Original Article

Analysis of Adverse Events With Janus Kinase Inhibitors Reported to Spontaneous Reporting System

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Article info:
Received: 22 Feb 2024
Accepted: 26 Apr 2024

Keywords:
Pharmacovigilance, Tofacitinib, Janus kinase (JAK), Pneumonia, Herpes zoster (HZ)

ABSTRACT

Background: Janus kinase (JAK) inhibitors are recently launched treatments with a new mechanism of action, so their safety needs to be verified through long-term usage.

Objectives: This study aimed to determine the clinical characteristics of JAK inhibitor-related adverse events (AEs) in a real-world setting, using data from the Japanese adverse drug event report (JADER) database.

Methods: AEs are defined using the preferred terms from the dictionary of medical terms for regulatory agencies and include pneumonia, herpes zoster (HZ), hematopoietic erythropenia, hematopoietic leukopenia, hematopoietic thrombocytopenia, liver disorder, renal impairment, interstitial lung disease (ILD), cardiac failure, embolic and thrombotic events, gastrointestinal perforation, and hyperglycemia. Adjusted reported odds ratios (ROR) are used to assess disproportionality in the pharmacovigilance data, and time-to-onset analysis is performed using Weibull shape parameters.

Results: The JADER database contained 823662 reports published between April 2004 and March 2023. Pneumonia and HZ are associated with all JAK inhibitors except filgotinib. Adjusted RORs for pneumonia with peficitinib, tofacitinib, baricitinib, ruxolitinib, filgotinib, and upadacitinib are 4.4 (95% CI, 3.36%, 5.75%), 6.93 (95% CI, 6.18%, 7.77%), 6.51 (95% CI, 5.52%, 7.67%), 3.3 (95% CI, 2.76%, 3.95%), 4.39 (95% CI, 2.55%, 7.58%), and 6.11 (95% CI, 4.53%, 8.23%), respectively. Adjusted RORs for HZ with peficitinib, tofacitinib, baricitinib, ruxolitinib, and upadacitinib are 8.94 (95% CI, 5.69%, 14.05%), 31.82 (95% CI, 27.58%, 36.71%), 34.96 (95% CI, 28.92%, 42.26%), 5.24 (95% CI, 3.57%, 7.7%), and 33.19 (95% CI, 23.81%, 46.27%), respectively. The median time-to-onset of pneumonia and HZ with JAK inhibitor usage ranged from 2 to 6 months and 4 to 7 months, respectively.

Citation Tanaka H, Maezawa M, Nakao S, Miyasaka K, Hirofuji S Yamashita M, et al. Analysis of Adverse Events With Janus Kinase Inhibitors Reported to Spontaneous Reporting System. Pharmaceutical and Biomedical Research. 2024; 10(3):203-228. http://dx.doi.org/10.32598/PBR.10.3.1207.3

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Conclusion: We demonstrated the potential risks of JAK inhibitor use with real-world data. The present analysis shows that patients receiving peficitinib, tofacitinib, baricitinib, ruxolitinib, filgotinib, or upadacitinib should be closely monitored for AEs. The most common AEs associated with JAK inhibitors were pneumonia and HZ.

Introduction

Janus kinase (JAK) inhibitors act on cytokine signaling pathways involved in inflammatory diseases and immune system abnormalities [1-4]. JAKs are essential for many cytokine families, and biological therapies targeting inflammatory cytokines have critically changed the treatment of rheumatoid arthritis (RA) and other autoimmune diseases. RA, for instance, is associated with the overproduction of interleukin (IL)-6, IL-12, IL-15, IL-23, granulocyte macrophage-colony stimulating factor, and interferons [4].

Four members of the JAK family, JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), are involved in different cytokine signaling pathways. JAK1, JAK2, and TYK2 are ubiquitously expressed, while expression of JAK3 is mainly restricted to cells of hematopoietic origin [2]. JAK1 is primarily involved in inflammatory and innate immune responses. Inhibition of JAK1 suppresses IL-6 signaling, which is central to inflammatory disease [1]. JAK2 is essential for erythropoiesis, myelopoiesis, and platelet production. JAK3 is vital for lymphocyte proliferation and homeostasis [2-4]. The IL-2 family of cytokines (IL-2, -4, -7, -9, -15, and -21) signal through JAK3-bound receptors [3]. IL-2 is a cytokine secreted by antigen stimulation of T cell receptors that drives T cell growth, augments natural killer (NK) cytolytic activity, induces the differentiation of regulatory T cells, and mediates activation-induced cell death [5-7]. The function of IL-15 is the maintenance of NK cells and $CD8^{+}CD44^{h}$ memory T cells to provide a long-term immune response to pathogens [7]. TYK2 is associated with antiviral responses [1-4]. Therefore, differences in JAK inhibitor selectivity for cytokine signaling via distinct JAK pairs may provide a mechanistic rationale for reported differences in safety profiles (Figure 1) [1].

The main action of JAK inhibitors is suppression of inflammation and immune responses [8-12]. Drugs that selectively inhibit JAK1 and JAK3 treat autoimmune diseases such as RA, psoriatic arthritis, ulcerative colitis (UC), and Crohn disease [8-12]. JAK2 inhibitors, however, are used in the treatment of myeloid tumors such as myelofibrosis (MF) and primary myeloproliferative disorders [13, 14].

Tofacitinib is a first-generation selective oral JAK1 and JAK3 inhibitor with low activity against JAK2 and TYK2 [15]. Baricitinib is a JAK1 or JAK2 inhibitor with moderate activity against JYK2 and minimal activity against JAK3 [15]. Upadacitinib and filgotinib increase efficacy by selectively inhibiting JAK1, which is involved in the transmission of inflammatory cytokines, and reduce the risk of hematological adverse events (AEs) by preventing JAK2 inhibition [16-18]. Peficitinib inhibits the enzymatic activity of JAK1, JAK2, JAK3, and TYK2 and is expected to have moderate selectivity for JAK3 inhibition and relatively mild inhibition of JAK2, which may have less impact on red blood cells and platelets [19]. Ruxolitinib, a JAK1 and JAK2 inhibitor, is used for the treatment of polycythemia vera (PV), which is known to be associated with inappropriate JAK2 activation and intermediate- and high-risk primary MF [13, 14].

The common AEs of JAK inhibitor usage include infection, anemia, lymphopenia, liver dysfunction, renal dysfunction, and tumor exacerbation. Upper respiratory tract infections, pneumonia, bronchitis, and gastroenteritis are higher in patients treated with JAK inhibitors than in the general population [20]. Opportunistic infections such as herpes zoster (HZ), tuberculosis, and candidiasis have also been reported. Mainly, HZ is widely known as a high-frequency AE associated with JAK inhibitors, with a high incidence in Japan and other Asian countries [21]. The use of JAK inhibitors may increase the risk of thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), cardiovascular events, and malignancy [22, 23]. Safety data have been critical to the research and development of JAK inhibitors in recent years [23].

Understanding the incidence profile of AEs in patients with complex backgrounds and drug treatments is essential in clinical practice. The spontaneous reporting system (SRS) is a valuable tool for pharmacovigilance, reflecting the realities of clinical practice. In Japan, post-marketing AEs are managed by the Pharmaceuticals and Medical Devices Agency (PMDA), a regulatory authority. The Japanese adverse drug event report (JADER) database is an SRS that compiles data voluntarily submitted by healthcare professionals, pharmaceutical companies, and patients. The incidence profile for AEs associated with JAK inhibitors is unclear, and there are relatively fewer reports affecting the onset time of AEs

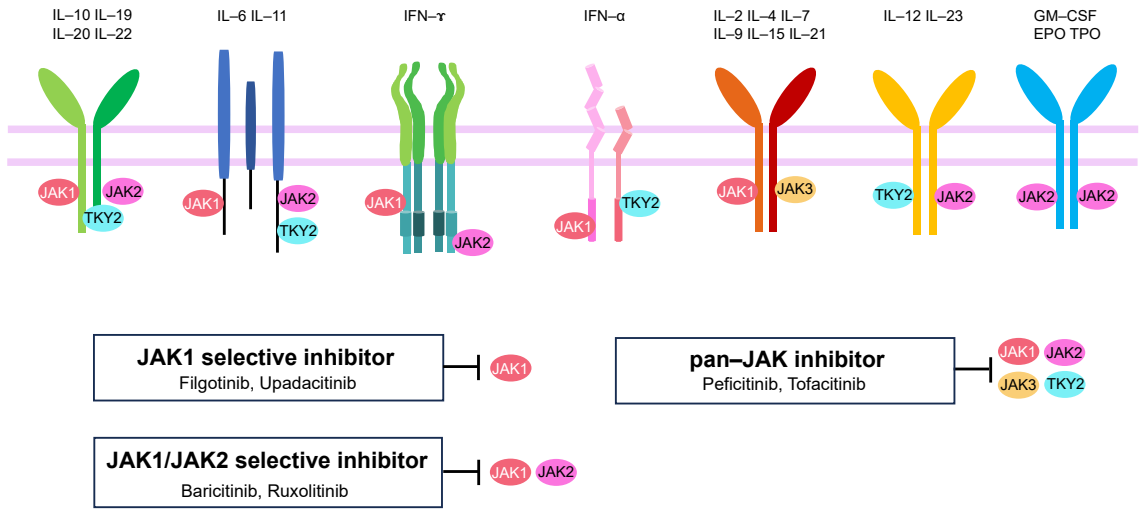

Figure 1. Main cytokine receptors and mechanism of action of inhibitors

caused by JAK inhibitors in actual clinical practice. This study evaluated the incidence profiles of AEs associated with JAK inhibitors by analyzing data from the JADER database.

