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CLINICAL SCIENCE

Janus kinase inhibitors and tumour necrosis factor inhibitors show a favourable safety profile and similar persistence in rheumatoid arthritis, psoriatic arthritis and spondyloarthritis: real-world data from the BIOBADASER registry

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ABSTRACT

Objectives To compare the safety of Janus kinase inhibitors (JAKi) with that of tumour necrosis factor inhibitors (TNFi) and determine drug persistence among patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA).

Methods We analysed data from patients included in BIOBADASER 3.0 and treated with JAKi or TNFi from 2015 to 2023 and estimated the incidence rate ratio (IRR) of adverse events and persistence.

Results A total of 6826 patients were included. Of these, 52% had RA, 25% psoriatic arthritis and 23% axial SpA. Treatment was with TNFi in 86%. The mean duration of treatment was 2.2 ± 2.0 years with TNFi versus 1.8 ± 1.5 with JAKi. JAKis were prescribed in older patients with longer term disease, greater comorbidity and later treatment lines and more frequently as monotherapy. The IRR of all infections and gastrointestinal events was higher among patients with RA treated with JAKi. Drug persistence at 1, 2 and 3 years was 69%, 55% and 45% for TNFi and 68%, 54% and 45% for JAKi. Multivariate regression models showed a lower probability of discontinuation for JAKi (HR=0.85; 95% CI 0.78–0.92) and concomitant conventional synthetic disease-modifying antirheumatic drugs (HR=0.90; 95% CI 0.84–0.96). The risk of discontinuation increased with glucocorticoids, comorbidities, greater disease activity and later treatment lines.

Conclusions Infections, herpes zoster and gastrointestinal adverse events in patients with RA tended to be more frequent with JAKi. However, prognosis was poor in patients receiving JAKi. Persistence was similar for TNFi and JAKi, although factors associated with discontinuation differed by diagnostic group.

INTRODUCTION

Janus kinase inhibitors (JAKi) are oral targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) used frequently as second-line

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The safety and persistence of Janus kinase inhibitors (JAKi) and tumour necrosis factor inhibitors (TNFi) for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) has been demonstrated in clinical trials. However, real-world data are needed.

WHAT THIS STUDY ADDS

⇒ Treatment with JAKi is associated with a slight increase in the frequency of all infections, herpes zoster and gastrointestinal events. This increase is greater in patients with RA. However, adverse events were mild and had no effect on mortality.
⇒ Persistence of JAKi was similar to that of TNFi in RA and axSpA, and slightly better for TNFi in PsA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In a real-world setting, the use of JAKi for treatment of RA, PsA or axSpA is an alternative with an acceptable balance between efficacy and safety. Rheumatologists should consider a personalised 'treat-to-target' strategy depending on the disease, patient profile and preferences, cost for the health system and availability.

therapy in rheumatoid arthritis (RA) and spondyloarthritis (SpA).¹ With more than 20 years of use in clinical practice, biological DMARDs (bDMARDs) have a robust efficacy and safety profile.^{2–4} Tumour necrosis factor inhibitors (TNFi) are recommended as the first-line biologic for RA, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), either in

monotherapy or in combination with methotrexate after failure of conventional synthetic DMARDs (csDMARDs).^{5–7}

JAKis were initially designed for treatment of RA and has now been approved for SpA. They have been marketed since 2012 in the USA and have been evaluated in multiple randomised clinical trials. However, safety in daily clinical practice is still under evaluation, especially after reports of potentially associated cardiovascular events and cancer.^{8,9} Data from the ORAL Surveillance study prompted the US Food and Drug Agency and the European Medicines Agency to issue an initial warning concerning the safety of tofacitinib and a subsequent warning about JAKi as a group.^{10,11}

The four JAKis marketed in Spain (as of October 2023) are tofacitinib, baricitinib, upadacitinib and filgotinib,^{1–4} all of which are prescribed and reimbursed by the National Health System.¹² Considering the increasing number of currently available options, an estimation of real-world safety and relative effectiveness could help rheumatologists to choose the appropriate therapy.

Real-world registries provide a unique opportunity to compare the safety and efficacy of JAKi and treatments with longer experience of use, such as TNFi, in daily clinical practice. In this study, we used data from the Spanish registry BIOBADASER 3.0 to evaluate and compare the safety profile of JAKi with that of TNFi and determine drug persistence in patients with RA and SpA.

METHODS

Study design

BIOBADASER 3.0 (Spanish registry on adverse events (AE) of advanced therapies in rheumatic diseases; <https://biobadaser.ser.es/>) is an observational, nationwide prospective registry of patients with chronic inflammatory rheumatic diseases starting treatment with a bDMARD (original or biosimilar) or tsDMARD. BIOBADASER 3.0 has been continuously collecting patient data from routine clinical practice since it was first established in 2000.¹³ The main objectives of the registry are to assess the long-term safety of patients undergoing treatment with bDMARDs/tsDMARDs and to determine effectiveness.¹⁴ The registry was established by the Spanish Agency of Medicines and Medical Devices and the Spanish Foundation of Rheumatology in 2000. Phase III was initiated in 2015. The full protocol of BIOBADASER 3.0 is available online (<https://biobadaser.ser.es/protocolo.aspx>). The study was reported in accordance with the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology and their extension for longitudinal observational drug studies in rheumatology.^{15,16}

Participants

We included adult patients (≥ 18 years) diagnosed with RA and SpA (PsA and axSpA) according to the criteria of the treating rheumatologist and initiating TNFi or JAKi between 2015 and 2023.

