

Ruxolitinib in myelofibrosis: to be or not to be an immune disruptor

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Abstract: Primary myelofibrosis (PMF) is a myeloproliferative neoplasm classified according to the 2016 revision of World Health Organization Classification of Tumors and Haematopoietic and Lymphoid Tissue. Ruxolitinib is an oral inhibitor of Janus kinase approved in the USA for the treatment of intermediate or high-risk PMF and approved in Europe for the treatment of splenomegaly and constitutional symptoms of the disease. More recently, case reports described serious opportunistic infections in this neoplasm treated with ruxolitinib. Research studies demonstrated the immunological derangement of this compound mainly based on T, dendritic, and natural killer cell defects. The purpose of this review of the literature was to analyze the relationship among ruxolitinib, immune system and bacterial, viral, fungal, and protozoan infections. A literature search was conducted using PubMed articles published between January 2010 and November 2016. The efficacy of drug in patients with PMF was demonstrated in two phase III studies, Controlled MyeloFibrosis Study with ORal Jak inhibitor Treatment (COMFORT-I and COMFORT-II). Grade 3 and 4 neutropenia were recognized in 7.1% and 2% of patients in the ruxolitinib and placebo arm of COMFORT-I. Grade 3 or 4 neutropenia or leukopenia were observed in 8.9% and 6.3% of ruxolitinib treated patients of 5-year follow-up of COMFORT-II. In addition, leukocyte subpopulations, lymphocyte functions, or antibody deficiency were not documented in either of the studies. The complex interactions between ruxolitinib, bone marrow, immune system, and infections in PMF need further investigation, robust data from a randomized clinical trial, registry, or large case-series.

Keywords: myelofibrosis, JAK/STAT pathway, immune system, infections, inflammation

Introduction

Myeloproliferative neoplasms (MPNs) according to the fourth edition of the World Health Organization (WHO) Classification of Tumors of the Haematopoietic and Lymphoid Tissues and the 2016 revision represent a group of heterogeneous diseases, which include polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocythemia (ET).¹⁻³

At the “early stage” of PMF, mandatory major criteria include megakaryocytic proliferation and atypia, clonal mutations of genes, such as Janus kinase 2 (JAK2), calreticulin (CALR), thrombopoietin receptor, or myeloproliferative leukemia virus oncogene (MPL). The minor criteria, confirmed in two determinations, include at least one of following: anemia, palpable splenomegaly, increased lactate dehydrogenase (LDH), and leukocytosis. In “overt PMF” mandatory major criteria include clonal mutations and megakaryocytic atypia associated with diffuse or dense increase of reticulin fibrosis or collagen fibrosis or osteosclerosis. The minor criteria, confirmed in two determinations, include at least one of the following: anemia, splenomegaly, increased LDH, and leukoerythroblastosis.¹⁻³

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Pathogenetically, PMF represents a stem cell-derived MPN associated with ineffective erythropoiesis and extramedullary hematopoiesis, cytokine-mediated stromal changes, including fibrosis and constitutional symptoms, poor prognosis due to thrombohemorrhagic complications and acute myeloid leukemic transformation. Lower risk of acute myeloid leukemia and better prognosis were recognized in PV and ET.^{4,5}

The Mayo Clinic Dynamic International Prognostic Scoring System-plus (DIPSS-plus), clinical and cytogenetic risk score discriminates 4 risk groups of PMF: low, intermediate 1 and 2, high-risk disease in the presence of 0, 1, 2 or 3, 4 or more factors. Age, constitutional symptoms, hemoglobin, peripheral blasts, leukocytes, platelets, karyotype, and transfusion dependency influence median overall survival (OS) of the disease. In fact, the OS varies from 15.4 to 1.3 years.⁶ Currently, molecular genetic DIPSS-independent factors are being studied to better stratify the outcome of MF.^{7,8}

Hematopoietic stem cell transplantation (HSCT) represents a curative approach reserved to a small group of intermediate-2 or high-risk PMF patients. However, novel agents targeting MPN molecular mechanisms, such as JAK, are available in clinical practice and trials to improve constitutional symptoms, splenomegaly, and quality of responses.⁹