Materials and Methods

Data source

Relevant information from the JADER database, from April 2004 to March 2023, was downloaded from the PMDA website [24]. The data from the JADER database was fully anonymized by the regulatory authority (PMDA) before we accessed it. The JADER database comprises four tables: DEMO table, including patient's demographic information like gender, age, weight, etc.; DRUG table, including drug information like drug name, causality of drug, etc.; REAC table, including adverse drug reaction, name, outcome, etc.; and HIST table, including medical history like primary diseases, etc. The DEMO table was linked to the DRUG, REAC, and HIST tables using ID numbers. We integrated the relational databases of the four tables from the JADER dataset using MariaDB version. 10.5 [25]. In the DRUG table, each drug was categorized into three codes according to its association with an AE: Suspected drug, concomitant drug, and interacting drug. We only analyzed cases that were categorized as suspected drugs.

Definition of AEs

The definition of AEs used in the JADER database is based on MedDRA (medical dictionary for regulatory activities) version 23.1 [26] (Table 1). Standardized MedDRA queries (SMQs) are widely used to analyze SRS reports [26]. SMQs, built by the Maintenance and Support Services Organization, are groups of preferred terms (PTs) categorized according to the level related to a defined medical condition. The grouping of SMQs allows for valuable data retrieval and the presentation of relevant individual case safety reports. The PTs retrieved with the respective SMQs were as follows: "Pneumonia" with 24 PTs for infective pneumonia (SMQ code: 20000231); "interstitial lung disease (ILD)" with 3 PTs for ILD (SMQ code: 20000042); "herpes zoster" with 11 PTs for ocular infections (SMQ code: 20000183); infective pneumonia (SMQ code: 20000231); opportunistic infections (SMQ code: 20000235); "embolic and thrombotic events" with 26 PTs for embolic and thrombotic events, arterial (SMQ code: 20000082); embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ code: 20000083); embolic and thrombotic events, venous (SMQ code: 20000084); "gastrointestinal perforation (GP)" with 11 PTs for GP (SMQ code: 20000107); "liver disorder" with 14 PTs for liver related investigations, signs and symptoms (SMQ code: 20000008); cholestasis and jaundice of hepatic origin (SMQ code: 20000009); hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions (SMQ code: 20000013); "renal impairment" with 12 PTs for acute renal failure (SMQ code: 20000003); drug reaction with eosinophilia and systemic symptoms syndrome (SMQ code: 20000225); "cardiac failure" with 11 PTs for cardiac failure (SMQ code: 20000004); "hematopoietic erythropenia" with 8 PTs for hematopoietic erythropenia (SMQ code: 20000029); "hematopoietic leukopenia" with 11 PTs for hematopoietic leukopenia (SMQ code: 20000030); "hematopoietic thrombocytopenia" with 2 PTs for hematopoietic thrombocytopenia (SMQ code: 20000031); and "hyperglycemia" with 6 PTs for hyperglycemia/new onset diabetes mellitus (SMQ code: 20000041) (Table 1).

Table 1. PTs associated with JAK inhibitors related AEs in MedDRA and the number of reports

Categories	PT[a] Name	PT Code	Peficitinib	Tofacitinib	Baricitinib	Ruxolitinib	Filgotinib	Upadacitinib
Pneumonia	Pneumonia	10035664	50	222	125	98	9	22
	Pneumonia bacterial	10060946	9	68	28	15	2	7
	Pneumocystis jirovecii pneumonia	10073755	2	66	18	11	3	24
	Pneumonia cytomegaloviral	10035676	0	10	2	3	1	2
	Bronchopulmonary aspergillosis	10006473	0	8	9	12	0	1
	Pneumonia cryptococcal	10067565	0	5	0	7	0	0
	Pneumonia pneumococcal	10035728	1	5	1	2	0	0
	Pneumonia influenzal	10035714	0	3	2	1	0	0
	Pneumonia legionella	10035718	0	3	2	0	0	0
	Pneumonia fungal	10061354	0	2	0	2	1	1
	Pneumonia pseudomonal	10035731	0	2	1	0	0	1
	Pneumonia mycoplasmal	10035724	2	2	0	1	0	0
	Pneumonia viral	10035737	0	2	2	1	0	1
	Pneumonia haemophilus	10035702	0	1	0	0	0	0
	Pneumonia herpes viral	10035703	0	1	0	0	0	0
	Pneumonia klebsiella	10035717	0	1	0	0	0	0
	Pneumonia chlamydial	10035673	0	1	0	0	0	0
	Mycoplasma infection	10061300	0	1	0	0	0	0
	Pneumonia streptococcal	10035735	0	1	0	1	0	0
	Pneumonia escherichia	10035699	1	0	0	0	0	0
	Pneumonia staphylococcal	10035734	1	0	1	1	0	0
	Pneumonia necrotising	10055672	0	0	1	0	0	0
	Pneumococcal infection	10061353	0	0	1	0	0	0
	Pneumonia moraxella	10035723	0	0	1	0	0	0
ILD	ILD	10022611	20	120	38	25	10	23
	Organising pneumonia	10067472	1	10	6	4	0	3
	Pulmonary fibrosis	10037383	0	3	0	0	0	0
Herpes zoster	Herpes zoster	10019974	21	252	138	27	1	40
	Herpes zoster oticus	10063491	0	5	3	0	0	1
	Varicella zoster pneumonia	10074254	0	3	0	0	0	0
	Varicella zoster virus infection	10075611	0	3	0	1	0	0
	Herpes zoster meningitis	10074259	0	3	1	0	1	1
	Ophthalmic HZ	10030865	0	2	3	0	0	0
	Herpes zoster meningoencephalitis	10074248	0	2	0	0	0	0
	Herpes zoster infection neurological	10061208	0	1	0	0	0	0
	Herpes zoster meningomyelitis	10074251	0	1	0	0	0	0
	Genital HZ	10072210	0	1	0	0	0	0
	Disseminated varicella zoster virus infection	10084396	0	0	0	0	0	1

Categories	PT[a] Name	PT Code	Peficitinib	Tofacitinib	Baricitinib	Ruxolitinib	Filgotinib	Upadacitinib
Embolic and thrombotic events	Deep vein thrombosis	10051055	5	22	17	2	2	5
	Disseminated intravascular coagulation	10013442	1	17	3	1	0	1
	Cerebral infarction	10008118	4	15	13	10	2	1
	Pulmonary embolism	10037377	2	10	12	6	0	5
	Embolism venous	10014522	0	6	0	0	0	1
	Myocardial infarction	10028596	5	5	4	1	1	1
	Acute myocardial infarction	10000891	0	4	3	2	2	1
	Thrombosis	10043607	0	3	4	2	0	0
	Venous thrombosis limb	10061408	0	3	1	0	0	1
	Thrombotic thrombocytopenic purpura	10043648	0	3	0	0	0	0
	Thrombophlebitis	10043570	0	2	0	0	0	0
	Embolism	10061169	0	1	0	1	0	0
	Cerebral thrombosis	10008132	0	1	1	0	1	1
	Pulmonary artery thrombosis	10037340	0	1	1	1	0	0
	Lacunar infarction	10051078	2	1	1	0	0	0
	Brain stem infarction	10006147	0	1	3	0	0	0
	Peripheral embolism	10061340	0	1	0	0	0	0
	Aortic thrombosis	10002910	0	1	0	1	0	0
	Embolic cerebral infarction	10060839	1	0	0	0	0	0
	Haemorrhagic cerebral infarction	10019005	1	0	0	0	1	1
	Cerebellar infarction	10008034	1	0	3	0	0	0
	Retinal vein occlusion	10038907	0	0	2	1	0	0
	Thrombotic cerebral infarction	10067347	0	0	2	0	1	1
	Pulmonary infarction	10037410	0	0	1	0	0	0
	Peripheral arterial occlusive disease	10062585	0	0	1	0	0	0
	Cardiac ventricular thrombosis	10053994	0	0	1	0	0	0
Cardiac failure	Cardiac failure	10007554	9	11	3	39	1	1
	Cardiac failure congestive	10007559	1	6	3	10	0	0
	Oedema peripheral	10030124	0	6	1	3	0	0
	Cardiac failure acute	10007556	3	5	1	4	0	0
	Peripheral swelling	10048959	0	1	0	0	0	0
	Cardiac dysfunction	10079751	0	1	0	0	0	0
	Pulmonary oedema	10037423	0	1	0	2	0	0
	Brain natriuretic peptide increased	10053405	0	1	0	0	0	0
	Oedema	10030095	0	1	0	3	0	0
	Cardiac failure chronic	10007558	2	1	0	3	0	0
	Cor pulmonale	10010968	1	0	0	0	0	0