Time points

Baseline was defined as the initiation date for each course of treatment since January 2015. The course of treatment ran from the initiation date to the earliest discontinuation, the end of participation in the registry (patient withdrawal, death or loss to follow-up) or the end of the study period (October 2023).

Treatment groups

The treatment groups were patients with RA, patients with PsA and patients with axSpA treated with TNFi or JAKi. For patients who switched between TNFi and JAKi, each treatment course contributed to the corresponding treatment group; therefore, a patient could be counted in both groups.

Outcomes of interest

AEs during follow-up are collected routinely in BIOBADASER 3.0 (date of occurrence, type and classification according to the Medical Dictionary for Regulatory Activities (version 26.1),¹⁷ severity, outcome and concomitant treatment at the time of the AE). Safety was measured as the incidence of AEs during the risk window for each treatment (ie, duration of exposure plus a lag period).

Drug persistence was defined as the drug retention rate at 1, 2 and 3 years after initiation of therapy.

Variables

The data collected were as follows: (1) patient data, namely sex, date of birth, diagnosis, date of diagnosis and comorbidities (Charlson Comorbidity Index)¹⁸; (2) data on treatment, including type of TNFi (originals and biosimilars) and tsDMARD, dates of initiation and discontinuation and reason for discontinuation. Sex, age, disease duration, Charlson Comorbidity Index, line of treatment, concomitant medications and disease activity were considered confounding variables for adjustment. Disease activity was categorised as low, medium and high according to the thresholds defined for each disease activity index.^{19–24}

Statistical analysis

Patient characteristics at baseline (initiation of treatment) were described using percentages and mean and SD according to the type and distribution of the variables. We estimated the incidence rate of AEs per 1000 person-years and 95% CI by group. We used the ‘ever taken drug’ risk attribution model for AEs with long latency periods (malignancy and mortality), attributing all remaining AEs while the patient is actively receiving therapy plus a lag period beyond discontinuation. The risk window lag period was twice the drug half life and an additional 30–180 days depending on the type of event (eg, 30 days for respiratory disorders, 90 days for infections and 180 days for cardiovascular disorders).²⁵ Comparisons of the incidence rate between groups were expressed as the incidence rate ratio (IRR), which was obtained by Poisson regression and adjusted for the confounding variables.

Drug persistence was calculated as the number of patients remaining on treatment divided by the number of patients at risk of discontinuation using Kaplan-Meier survival curves (excluding censored patients) and considering any of the reasons for discontinuation (eg, loss of efficacy, AEs) as a completion event. Log-rank tests were used to compare the survival curves of JAKi and TNFi across the different diagnoses. Cox regression (proportional hazards) was used to analyse the factors associated with differences in drug retention rates between JAKi and TNFi. All analyses were performed using Stata V.13.1 (StataCorp, College Station, Texas, USA).

RESULTS

We included 6826 patients, 3513 (51.5%) with RA and 3313 (48.5%) with SpA, including 1742 (25.5%) with PsA and 1571 (23.0%) with axSpA. A total of 5899 (86.4%) patients received 7661 courses of treatment with TNFi, 1642 (24.0%) patients

Table 1 Main clinical characteristics, by disease and group of treatment

Variables	Spondyloarthritis			All SpA	All patients
	Rheumatoid arthritis	Psoriatic arthritis	Axial SpA		
Total patients, n (%)	3513 (51.5)	1742 (25.5)	1571 (23.0)	3313 (48.5)	6826 (100)
Women, n (%)	2806 (79.9)	952 (54.7)	535 (34.1)	1487 (44.9)	4293 (62.9)
TNF inhibitors					
Number of patients, n (%)	2681 (45.4)	1675 (28.4)	1545 (26.2)	3218 (54.6)	5899 (86.4)
Number of patients with prior exposure to JAKi, n (%)	428 (16.0)	113 (6.8)	31 (2.0)	144 (4.5)	572 (9.7)
Age at treatment start in years, mean (SD)	55.7 (12.4)	50.6 (11.9)	48.2 (13.0)	49.4 (12.5)	52.1 (12.8)
Disease duration at treatment start in years, mean (SD)	9.3 (8.7)	7.5 (7.4)	10.3 (10.7)	8.9 (9.3)	9.1 (9.0)
Follow-up time in years, mean (SD)	1.9 (1.8)	2.2 (2.1)	2.5 (2.1)	2.4 (2.1)	2.2 (2.0)
Follow-up time in years, min-max	0, 8.7	0, 8.8	0, 8.7	0, 8.8	0, 8.8
Charlson Comorbidity Index, n (%)					
0	0 (0)	1361 (81.4)	1292 (83.6)	2653 (82.4)	2653 (45.0)
1	2158 (80.5)	192 (11.5)	156 (10.1)	348 (10.8)	2506 (42.5)
2	319 (11.9)	80 (4.8)	64 (4.1)	144 (4.5)	463 (7.9)
3 or more	204 (7.6)	40 (2.4)	33 (2.1)	73 (2.3)	277 (4.7)
Number of treatments, n (%)	3323 (43.4)	2202 (28.7)	2136 (27.9)	4338 (56.6)	7661 (100)
Lines of treatment, n (%)					
First	1787 (53.8)	1069 (48.6)	1014 (47.5)	2083 (48.0)	3870 (50.5)
Second	743 (22.4)	578 (26.3)	547 (25.6)	1125 (25.9)	1868 (24.4)
Third or higher	793 (23.9)	555 (25.2)	575 (26.9)	1130 (26.1)	1923 (25.1)
Concomitant use of csDMARD at treatment start, n (%)	2571 (77.4)	1272 (57.8)	410 (19.2)	1682 (38.8)	4253 (55.5)
Concomitant use of GCs at treatment start, n (%)	1912 (57.5)	570 (25.9)	184 (8.6)	754 (17.4)	2666 (34.8)
Type of TNFi, n (%)					
Originals	1019 (30.7)	933 (42.4)	949 (44.4)	1882 (43.4)	2901 (37.9)
MOA	861 (84.5)	768 (82.3)	843 (88.8)	1161 (85.6)	2472 (85.2)
Soluble receptor	158 (15.5)	165 (17.7)	106 (11.2)	271 (14.4)	429 (14.8)
Biosimilars	2304 (69.3)	1269 (57.6)	1187 (55.6)	2456 (56.6)	4760 (62.1)
MOA	1370 (59.5)	941 (79.3)	982 (77.4)	1923 (78.3)	3293 (69.2)
Soluble receptor	934 (40.5)	246 (20.7)	287 (22.6)	533 (21.7)	1467 (30.8)
Disease activity at treatment start, mean (SD)					
DAS28-ESR	4.5 (1.4)	4.0 (1.4)	–	4.0 (1.4)	4.2 (1.4)
DAS28-CRP	3.4 (1.2)	3.1 (1.1)	–	3.1 (1.1)	3.2 (1.2)
ASDAS	–	3.2 (1.4)	3.2 (1.2)	3.2 (1.3)	3.2 (1.3)
BASDAI	–	4.7 (2.9)	5.2 (2.5)	5.1 (2.6)	5.1 (2.6)
DAPSA	–	26.3 (16.1)	–	26.1 (16.1)	26.1 (16.1)
Reasons for discontinuation, n (%)					
Inefficacy	885 (57.9)	623 (58.8)	485 (52.3)	1108 (55.7)	1993 (56.7)
Adverse event	354 (23.2)	205 (19.3)	181 (19.5)	386 (19.4)	740 (21.0)
Other*	290 (18.9)	232 (21.9)	262 (28.2)	494 (24.9)	784 (22.3)
Total	1529 (100)	1060 (100)	928 (100)	1988 (100)	3517 (100)