Mutations of JAK2, CALR, and MPL are mutually exclusive in the pathogenesis of myeloproliferative Philadelphia-negative neoplasms. In this regard, 10%–15% of PMF are reported “triple negative” for JAK2, CALR, and MPL mutations; 50%–60% of PMF are JAK2 mutated, 20%–25% and 6%–7% are CALR and MPL mutated, respectively.²

Janus kinase signal transducers and activators of transcription pathway (JAK/STAT) transmit information from outside on the DNA of the cell. JAKs are associated with growth factor receptors (eg, erythropoietin receptor and thrombopoietin receptor). After binding of interferon or interleukin, cytokine receptors recruit JAKs, which phosphorylate the receptor protein and bind STAT proteins. STATs initiate transcription of target genes involved in cell growth, differentiation, and apoptosis.⁹ Specifically, JAK2V617F somatic mutation leads to constitutive activation of JAK/STAT pathway. The mechanism of CARL mutations or more rare mutations of epigenetic modifiers are still uncertain.^{10,11}

Four JAK family members and seven STATs are recognized. The JAK family has a key role in myeloid and lymphoid cell proliferation and differentiation. JAK1 mediates the effect of proinflammatory cytokines: interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-alpha). JAK2 mediates differentiation, proliferation, and

avoidance of apoptosis. Ruxolitinib, an oral inhibitor of JAK1 and JAK2, is associated with reduction in the levels of inflammatory markers: IL-6, TNF-alpha, and C-reactive protein (CRP).^{12,13} Inflammatory cytokines are considered responsible for the constitutional symptoms (night sweats, pruritus and fever, fatigue, and weight loss) of myelofibrosis (MF).¹⁴

Ruxolitinib (JAKAFI, Incyte Corporation; JAKAVI, Novartis) is approved in the USA for the treatment of intermediate or high-risk disease and in Europe for the treatment of splenomegaly or constitutional symptoms. In addition, this drug is not specific for the mutated form of JAK2 and inhibits both the wild-type and JAK2V617F. The efficacy of this compound in patients with PMF was demonstrated in two phase III studies, Controlled MyeloFibrosis Study with Oral Jak inhibitor Treatment (COMFORT-I and COMFORT-II).^{15,16}

More recently, case reports described serious opportunistic infections in ruxolitinib-treated PMF patients and research studies demonstrated the immunological derangement of this treatment.

Methods

The purpose of this review of the literature was to analyze the relationship among ruxolitinib, immune system, and infections. A literature search was conducted using PubMed for articles published from January 2010 to November 2016 using the terms “myelofibrosis and infections or myelofibrosis and immune system”, “ruxolitinib and infections or ruxolitinib and immune system”. Only articles published in English were considered. The contribution of ruxolitinib to the immune balance is focused on bacterial, viral, fungal, and protozoan infections.

Results

In COMFORT-I study, ruxolitinib was compared with placebo in intermediate-2 and high-risk MF. In COMFORT-II, ruxolitinib was compared with the best available therapy in intermediate-2 and high-risk MF. More specifically, COMFORT-I is a double-blind trial, included 309 patients with International Prognostic Scoring System (IPSS) high-risk or intermediate-2 MF, palpable spleen of at least 5 cm, and platelet count of at least 100,000/mm³. COMFORT-II is an open-label phase III trial, which enrolled 219 patients considering the same criteria of inclusion of the previous trial. In both the trials, the starting dose of drug was 15 or 20 mg twice daily based on platelet count >200,000/mm³ or between 100,000 and 200,000/mm³. Drug was reduced appropriately in patients with renal or hepatic impairment or platelet count <100,000/mm³. In both studies, reduction

in spleen size was confirmed by imaging at 24 and 48 weeks of treatment.^{15,16}

In the first month of the treatment of both trials, grade 3 or 4 anemia or thrombocytopenia were reported. These cytopenias result from the inhibitory effects of drug on JAK2 and erythropoietin/thrombopoietin signals.¹⁷ These adverse events (AE) can be managed adequately by prompt red blood cell transfusions and gradual tapering of dose due to “withdrawal syndrome” and rebound of inflammatory cytokines.^{18–20}