Categories	PT[a] Name	PT Code	Peficitinib	Tofacitinib	Baricitinib	Ruxolitinib	Filgotinib	Upadacitinib
Gastrointestinal perforation	Large intestine perforation	10023804	2	6	2	1	0	0
	Duodenal perforation	10013832	0	3	0	0	0	0
	Intestinal perforation	10022694	0	3	0	0	0	0
	Gastrointestinal perforation	10018001	1	3	0	1	1	1
	Rectal perforation	10038073	1	2	0	0	0	0
	Diverticular perforation	10061820	0	2	3	0	0	1
	Gastric ulcer perforation	10017835	0	1	0	0	0	0
	Small intestinal perforation	10041103	0	1	0	1	0	0
	Gastric perforation	10017815	1	0	0	1	0	0
	Enterovesical fistula	10062570	0	0	1	0	0	0
	Oesophageal rupture	10052211	0	0	0	0	2	2
Liver disorder	Hepatic function abnormal	10019670	2	23	6	35	1	1
	Liver disorder	10024670	1	13	2	17	2	1
	Aspartate aminotransferase increased	10003481	0	10	0	12	0	0
	Gamma-glutamyltransferase increased	10017693	1	8	0	11	0	0
	Alanine aminotransferase increased	10001551	0	7	1	8	0	0
	Transaminases increased	10054889	0	3	0	1	0	0
	Liver function test increased	10077692	0	2	4	0	0	0
	Blood alkaline phosphatase increased	10059570	0	2	0	14	0	0
	Blood cholinesterase decreased	10005430	0	1	0	0	0	0
	Blood bilirubin increased	10005364	0	1	0	4	0	0
	Liver function test abnormal	10024690	1	1	0	0	0	0
	Drug-induced liver injury	10072268	1	1	1	6	0	1
	Hepatic enzyme increased	10060795	0	1	2	5	0	0
	Jaundice cholestatic	10023129	0	0	1	0	0	0
Renal impairment	Renal impairment	10062237	38	29	8	45	10	10
	Acute kidney injury	10069339	2	7	4	8	0	2
	Renal failure	10038435	1	4	0	6	1	1
	Protein urine present	10053123	0	4	0	1	0	0
	Blood urea increased	10005851	0	3	0	1	0	0
	Blood creatinine increased	10005483	0	2	0	3	0	0
	Renal disorder	10038428	0	2	0	5	0	0
	Urine output decreased	10059895	0	1	0	0	0	0
	Creatinine renal clearance decreased	10011372	0	1	0	0	0	0
	Tubulointerstitial nephritis	10048302	2	1	0	1	0	0
	Glomerular filtration rate decreased	10018358	0	0	3	0	0	0
	Nephritis	10029117	0	0	0	0	1	1

Categories	PT[a] Name	PT Code	Peficitinib	Tofacitinib	Baricitinib	Ruxolitinib	Filgotinib	Upadacitinib
Hematopoietic erythropenia	Anaemia	10002034	3	26	26	374	2	4
	Haemoglobin decreased	10018884	0	19	1	131	1	1
	Red blood cell count decreased	10038153	0	11	0	5	0	0
	Haematocrit decreased	10018838	0	8	0	1	0	0
	Anaemia macrocytic	10002064	0	4	0	0	0	0
	Aplasia pure red cell	10002965	0	2	0	1	0	0
	Microcytic anaemia	10027538	0	1	0	0	0	0
	Aplastic anaemia	10002967	0	0	1	0	0	0
Hematopoietic leukopenia	Lymphocyte count decreased	10025256	3	28	4	32	0	0
	White blood cell count decreased	10047942	0	13	5	49	1	1
	Febrile neutropenia	10016288	0	9	0	6	0	0
	Neutrophil count decreased	10029366	0	7	6	29	0	3
	Leukopenia	10024384	1	4	18	9	0	0
	Lymphocyte percentage decreased	10052231	0	4	0	0	0	0
	Lymphopenia	10025327	0	4	0	7	0	0
	Basophil percentage decreased	10052219	0	2	0	0	0	0
	Neutropenia	10029354	3	2	0	9	1	1
	Eosinophil percentage decreased	10052221	0	1	0	0	0	0
	Granulocyte count decreased	10018681	0	0	1	0	0	0
Hematopoietic thrombocytopenia	Platelet count decreased	10035528	0	11	3	252	0	0
	Thrombocytopenia	10043554	2	6	0	42	0	0
Hyperglycemia	Blood glucose increased	10005557	0	5	0	1	0	0
	Diabetes mellitus	10012601	1	3	0	1	0	0
	Hyperglycaemic hyperosmolar nonketotic syndrome	10063554	0	2	0	0	0	0
	Glucose urine present	10018478	0	1	0	0	0	0
	Diabetes mellitus inadequate control	10012607	0	1	0	0	0	0
	Type 2 diabetes mellitus	10067585	0	0	0	1	0	0

[a]Preferred terms by the MedDRA version 23.1.

PBR

Drug selection

Six oral JAK inhibitors approved in Japan as of 2022 were examined. The JAK inhibitors analyzed in this study, along with the indications in parenthesis, are ruxolitinib (MF, PV), tofacitinib (RA, UC), baricitinib (RA, atopic dermatitis, pneumonia due to SARS-CoV-2, alopecia areata), upadacitinib (RA, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis), filgotinib (RA, UC), and peficitinib (RA, UC).

Signal detection

To detect AEs associated with JAK inhibitors, we calculated the crude reporting odds ratio (ROR) using a 2-by-2 contingency table. Using multiple-logistic regression analysis, we also calculated the adjusted RORs to control for the covariates. We considered a signal detected if the estimated ROR and the lower limit of the corresponding 95% confidence interval (CI) was greater than one and if at least two cases were reported [27]. The reports were stratified by reporting age ≤59 and ≥60 years and sex (male and female). The following multiple logistic regression model (Equation 1) was used for the analysis:

1. $\log(\text{odds}) = \beta_0 + \beta_1 Y + \beta_2 S + \beta_3 A + \beta_4 D$

where, Y is the reporting year, S denotes sex, A is the stratified age group, and D is the JAK inhibitor. Data analyses were performed using the statsmodels version 0.13.2 in Python (version 3.8.13) [28].

Time-to-onset analysis

Recently, time-to-onset analysis has been proposed to detect AE signals in SRSs. It has been reported that the incidence of AEs after prescription depends on causative factors and often changes over time. In contrast, AEs not drug-related occur constantly as a background. Therefore, changes in the incidence of AEs over time may indicate a relationship between a drug and the AE [29, 30]. The specific parameter α of the Weibull probability density function determines the scale of the function, and the shape parameter β determines the shape of the function. The shape parameter β of the Weibull distribution was used to display the hazard without a reference population as follows. If the 95% CI of β included 1, the hazard was estimated to be constant (random failure type). If the lower limit of the 95% CI of β was greater than 1, the hazard was considered to increase over time (wear-out failure type). Finally, if the upper limit of the 95% CI of β was less than 1, the hazard was considered to decrease over time (initial failure type). Reports in which the time of occurrence of the AE and the time of prescription initiation were incomplete were excluded from the analysis. We calculated the period from the date of the dose to the date of the first onset of the AE and fitted it to a Weibull function using the parametric SurPyval model in SurPyval (version 0.10.1.0) in Python (version 3.8.13) [31].

Results

A total of 823662 reports were submitted to the JADER database during the study period. Also, 5524 cases were reported with JAK inhibitors as suspected drugs, with the following reporting rates: Peficitinib 8.6% (n=476), tofacitinib 39.2% (n=2164), baricitinib 19.1% (n=1054), ruxolitinib 25.8% (n=1427), filgotinib 2.3% (n=127), and upadacitinib 5.7% (n=314). Women reported 67.6% use of the JAK inhibitors, excluding ruxolitinib, whereas men reported 57.6% use of ruxolitinib. The reporting ratios of AEs in patients in their 80s, 70s, 60s, and 50s who were administered the JAK inhibitors, except for ruxolitinib, were 13.0%, 38.1%, 21.9%, and 7.6%, respectively. Among the reports on ruxolitinib, the percentages of patients with MF and PV were 76.9% and 20.6%, respectively. Of the reports on peficitinib, tofacitinib, baricitinib, filgotinib, and upadacitinib, the percentages of patients with RA history were 98.5%, 83.4%, 85.8%, 81.8%, and 89.7%, respectively.

ROR analysis

The crude and adjusted RORs for the categorized AEs of JAK inhibitors are summarized in Table 2. The coefficients of the confounding factors adjusted by multiple logistic regression are shown in Table 3. Adjusted RORs for pneumonia with peficitinib, tofacitinib, baricitinib, ruxolitinib, filgotinib, and upadacitinib were 4.40 (95% CI, 3.36%, 5.75%), 6.93 (95% CI, 6.18%, 7.77%), 6.51 (95% CI, 5.52%, 7.67%), 3.30 (95% CI, 2.76%, 3.95%), 4.39 (95% CI, 2.55%, 7.58%), and 6.11 (95% CI, 4.53%, 8.23%). The adjusted RORs for HZ with peficitinib, tofacitinib, baricitinib, ruxolitinib, and upadacitinib were 8.94 (95% CI, 5.69%, 14.05%), 31.82 (95% CI, 27.58%, 36.71%), 34.96 (95% CI, 28.92%, 42.26%), 5.24 (95% CI, 3.57%, 7.7%), and 33.19 (95% CI, 23.81%, 46.27%), respectively. Adjusted RORs with ruxolitinib for hematopoietic erythropenia, hematopoietic leukopenia, hematopoietic thrombocytopenia, liver disorder, and cardiac failure were 23.51 (95% CI: 20.92%, 26.42%), 1.57 (95% CI: 1.29%, 1.9%), 8.36 (95% CI, 7.3%, 9.57%), 1.71 (95% CI, 1.39%, 2.11%), and 1.85 (95% CI, 1.41%, 2.42%), respectively.

