Reactivation of a Common Infection Following Treatment with a Novel Agent for an Uncommon Disease - Ruxolitinib Associated Tuberculosis: Two Cases

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Abstract
Ruxolitinib, a JAK 1 and 2 inhibitor is the targeted therapy for myelofibrosis, which is a myeloproliferative neoplasm causing bone marrow fibrosis. The drug produces a rapid improvement in the myelofibrosis associated spleenomegaly and an overall improvement in MF associated symptoms. Ruxolitinib has been rarely known to cause tuberculosis. Very few case reports are available depicting opportunistic infections associated with the drug. We report 2 cases of patients who developed tuberculosis while on treatment with ruxolitinib.

Keywords: ruxolitinib, immunosuppression, tuberculosis

INTRODUCTION
Myelofibrosis (MF), is a myeloproliferative neoplasm, typified by progressive fibrosis of bone marrow and inefficient hematopoiesis. Clinical hallmarks include anemia, splenomegaly, and enfeebling symptoms being bone pain, fatigue, fever, night sweats, pruritus, and weight loss[1,2,3]. Treatment with ruxolitinib which is a dual JAK1/2 inhibitor represents the sole approved targeted therapy for reducing spleenomegaly and systemic symptoms of myelofibrosis. It may also have favourable effect on survival[4].

The main mode of action of ruxolitinib is by the down-regulation of pro-inflammatory cytokines that perform a cardinal role in MF induction and advancement[5]. Its major cellular and systemic effects are inhibition of proliferation, induction of apoptosis and reduction in plasma levels of cytokine, all of which are mediated by the inhibition of JAKs’ ability to phosphorylate STAT by the drug.

However, the disruption of JAK-STAT signaling also affects immune homeostasis. Notably, the anti-inflammatory activity of ruxolitinib is likely to impair the maturation and function of dendritic and T cells, culminating in attenuated control of silent infections and overall increased risk of infection[6].

Ruxolitinib is initiated at a dose of 20 mg given orally twice a day in patients with platelet count above 200 X 10^9/L, and 15 mg twice a day for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L. Common ADRs of this drug include dizziness, headache, fatigue, bruise, increased serum cholesterol, increased AST and ALT, diarrhoea, and thrombocytopenia. Ruxolitinib has been known to cause tuberculosis at a frequency less than 1 %.

CASE DESCRIPTION
Here, we report 2 cases of MF who developed TB while on ruxolitinib treatment.