Grade 3 and 4 neutropenia were recognized in 7.1% and 2% of patients in the ruxolitinib and placebo arm of COMFORT-I trial. Urinary infections and herpes zoster were documented in patients treated with ruxolitinib in COMFORT-I.¹⁵ More recently, 5-year follow-up of COMFORT-II noted grade 3 or 4 neutropenia or leukopenia in 8.9% and 6.3% of ruxolitinib-treated patients. Urinary tract infections, pneumonia, herpes zoster, sepsis, and tuberculosis (TBC) infections were observed in 24.6%, 13.1%, 11.5%, 7.9%, and 1% of ruxolitinib subgroup of patients, respectively.¹⁶

Leukocytes subpopulations and functions or antibody deficiency were not documented in both studies. Interestingly, Theocharides et al recognized that omozygous calcitriol mutations in PMF lead to acquired myeloperoxidase deficiency.²¹

Ruxolitinib and immune system: dendritic cell, natural killer, and T regulatory

The immune “orchestra” includes innate and adaptive arms. The former includes anatomic barriers, antimicrobial molecules, such as complement and cellular components: neutrophils, eosinophils, basophils, mast cell, natural killer (NK), monocytes/macrophages, and dendritic cells (DC). The latter includes B lymphocytes, CD4+ T-helper lymphocytes

(Th1, Th2, Th17, and T regulatory [T reg]) and CD8+ cytotoxic T lymphocytes.

Figure 1 summarizes the complex relationship between the drug and the immune “orchestra”. More recently, Heine et al demonstrated that ruxolitinib affects DC differentiation, phenotype, and function leading to impaired T-cell activation.²²

DC are important antigen presenting and phagocytic cells. They induce CD8+ T cells to destroy infected and neoplastic cells. In addition, DC control adaptive response producing IL-12 and IL-23, cytokines that drive Th1 and Th17 lymphocytes phenotypes. More specifically, Th1 cells produce cytokine interferon gamma (INF-gamma), IL-2, and TNF-alpha. TNF-alpha improves Th1 against intracellular pathogens. Th17 secrete IL-17 and IL-22, key cytokines against extracellular bacteria. More mature DC mediate the induction of T-reg cells.

In addition, Rudolph et al published very interesting data on the mechanism of ruxolitinib impairment of DC migration and inhibition of Rho-associated coil kinase.²³

Schonberg et al reported a reduction of NK in ruxolitinib-treated patients.²⁴ NK are lymphocytes, immune effector cells known to eliminate both virus and cancers and produce important inflammatory cytokines, such as INF-gamma and TNF-alpha.

Massa et al observed a rapid and long-lasting decrease of T-reg cell in patients treated with the drug.²⁵ Keohane et al noted that T-reg cells are reduced in MPN patients compared with healthy, especially in those treated with ruxolitinib.²⁶ Finally, Paramalli Yajnanarayana et al recognized a decreased T reg, Th1, and Th 17 in ruxolitinib exposure.²⁷

T-reg cells control viral, fungal, and protozoan infections and are involved in moderating inflammation and maintaining

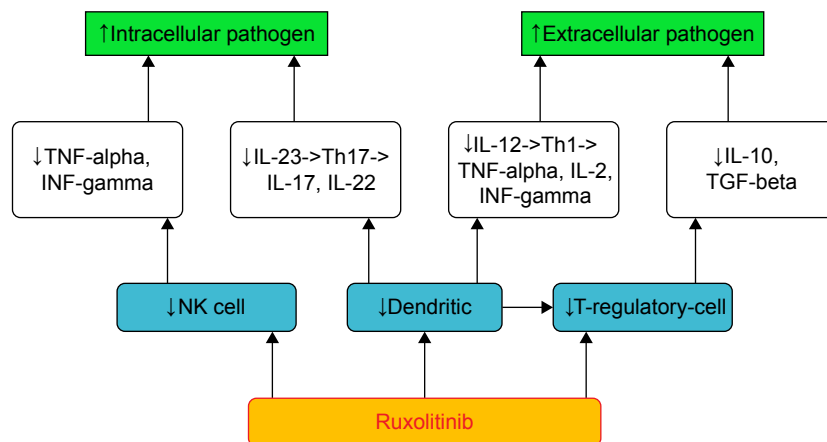


Figure 1 Ruxolitinib and immune system.