Time-to-onset analysis

For the time-to-onset analysis, we used only combinations for which we had complete information on the drug start date and AE onset date. Boxplots were created for each JAK inhibitor with respect to the time of onset of each AE (Figure 2). We summarize the median number of days, from the start of treatment to disease

Table 2. Number of reports and crude ROR and adjusted ROR of JAK inhibitor related AEs

AE Category	Drug	No.		Crude ROR[a] (95% CI)[b]	Adjusted ROR (95% CI)
		Total case	Case		
Pneumonia	Peficitinib	23677	62	4.68 (4.08-5.37)	4.4 (3.36-5.75)
	Tofacitinib	23677	371	6.99 (6.6-7.41)	6.93 (6.18-7.77)
	Baricitinib	23677	178	6.7 (6.17-7.28)	6.51 (5.52-7.67)
	Ruxolitinib	23677	136	3.7 (3.37-4.05)	3.3 (2.76-3.95)
	Filgotinib	23677	15	4.62 (3.5-6.09)	4.39 (2.55-7.58)
	Upadacitinib	23677	53	6.45 (5.55-7.51)	6.11 (4.53-8.23)
Herpes zoster	Peficitinib	3099	20	10.78 (8.57-13.56)	8.94 (5.69-14.05)
	Tofacitinib	3099	239	34.92 (32.51-37.51)	31.82 (27.58-36.71)
	Baricitinib	3099	136	39.7 (36.13-43.62)	34.96 (28.92-42.26)
	Ruxolitinib	3099	27	5.27 (4.33-6.4)	5.24 (3.57-7.7)
	Filgotinib	3099	1	c	c
	Upadacitinib	3099	42	38.94 (32.94-46.03)	33.19 (23.81-46.27)
Haematopoietic erythropenia	Peficitinib	18823	3	0.25 (0.14-0.45)	0.27 (0.09-0.85)
	Tofacitinib	18823	52	1.02 (0.89-1.18)	1.06 (0.81-1.4)
	Baricitinib	18823	27	1.08 (0.89-1.31)	1.18 (0.8-1.73)
	Ruxolitinib	18823	459	22.68 (21.38-24.06)	23.51 (20.92-26.42)
	Filgotinib	18823	2	0.69 (0.34-1.4)	0.78 (0.19-3.15)
	Upadacitinib	18823	5	0.64 (0.41-1.01)	0.73 (0.3-1.77)
Hematopoietic leukopenia	Peficitinib	46098	7	0.23 (0.16-0.34)	0.27 (0.13-0.57)
	Tofacitinib	46098	62	0.48 (0.42-0.55)	0.52 (0.41-0.68)
	Baricitinib	46098	32	0.39 (0.32-0.48)	0.45 (0.3-0.67)
	Ruxolitinib	46098	112	1.48 (1.34-1.63)	1.57 (1.29-1.9)
	Filgotinib	46098	2	0.27 (0.13-0.55)	0.32 (0.08-1.31)
	Upadacitinib	46098	4	0.20 (0.12-0.33)	0.24 (0.09-0.64)
Hematopoietic thrombocytopenia	Peficitinib	25580	2	0.12 (0.06-0.25)	0.15 (0.04-0.61)
	Tofacitinib	25580	17	0.24 (0.19-0.3)	0.27 (0.17-0.44)
	Baricitinib	25580	3	0.08 (0.05-0.15)	0.11 (0.03-0.33)
	Ruxolitinib	25580	275	7.92 (7.4-8.49)	8.36 (7.3-9.57)
	Filgotinib	25580	0	c	c
	Upadacitinib	25580	0	c	c

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AE Category	Drug	No.		Crude ROR[a] (95% CI)[b]	Adjusted ROR (95% CI)
		Total case	Case		
Liver disorder	Peficitinib	43202	5	0.18 (0.11-0.28)	0.29 (0.12-0.71)
	Tofacitinib	43202	54	0.45 (0.39-0.51)	0.61 (0.46-0.8)
	Baricitinib	43202	16	0.27 (0.21-0.34)	0.42 (0.26-0.69)
	Ruxolitinib	43202	94	1.31 (1.17-1.46)	1.71 (1.39-2.11)
	Filgotinib	43202	3	0.44 (0.24-0.79)	0.77 (0.24-2.42)
	Upadacitinib	43202	3	0.16 (0.09-0.29)	0.28 (0.09-0.87)
Renal impairment	Peficitinib	28912	43	2.52 (2.14-2.95)	2.38 (1.73-3.25)
	Tofacitinib	28912	36	0.45 (0.38-0.53)	0.44 (0.32-0.61)
	Baricitinib	28912	11	0.28 (0.2-0.37)	0.27 (0.15-0.48)
	Ruxolitinib	28912	55	1.13 (0.98-1.3)	1.02 (0.78-1.33)
	Filgotinib	28912	9	2.12 (1.5-3)	2.02 (1.02-3.99)
	Upadacitinib	28912	3	0.25 (0.14-0.44)	0.23 (0.07-0.72)
ILD	Peficitinib	34389	21	0.97 (0.78-1.22)	1.02 (0.66-1.59)
	Tofacitinib	34389	123	1.35 (1.23-1.48)	1.44 (1.19-1.73)
	Baricitinib	34389	41	0.89 (0.76-1.04)	0.96 (0.7-1.32)
	Ruxolitinib	34389	25	0.42 (0.34-0.51)	0.36 (0.24-0.53)
	Filgotinib	34389	8	1.56 (1.08-2.25)	1.72 (0.84-3.55)
	Upadacitinib	34389	24	1.77 (1.43-2.19)	1.90 (1.25-2.89)
Cardiac failure	Peficitinib	15830	15	1.53 (1.18-1.99)	1.23 (0.73-2.06)
	Tofacitinib	15830	28	0.65 (0.54-0.79)	0.57 (0.39-0.82)
	Baricitinib	15830	6	0.28 (0.19-0.42)	0.23 (0.1-0.52)
	Ruxolitinib	15830	55	2.10 (1.83-2.41)	1.85 (1.41-2.42)
	Filgotinib	15830	1	c	c
	Upadacitinib	15830	1	c	c
Embolic and thrombotic events	Peficitinib	23591	14	0.95 (0.72-1.24)	0.83 (0.48-1.41)
	Tofacitinib	23591	76	1.20 (1.07-1.35)	1.12 (0.89-1.4)
	Baricitinib	23591	56	1.83 (1.59-2.1)	1.64 (1.25-2.15)
	Ruxolitinib	23591	21	0.52 (0.41-0.64)	0.46 (0.3-0.72)
	Filgotinib	23591	9	2.62 (1.85-3.71)	2.30 (1.16-4.54)
	Upadacitinib	23591	10	1.04 (0.75-1.43)	0.91 (0.49-1.72)

AE Category	Drug	No.		Crude ROR[a] (95% CI)[b]	Adjusted ROR (95% CI)
		Total case	Case		
Gastrointestinal perforation	Peficitinib	6051	5	1.32 (0.84-2.07)	1.23 (0.51-2.98)
	Tofacitinib	6051	21	1.29 (1.03-1.61)	1.24 (0.81-1.91)
	Baricitinib	6051	6	0.74 (0.49-1.12)	0.70 (0.31-1.56)
	Ruxolitinib	6051	4	0.39 (0.23-0.64)	0.37 (0.14-0.98)
	Filgotinib	6051	3	3.30 (1.84-5.92)	3.09 (0.98-9.73)
	Upadacitinib	6051	2	0.81 (0.4-1.64)	0.76 (0.19-3.04)
Hyperglycemia	Peficitinib	4719	1	c	c
	Tofacitinib	4719	11	0.86 (0.64-1.17)	0.89 (0.49-1.62)
	Baricitinib	4719	0	c	c
	Ruxolitinib	4719	3	0.37 (0.21-0.67)	0.37 (0.12-1.14)
	Filgotinib	4719	0	c	c
	Upadacitinib	4719	0	c	c

[a]Odds ratio, [b]Confdence interval, [c]Number of cases was <2.

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onset, and the calculated Weibull parameters in Table 4. The time-to-onset of pneumonia and HZ were highly variable for all JAK inhibitors. For tofacitinib, which was reported most frequently, the median time-to-onset (interquartile range: IQR) and the Weibull parameter β (95% CI) for pneumonia were 166.0 (IQR: 57–309) days and 1.04 (95% CI, 0.94%, 1.13%), and for HZ they were 232 (IQR: 73–402.8) days and 1.23 (95% CI, 1.08%, 1.38%), respectively. Hematopoietic erythropenia, leukopenia, and thrombocytopenia were most frequently reported with ruxolitinib and occurred early in the initiation of treatment. The median time-to-onset (IQR) and the Weibull β values were 50.0 (IQR: 25.5–105.5) days and 0.91 (95% CI, 0.81%, 1.00%) for erythropenia, 31.0 (IQR: 11–139) days and 0.72 (95% CI, 0.55%, 0.89%) for leukopenia, and 37.0 (IQR: 17.8–105.3) days and 0.84 (95% CI, 0.74%, 0.95%) for thrombocytopenia. The incidence of hepatic and renal disorders varied according to the formulation; however, the number of reports was small. ILD was reported at a median of 3 to 4 months after drug initiation. Cardiac failure, embolic and thrombotic events, and GP were reported less frequently; trends in the duration of these AEs could not be ascertained.