Continued

Table 1 Continued

Variables	Spondyloarthritis				All patients
	Rheumatoid arthritis	Psoriatic arthritis	Axial SpA	All SpA	
JAK inhibitors					
Number of patients, n (%)	1386 (84.4)	198 (12.1)	58 (3.5)	256 (15.6)	1642 (24.0)
Number of patients with prior exposure to TNFi, n (%)	216 (15.6)	39 (19.7)	4 (6.9)	43 (16.8)	259 (15.8)
Age at treatment start in years, mean (SD)	57.0 (12.1)	52.6 (10.1)	52.4 (10.9)	52.6 (10.3)	56.3 (11.9)
Disease duration at treatment start in years, mean (SD)	11.8 (8.8)	10.1 (8.2)	15.1 (11.1)	11.2 (9.1)	11.7 (8.9)
Follow-up time in years, mean (SD)	1.9 (1.6)	1.3 (1.2)	1.1 (0.7)	1.3 (1.1)	1.8 (1.5)
Follow-up time in years, min-max	0, 6.2	0, 5.6	0, 4.1	0, 5.6	0, 6.2
Charlson Comorbidity Index, n (%)					
0	0 (0.0)	162 (81.8)	45 (77.6)	207 (80.9)	207 (12.6)
1	1089 (78.6)	20 (10.1)	5 (8.6)	25 (9.8)	1114 (67.8)
2	164 (11.8)	12 (6.1)	6 (10.3)	18 (7.0)	182 (11.1)
3 or more	133 (9.6)	4 (2.0)	2 (3.5)	6 (2.3)	139 (8.5)
Number of treatments, n (%)	1686 (85.4)	226 (11.5)	62 (3.1)	288 (14.6)	1974
Lines of treatment, n (%)					
First	401 (23.8)	23 (10.2)	5 (8.1)	28 (9.7)	429 (21.7)
Second	317 (18.8)	38 (16.8)	12 (19.4)	50 (17.4)	367 (18.6)
Third or higher	968 (57.4)	165 (73)	45 (72.6)	210 (72.9)	1178 (59.7)
Concomitant use of csDMARD at treatment start, n (%)	924 (54.8)	113 (50)	12 (19.4)	125 (43.4)	1049 (53.1)
Concomitant use of GCs at treatment start, n (%)	959 (56.9)	100 (44.3)	13 (21.0)	113 (39.2)	1072 (54.3)
Type of JAKi, n (%)					
Baricitinib	738 (43.8)	6 (2.7)	1 (1.6)	7 (2.4)	745 (37.7)
Tofacitinib	460 (27.3)	125 (55.3)	7 (11.3)	132 (45.8)	592 (30.0)
Upadacitinib	373 (22.1)	94 (41.6)	54 (87.1)	148 (51.4)	521 (26.4)
Filgotinib	115 (6.8)	1 (0.4)	0 (0.0)	1 (0.4)	117 (5.9)
Disease activity at treatment start, mean (SD)					
DAS28-ESR	4.7 (1.4)	4.5 (1.4)	–	4.5 (1.4)	4.6 (1.4)
DAS28-CRP	3.6 (1.1)	3.5 (1.2)	–	3.5 (1.2)	3.5 (1.1)
ASDAS	–	4.1 (2.0)	3.4 (1.0)	3.7 (1.5)	3.7 (1.5)
BASDAI	–	5.1 (3.0)	5.1 (2.9)	5.1 (3.0)	5.2 (3.0)
DAPSA	–	31.0 (26.5)	–	31.0 (26.5)	31.0 (26.5)
Reasons for discontinuation, n (%)					
Inefficacy	439 (58.9)	69 (67.7)	8 (72.7)	77 (88.1)	516 (60.1)
Adverse event	203 (27.3)	22 (21.6)	3 (27.3)	25 (22.1)	228 (26.6)
Other*	103 (13.8)	11 (10.7)	0 (0.0)	11 (9.8)	114 (13.3)
Total	745 (100)	102 (100)	11 (100)	113 (100)	858 (100)

For those patients treated with both mechanisms of action, each treatment course contributed to the corresponding treatment group.