self-tolerance. In fact, they produce inhibitory cytokines such as IL-10 and transforming growth factor-beta (TGF-beta) that promote fibrosis, affect the function, and induce apoptosis of T-effector lymphocytes.

Beyond immune derangement

Al-Ali et al²⁸ recently reported an open-label, multicenter, single-arm phase IIIb expanded-access study in patients with MF. This study included patients treated with this compound outside a clinical trial. The analysis included a large cohort of 1,144 intermediate and high-risk MF patients, including 163 intermediate-1 diseases. Among nonhematologic AE, grade 3 or 4 neutropenia was reported. Herpes zoster and influenza were observed in 3.6% and 3% in the whole cohort of intermediate and high-risk MF, respectively. One case of hepatitis B reactivation was documented in intermediate-1 subgroup.²⁸

MF is a rare myeloproliferative of elderly patients, it may be a primary disease or secondary transformation of PV/TE. PMF patients who undergo ruxolitinib treatment may have or develop defects involving innate and adaptive immune system, more specifically T, dendritic, and NK cells. In addition, these patients may have functional hyposplenism and agranulocytosis. Severe and prolonged neutropenia is a well-recognized risk factor for infections, such as neoplastic dysfunctional granulocytes, including myeloperoxidase deficiency. In summary, biological studies are consistent with the assumption of a combination of immune defects.²²⁻²⁷ Obviously, previous treatments, patient age and comorbidities, and environmental exposure may influence the risk of infections.²⁹⁻³¹

Recently, a Cochrane study pointed out the small number of patients included in COMFORT-I and COMFORT-II.³² Therefore, more robust data are mandatory to answer the question of possible immune derangement of ruxolitinib treatment in MF. Randomized clinical trial (RCT) data or longer follow-up studies are not always available for rare diseases.³³ Hultcrantz et al observed a higher mortality rate due to infections in patients diagnosed with MPNs than that of matched controls in Sweden between 1973 and 2005. In addition, big data from registry or large case series should be analyzed considering the 2016 revision of WHO.³⁴

Bacterial, viral, fungal, and protozoan infections

Table 1 summarizes bacterial infections recently reported during JAKAFI/JAKAVI treatment.³⁵⁻⁴³ Bacterial infections are recognized early and late after treatment. The majority of

case reports describe TBC disseminated disease, including Pott's disease. The possible explanation of TBC reactivation during ruxolitinib may be the impairment of DC and IL-12 production, a key cytokine involved in the transcription of INF-gamma. In addition, ruxolitinib induces depression of Th1 lymphocyte responses and production of INF-gamma and TNF-alpha. Specifically, the former activates macrophage to produce reactive oxygen and the latter plays a critical role in protection against TBC.

Certainly, the screening for latent TBC must be considered if epidemiological risk factors are significant. Quantiferon TBC test may be negative due to immune dysregulation of disease or treatments. Furthermore, mild symptoms and low CRP are probably due to the reduction of inflammatory cytokines. Therefore, prompt and accurate physical examination and decisions are mandatory in this setting of patients. Indeed, patients with firmly suspected or documented active TBC should be isolated in single rooms using airborne precautions. Interestingly, some authors demonstrated that the drug may be safely administered in serious infections providing optimal monitoring of disease and TBC treatment.^{42,43}

Viral infections were recognized early and late after this treatment (Table 2).⁴⁴⁻⁵⁰ The majority of case report describes herpes simplex virus (HSV) possible reactivation and hepatitis B virus (HBV) reactivation. The possible explanations include impairment of NK cells, which have a key role in controlling herpes infections, especially when T cells are low and a reduction of T-reg protective against virus occurs. Acyclovir/valacyclovir HSV prophylaxis may be considered in selected cases, for example, low CD4+ lymphocyte count. Frequently immunocompromised patients with defects in cell-mediated immunity experienced more severe and disseminate HSV than those with agammaglobulinemia.