Discussion

Pneumonia is a serious infectious event observed in clinical trials involving JAK inhibitors [13, 32-36]. In our study, pneumonia was the most reported infection-related AE, with ROR signals detected. The median time-to-onset of pneumonia ranged from 2 to 6 months with all JAK inhibitors. Multiple logistic regression analysis showed that pneumonia was reported more frequently in males over 60. In safety reports of tofacitinib, males and older people are reported to be at risk of serious infections, including pneumonia [32].

Herpes zoster is also a frequent AE of JAK inhibitor use, as per our study. Severe cases have been reported to date, but infrequently so [32-36]. Irreversible ganglion cell necrosis may result in residual postherpetic neuralgia and sequelae, such as physical disability and mental anguish, making it an AE that requires sufficient vigilance, with a poor prognosis in severe cases of HZ [37]. The degree of inhibition of the JAK3-dependent pathway is low and thus appears to have little effect on homeostatic immune functions that control infection and HZ [1]. A family history of HZ, physical trauma, older age, female gender, psychological stress, and the presence of comorbidities such as diabetes, RA, cardiovascular diseases, kidney disease, systemic lupus erythematosus, and inflammatory bowel disease have been reported as

Table 3. Variable and adjusted ROR in multiple logistic regression analysis

AE Category	Drug	Variables	Estimated Beta		Wald Test	Adjusted ROR[a] (95% CI)[b]
Pneumonia	Peficitinib	Reporting year	β1	0	0.0178	1 (1–1.01)
		Female	β2	-0.19	<0.0001	0.83 (0.81–0.85)
		≥60 years old	β3	0.51	<0.0001	1.66 (1.61–1.71)
	Tofacitinib	Reporting year	β1	0	0.1507	1(1–1)
		Female	β2	-0.2	<0.0001	0.82 (0.8–0.84)
		≥60 years old	β3	0.5	<0.0001	1.65 (1.6–1.7)
	Baricitinib	Reporting year	β1	0	0.0859	1.00 (1–1)
		Female	β2	-0.19	<0.0001	0.82 (0.8–0.85)
		≥60 years old	β3	0.5	<0.0001	1.66 (1.61–1.71)
	Ruxolitinib	Reporting year	β1	0	0.0147	1 (1–1.01)
		Female	β2	-0.19	<0.0001	0.83 (0.81–0.85)
		≥60 years old	β3	0.5	<0.0001	1.66 (1.61–1.71)
	Filgotinib	Reporting year	β1	0	0.0085	1.00 (1–1.01)
		Female	β2	-0.19	<0.0001	0.83 (0.81–0.85)
		≥60 years old	β3	0.51	<0.0001	1.66 (1.61–1.71)
	Upadacitinib	Reporting year	β1	0	0.0177	1.00 (1–1.01)
		Female	β2	-0.19	<0.0001	0.83 (0.81–0.85)
		≥60 years old	β3	0.51	<0.0001	1.66 (1.61–1.71)
Herpes zoster	Peficitinib	Reporting year	β1	0.02	<0.0001	1.02 (1.01–1.02)
		Female	β2	0.5	<0.0001	1.65 (1.54–1.78)
		≥60 years old	β3	-0.08	0.0427	0.93 (0.86–1)
	Tofacitinib	Reporting year	β1	0.01	0.0286	1.01 (1–1.02)
		Female	β2	0.45	<0.0001	1.57 (1.46–1.69)
		≥60 years old	β3	-0.11	0.0031	0.90 (0.83–0.96)
	Baricitinib	Reporting year	β1	0.01	0.0199	1.01 (1–1.02)
		Female	β2	0.47	<0.0001	1.60 (1.49–1.72)
		≥60 years old	β3	-0.1	0.0084	0.91 (0.84–0.98)
	Ruxolitinib	Reporting year	β1	0.02	<0.0001	1.02 (1.01–1.02)
		Female	β2	0.51	<0.0001	1.66 (1.55–1.79)
		≥60 years old	β3	-0.08	0.0382	0.93 (0.86–1)
	Filgotinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
	Upadacitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.02)
		Female	β2	0.5	<0.0001	1.65 (1.53–1.77)
		≥60 years old	β3	-0.08	0.0321	0.92 (0.86–0.99)

AE Category	Drug	Variables	Estimated Beta		Wald Test	Adjusted ROR[a] (95% CI)[b]
Hematopoietic erythropenia	Peficitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.97)
		Female	β2	0.17	<0.0001	1.19 (1.15–1.22)
		≥60 years old	β3	0.42	<0.0001	1.53 (1.48–1.58)
	Tofacitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.97)
		Female	β2	0.17	<0.0001	1.19 (1.15–1.22)
		≥60 years old	β3	0.42	<0.0001	1.53 (1.48–1.58)
	Baricitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.97)
		Female	β2	0.17	<0.0001	1.19 (1.15–1.22)
		≥60 years old	β3	0.42	<0.0001	1.53 (1.48–1.58)
	Ruxolitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.96–0.97)
		Female	β2	0.17	<0.0001	1.19 (1.16–1.23)
		≥60 years old	β3	0.41	<0.0001	1.50 (1.45–1.55)
	Filgotinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.97)
		Female	β2	0.17	<0.0001	1.19 (1.15–1.22)
		≥60 years old	β3	0.42	<0.0001	1.53 (1.48–1.58)
	Upadacitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.97)
		Female	β2	0.17	<0.0001	1.19 (1.15–1.22)
		≥60 years old	β3	0.42	<0.0001	1.53 (1.48–1.58)
Hematopoietic leukopenia	Peficitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.98)
		Female	β2	0	0.6748	1 (0.99–1.02)
		≥60 years old	β3	0.1	<0.0001	1.10 (1.08–1.13)
	Tofacitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.98)
		Female	β2	0	0.629	1 (0.99–1.02)
		≥60 years old	β3	0.1	<0.0001	1.10 (1.08–1.13)
	Baricitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.98)
		Female	β2	0	0.6573	1 (0.99–1.02)
		≥60 years old	β3	0.1	<0.0001	1.10 (1.08–1.13)
	Ruxolitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.98)
		Female	β2	0	0.7018	1 (0.98–1.02)
		≥60 years old	β3	0.1	<0.0001	1.10 (1.08–1.12)
	Filgotinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.98)
		Female	β2	0	0.6994	1.00 (0.98–1.02)
		≥60 years old	β3	0.1	<0.0001	1.10 (1.08–1.13)
	Upadacitinib	Reporting year	β1	-0.03	<0.0001	0.97 (0.97–0.98)
		Female	β2	0	0.6891	1 (0.99–1.02)
		≥60 years old	β3	0.1	<0.0001	1.10 (1.08–1.13)

AE Category	Drug	Variables	Estimated Beta		Wald Test	Adjusted ROR[a] (95% CI)[b]
Hematopoietic thrombocytopenia	Peficitinib	Reporting year	β1	-0.05	<0.0001	0.96 (0.95–0.96)
		Female	β2	-0.05	0.0002	0.95 (0.93–0.98)
		≥60 years old	β3	0.49	<0.0001	1.63 (1.58–1.68)
	Tofacitinib	Reporting year	β1	-0.05	<0.0001	0.96 (0.95–0.96)
		Female	β2	-0.05	0.0003	0.95 (0.93–0.98)
		≥60 years old	β3	0.49	<0.0001	1.63 (1.59–1.68)
	Baricitinib	Reporting year	β1	-0.05	<0.0001	0.96 (0.95–0.96)
		Female	β2	-0.05	0.0003	0.95 (0.93–0.98)
		≥60 years old	β3	0.49	<0.0001	1.63 (1.58–1.68)
	Ruxolitinib	Reporting year	β1	-0.05	<0.0001	0.95 (0.95–0.96)
		Female	β2	-0.05	0.0002	0.95 (0.93–0.98)
		≥60 years old	β3	0.48	<0.0001	1.62 (1.57–1.66)
	Filgotinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
	Upadacitinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
Liver disorder	Peficitinib	Reporting year	β1	-0.07	<0.0001	0.94 (0.93–0.94)
		Female	β2	-0.04	0.0002	0.96 (0.94–0.98)
		≥60 years old	β3	-0.16	<0.0001	0.85 (0.84–0.87)
	Tofacitinib	Reporting year	β1	-0.07	<0.0001	0.94 (0.93–0.94)
		Female	β2	-0.04	0.0002	0.96 (0.94–0.98)
		≥60 years old	β3	-0.16	<0.0001	0.85 (0.84–0.87)
	Baricitinib	Reporting year	β1	-0.07	<0.0001	0.94 (0.93–0.94)
		Female	β2	-0.04	0.0002	0.96 (0.94–0.98)
		≥60 years old	β3	-0.16	<0.0001	0.85 (0.84–0.87)
	Ruxolitinib	Reporting year	β1	-0.07	<0.0001	0.93 (0.93–0.94)
		Female	β2	-0.04	0.0002	0.96 (0.94–0.98)
		≥60 years old	β3	-0.16	<0.0001	0.85 (0.84–0.87)
	Filgotinib	Reporting year	β1	-0.07	<0.0001	0.94 (0.93–0.94)
		Female	β2	-0.04	0.0002	0.96 (0.94–0.98)
		≥60 years old	β3	-0.16	<0.0001	0.85 (0.84–0.87)
	Upadacitinib	Reporting year	β1	-0.07	<0.0001	0.94 (0.93–0.94)
		Female	β2	-0.04	0.0002	0.96 (0.94–0.98)
		≥60 years old	β3	-0.16	<0.0001	0.85 (0.84–0.87)