*Other reasons for discontinuation: patient loss of follow-up, pregnancy, remission, non-medical switch, others, unknown.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; csDMARD, conventional synthetic DMARD; DAPSA, Disease Activity in Psoriatic Arthritis Score; DAS28-CRP, Disease Activity Score with 28 joints count and C reactive protein; DAS28-ESR, Disease Activity Score with 28 joints count and erythrocyte sedimentation rate; GC, glucocorticoid; JAKi, Janus kinase inhibitor; MAb, monoclonal antibodies; SpA, spondyloarthritis; TNFi, tumour necrosis factor inhibitor.

Table 2 Incidence rate per 1000 person-years of main adverse events

	Rheumatoid arthritis			Spondyloarthritis		
	TNFI	JAKi	JAKi	TNFI	JAKi	JAKi
Total exposure time (years)	6432.3	3165.1	3165.1	10 302.9	375.8	375.8
Type of adverse event	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)
Mortality*	4.4 (3.0 to 6.3)	6.0 (3.8 to 9.4)	1.4 (0.8 to 2.5) P=0.28	1.4 (0.8 to 2.3)	2.7 (0.4 to 18.9)	2.0 (0.3 to 14.9) P=0.52
Malignancies*	19.9 (16.7 to 23.7)	19.9 (15.5 to 25.5)	1.0 (0.7 to 1.4) P=0.99	13.4 (11.3 to 15.8)	10.6 (4.0 to 28.4)	0.8 (0.3 to 2.2) P=0.65
All infections	221.8 (210.6 to 233.7)	280.9 (263.0 to 300.0)	1.3 (1.2 to 1.4) P<0.001	1.1 (1.0 to 1.3) P=0.005	170.5 (162.7 to 178.7)	1.5 (1.2 to 1.8) P<0.001
Serious infections	30.9 (26.9 to 35.5)	49.3 (42.1 to 57.7)	1.6 (1.3 to 2.0) P<0.001	1.1 (0.9 to 1.4) P=0.37	18.8 (16.4 to 21.7)	1.0 (0.5 to 2.1) P=0.98
Herpes zoster	8.7 (6.7 to 11.3)	18.6 (14.4 to 24.1)	2.1 (1.5 to 3.1) P<0.001	2.2 (1.5 to 3.3) P<0.001	10.6 (4.0 to 28.4)	2.2 (0.8 to 6.2) P=0.12
Tuberculosis	1.4 (0.7 to 2.7)	0.3 (0.0 to 2.2)	0.2 (0.0 to 1.8) P=0.16	0.2 (0.0 to 1.4) P=0.10	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Cardiac	11.0 (8.7 to 13.9)	15.8 (12.0 to 20.8)	1.7 (1.1 to 2.4) P=0.008	1.1 (0.7 to 1.6) P=0.71	8.3 (6.7 to 10.2)	1.0 (0.3 to 3.1) P=0.96
Thrombotic/vascular	11.6 (9.6 to 14.1)	17.2 (11.6 to 25.5)	1.4 (1.0 to 2.1) P=0.052	1.3 (0.9 to 2.0) P=0.16	8.0 (2.6 to 24.8)	1.1 (0.3 to 3.4) P=0.91
Pulmonary	30.2 (26.2 to 34.7)	38.9 (32.6 to 46.4)	1.3 (1.0 to 1.6) P=0.028	1.1 (0.9 to 1.4) P=0.39	22.0 (19.3 to 25.1)	1.3 (0.7 to 2.4) P=0.36
Gastrointestinal	13.1 (11.2 to 15.1)	50.6 (43.3 to 59.0)	1.6 (1.3 to 2.0) P<0.001	1.5 (1.2 to 1.8) P=0.001	55.9 (35.4 to 85.7)	1.4 (0.9 to 2.2) P=0.11
Gastrointestinal perforation	2.5 (1.5 to 4.1)	3.8 (2.2 to 6.7)	1.5 (0.7 to 3.2) P=0.27	1.1 (0.5 to 2.4) P=0.90	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)

Adjusted IRR by age, sex, years of disease and Charlson Comorbidity Index, line of treatment, concomitant use of methotrexate, concomitant use of glucocorticoids and disease activity at baseline.
p<0.05 are shown in bold.

*Mortality and malignancy events followed the 'ever taken drug' risk attribution model. All the remaining adverse events were attributed to a drug while the patient was actively receiving therapy plus a lag window beyond drug discontinuation.
IR, incidence rate (per 1,000 patient-years); IRR, incidence rate ratio (calculated using the TNFI as reference); JAKi, Janus kinase inhibitor; TNFI, tumour necrosis factor inhibitor.

received 1974 courses of treatment with JAKi and 715 (10.5%) received both treatments. Demographic and disease-related variables are shown in table 1. Patients with RA were older, mostly female and had a higher comorbidity index. They received concomitant csDMARDs and glucocorticoids more frequently than patients with SpA.