In addition, surveillance of HBV markers and viral load are important due to the high incidence of latent HBV and reactivation during steroids or immunosuppression. More than one third of the world population has been infected with HBV, 350 million people present chronic infection, and the majority live in Southwest Asia and the Western Pacific regions. Reactivation of hepatitis B after steroids, chemotherapy and immunosuppressive therapy is a recognized complication. The timeframe of reactivation and rate varies from 20% to 50%, while in the HSCT setting this rate increases further. Interestingly, HBV-DNA contains corticosteroid elements stimulating virus replication.⁵¹

Most HBV reactivation occurs in hepatitis B surface Australia antigen (HbsAg)-positive patients and more rarely in patients without Australia but with antibodies against

Table 1 Bacterial infections associated with ruxolitinib in myelofibrosis

Clinical features	Laboratory features	Diagnosis and management	Outcomes	Reference
Male of 73 years Diagnosis of MF: 2009 6 weeks of RU treatment	Microbiological analysis of the debrided tissue positive Blood cultures <i>Escherichia coli</i> positive	Fever and necrotizing fasciitis of the scrotum Drug discontinuation and ABT plus surgical approach	Improvement	35
Male of 78 years Diagnosis of MF: May 2015 8 months of RU treatment	Microbiological analysis of <i>Klebsiella pneumoniae</i> of liver abscess drainage	Fever and abdominal pain Drug discontinuation and ABT plus surgical approach	Improvement	36
Male of 82 years Diagnosis of PMF: 2005 Treatments reported: hydroxyurea, danazol, prednisolone 2 months of RU treatment	Culture of sputum positive	Pulmonary TBC reactivation Drug discontinuation and ABT	Improvement	37
Male of 69 years Diagnosis of PMF: May 2015 3 weeks of RU treatment	Histological analysis of cervical lump Quantiferon gold positive	Pulmonary TBC reactivation Drug discontinuation and ABT Ruxolitinib retreatment after ABT	Improvement of infection and MF	38
Male of 78 years Diagnosis of MF in RU treatment	Histological and microbiological analysis of lump	Disseminated TBC (lungs and lump) Drug discontinuation and ABT	Improvement	39
Male of 62 years Diagnosis of PMF: 1996 7–9 weeks of RU treatment	Microbiological analysis, PCR and culture of BAL Blood culture positive	Disseminated TBC (lungs and lump) Drug discontinuation and ABT Ruxolitinib retreatment after ABT	Improvement of infection and MF	40
Male Diagnosis of PMF: 1990	Histological and microbiological analysis of lump Culture of sputum positive Quantiferon gold positive	Disseminated TBC Drug discontinuation and ABT	Improvement	41
Female of 65 years Diagnosis of post-PV MF 4 months of RU treatment	Histological and culture analysis of lump	Extrapulmonary TBC Drug discontinuation and ABT Drug retreatment associated with secondary TBC prophylaxis	Improvement of infection and MF	42
Female of 78 years Diagnosis of PMF: 2011 Treatment reported: splenic irradiation 21 months of RU treatment	Histological analysis, PCR and culture of lump Quantiferon positive	Disseminated tuberculosis, spondylodiscitis Drug was continued and ABT	Improvement	43

Abbreviations: ABT, antibiotic therapy; BAL, bronchoalveolar lavage; MF, myelofibrosis; PCR, polymerase chain reaction; RU, ruxolitinib; PMF, primary myelofibrosis; TBC, tuberculosis.

hepatitis B core antigen (anti-Hbc) and/or Australia.⁵¹ In addition, the host immune system may affect on hepatocellular damage and viral clearance, such as viral factors. Therefore, a prompt antiviral prophylaxis should be considered in high risk of HBV reactivation hematological patients according to the American Association for Study of Liver Diseases and European guidelines.^{52,53} However, another important point is a careful clinical monitoring due to the incidence of prophylactic drug resistance, such as an adequate monitoring of HBV-DNA and transaminases considering the occurrence of viral replication before evidence of hepatitis. In addition, the exact duration of prophylaxis may be guided by monitoring the immune reconstitution by flow cytometry, for example.

