The Journal of Rheumatology 2022;49 Suppl 1:44–7
doi:10.3899/jrheum.211329
First Release March 15 2022

The Journal of Rheumatology

Janus Kinase Inhibitors: Safety in Patients With Psoriatic Arthritis

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ABSTRACT. Janus kinase inhibitors (JAKi; or Jakinibs) have become widely prescribed around the world for a variety of immune-mediated inflammatory diseases, including psoriatic arthritis. A previous noninferiority surveillance study of patients aged > 50 years with rheumatoid arthritis and ≥ 1 additional cardiac risk factor raised a number of safety concerns. This review focuses on available safety data from peer-reviewed publications, as well as the most recent presentations from major conferences highlighting JAKi-associated adverse effects. The safety data for several types of JAKi are reviewed. The latest available safety data for tofacitinib, upadacitinib, filgotinib, deucravacitinib, and brepocitinib is presented. In addition, the findings from the oral surveillance study will be discussed to put safety concerns into context.

Key Indexing Terms: GRAPPA, psoriasis, psoriatic arthritis

Introduction

There has been a dramatic uptake in the use of Janus kinase inhibitors (JAKi; or Jakinibs) by rheumatologists across the immune-mediated inflammatory disease (IMID) spectrum in recent years. For patients with rheumatoid arthritis (RA), the JAKi class commands upwards of 25% of the market share, with 1–3 initiations for patients who had an inadequate response or are intolerant to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate (MTX). A comprehensive clinical trial program has led to registration and reimbursement for the PsA indication in a number of countries, but it is the safety of the JAKi class in PsA that is the focus of this review. Our study is also a result of the recent safety concerns that have led the U.S. Food and Drug Administration to impose a black box warning across the JAKi class for all IMID indications, as well as the recommendation that JAKi should be used as a second-line treatment once tumor necrosis factor (TNF) agents have been found to be inadequate or contraindicated.

The choice of JAKi or biologic DMARDs (bDMARDs) as strategies for treatment of PsA can be based on their different characteristics (Table 1). The efficacy of JAKi has been tested by comparing these treatments to the "gold standard" (ie, MTX combined with adalimumab [ADA]) across domains, for patient-reported outcomes and slowing retardation of radiological progression. The efficacy of JAKi in patients with axial PsA has not been specifically studied, but efficacy has been demonstrated in studies of patients with radiographic axial spondyloarthropathy.

Safety Data From Clinical Trials

A comprehensive clinical trial program (Table 2) assessing

Table 1. Comparison of distinguishing characteristics of JAKi with bDMARDs.

JAKi	bDMARDs
Oral route	Parenteral route
Small-molecule protein	Monoclonal antibody
Intracellular targets	Extracellular receptor and soluble targets
Nonimmunogenic	Potentially immunogenic
Multiple cytokine inhibition	Single cytokine inhibition
Generic potential	Biosimilars
Short half-life	Longer half-lives
Stable	Heat sensitive
Monotherapy efficacy	Combination therapy most effective
No demyelination	Demyelination
No PsO induction	PsO induction
No SLE induction	SLE induction
Zoster signal	No increased zoster signal
No cardiac failure signal	Cardiac failure signal
Not applicable	Injection site and infusion reactions
Hepatic metabolism, renal and fecal excretion	Proteolytic degradation
Drug interactions with CyP3A4 pathway	No drug interactions
Metabolites	No metabolites

bDMARD: biologic disease-modifying antirheumatic drug; JAKi: Janus kinase inhibitors; PsO: psoriasis; SLE: systemic lupus erythematosus.

As part of the supplement series GRAPPA 2022, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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PN has received funding for clinical trials and honoraria for advice and lectures on behalf of AbbVie, BMS, Celgene, Pfizer, Novartis, Eli Lilly, Samsung, Boehringer Ingelheim, Janssen, and Galapagos.

This paper does not require institutional review board approval.

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Accepted for publication December 8, 2021.

Table 2. Five types of JAKi tested in clinical trials in patients with PsA.