The first case was a 67 year old gentleman, presented with transfusion dependent anemia of 2 months duration and a massive spleenomegaly. A peripheral blood smear and a bone marrow study confirmed the diagnosis of primary myelofibrosis. The karyotype was normal. Molecular evaluation(JAK mutation, CAL-R, cMPL) was not done as it was not covered by insurance and patient could not afford the tests from his pocket. DIPSS was intermediate 2 risk status with a score of 3. His platelet count was 374 k/uL, WBC – 4.6 x 10 k/uL, Hb – 10.5 g/dL(after PRBC transfusions). He was initiated on ruxolitinib 20 mg twice daily in view of DIPSS advanced risk status and symptomatic spleenomegaly. He had an excellent response to ruxolitinib with spleen size decreasing to more than 30 % by week 10 as measured by ultrasound. 12 weeks after starting ruxolitinib, the patient presented with complaints of high grade fever associated with chills, generalized weakness and tiredness. Chest X-ray confirmed clinical findings of a moderate right sided pleural effusion for which pleural fluid tapping was done. Pleural fluid culture, AFB smear, cytology, cultures sent were negative. Mantoux test was done which was also negative. He was treated with antimicrobials and he improved. He was continued on ruxolitinib and maintained the excellent response. At 10 months of therapy he was again presented with fever and generalised tiredness of 2 weeks duration. A chest radiograph revealed pulmonary infiltrates in bilateral lung areas. CT scan of chest revealed multiple cavitatory randomly distributed nodules, bilaterally evident miliary motting, right mild pleural effusion and prominent mediastinal nodes suggestive of tuberculosis. Bronchoscopy, BAL Cytology, Smear for AFB was carried out. BAL Cytology revealed AFB. Gene Xpert was positive for AFB. Though there was no previous history of TB, the fact that he lives in a TB endemic country suggests that he must have had latent infection in the past which reactivated when he was exposed to ruxolitinib as the drug decreases T cell and dendritic cell function. The patient was started on anti tubercular regimen with isoniazid, rifampicin, pyrazinamide and ethambutol, with which the symptoms markedly improved. The causality of ADR was...
Two of these cases did not have any previous history of TB, were of reactivation of pulmonary TB, 1 case of extra TB following use of ruxolitinib till date, of which 2 cases neutropenia and thrombocytopenia. Dose-related hematologic toxicity such as anemia, are rarely reported. The major reported side effects are the use of Ruxolitinib [7]. Ruxolitinib induced TB infections herpes simplex and pneumocystis jiroveci associated with chorioretinitis, cryptococcus neoformans, mucormycosis, studies have shown reactivation of Hepatitis B, toxoplasma opportunistic infections associated with the drug. Several immune system can be profound and can be the cause of prevention of TB infection. The impact of ruxolitinib on such as IFN -ruxolitinib leads to depressed T helper cell type 1 response and TNF–α which play a crucial role in the prevention of TB infection. The impact of ruxolitinib on immune system can be profound and can be the cause of opportunistic infections associated with the drug. Several studies have shown reactivation of Hepatitis B, toxoplasma chorioretinitis, cryptococcus neoformans, mucormycosis, herpes simplex and pneumocystis jiroveci associated with the use of Ruxolitinib[9]. Ruxolitinib induced TB infections are rarely reported. The major reported side effects are dose-related hematologic toxicity such as anemia, neutropenia and thrombocytopenia. With reference to the literature, there has been 8 cases of TB following use of ruxolitinib till date, of which 2 cases were of reactivation of pulmonary TB, 1 case of extra pulmonary TB and 5 cases of disseminated TB. Though two of these cases did not have any previous history of TB, the close temporal relation between the start of ruxolitinib and the diagnosis of TB points to reactivation of TB as the most likely pathophysiology. Cases have been reported even from non-endemic areas. In all the cases except one, ruxolitinib was withheld and standard TB treatment was started[8].

We could report cases of two patients who developed pulmonary TB and ascitic fluid TB while on treatment with ruxolitinib. In both cases ruxolitinib was discontinued after diagnosis of TB. It was possible to re initiate therapy with ruxolitinib in one of the patient. A case report from UK describes a case of ruxolitinib induced tuberculosis presented as a neck lump but most other cases came with complains of fever, cough, weakness and chills. Francesca Palandri reported a case of ruxolitinib who developed extrapulmonary TB (lymph node) while on ruxolitinib[10]. They suggest that clinicians should consider tuberculosis as a differential diagnosis in patients on ruxolitinib, as immunosuppressant medications can cause opportunistic infections[9]. In our both cases the patients became symptomatically better after initiating the anti TB therapy which shows the association of increased risk of TB while on ruxolitinib. So there is a need for periodically monitoring the patient for latent TB infection while on therapy with this drug. Also, one should look for signs of TB on a chest x-ray prior to initiating treatment with ruxolitinib.

CONCLUSION

Treatment with ruxolitinib which has potent activity against JAK 1 and 2[11] may have triggered tuberculosis as it is an immuno suppressant drug and increases the risk of infection. The clinicians must be cognizant of the possibility of opportunistic infection associated with ruxolitinib. Our cases emphasize the need of careful screening for tuberculosis prior to initiating ruxolitinib. After initiating ruxolitinib, periodic follow up of the patients is recommended, to check for the development of opportunistic infection.

REFERENCE