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Sex differences in the safety profile of Janus kinase inhibitors in rheumatoid arthritis: results from the JAK-POT international collaboration

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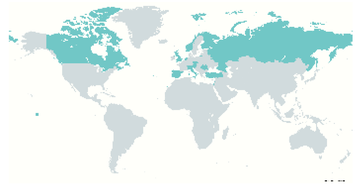

INTRODUCTION

- The safety and efficacy of Janus Kinase inhibitors (JAKi) has been broadly studied in clinical trials, and post-authorization observational studies contribute to the knowledge about their safety in routine clinical practice.
- While JAKi safety is being scrutinized, it is important to explore the role of well-known risk factors like sex on the occurrence of adverse events of interest.

OBJETIVES

To explore the potential impact of sex on the incidence of malignancies, infections and cardiovascular events, using real-world data from the JAK-pot collaboration.

METHODS

- Adult rheumatoid arthritis (RA) patients starting JAKi from 12 registers across Europe and Québec were included.
- Adverse events of interest were categorized into: all malignancies stratified by “non-melanoma skin cancer (NMSC)” and “malignancy excluding NMSC”, serious infections, major adverse cardiovascular events (MACE) and venous thromboembolism (VTE).
- Adverse events were attributed to the JAKi treatment if these occurred while on therapy or during a risk window after discontinuation until follow-up loss, death, or study end, whichever came first. The risk windows were 5 years for malignancies, 6 months for cardiovascular events (MACE and VTE), and 3 months for infections.
- Incidence rates (IR) per 100 patient-years (PY) and per 1000 PY with 95% confidence intervals (CI) were computed. Poisson regression was used to obtain adjusted incidence rate ratios (aIRR) with 95% CI, accounting for the following covariates: age, disease duration at treatment start, line of treatment, and prior history of each type of event – see Table 2 footnotes.

RESULTS

- Of the 65,203 RA patients, 12,394 initiated JAKi treatment between 2013 and 2024. Patients were mostly females (80.7%), initiated JAKi treatment at a mean age of 57.9 years, and most treatments were received as a third or later line (30.0%) (Table 1). Overall, patients had similar clinical characteristics, although males seemed to have a later onset of RA and thus a shorter disease duration at treatment start. In addition, males had a higher proportion of overweight/obesity, smoking and cardiovascular disease compared to females. A total of 286 malignancies (93 NMSC), 1775 infections (319 serious), 69 MACE and 61 VTE were reported.
- IRs and crude IRRs were lower among females for all events of interest. While the incidence of all malignancies (including NMSC) was significantly lower among female patients (aIRR=0.48 [95% CI: 0.25-0.93]), no differences were found when stratifying by malignancies excluding NMSC, and by NMSC (Table 2).

Table 1. Baseline characteristics

	Males N=2,391	Females N=10,003	Total N=12,394
Age at diagnosis (years), mean (SD)	47.9 (13.1)	44.8 (13.7)	45.4 (13.7)
Age at treatment start (years), mean (SD)	58.8 (11.5)	57.7 (12.4)	57.9 (12.2)
Disease duration at treatment start (years), mean (SD)	10.9 (9.0)	12.9 (9.7)	12.5 (9.6)
Treatment duration (years), mean (SD)	2.2 (1.8)	2.2 (1.8)	2.2 (1.8)
Seropositivity (RF or ACPA), n (%)	1681 (80.9)	6852 (80.4)	8533 (80.5)
Previous b/tsDMARDs, median (IQR)	2.0 [0.0; 3.0]	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]
Previous b/tsDMARD, n (%)			
0	604 (25.3)	2460 (24.6)	3064 (24.7)
1	566 (23.7)	2357 (23.6)	2923 (23.6)
2	502 (21.0)	2190 (21.9)	2692 (21.7)
≥ 3	719 (30.1)	2996 (30.0)	3715 (30.0)
Concomitant csDMARD (%)	1281 (53.8)	5133 (51.3)	6414 (51.8)
Concomitant GC, n (%)	1053 (46.5)	4035 (42.5)	5088 (43.2)
DAS 28 CRP at baseline, mean (SD)	3.7 (1.6)	3.8 (1.5)	3.8 (1.5)
DAS 28 ESR at baseline, mean (SD)	4.0 (1.7)	4.3 (1.6)	4.2 (1.6)
BMI, median [IQR]	26.8 [24.3; 29.9]	25.7 [22.6; 29.9]	26.0 [22.9; 29.9]
Tobacco (ever), n (%)	1013 (54.5)	2265 (29.8)	3278 (34.6)
History of cardiovascular disease, n (%)	100 (15.6)	187 (7.2)	287 (8.9)
Current or past malignancy, n (%)	71 (3.5)	337 (4.0)	408 (3.9)
Past serious infection, n (%)	197 (13.6)	802 (12.3)	999 (12.5)

SD = standard deviation, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibody, b/tsDMARDs = biological or targeted synthetic DMARDs, csDMARDs = conventional synthetic DMARDs, GC = glucocorticoids, DAS 28 = Disease Activity Score 28, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, BMI = Body Mass Index, IQR = interquartile range.

Table 2. Incidence rates of adverse events of interest stratified by sex and incidence rate ratios (adjusted by age, disease duration at treatment start, and line of treatment)

Type of adverse events		Nº of events	IR (95% CI)	Per	Crude IRR (95% CI)	Adjusted IRR (95% CI)
Malignancies (all)*	Females	175	0.45 (0.39 - 0.52)	100PY	0.38 (0.19 - 0.79)	**0.48 (0.25 - 0.93)**
	Males	111	1.22 (1.00 - 1.47)			
Malignancies excluding NMSC	Females	119	0.31 (0.26 - 0.37)	100PY	0.40 (0.17 - 0.93)	0.44 (0.18 - 1.08)
	Males	74	0.81 (0.64 - 1.02)			
NMSC	Females	56	0.15 (0.11 - 0.19)	100PY	0.37 (0.09 - 1.54)	0.63 (0.29 - 1.36)
	Males	37	0.41 (0.28 - 0.56)			
Serious infections**	Females	242	1.07 (0.94 - 1.22)	100PY	0.77 (0.60 - 0.99)	0.84 (0.65 - 1.08)
	Males	77	1.39 (1.10 - 1.74)			
MACE***	Females	42	1.87 (1.35 - 2.53)	1000PY	0.38 (0.23 - 0.62)	**0.39 (0.25 - 0.63)**
	Males	27	4.92 (3.24 - 7.16)			
VTE***	Females	43	1.91 (1.38 - 2.57)	1000PY	0.58 (0.29 - 1.01)	0.60 (0.35 - 1.04)
	Males	18	3.26 (1.93 - 5.15)			

*Additionally adjusted by "current or past malignancy"
**Additionally adjusted by "past serious infection"
***Additionally adjusted by "history of cardiovascular disease"

- Females had a significantly lower incidence of MACE (aIRR=0.39 [95% CI: 0.25-0.63]), yet no significant difference in the incidence of VTE was observed between females and males.

CONCLUSIONS

- In this real-world study, differences were found between males and females in the safety profile: a significantly lower risk of MACE was observed among females compared to males.
- Results should be interpreted with caution given the limitations of this work, including the unmeasured or residual confounding that could potentially explain some of these findings.
- Future analyses are planned to further assess sex differences with regards to time from treatment start until the occurrence of the first adverse event, for all outcomes of interest.

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