International Journal of Infectious Diseases 80 (2019) 134–136

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Tuberculosis and atypical mycobacterial infections in ruxolitinib-treated patients with primary or secondary myelofibrosis or polycythemia vera

Sylvain Lescuyer[a,*], Marie-Pierre Ledoux[a], Simon Gravier[a], Shanti Natarajan-Amé[a], Céline Duval[a], Fréderic Maloisel[b], Laurent Mauvieux[c,d], Elise Toussaint[a], Luc-Matthieu Fornecker[a,c], Raoul Herbrecht[a,c]

[a] Department of Oncology and Haematology, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
[b] Clinique Sainte Anne, Strasbourg, France
[c] Université de Strasbourg, Inserm UMR-S1113/IRFAC, Strasbourg, France
[d] Laboratory of Haematology, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

ARTICLE INFO

Article history:
Received 17 September 2018
Received in revised form 23 December 2018
Accepted 4 January 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Ruxolitinib
Mycobacteria
Tuberculosis
Mycobacterium tuberculosis
Mycobacterium avium complex

ABSTRACT

Ruxolitinib is a JAK-1/JAK-2 inhibitor indicated for the treatment of polycythemia vera and primary or secondary myelofibrosis. Only one patient (0.2%) was diagnosed with tuberculosis among the 485 patients receiving ruxolitinib in the four pivotal trials. Fourteen cases of tuberculosis have since been reported. We observed two (3%) mycobacterial infections (one due to *Mycobacterium tuberculosis* and one due to *Mycobacterium avium* complex) in our cohort of 65 patients receiving ruxolitinib. This observation suggests that the rate of mycobacterial infection might be higher than that observed in the pivotal trials and that atypical mycobacterial infections can also occur.

Introduction

Ruxolitinib, a Janus kinase (JAK-1 and JAK-2) inhibitor, is indicated for primary myelofibrosis or myelofibrosis secondary to polycythemia vera or essential thrombocythemia and for patients with polycythemia vera failing or intolerant to hydroxyurea. Pivotal studies conducted in patients with myelofibrosis proved efficacy by the reduction in spleen size, amelioration of symptoms, and improvements in survival (Harrison et al., 2012; Verstovsek et al., 2012). Patients with polycythemia vera with an inadequate response to or adverse events from hydroxyurea also benefit from ruxolitinib, with improved control of haematocrit and a reduced spleen volume (Passamonti et al., 2016; Vannucchi et al., 2015). Rates of infection were similar in the ruxolitinib and control groups in all of these previous studies, with the exception of herpes zoster infections, which were all of grade 1 or 2 severity and were more frequent in the ruxolitinib-treated patients in only one of these studies (Vannucchi et al., 2015). This excess in herpes zoster infections was confirmed in a meta-analysis of five phase III trials (Lussana et al., 2018). Only one mycobacterial infection was reported among the 485 patients who received ruxolitinib in one of the four pivotal trials (Harrison et al., 2016). Since these studies, 14 other cases of tuberculosis (TB) have been published (Lussana et al., 2018; Tsukamoto et al., 2018; Dioverti et al., 2018; Palandri et al., 2018; Polverelli et al., 2018). Ten of these were miliary or disseminated forms and four patients died. No atypical mycobacterial infection has been reported to date.

The mechanisms hypothesized for the increased susceptibility to infection in ruxolitinib-treated patients include the inhibition of the JAK–STAT pathway resulting in a decreased type 1 helper T cell (Th1) response and inflammatory cytokine production, a long-lasting down-regulation of regulatory T cells (Tregs), an impairment of dendritic cell functions, and an impairment of maturation of natural killer (NK) cells (Lussana et al., 2018; Heine et al., 2013; Massa et al., 2014; Schonberg et al., 2015).

The objective of this study was to perform a retrospective analysis of the rate of mycobacterial infections in a cohort of patients treated with ruxolitinib for polycythemia vera or symptomatic primary or secondary myelofibrosis. Patients

* Corresponding author at: Department of Oncology and Haematology, Hôpital de Hautepierre, 67098 Strasbourg, France.
E-mail address: sylvain.lescuyer@chru-strasbourg.fr (S. Lescuyer).

https://doi.org/10.1016/j.ijid.2019.01.002

receiving off-label ruxolitinib, for example for chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation, were excluded. This study is part of a larger analysis of infections in immunosuppressed and frail patients. The Comité d'Ethique des Facultés de Médecine, d'Odontologie, de Pharmacie, des Ecoles d'Infirmières, de Kinésithérapie, de Maïeutique et des Hôpitaux Universitaires de Strasbourg approved this global study. Surviving patients gave informed consent.