Epstein–Barr virus (EBV) lymphoproliferative disorder represents a life-threatening complication after HSCT with a major risk factor for profound T-cell depletion.⁵⁴ Probably, previous treatments and comorbidities may justify the fatal

possible case of EBV-lymphoproliferative of central nervous system as reported in Table 2.

Progressive multifocal leukoencephalopathy is due to reactivation of John Cunningham polyomavirus. At present, rare data are reported on the epidemiology of disease in non-HIV setting and its treatment.⁵⁵

Fungal and protozoan infections after ruxolitinib are summarized in Table 3.^{56–59} *Toxoplasma* is commonly related to cat exposure. In addition, *Toxoplasma gondii* release kinase that interact with JAK–STAT pathway and drug downregulate cytokines, including TNF-alpha, which play an essential role in controlling intracellular fungal pathogen. Toxoplasmosis is likely to be an underestimated complication after allogeneic stem cell transplantation with a high mortality rate.

Furthermore, *Pneumocystis jiroveci* (PJP) is responsible for severe infections in HSCT patients. Rare data are reported in non-HSCT setting. For clinical point of view, serum

Table 2 Viral infections associated with ruxolitinib in myelofibrosis

Clinical features	Laboratory features	Diagnosis and management	Outcomes	Reference
Male of 67 years Diagnosis of PMF: 2009 1 months of RU treatment	PCR of aqueous humor positive	Bilateral CMV retinitis Drug discontinuation and AVT intravenously and intravitreally	Improvement	44
Female of 57 years Diagnosis of PV: 1990, MF: 2015 Treatments: splenectomy, hydroxyurea, anagrelide, prednisone, tacrolimus due to focal segmental glomerulosclerosis, interferon alfa 9 weeks of RU treatment	PCR of CSF positive No biopsy	EBV lymphoproliferative disorder of central nervous system plausible Drug discontinuation, Rituximab and temozolomide	Death 5 weeks after diagnosis	45
Male of 77 years Diagnosis of MF 6 months of RU treatment	PCR from gastric ulcer	EBV-related gastric ulcer Drug discontinuation AVT	Improvement	46
Male of 67 years Diagnosis of PMF 2014 4 days of RU treatment	Punch biopsy of cheek Cultures of lip positive for HSV-1	Dissemination HSV infection Drug discontinuation and AVT	Permanent vision loss	47
Male of 75 years Diagnosis of MF: 2013 10 weeks of RU treatment	Brain biopsy	PML Drug discontinuation	Worsening of neurologic signs	48
Female of 49 years Diagnosis of ET and MF: 2008 Treatments: hydroxyurea 4 weeks of RU treatment, carrier of HBV	Increased HBV-DNA titers	Reactivation of HBV Drug discontinuation and AVT	Improvement	49
Female of 72 years Diagnosis of ET and MF: 2014 8 months of RU treatment, carrier of HBV	Increased transaminases and HBV-DNA titers	Reactivation of HBV Drug discontinuation AVT	Transaminases and HBV-DNA titers improved	50

Abbreviations: ABT, antibiotic therapy; AVT, antiviral therapy; EBV, Epstein-Barr; CSF, cerebrospinal fluid; CMV, cytomegalovirus; ET, essential thrombocythemia; HBV, hepatitis B Virus; HSV, herpes simplex virus; MF, myelofibrosis; PCR, polymerase chain reaction; PMF, primary myelofibrosis; PML, progressive multifocal leukoencephalopathy; PV, polycythemia vera; RU, ruxolitinib.

diagnosis in immunocompromised hematological patients sometimes varies independently from reactivation.

