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LETTER TO THE EDITOR

Infections associated with ruxolitinib: study in the French Pharmacovigilance database

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Dear Editor,

Ruxolitinib, an orally bioavailable potent and selective inhibitor of Janus kinases (JAKs) 1 and 2, has been approved in Europe for the treatment of myelofibrosis and polycythemia vera.

Ruxolitinib improves disease-related constitutional symptoms, splenomegaly and overall survival in myelofibrosis. However, studies suggest that the drug exerts immunosuppressive activity and may predispose patients to infections [1].

Here, we report all the infectious adverse events (I-AEs) registered in the French Pharmacovigilance database between August 23, 2012 and August 31, 2017 with ruxolitinib as "suspect" or "interacting drug" and adverse drug reactions (ADRs) coded as "infections and infestations" with MedDRA System Organ Class (SOC).

The French Pharmacovigilance database was established in 1985 to record spontaneous reporting of adverse drug reactions reported to the network of 31 French Regional Pharmacovigilance Centers.

In this retrospective study, based on spontaneous physicians'report, we identified 30 cases of infectious events including opportunistic infections which occurred in 26 patients; 28 were serious. The median age of patients was 69 years (range 53–89) and 54% were male. The indications of ruxolitinib were primary myelofibrosis ($n = 5$), secondary myelofibrosis ($n = 7$), unspecified myelofibrosis ($n = 8$), polycythemia vera ($n = 3$), atypical myeloproliferative neoplasm ($n = 1$), and graft versus host disease ($n = 2$). The median daily dose was 30 mg (range 10–60) unknown (UK) for two patients. No concomitant immunosuppressive therapy was mentioned. The immune status was unknown except for two patients (normal). The median time to onset was 465 days (range 98–1550) (UK for 12/26 patients). Infections were bacterial ($n = 9$), mycobacterial ($n = 5$), viral ($n = 10$), fungal ($n = 4$), protozoan ($n = 1$), and non specified opportunistic infection ($n = 1$). The most frequent pathogen identified was zoster virus (20%). Five sepsis were reported (16.6%). Ruxolitinib was discontinued in 13 and reduced in two patients (UK in 11 patients). Six deaths were reported—three due to sepsis, two multivisceral failure, and one respiratory distress.

Table 1 resumes the characteristics of infections.

Several opportunistic and non opportunistic infections, generally mild, were reported in patients treated with ruxolitinib in clinical trials and in post marketing. There have been recent isolated reports of toxoplasma retinitis, cryptococcal pneumonia and meningoencephalitis, disseminated tuberculosis, progressive multifocal leukoencephalopathy, *Klebsiella pneumoniae* primary liver, and sino-orbital mucormycosis in patients receiving ruxolitinib. Treatment with ruxolitinib has also been associated with the reactivation of latent infections with hepatitis B virus, Epstein Barr virus, and herpes simplex virus [2–9].

The occurrence of infections could be explained by the mechanism of action of ruxolitinib. This drug causes inhibition of the JAK signal transducer and STAT pathway. This pathway is essential for host immunity and defense. Studies suggest that ruxolitinib impaired several cytokines (IL1, IL6, TNFα, and IFN-γ), modulates dendritic cell function and T cell response, and reduces NK cell levels in myeloproliferative

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Table 1 Description of infections reported in the French Pharmacovigilance database in patients treated by ruxolitinib

Type of infection	Number of cases	Localization	Antimicrobial agents
Bacterial	9	Sepsis (5)	*Escherischia coli* (2), non specified *Streptococcus* (1), non identified (2)
		Pulmonary (2)	*Legionella pneumophila* (2)
		Urinary tract (2)	*Klebsiella pneumoniae* (1), non identified (1)
Mycobacterial	5	Nodal (2)	*Mycobacterium avium* (1), non identified (1)
		Cerebral (1)	Unspecified (1)
		Disseminated (2)	*Mycobacterium avium* (1) *Mycobacterium tuberculosis* (1)
Viral	10	Cutaneous (5)	*Varicella Zoster virus* (VZV) (5)
		Respiratory tract (3)	*Influenza A virus* (2), VZV (1)
		Hepatic (1)	*Epstein Barr virus* (1)
		Occular (1)	*Herpes Simplex virus* (1)
Fungal	4	Pulmonary (4)	*Aspergillus fumigatus* (1) *Cryptococcus neoformans* (1) *Pneumocystis jiroveci* (1) *Lichtheimia rhizomucor* (1)
Protozoan	1	Occular (1)	*Toxoplasma gondii* (1)
Unknown	1	Pulmonary (1)	*Non specified opportunistic infection* (1)

neoplasms patients which may lead to increased risk of or opportunistic infections or reactivation of latent infections [9–10]. Physicians must be alerted of this risk, and antimicrobial prophylaxis should to be discussed in patients at risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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