JAKi	Preferred/ Selective	Clinical Trial	Duration	Enrolled Population	JAKi Doses	Comparator
Tofacitinib	JAK1/3	OPAL Broaden OPAL Beyond OPAL Balance	12 months	csDMARD-IR TNF-IR LTE	5 or 10 mg bid	ADA
Upadacitinib	JAK1	SELECT-PsA 1 SELECT-PsA 2	24/32 weeks 24/32 weeks	csDMARD-IR TNF-IR	15 or 30 mg	ADA
Filgotinib	JAK1	EQUATOR 1 EQUATOR 2	16 weeks 52 weeks	csDMARD-IR	200 mg qd	PBO
Deucravacitinib	TYK2	Phase II	16 weeks 52 weeks	csDMARD 1 TNF-IR < 30%	6 or 12 mg qd	PBO
Beprocitinib	TYK2/JAK1	Phase II	16 weeks 52 weeks	csDMARD TNF-IR < 30%	10, 30, or 60 mg qd	PBO

ADA: adalimumab; bid: twice per day; csDMARD: conventional synthetic disease-modifying antirheumatic drug; IR: inadequate responders; JAKi: Janus kinase inhibitor; LTE: long-term extension; PBO: placebo; qd: once per day; TNF: tumor necrosis factor; TYK2: tyrosine kinase 2.

different types of JAKi has established the efficacy and safety of tofacitinib (TOF), upadacitinib, filgotinib, deucravacitinib, and brepocitinib. Baricitinib has been studied in patients with psoriasis but not in those with PsA, and thus will not be considered further.

TOF clinical trials. The OPAL program included 3 clinical trials. The OPAL Broaden trial was a 12-month study comparing 2 doses of TOF (5 mg twice/d [bid] or 10 mg bid) with placebo and ADA (40 mg subcutaneously every 2 weeks) as an active comparator arm.[1] Enrolled patients had active PsA, and were TNF-naïve and inadequate responders (IR) to csDMARDs (including MTX). The OPAL Beyond study was a 6-month study of patients with PsA who were TNF-IR.[2] Patients completing these studies were invited to enter the long-term extension OPAL Balance study.[3] An analysis of the OPAL Balance study at 3 years included a total of 686 patients given TOF with 1153 patient-years (PY) of exposure. Most of the patients were in the TOF 5-mg bid group (680 patients with 687 PY). Baseline demographics included a mean age of 48 years and a mean PsA duration of 7.6 years; two-thirds had enthesitis and half had dactylitis. In addition, data from various registries for TOF with safety data have been reported, but not for the PsA indication.[4] TOF has an extensive RA clinical trial program with 9.5 years of follow-up and an established list of adverse effects for JAKi that are of particular interest (Table 3).[5]

From these studies, the safety profile of TOF can be described. Serious adverse events (SAEs) were reported in 10.6% of patients, with 8.6% discontinuing treatment and 30.9% reducing or temporarily discontinuing therapy. Herpes zoster (HZ) was reported in 19 patients, with an incidence rate of 1.7/100 PY, including 1 case of facial involvement classified as an SAE. Opportunistic infections were seen with an incidence rate of 0.3/100 PY, which were exclusively due to 4 cases of HZ. Serious infective events (SIEs) occurred with an incidence rate of 0.9/100 PY (11 patients). Malignancies (excluding nonmelonoma skin cancer [NMSC]) were seen at a rate of 0.8/100 PY, whereas NMSC was reported at 1.0/100 PY. Major cardiac events (MACEs) occurred in 0.3/100 PY in the TOF 5-mg bid group. Low rates of other laboratory variable safety outcomes were reported (data not shown).