Patients treated with JAKi were older at initiation of treatment (56.3 vs 52.1 years), had a longer disease duration (11.7 vs 9.1 years) and presented a higher comorbidity index. The prescription pattern was also different, with JAKi being more frequently prescribed in later treatment lines in both diagnostic groups and JAKi monotherapy more common in patients with RA. The use of glucocorticoids was more frequent in combination with JAKi than with TNFi in patients with SpA.

The most frequently prescribed JAKi was baricitinib (37.7%), followed by tofacitinib (30.0%), upadacitinib (26.4%) and filgotinib (5.9%). As some of these therapies have no indication in SpA, differences by diagnostic group were recorded. Mean baseline disease activity indices at initiation of therapy were similar in both groups. Patients discontinued TNFi and JAKi for similar reasons, namely inefficacy (56.7% and 60.1%, respectively) and AEs (21% and 26.6%, respectively).

Safety profile

The cumulative duration of exposure for RA was 6432.3 patient-years in the case of TNFi and 3165.1 patient-years in the case of JAKi. The equivalent values for SpA were 10302.9 and 375.8 patient-years, respectively.

The incidence rate of AEs per 1000 patient-years and the crude and adjusted IRR comparing JAKi with TNFi are shown in table 2. The IRR of fatal AEs and cancer was similar between treatments, with no clinical or statistically significant differences in the crude or the adjusted analysis.

The risk of all infections, serious infections and herpes zoster was onefold to twofold higher among patients with RA treated with JAKi in the crude analyses. In the adjusted IRR analyses, the IRR was statistically significant only for all infections and herpes zoster. In patients with SpA, this difference was only statistically significant for all infections in the crude analysis, but not in the adjusted. The incidence of tuberculosis was similar in patients with RA treated with TNFi and JAKi. No cases of tuberculosis were reported among patients with SpA treated with JAKi. The

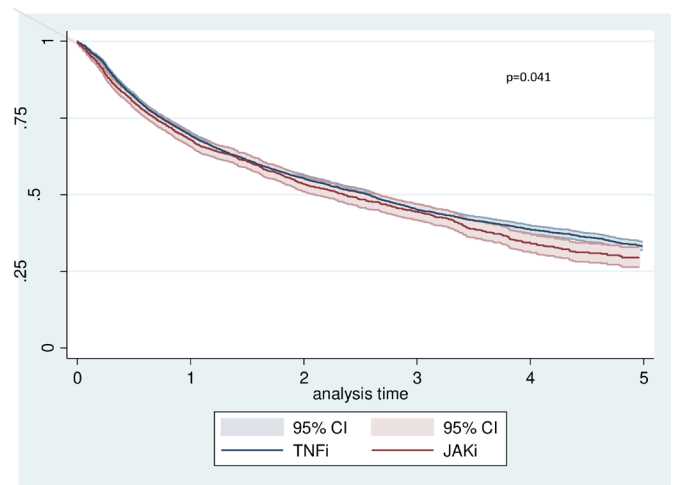


Figure 1 Kaplan-Meier drug persistence curves by treatment, all patients. JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor.

most common infections were upper and lower respiratory tract infections, followed by SARS-CoV-2 infection.

The IRR of cardiac AEs was higher in patients with RA treated with JAKi in the crude but not in the adjusted analyses. No differences were found in the IRR of thrombotic/vascular AEs for patients with RA or SpA. The main presentations for cardiovascular AEs were atrial fibrillation, tachyarrhythmia, chest pain and myocardial infarction.

The IRR of pulmonary and gastrointestinal AEs was higher in patients with RA for JAKi in the crude analysis; however, this difference was not confirmed in the adjusted IRR. The main presentations of pulmonary AE were cold, dyspnoea and cough. There were five cases of pulmonary embolism in patients with RA treated with TNFi, six cases in patients with RA treated with JAKi and four in patients with SpA treated with TNFi. The gastrointestinal AEs observed were diarrhoea, abdominal and oropharyngeal pain, oral ulcers and nausea. No gastrointestinal perforations were reported among patients with SpA treated with JAKi. Additional data for AEs are shown in the online supplemental material.

Table 3 Drug persistence by group of treatment

	1 year		2 years		3 years		P value
	Retention rate (%)	95% CI	Retention rate (%)	95% CI	Retention rate (%)	95% CI	
All patients							0.041
TNFi	69.2	68.2 to 70.3	55.3	54.1 to 56.5	45.2	43.9 to 46.5	
JAKi	68.3	66.0 to 70.6	54.0	51.4 to 56.5	44.9	42.1 to 47.7	
Rheumatoid arthritis							0.86
TNFi	67.4	65.7 to 69.0	52.9	51.0 to 54.7	42.6	40.5 to 44.6	
JAKi	68.3	66.0 to 70.6	54.0	51.4 to 56.5	44.9	42.1 to 47.7	
Spondyloarthritis							0.016
Psoriatic arthritis							0.016
TNFi	69.3	67.3 to 71.3	54.9	52.6 to 57.1	44.6	42.2 to 47.0	
JAKi	60.6	53.4 to 67.0	45.5	37.6 to 53.1	37.7	29.1 to 46.2	
Axial spondyloarthritis							0.30
TNFi	72.0	69.9 to 73.9	59.4	57.1 to 61.5	49.3	46.9 to 51.7	
JAKi	82.9	70.4 to 90.4	64.0	37.8 to 81.4	48.0	16.3 to 74.3	

Retention rate is expressed as estimated survival percentage, which accounted for the patients at risk in the denominator (ie, excluding censored subjects).

JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor.