AE Category	Drug	Variables	Estimated Beta		Wald Test	Adjusted ROR[a] (95% CI)[b]
Renal impairment	Peficitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.23	<0.0001	0.79 (0.77–0.81)
		≥60 years old	β3	0.37	<0.0001	1.45 (1.41–1.48)
	Tofacitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.23	<0.0001	0.79 (0.78–0.81)
		≥60 years old	β3	0.37	<0.0001	1.45 (1.41–1.49)
	Baricitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.23	<0.0001	0.79 (0.78–0.81)
		≥60 years old	β3	0.37	<0.0001	1.45 (1.41–1.49)
	Ruxolitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.23	<0.0001	0.79 (0.77–0.81)
		≥60 years old	β3	0.37	<0.0001	1.45 (1.41–1.48)
	Filgotinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.23	<0.0001	0.79 (0.77–0.81)
		≥60 years old	β3	0.37	<0.0001	1.45 (1.41–1.48)
	Upadacitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.23	<0.0001	0.79 (0.78–0.81)
		≥60 years old	β3	0.37	<0.0001	1.45 (1.41–1.48)
ILD	Peficitinib	Reporting year	β1	-0.02	<0.0001	0.98 (0.98–0.99)
		Female	β2	-0.45	<0.0001	0.64 (0.62–0.65)
		≥60 years old	β3	1.05	<0.0001	2.85 (2.77–2.93)
	Tofacitinib	Reporting year	β1	-0.02	<0.0001	0.98 (0.98–0.99)
		Female	β2	-0.45	<0.0001	0.64 (0.62–0.65)
		≥60 years old	β3	1.05	<0.0001	2.85 (2.77–2.93)
	Baricitinib	Reporting year	β1	-0.02	<0.0001	0.98 (0.98–0.99)
		Female	β2	-0.45	<0.0001	0.64 (0.62–0.65)
		≥60 years old	β3	1.05	<0.0001	2.85 (2.77–2.93)
	Ruxolitinib	Reporting year	β1	-0.02	<0.0001	0.98 (0.98–0.99)
		Female	β2	-0.45	<0.0001	0.64 (0.62–0.65)
		≥60 years old	β3	1.05	<0.0001	2.85 (2.77–2.94)
	Filgotinib	Reporting year	β1	-0.02	<0.0001	0.98 (0.98–0.99)
		Female	β2	-0.45	<0.0001	0.64 (0.62–0.65)
		≥60 years old	β3	1.05	<0.0001	2.85 (2.77–2.93)
	Upadacitinib	Reporting year	β1	-0.02	<0.0001	0.98 (0.98–0.99)
		Female	β2	-0.45	<0.0001	0.64 (0.62–0.65)
		≥60 years old	β3	1.05	<0.0001	2.85 (2.77–2.93)

AE Category	Drug	Variables	Estimated Beta		Wald Test	Adjusted ROR[a] (95% CI)[b]
Cardiac failure	Peficitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.02)
		Female	β2	0.18	<0.0001	1.2 (1.16–1.24)
		≥60 years old	β3	0.49	<0.0001	1.63 (1.58–1.69)
	Tofacitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.02)
		Female	β2	0.18	<0.0001	1.2 (1.16–1.24)
		≥60 years old	β3	0.49	<0.0001	1.63 (1.58–1.69)
	Baricitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.02)
		Female	β2	0.18	<0.0001	1.20 (1.16–1.24)
		≥60 years old	β3	0.49	<0.0001	1.63 (1.58–1.69)
	Ruxolitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.02)
		Female	β2	0.18	<0.0001	1.20 (1.16–1.24)
		≥60 years old	β3	0.49	<0.0001	1.63 (1.57–1.69)
	Filgotinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
	Upadacitinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
Embolic and thrombotic events	Peficitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.01	0.2858	0.99 (0.96–1.01)
		≥60 years old	β3	0.36	<0.0001	1.44 (1.40–1.48)
	Tofacitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.01	0.272	0.99 (0.96–1.01)
		≥60 years old	β3	0.36	<0.0001	1.44 (1.40–1.48)
	Baricitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.02	0.2517	0.98 (0.96–1.01)
		≥60 years old	β3	0.36	<0.0001	1.44 (1.39–1.48)
	Ruxolitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.01	0.2795	0.99 (0.96–1.01)
		≥60 years old	β3	0.36	<0.0001	1.44 (1.4–1.48)
	Filgotinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.01	0.2736	0.99 (0.96–1.01)
		≥60 years old	β3	0.36	<0.0001	1.44 (1.4–1.48)
	Upadacitinib	Reporting year	β1	0.01	<0.0001	1.01 (1.01–1.01)
		Female	β2	-0.01	0.2826	0.99 (0.96–1.01)
		≥60 years old	β3	0.36	<0.0001	1.44 (1.4–1.48)

AE Category	Drug	Variables	Estimated Beta		Wald Test	Adjusted ROR[a] (95% CI)[b]
Gastrointestinal perforation	Peficitinib	Reporting year	β1	0	0.0532	1 (1–1.01)
		Female	β2	-0.01	0.7942	0.99 (0.94–1.04)
		≥60 years old	β3	0.21	<0.0001	1.23 (1.16–1.3)
	Tofacitinib	Reporting year	β1	0	0.0556	1 (1–1.01)
		Female	β2	-0.01	0.782	0.99 (0.94–1.04)
		≥60 years old	β3	0.21	<0.0001	1.23 (1.16–1.3)
	Baricitinib	Reporting year	β1	0	0.0476	1 (1–1.01)
		Female	β2	-0.01	0.8115	0.99 (0.94–1.05)
		≥60 years old	β3	0.21	<0.0001	1.23 (1.16–1.3)
	Ruxolitinib	Reporting year	β1	0	0.0466	1 (1–1.01)
		Female	β2	-0.01	0.7968	0.99 (0.94–1.05)
		≥60 years old	β3	0.21	<0.0001	1.23 (1.17–1.3)
	Filgotinib	Reporting year	β1	0	0.0556	1 (1–1.01)
		Female	β2	-0.01	0.7881	0.99 (0.94–1.04)
		≥60 years old	β3	0.21	<0.0001	1.23 (1.16–1.3)
	Upadacitinib	Reporting year	β1	0	0.0502	1 (1–1.01)
		Female	β2	-0.01	0.8016	0.99 (0.94–1.05)
		≥60 years old	β3	0.21	<0.0001	1.23 (1.16–1.3)
Hyperglycemia	Peficitinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
	Tofacitinib	Reporting year	β1	0.01	0.0003	1.01 (1–1.02)
		Female	β2	-0.32	<0.0001	0.73 (0.69–0.77)
		≥60 years old	β3	-0.08	0.0111	0.93 (0.87–0.98)
	Baricitinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
	Ruxolitinib	Reporting year	β1	0.01	0.0003	1.01 (1–1.02)
		Female	β2	-0.32	<0.0001	0.73 (0.69–0.77)
		≥60 years old	β3	-0.08	0.012	0.93 (0.87–0.98)
	Filgotinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c
	Upadacitinib	Reporting year	β1	c	c	c
		Female	β2	c	c	c
		≥60 years old	β3	c	c	c

[a]The adjusted RORs were calculated with the estimates of betas, [b]Confdence interval, [c]Number of cases was <2.