Upadacitinib (JAK1 preferred/selective) clinical trials. The phase III, 24-week SELECT-PsA 1 trial compared upadacitinib (15 mg/d and 30 mg/d) and placebo to ADA 40 mg every other week (EOW) as an active comparator in csDMARD-IR patients with PsA.[6] In another phase III, 24-week SELECT-PsA 2 trial, bDMARD-IR patients with PsA received placebo or upadacitinib (either 15 mg/d or 30 mg/d).[7] From the 2 trials with a total of 2257 patients, 907 (1247 PY) received 15/mg/d of upadacitinib, 921 (1257 PY) received 30 mg/d, and 429 (550 PY) received ADA 40 mg EOW, for a median duration of 1.3 years

Table 3. List of JAKi adverse effects of special interest collected during clinical trials or in registries.

Clinical Events	Laboratory Variables
Serious adverse events	Anemia
Serious infective events	Neutropenia
Opportunist infections (in particular, herpes zoster or tuberculosis)	Lymphopenia, including natural killer cell numbers
Malignancy, including melanoma and nonmelanoma skin cancer	Transaminitis
Major cardiovascular events, including venous thromboembolism	Lipid profile
Gastric perforation	Creatinine
	Creatine phosphokinase

JAKi: Janus kinase inhibitor.

(IQR 2.9–3.0). Enrolled patients had a mean age of 51 years with a mean disease duration of 7 years.

The safety profile of upadacitinib showed low rates of AEs as reported in the 2 trials[8] (Table 4). SIE rates increased with age, especially for those aged > 75 years. Rates of HZ were increased compared with the TNF inhibitor (TNFi) but were nonserious and affected only 1 dermatome. Rates of NMSC, MACE, VTE, and laboratory variables were comparable across the groups.

Filgotinib (JAK1 preferred/selective) clinical trials. In the phase II, 16-week EQUATOR trial, 131 csDMARD-IR patients received filgotinib (200 mg/d) or placebo and afterwards were offered a 56-week open label extension to receive filgotinib 200 mg once per day (qd). Enrolled patients had a mean age of 50 years, a mean disease duration of 7 years, and 65% had enthesitis. Data from filgotinib exposure was available over 160 PY, with a mean duration of 66 weeks.

The safety profile of filgotinib showed a low rate of reported AEs (Table 5). There was 1 case of HZ. Mean change in hemoglobin concentrations (filgotinib 6 g/L [SD 8.2] vs placebo 1 g/L [SD 9.2]) and platelet counts (-16×10^9/L [SD 62.0] vs 7×10^9/L [SD 57.4]) differed between the filgotinib and placebo groups. Natural killer cell counts were stable in the filgotinib group (–4.2% [SD 46.9]) but increased in the placebo group (12.9% [SD 32.5]). Mean total cholesterol increased from baseline in patients treated with filgotinib (0.45 mmol/L [SD 1.0]) compared with placebo (0.09 mmol/L [SD 0.8]), mainly due to a 15% decrease in the low-density lipoprotein:high-density lipoprotein ratio in the filgotinib group (data not shown). Changes in other laboratory variables, vital signs, or electrocardiograms were similar in the 2 groups.[9,10]

Deucravacitinib (TYK2 selective) clinical trials. Deucravacitinib selectively inhibits tyrosine kinase 2 (TYK2), binding to the regulatory domain of the kinase. A 1-year phase II trial in patients with active PsA who had failed or were intolerant to csDMARDs and/or 1 TNFi (≤ 30%) is ongoing. Patients were randomized to deucravacitinib at 6 mg/qd or 12 mg/qd, or placebo.[11] The primary endpoint was achievement of American College of Rheumatology (ACR) swollen joint count response at week 16. In this trial, 203 patients were randomized and 180 (89%) completed 16 weeks of treatment. Mean age was 49.8 years, median PsA duration was 4.5 years, and half had enthesitis.

The 16-week safety data showed no SAEs, SIEs, VTE, HZ, opportunistic infections or malignancies, or clinically meaningful changes in laboratory variables given the small patient numbers who were followed for too short a period of time.

Brepocitinib (JAK1/TYK2 inhibitor) clinical trials. In a phase II dose-ranging study of 295 bDMARD-naïve patients with PsA, 218 were given brepocitinib (10, 30, or 60 mg/d) for 16 weeks, followed by 30 or 60 mg/day during weeks 16–52; 67 patients were given placebo.[12] These patients had a mean age of 48 years and a mean disease duration of 6 years; 60% had enthesitis and 30% had dactylitis at baseline.