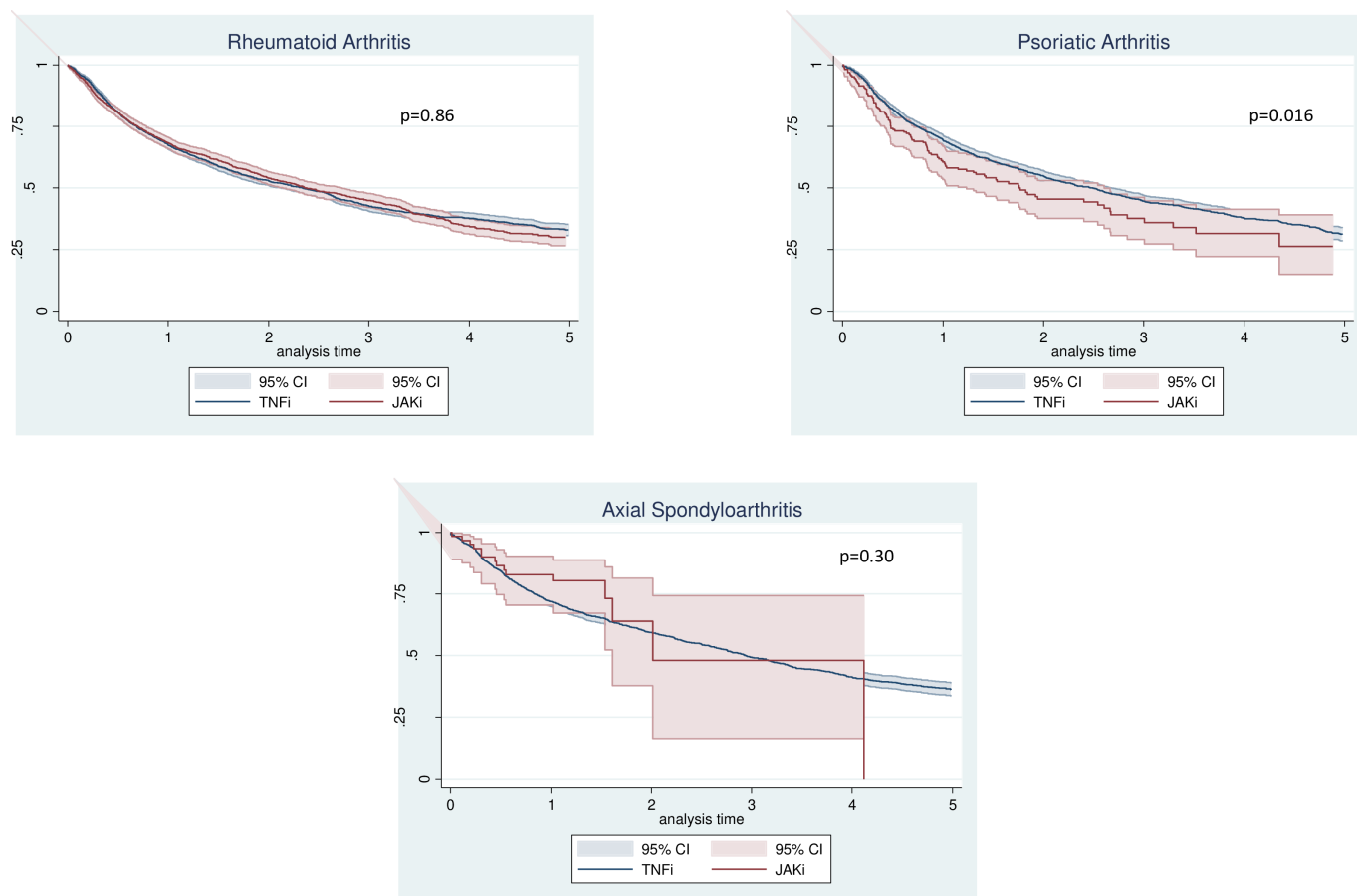


Figure 2 Kaplan-Meier drug persistence curves by treatment, stratified by disease. JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor.

The most common causes of death were serious infections, cardiovascular events and cancer.

Drug persistence and associated factors

Drug persistence at 1, 2 and 3 years was 69.2%, 55.3% and 45.2% for TNFi and 68.3%, 54.0% and 44.9% for JAKi, respectively, in the study population as a whole (table 3 and figure 1). When stratified by diagnostic group, persistence of TNFi and JAKi was similar in RA ($p=0.86$) and axSpA ($p=0.30$). Significant differences in favour of TNFi were observed in the PsA group ($p=0.016$) (figure 2). However, follow-up time was limited for patients with PsA and axSpA treated with JAKi, as approval for these indications was more recent (ie, December 2019).¹²

Hazard ratios (HRs) with their 95% CI were estimated in both the bivariate and multivariate analyses to identify the variables associated with drug persistence (table 4). In the model that included all diseases, treatment with JAKi (HR=0.85; 95% CI 0.78–0.92), having axSpA (0.84; 0.76–0.95) and concomitant use of csDMARDs (0.90; 0.84–0.96) were associated with lower probability of discontinuation. On the other hand, the variables associated with a greater probability of discontinuation were higher comorbidity index (1.07; 1.03–1.11), concomitant treatment with glucocorticoids (1.13; 1.05–1.21), female sex (1.16; 1.08–1.24), the use of a second line of treatment (1.30; 1.20–1.40) or ≥ 3 lines (1.53; 1.41–1.65), and medium baseline disease activity (1.19; 1.10–1.28) or high baseline disease activity (1.34; 1.23–1.46). When stratified by disease, the models differed slightly from the general model, especially in patients with PsA and axSpA. Unlike RA, in the SpA models, JAKi, glucocorticoids and the

comorbidity index were no longer associated with a lower probability of discontinuation, and female sex was associated with a greater risk of discontinuation, as were ≥ 3 lines of treatment and baseline disease activity.

