such challenges do not necessarily undermine the benefit of ruxolitinib therapy in a select group of patients with advanced MF. Such patients include those with severe constitutional symptoms, profound cachexia, and symptomatic splenomegaly. On the other hand, the drug can potentially exacerbate matters in other patients by causing anemia or thrombocytopenia. Furthermore, the observations from the current report underscore the need for complete disclosure to patients that they might have a difficult time with discontinuation of the drug. Patients should also be alerted about the need for gradual tapering of the drug under close physician supervision.

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