The safety profile of brepocitinib is described in Table 6 for the placebo group over 16 weeks and for the brepocitinib groups (30 or 60 mg/d) over 52 weeks. Adverse effects were consistent for JAKi, with dose-dependent transaminitis, creatine phosphokinase elevation (without rhabdomyolysis), and anemia.

Table 4. Safety outcomes from upadacitinib clinical trials over 24 weeks.

Events/100 PY	Placebo, n = 635	Upadacitinib, 15 mg, n = 907	Adalimumab, 40 mg, n = 429
Serious adverse events	8.2	10.3	9.6
Serious infective events	1.9	2.3	1.3
Opportunistic infections	0	0.4	0
Major cardiovascular event	0.4	0.3	0.5
Venous thromboembolism	0.4	0.3	0.4
Malignancy	0	0.7	0.7
Nonmelanoma skin cancer	0.4	0.7	0.4
Creatine phosphokinase	4.1	9.1	7.5
Alanine transaminase	5.6	5.4	9.6
Herpes zoster	1.9	3.4	0.5

PY: patient-years.

Table 5. Safety outcomes from filgotinib clinical trials.

Rates/100 PY	Filgotinib, PY = 160	Placebo, PY = 20
Serious adverse event	5.6	5.0
Serious infective event	1.9	0
Malignancy	0.6	0
Herpes zoster	0.6	0
Venous thromboembolism	0	0
Tuberculosis	0	0
Major cardiovascular events	0.6	0
Lymphopenia > Gr2	11.1	4.5
Neutropenia > Gr2	5.5	0
ALT increase > Gr2	1.6	1.5
Creatinine increase > Gr2	0.8	0

ALT: alanine aminotransferase; Gr2: grade 2; PY: patient-years.

Table 6. Safety outcomes from brepocitinib clinical trials at 16-week follow-up.

	Placebo, n = 67	Brepocitinib 30 mg, n = 108	Brepocitinib 60 mg, n = 110
Serious adverse event	1.5	9.3	1.8
Serious infective event	0	1.9	1.8
Herpes zoster	0	1.9	1.8
Malignancy	0	0.9	0
Major cardiovascular event, including VTE	0	0	0
Gastrointestinal perforation	0	0	0
ALT × 3 ULN	4.5	6.5	13.5
Hemoglobin < 0.8	1.5	1.9	3.6
Creatine phosphokinase > 2 ULN	7.5	21.5	26.4

Values are expressed as %. ALT: alanine transaminase; ULN: upper limit of normal; VTE: venous thromboembolism.

Safety Data From Oral Surveillance

Presentations at the ACR Convergence 2021 meeting described the head-to-head study of TOF (5 mg bid or 10 mg bid) compared to ADA or etanercept in patients with RA aged > 50 years with ≥ 1 cardiovascular risk factor.[13,14,15] Patients had a mean age of 60 years (30% > 65 yrs) and a mean RA disease duration of 10 years. The number needed to harm (NNH) for MACE events compared to TNFi was 567, with the risk driven by nonfatal myocardial infarction. The NNH for malignancies was 276, driven by lung cancer incidence. The NNH for serious infective episodes was 283.

Conclusion

The safety data for JAKi from the trials described above, while reassuring in that no unexpected safety issues were identified in patients with PsA when compared with the more extensive usage in RA patients, remains limited due to short durations of patient exposure and small study sizes. Our knowledge of the safety of these treatments will expand with the accumulation of registry data and more widespread use of JAKi as the PsA indication increases around the globe. People with PsA are at lower general risk than patients with RA for a number of reasons, including lower corticosteroid usage, lower age group, and fewer comorbidities. The oral surveillance data gives reason to pause but confirms the importance of appropriate patient selection and weighing risk vs benefit for the individual patient and their treatment journey. We should be careful not to throw the baby out with the bathwater.

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