PJP (formerly *Pneumocystis carinii*) pneumonia is a rare fungal infections observed in patients with a disrupted immune system, including HIV and HSCT recipients.⁶⁰ A recent meta-analysis of RCTs indicates that prophylaxis of PJP pneumonia in immunocompromised non-HIV-infected patients is useful when the risk of disease is >3.5% in adults.⁶¹

Rare data were recognized in non-HSCT setting. Therefore, a physician should consider trimethoprim/sulfamethoxazole evaluating its tolerability and activity against PJP and other opportunist pathogens, such as toxoplasma, encapsulated bacteria organisms, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and gram negative.

Cryptococcus is a yeast-like environmental fungus responsible for pneumonia or meningoencephalitis, especially

Table 3 Fungal and protozoan infections associated with ruxolitinib in myelofibrosis

Clinical features	Laboratory features	Diagnosis and management	Outcomes	Reference
Male of 65 years Diagnosis: PV and MF	PCR of aqueous fluid	Bilateral toxoplasmosis retinitis Drug discontinuation and ABT	Stable vision and retinal scar	56
Male of 66 years Diagnosis of PV and MF: 2001 Previous treatments: prednisone 18 months of RU treatment	Culture of BAL positive	Pneumony criptococcosis Drug discontinuation AF and subsequently drug reintroduction	Improvement of infection and MF	57
Female of 69 years Diagnosis MF: 2011 More than 3 years of RU treatment	CSF with India link positive Culture of CSF positive	Criptococcal meningoencephalitis AF	Improvement	58
Male of 69 years Diagnosis MF: 2009 More than 3 years of RU treatment	Transbronchial biopsy PCR of BAL positive	<i>Pneumocystis jiroveci</i> pneumonitis Drug discontinuation and ABT	Improvement	59

Abbreviations: ABT, antibacterial therapy; AF, antifungal; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; MF, myelofibrosis; PCR, polymerase chain reaction; PV, polycythemia vera; RU, ruxolitinib.

in immunocompromised patients, such as HIV with CD4+ lymphocyte count inferior to 200/mm³.^{62–64} Interestingly, a case report presented in Table 3 describes the possibility of reintroduction of ruxolitinib after the prompt treatment of fungal infections.⁵⁷

Conclusions

The complex interactions between the drug, bone marrow, and immune system (innate and adaptive arms) and infections (bacterial, viral, fungal, and protozoan) need further clinical and translational studies to confirm the significant influence of this relationship.

Biological studies are consistent with the assumption of a combination of immune defects mainly based on T, dendritic, and NK cell defects and dysfunctional granulocytes. Age and comorbidities, treatments (such as steroids), and environmental exposure may influence the risk of infections, for example, intracellular or extracellular pathogen. For clinical point of view, accurate screening and prompt treatment of infections are mandatory considering the reduction in the levels of inflammatory markers, for example, CRP (drug related) and the possibility of acquiring multidrug-resistant organisms' infections.^{65,66} Recently, new definitions and perspectives are recognized regarding sepsis and its high mortality rate.⁶⁷

More robust data are necessary to answer the question of possible immune derangement of ruxolitinib treatment in MF. In summary, precautions should be implemented to improve adequate screening, prophylaxis, and prompt treatment of infections. Furthermore, the patients should be warned about the possibility of reactivation of infections. Importantly, some authors demonstrated the possibility to cure infections and ultimately treat MF.

Ruxolitinib is the first drug approved in a rare disease of the elderly, MF. At present, it is also approved for the treatment of patients with PV nonresponders or intolerant of hydroxyurea.⁶⁸

In conclusion, RCT data on this topic are scarce, such as updated data from registry or large case series. At present, other JAK inhibitors are ongoing in phase III studies for the treatment of MPNs. Safety and tolerability of ruxolitinib and JAK inhibitors should be further clarified with the aim of improving responses using the combination of targeted therapies.⁶⁸

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Disclosure

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