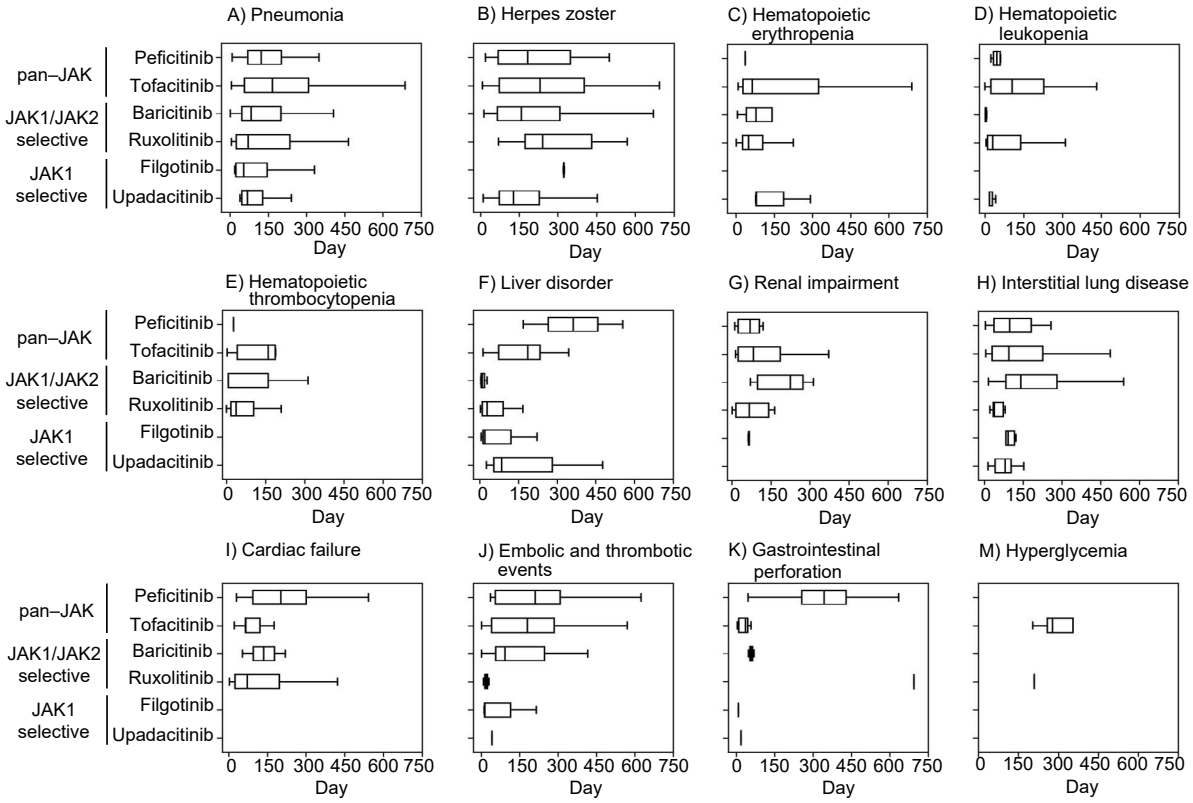

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Figure 2. Box plots for AEs

A) Pneumonia, B) HZ, C) Hematopoietic erythropenia, D) Hematopoietic leukopenia, E) Hematopoietic thrombocytopenia, F) Liver disorder, G) Renal impairment, H) ILD, I) Cardiac failure, J) Embolic and thrombotic events, K) Gastrointestinal perforation, L) Hyperglycemia, showing suspected drugs plotted against AE onset time, as observed in the JADER database

JADER: Japanese adverse drug event report.

risk factors for HZ and should be addressed according to patient risk [38]. In our study, multiple logistic regression results indicate that HZ is more commonly reported in females under 60. HZ may be underreported in older age groups. The median time-to-onset of HZ with JAK inhibitors ranges from 4 to 7 months. The incidence of severe infections, including pneumonia and HZ, has not been shown to increase with long-term JAK inhibitor use and remains stable over time [32, 33], suggesting the need for constant monitoring of signs of infection during JAK inhibitor use.

The ROR signals for hematopoietic erythropenia, leukopenia, and thrombocytopenia were detected only with ruxolitinib. The AEs associated with ruxolitinib are often anemia and thrombocytopenia due to JAK2 inhibition; however, the treatment discontinuation rate is low [13, 14, 39]. Rates of new or worsening grade 3 or 4 anemia and thrombocytopenia have been reported in clinical trials of MF, with most new or worsening events occurring within the first 6 months of treatment [14, 40]. In a double-blind, placebo-controlled trial of ruxolitinib for MF, anemia, and thrombocytopenia were more common in ruxolitinib-treated patients than in placebo-treated patients. Still, the discontinuation rate was reported to be low (1 patient in each group for each event), and these AEs were manageable [39]. In our study, the time-to-onset of AEs for ruxolitinib was concentrated around 4 months after the initiation of treatment, which is consistent with clinical trial reports. Erythropenia, leukopenia, and thrombocytopenia have also been reported in response to JAK inhibitors other than ruxolitinib. In a safety analysis of tofacitinib, lymphocytopenia was shown to be a risk factor for severe infections and HZ [41, 42]. Laboratory values in patients prescribed with JAK inhibitors should be closely monitored because lymphopenia may be missed if white blood cell percentages are not calculated.

Drug-induced liver injury is the leading cause of acute liver injury. In this study, AEs related to hepatitis B virus (HBV) reactivation were excluded to detect only drug-induced liver dysfunction signals. In previous studies, JAK inhibitors did not appear to be drugs with an excep-

Table 4. Interquartile range and Weibull shape parameter of JAK inhibiter related AEs

Category	Drug	Count	Median (IQR)[a]	α (95% CI)[b]	β (95% CI)[b]
Pneumonia	Peficitinib	20	123 (70.5–201)	114.07 (170.23–226.4)	1.18 (0.84–1.51)
	Tofacitinib	205	166 (57–309)	191.99 (217.4–242.82)	1.04 (0.94–1.13)
	Baricitinib	72	82.5 (46.0–200.5)	107.56 (132.99–158.42)	1.07 (0.91–1.23)
	Ruxolitinib	42	71.5 (25.3–235.5)	95.12 (134.42–173.73)	0.92 (0.73–1.1)
	Filgotinib	4	54.5 (22.8–146.8)	2.59 (108.32–214.05)	0.9 (0.33–1.46)
	Upadacitinib	23	69 (46.5–128.5)	83.66 (103.96–124.25)	1.86 (1.39–2.34)
Herpes zoster	Peficitinib	5	183 (69–349)	68.81 (231.67–394.53)	1.1 (0.43–1.77)
	Tofacitinib	116	232 (73–402.8)	236.29 (271.78–307.27)	1.23 (1.08–1.38)
	Baricitinib	33	159 (66–308)	167.56 (228.19–288.83)	1.14 (0.88–1.4)
	Ruxolitinib	7	242 (173.5–431.5)	213.41 (336.30–459.19)	1.79 (0.88–2.7)
	Filgotinib	2	323.5 (322.3–324.8)	322.16 (324.73–327.3)	155.24 (4.73–305.74)
	Upadacitinib	19	129 (73.5–228)	107.32 (166.54–225.77)	1.11 (0.77–1.46)
Hematopoietic erythropenia	Peficitinib	1	36 (36–36)	c	c
	Tofacitinib	24	64 (26.8–325)	93.71 (172.25–250.8)	0.78 (0.57–0.98)
	Baricitinib	13	78 (40–141)	66.69 (147.53–228.37)	0.88 (0.57–1.19)
	Ruxolitinib	135	50 (25.5–105.5)	75.7 (90.67–105.64)	0.91 (0.81–1)
	Filgotinib	0			
	Upadacitinib	3	80 (78.5–186.5)	62.83 (169.15–275.48)	1.61 (0.44–2.78)
Hematopoietic leukopenia	Peficitinib	4	47 (33–58.8)	37.33 (50.11–62.88)	3.39 (1.03–5.75)
	Tofacitinib	27	105 (24–228.5)	68.65 (121.5–174.34)	0.76 (0.56–0.97)
	Baricitinib	7	3 (2–5.5)	1.52 (7.53–13.54)	0.83 (0.47–1.19)
	Ruxolitinib	29	31 (11–139)	43.82 (79.48–115.13)	0.72 (0.55–0.89)
	Filgotinib	0	–	–	–
	Upadacitinib	3	17 (17–29.5)	16.37 (28.80–41.23)	2.34 (0.64–4.04)
Hematopoietic thrombocytopenia	Peficitinib	1	27 (27–27)	c	c
	Tofacitinib	6	161 (41.8–187.3)	5.98 (158.16–310.34)	0.73 (0.32–1.14)
	Baricitinib	3	7 (7–160.5)	52.37 (-64.26–180.89)	0.56 (0.15–0.96)
	Ruxolitinib	100	37 (17.8–105.3)	61.75 (77.88–94.01)	0.84 (0.74–0.95)
	Filgotinib	0	–	–	–
	Upadacitinib	0	–	–	–