Methods and results

Sixty-five patients with polycythemia vera or symptomatic primary or secondary myelofibrosis were treated with ruxolitinib in the Department of Oncology and Haematology at the University Hospital of Strasbourg and the Haematology Unit of the Clinique Sainte-Anne between July 2011 and June 2018. The total duration of exposure to ruxolitinib was 58 375 days (mean 898 days, median 442 days, range 32–2211 days). Two cases of disseminated mycobacterial infection were observed in this cohort: one case each of *Mycobacterium tuberculosis* and *Mycobacterium avium* complex.

The first case was a 73-year-old male with JAK2 V617F mutated primary myelofibrosis diagnosed in 2012. He had no prior history of TB. Ruxolitinib was introduced in March 2014 because of weight loss and symptomatic splenomegaly. The dose was limited to 15 mg twice daily because of mild thrombocytopenia. The patient's weight stabilized and splenomegaly decreased considerably. There was no change in ruxolitinib dosage over the 6 months of treatment. An intermittent fever started on day 136 of ruxolitinib therapy. He was hospitalized in September 2014 for persistent fever and confusion. A white blood cell count revealed a normal neutrophil count (1.90×10^9/l), lymphocytopenia (0.41×10^9/l), and monocytopenia (0.07×10^9/l). Imaging showed multiple pulmonary and cerebral micronodules. TB was suspected despite negative bacteriology. The interferon-gamma release assay (IGRA) result was positive. Ruxolitinib was discontinued without tapering and anti-TB therapy was initiated. In the absence of improvement, a cerebral biopsy was performed in October 2014 and cultures grew *M. tuberculosis*. The patient died in December 2014 from a cerebral haemorrhage.

The second case was a 65-year-old female with JAK2 V617F mutated polycythemia vera diagnosed in March 1992 following a stroke. She was treated with phlebotomy and hydroxyurea. Secondary myelofibrosis developed gradually and became symptomatic in November 2011. In November 2012 following weight loss and symptomatic splenomegaly, hydroxyurea was discontinued and ruxolitinib 20 mg twice daily was started with marked reduction in splenomegaly. There was no change in the ruxolitinib dose over the following 47 months. She was admitted in November 2016 (first sign on day 1410 of ruxolitinib therapy) for weight loss, asthenia, confusion, pancytopenia, hepatomegaly, and worsening splenomegaly. A white blood cell count revealed a normal neutrophil count (2.33×10^9/l) and lymphocyte count (2.14×10^9/l), with monocytopenia (0.07×10^9/l). A computed tomography scan showed an excavated pulmonary lesion, multiple enlarged lymph nodes, and massive hepatosplenomegaly. Marrow examination showed the negative shadow of a bacillus in a macrophage, suggesting a mycobacterial infection. Bone marrow, blood, and gastric lavage cultures grew *M. avium* complex. Ruxolitinib was discontinued and a combination of clarithromycin, rifabutin, ethambutol, and amikacin was initiated. The patient died of respiratory failure 11 days after the initiation of therapy.

This experience of two fatal disseminated mycobacterial infections in a cohort of 65 patients treated with ruxolitinib indicates a rate of 3%. All patients treated with ruxolitinib had at least one of the following: symptomatic splenomegaly or constitutional symptoms. With a mean duration of treatment of 898 days (2.46 years), the person-time rate is 0.013 cases per person-year. The case of TB occurred after 136 days (20 weeks), which is within the range reported in the literature (median 8 weeks, range 3–76 weeks), while the case of atypical mycobacterial infection occurred after a much longer duration of exposure (1410 days, 201 weeks).

Discussion

The rate of mycobacterial infection observed in this cohort is in complete contrast to the unique case of TB in the ruxolitinib-treated groups in the randomized clinical trials. None of the present study patients had a past history of mycobacterial infection. The patients were not screened for TB. It is recognized that this single-centre experience may overestimate the true rate of mycobacterial infection in this setting, especially regarding atypical mycobacterial infection, as no other case has so far been reported. An Italian multicenter study reported three cases of mycobacterial infection in a cohort of 446 consecutive patients receiving ruxolitinib for primary or secondary myelofibrosis, a finding similar to our experience, suggesting that the rate of mycobacterial infection could be much higher in real life than in clinical trials (Polverelli et al., 2018).

Clinicians need to be aware of this risk, as cases of TB and other opportunistic infections continue to be reported in the literature. A prior history of TB should be considered a contraindication to the use of ruxolitinib. Screening for TB by IGRA has been recommended by an Austrian group (Krauth et al., 2018). It should not, however, result in a reduction in the use of ruxolitinib, as the vast majority of patients greatly benefit from this treatment.

Funding source

None.

Ethical approval

Comité d'Ethique des Facultés de Médecine, d'Odontologie, de Pharmacie, des Ecoles d'Infirmières, de Kinésithérapie, de Maïeutique et des Hôpitaux Universitaires de Strasbourg.

Conflict of interest

None.

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