DISCUSSION

The real-world safety of JAKi has been compared with that of TNFi in a limited number of studies. This analysis of BIOBADASER 3.0 included 6826 patients treated with TNFi and JAKi in daily clinical practice between 2015 and 2023. We provide real-world evidence of a similar safety profile for JAKi and TNFi.

A higher incidence of infection including herpes zoster, all infections and gastrointestinal events was recorded for patients with RA treated with JAKi; in patients with SpA, incidence was only high for all infections in the crude, but not in the adjusted analysis. However, patients initiating JAKi were older and biologic experienced and had a longer disease duration and higher comorbidity, as reported in other registries.^{26–29} In the JAK-pot study, a collaboration of European registries of patients with RA treated with bDMARDs and tsDMARDs including data from BIOBADASER, the probability of stopping treatment owing to AE was higher for JAKi than for TNFi.²⁸

Our safety results confirm findings from a pooled safety analysis based on data from randomised clinical trials in patients with RA for tofacitinib,³⁰ baricitinib,³¹ upadacitinib³² and filgotinib.³³ Safety data for SpA are restricted to tofacitinib and upadacitinib, although the results are similar.^{34 35}

Most real-world evidence is for tofacitinib³⁶ because of its earlier market release. Our data are consistent with this finding

Table 4 Cox proportional hazards regression models for drug discontinuation

Variable	Reference	Bivariate			Multivariate		
		HR	95% CI	P value	HR	95% CI	P value
All diseases							
JAKi	TNFi	1.06	0.98 to 1.14	0.15	0.85	0.78 to 0.92	<0.001
Disease							
Psoriatic arthritis	Rheumatoid arthritis	0.98	0.91 to 1.05	0.61	1.07	0.98 to 0.95	0.14
Axial spondyloarthritis	Rheumatoid arthritis	0.80	0.74 to 0.86	<0.001	0.84	0.76 to 0.95	0.003
Concomitant csDMARDs	Monotherapy	0.96	0.90 to 1.02	0.18	0.90	0.84 to 0.96	0.001
Disease duration		1.00	1.00 to 1.00	0.48	0.99	0.99 to 1.00	<0.001
Age at the start of treatment		1.00	1.00 to 1.01	0.002	1.00	1.00 to 1.00	0.57
GCs	No GCs	1.18	1.11 to 1.26	<0.001	1.13	1.05 to 1.21	<0.001
Charlson Comorbidity Index		1.09	1.06 to 1.12	<0.001	1.07	1.03 to 1.11	0.001
Sex, female	Male	1.23	1.16 to 1.31	<0.001	1.16	1.08 to 1.24	<0.001
Lines of treatment	First						
Second		1.22	1.13 to 1.32	<0.001	1.30	1.20 to 1.40	<0.001
Third or higher		1.41	1.31 to 1.51	<0.001	1.53	1.41 to 1.65	<0.001
Disease activity (baseline)							
Low							
Medium		1.19	1.11 to 1.28	<0.001	1.19	1.10 to 1.28	<0.001
High		1.23	1.14 to 1.33	<0.001	1.34	1.23 to 1.46	<0.001
Rheumatoid arthritis							
JAKi	TNFi	0.96	0.88 to 1.05	0.36	0.80	0.72 to 0.87	<0.001
Concomitant csDMARDs	Monotherapy	0.88	0.80 to 0.96	0.004	0.92	0.83 to 1.01	0.072
Disease duration		1.00	1.00 to 1.01	0.55	0.99	0.99 to 1.00	0.001
Age at the start of treatment		1.00	1.0 to 1.00	0.61	1.00	1.00 to 1.00	0.65
GCs	No GCs	1.17	1.07 to 1.27	<0.001	1.15	1.05 to 1.25	0.002
Charlson Comorbidity Index		1.08	1.03 to 1.13	0.002	1.07	1.01 to 1.12	0.014
Sex, female	Male	1.01	0.91 to 1.12	0.90	1.01	0.90 to 1.12	0.92
Lines of treatment	First						
Second		1.26	1.13 to 1.41	<0.001	1.37	1.22 to 1.53	<0.001
Third or higher		1.57	1.43 to 1.73	<0.001	1.80	1.62 to 2.0	<0.001
Disease activity (baseline)							
Low							
Medium		1.15	1.04 to 1.27	0.006	1.19	1.08 to 1.32	0.001
High		1.36	1.20 to 1.53	<0.001	1.34	1.18 to 1.52	<0.001
Psoriatic arthritis							
JAKi	TNFi	1.30	1.05 to 1.59	0.013	1.04	0.84 to 1.30	0.70
Concomitant csDMARDs	Monotherapy	0.87	0.77 to 0.97	0.014	0.90	0.08 to 1.02	0.10
Disease duration		0.99	0.99 to 1.00	0.10	0.99	0.98 to 1.00	0.004
Age at the start of treatment		1.00	1.00 to 1.01	0.16	1.00	1.00 to 1.01	0.17
GCs	No GCs	1.14	1.01 to 1.30	0.037	1.12	0.98 to 1.28	0.089
Charlson Comorbidity Index		1.01	0.94 to 1.09	0.82	1.00	0.92 to 1.08	0.94
Sex, female	Male	1.44	1.28 to 1.62	<0.001	1.36	1.20 to 1.54	<0.001
Lines of treatment	First						
Second		1.23	1.06 to 1.41	0.005	1.26	1.09 to 1.46	0.002
Third or higher		1.31	1.14 to 1.50	<0.001	1.35	1.15 to 1.59	<0.001
Disease activity (baseline)							
Low							
Medium		1.22	1.06 to 1.40	0.005	1.23	1.07 to 1.42	0.004
High		1.40	1.20 to 1.64	<0.001	1.36	1.16 to 1.60	<0.001
Axial spondyloarthritis							
JAKi	TNFi	0.62	0.34 to 1.13	0.12	0.58	0.32 to 1.06	0.079
Concomitant csDMARDs	No csDMARDs	0.86	0.73 to 1.02	0.075	0.85	0.71 to 1.01	0.059
Disease duration		1.00	0.99 to 1.01	0.73	1.00	0.99 to 1.00	0.19
Age at the start of treatment		1.00	1.00 to 1.01	0.12	1.00	1.00 to 1.01	0.45
GCs	No GCs	0.91	0.72 to 1.13	0.38	0.94	0.74 to 1.19	0.59
Charlson Comorbidity Index		1.13	1.06 to 1.21	<0.001	1.12	1.05 to 1.21	0.001
Sex, female	Male	1.21	1.06 to 1.38	0.005	1.20	1.04 to 1.37	0.01
Lines of treatment	First						
Second		1.15	0.99 to 1.35	0.074	1.19	1.01 to 1.40	0.033