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Category	Drug	Count	Median (IQR)[a]	α (95% CI)[b]	β (95% CI)[b]
Liver disorder	Peficitinib	2	362 (265.5–458.5)	160.85 (410.97–661.09)	2.02 (0.06–3.97)
	Tofacitinib	21	186 (73–234)	146.12 (208.64–271.17)	1.26 (0.90–1.62)
	Baricitinib	6	10 (5–18.8)	7.31 (14.41–21.51)	1.44 (0.68–2.21)
	Ruxolitinib	25	29 (10–91)	34.31 (71–107.68)	0.68 (0.51–0.84)
	Filgotinib	3	19 (12–120.5)	30.60 (-61.91–154.43)	0.67 (0.18–1.17)
	Upadacitinib	3	85 (55–281)	21.98 (-185.48–392.95)	0.90 (0.23–1.57)
Renal impairment	Peficitinib	12	70.5 (24–105.8)	49.00 (82.94–116.87)	1.23 (0.77–1.68)
	Tofacitinib	10	83 (24.8–185.8)	57.70 (120.73–183.76)	1.05 (0.62–1.49)
	Baricitinib	7	225 (98.5–273)	145.22 (259.77–374.31)	1.50 (0.79–2.2)
	Ruxolitinib	16	67.5 (16.5–141.3)	48.08 (89.76–131.44)	0.93 (0.63–1.24)
	Filgotinib	2	65.5 (64.3–66.8)	64.09 (66.70–69.31)	31.42 (0.96–61.87)
	Upadacitinib	0	–	–	–
ILD	Peficitinib	10	98.5 (37.8–182.8)	53.18 (141.34–229.51)	0.88 (0.52–1.24)
	Tofacitinib	75	96 (30.5–227)	128.15 (160.26–192.37)	1 (0.85–1.15)
	Baricitinib	21	142 (85–282)	163.53 (227.85–292.16)	1.34 (0.96–1.72)
	Ruxolitinib	7	40 (35–74)	35.32 (84.57–133.83)	1.14 (0.64–1.64)
	Filgotinib	5	93 (84–117)	64.58 (96.45–128.31)	2.29 (0.74–3.85)
	Upadacitinib	14	81 (43–105)	66.43 (93.28–120.13)	1.61 (1.05–2.17)
Cardiac failure	Peficitinib	6	202.5 (94.3–300.3)	110.00 (246.21–382.42)	1.28 (0.58–1.97)
	Tofacitinib	9	67 (65.0–122.)	64.70 (137.62–210.55)	1.10 (0.68–1.53)
	Baricitinib	2	136.5 (94.8–178.3)	41.69 (153.54–265.4)	1.69 (0.05–3.32)
	Ruxolitinib	23	72 (25.0–197)	78.98 (141.24–203.51)	0.82 (0.61–1.04)
	Filgotinib	0	–	–	–
	Upadacitinib	0	–	–	–
Embolic and thrombotic events	Peficitinib	13	211 (55–309)	160.09 (247.59–335.08)	1.36 (0.86–1.86)
	Tofacitinib	27	181 (41–285)	118.63 (196.43–274.22)	0.84 (0.62–1.06)
	Baricitinib	26	93 (56.3–247)	109.97 (166.85–223.74)	0.99 (0.74–1.25)
	Ruxolitinib	2	19.5 (14.3–24.8)	8.49 (22.13–35.77)	1.99 (0.06–3.92)
	Filgotinib	3	15 (13–115.5)	23.12 (-66.67–156.46)	0.75 (0.2–1.3)
	Upadacitinib	2	42 (42–42)	c	c

Category	Drug	Count	Median (IQR)[a]	α (95% CI)[b]	β (95% CI)[b]
Gastrointestinal perforation	Peficitinib	4	344 (256–430.3)	160.47 (375.28–590.1)	1.5 (0.43–2.56)
	Tofacitinib	12	36 (10–45.3)	15.65 (69.16–122.66)	0.65 (0.43–0.88)
	Baricitinib	2	58.5 (52.8–64.3)	50.39 (63.3–76.2)	6.02 (0.18–11.86)
	Ruxolitinib	1	695 (695–695)	c	c
	Filgotinib	2	8 (8–8)	c	c
	Upadacitinib	1	18 (18–18)	c	c
Hyperglycemia	Peficitinib	0	–	–	–
	Tofacitinib	4	278.5 (258-356)	380.17 (245.9-514.44)	2.48 (0.97-3.99)
	Baricitinib	0	–	–	–
	Ruxolitinib	1	209 (209-209)	c	c
	Filgotinib	0	–	–	–
	Upadacitinib	0	–	–	–

[a]Interquartile range, [b]Confident interval, [c]Singular value decomposition did not converge in linear least squares. PBR

tionally high risk of HBV-reactivation [43, 44]. The exact mechanism underlying JAK inhibitor-induced liver injury is not understood yet. The ROR signals of liver injury were detected only with ruxolitinib but not with the other JAK inhibitors. Liver injury is not the major AE for JAK inhibitors; however, monitoring liver enzymes is necessary because severe outcomes, including the development of liver failure, have been reported [45]. In our study, with ruxolitinib, most reports of liver injury occur about 3 months after initiation of treatment. Tofacitinib has a wider distribution at the time of hepatic injury onset than ruxolitinib. Therefore, it is considered necessary to monitor liver function not only during the initial period of drug initiation but also throughout its use.

The ROR signals for renal impairment were detected using peficitinib and filgotinib. A safety analysis of clinical trials of tofacitinib in RA reported a serum creatinine elevation of 1.5% as an AE, leading to discontinuation. In contrast, no serum creatinine elevation with long-term use was reported [41]. Serum creatinine should always be monitored during JAK inhibitor use, with early action warranted for elevated creatinine.

JAK inhibitors have not yielded consistent results in detecting ROR signals for interstitial pneumonia. ILD is the most common pulmonary manifestation of lung disease due to RA; hence, JAK inhibitors may not be a risk factor for interstitial pneumonia [46]. Although difficult in patients with pre-existing RA-related ILD, the development of parenchymal abnormalities should be appropriately evaluated before treatment, to differentiate between drug-induced pulmonary toxicity and pulmonary involvement due to the underlying disease. In our study, the shortest median time-to-onset of ILD with JAK inhibitors was 40.0 days for ruxolitinib, and the longest was 142.0 days for baricitinib. Patients should be monitored for symptoms of interstitial pneumonia, such as fever, cough, and dyspnea, especially during the first four months of using JAK inhibitors. They should be instructed to discontinue the drug immediately upon symptom onset.

ROR signals for thromboembolic-related events were detected with baricitinib and filgotinib, whereas those for heart failure were detected only with ruxolitinib. Dose-dependent increases in total, high-density, and low-density lipoprotein cholesterol levels have been reported following JAK inhibitor treatment [47]. However, no association has been reported with major adverse cardiovascular events [48, 49]. Inflammation causes hypercoagulability and is a risk factor for venous thromboembolism (VTE) and arterial thromboembolism, including DVT and PE. It has been reported that RA disease correlates with an increased risk of VTE [50]. Currently, there are reports of DVT and PE during JAK inhibitor use. However, the relationship between JAK inhibitors and an increased risk of these events is unclear [49]. In addition to the underlying disease, patient risk factors and case history should be carefully considered.

Gastrointestinal perforation can occur at any site in the gut, with the contents of the stomach or intestinal tract released into the abdominal cavity. In our study, JAK inhibitors were not associated with ROR signals for GP-related AEs. In a report on tofacitinib, most GPs occurred in the lower gastrointestinal tract, and most cases were treated with concomitant NSAIDs or glucocorticoids [32].

The incidence of GP has been reported to be higher with interleukin (IL)-6 inhibitors than with other antirheumatic drugs [51]. Although the detailed mechanism is unclear, IL-6 regulates vascular endothelial growth factor, which is involved in angiogenesis and tissue repair [52]. Dendritic cells derived from Peyer's patches in the intestinal submucosa express high levels of IL-6 and strongly induce IgA [53], which may derange the intestinal microbiota and delay tissue repair processes. Suppression of IL-6 signaling by JAK1 inhibition may result in GP. Timely diagnosis of GP is difficult as it is infrequent, and the timing of its occurrence is unpredictable. Nevertheless, it is a potentially serious AE that should not be overlooked.

Although reported infrequently, our study found no association between JAK inhibitor use and hyperglycemia (Table 1). To our knowledge, few reports exist on the relationship between JAKs and impaired glucose tolerance.

Analyses using SRS, such as the JADER database, have several notable limitations. Intrinsic problems with the SRS data include over-reporting, under-reporting, missing data, exclusion of healthy individuals, lack of denominators, and confounding factors [54]. It is improbable that the "true" risk of AEs will be evaluated without information on the total number of patients administered with JAK inhibitors. We adjusted for possible confounders in the database using multiple logistic regression methods. The adjusted ROR offers a rough indication of the signal strength, which can be used to generate hypotheses to search for unknown potential AEs. In clinical practice, the AE profile of JAK inhibitors in post-marketing real-world data remains to be established. The JADER is the primary tool available for pharmacovigilance because it is the world's largest and one of the most widely used databases. Although our results only support the basis of a phenomenon already known in the literature, our results, based on the evaluation of JADER, provide essential knowledge to improve our understanding of this issue. The timing of AE occurrence is also affected by different patient backgrounds. However, our results provide useful findings that reflect real-life scenarios, including the median timing of AE occurrence. This information may be particularly beneficial to prescribers.

Conclusion

Despite the inherent limitations of the SRS, we demonstrated the potential risks of JAK inhibitor use with real-world data. The present analysis shows that patients receiving peficitinib, tofacitinib, baricitinib, ruxolitinib, filgotinib, or upadacitinib should be closely monitored for AEs. The median onset of pneumonia and HZ with JAK inhibitor usage ranged from 2 to 6 months and 4 to 7 months, respectively. We believe that the data presented in this study will aid in detecting various AEs associated with JAK inhibitors early.

Ethical Considerations

Compliance with ethical guidelines

Ethical approval was not sought for this study because the study was a database-related observational study without directly involving any research subjects. All results were obtained from data openly available online from the PMDA website. All data from the JADER database were fully anonymized by the relevant regulatory authority before we accessed them.

Funding

This research was partially supported by Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant No.: 21K06646 and 21K11100).

Authors' contributions

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Conflict of interest

The authors declared no conflict of interest.

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