Continued

Table 4 Continued

Variable	Reference	Bivariate			Multivariate		
		HR	95% CI	P value	HR	95% CI	P value
Third or higher		1.13	0.97 to 1.32	0.11	1.17	0.99 to 1.39	0.059
Disease activity (baseline)	Low						
Medium		1.08	0.87 to 1.34	0.45	1.11	0.90 to 1.32	0.34
High		1.25	1.06 to 1.47	0.008	1.26	1.07 to 1.49	0.007

csDMARD, conventional synthetic DMARD; GC, glucocorticoid; JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor.

based on the doses marketed in the summary of product characteristics and authorised by regulatory agencies.^{10–12}

Patients with RA, PsA and axSpA have a higher cardiovascular risk, with the result that AEs such as major cardiovascular and thromboembolic events are expected.^{37,38} However, a higher incidence rate for cardiac AEs was only observed in patients with RA treated with JAKi in the crude analyses. The most common presentations of cardiovascular AEs were atrial fibrillation, tachyarrhythmia, chest pain and myocardial infarction, as reported elsewhere.³⁸ Compared with patients with SpA, patients with RA treated with JAKi were older, had a longer disease duration and a higher comorbidity index, received glucocorticoids more frequently and had higher levels of disease activity. Although we tried to reduce the effect of these variables in the adjusted analysis, there is still residual confounding that may contribute to the observed results. In addition, since 2019, treatment with tofacitinib for RA and SpA has been limited to 5 mg two times per day and to patients under 50 years of age, while in older patients, it can be used if no other options are available.^{9–12 34 35} No differences were found in the IRR of thrombotic/vascular AEs for patients with RA or SpA.

Global drug persistence rates at 1, 2 and 3 years were good. In patients with RA and axSpA, persistence was similar for TNFi and JAKi; in PsA it was slightly better for TNFi. Data from the DANBIO and DERMIO registries showed similar persistence rates. In patients with RA, the highest drug retention rates were for baricitinib, adalimumab and etanercept, with differences according to the line of treatment. In patients with PsA, persistence was better for TNFi and poorer for tofacitinib. In axSpA, the highest retention rates were for TNFi and the poorest were for tofacitinib.²⁷ Other real-world studies on persistence of TNFi and JAKi in these three diagnoses are scarce and with limited follow-up, although they report results similar to ours.^{26–29 36 39–41}

In our models, the variables associated with drug persistence were different for each diagnostic group. JAKis were associated with a lower probability of discontinuation in the general model and the RA-specific model. In patients with SpA, female sex increased the risk of discontinuation. These results confirm previous observations, although the data published for PsA and axSpA are scarce and limited to 1 year.^{40 42}

In patients with RA, glucocorticoids were associated with a higher probability of discontinuation. This association may be confounded by prescription bias, as glucocorticoids are prescribed to patients with more severe disease. Further research is necessary to clarify the relationship between glucocorticoids and drug persistence.

The strengths of our study include the large group of patients with different diagnoses treated in routine clinical practice. In addition, BIOBADASER is a consolidated registry that has followed up patients from throughout Spain for more than 20 years and in which data quality is monitored.

The main limitation of our study is the complexity involved in measuring variables associated with prescription bias in observational studies. An additional limitation is last resort bias, which is difficult to identify in secondary-use data. For this reason, we also included the line of treatment as an adjustment variable in the Cox regression model, after which the difference between JAKi and TNFi persisted. Similarly, some clinical and important variables associated with various risks (mortality, infection, gastrointestinal perforations and cardiovascular conditions, including thromboembolic risk) are difficult to measure and were not evaluated. Examples include a personal history of previous atherosclerotic disease, thromboembolic events, severe infections, colon diverticulitis, concomitant non-steroidal anti-inflammatory drugs,⁴³ opioids,⁴⁴ contraceptives with oestrogens and other drugs associated with these risks. For this reason, despite the attempts to model AE risks between treatment groups through adjusted IRR, there might still be residual confounding. In addition, JAKis were recently approved for treatment of axSpA, and the number of patients and long-term data decreased because of censored observations.

CONCLUSIONS

We recorded significant differences between patients with RA, PsA and axSpA treated with JAKi and TNFi in a real-world setting. In patients with RA, treatment with JAKi was associated with a slight increase in the frequency of AEs, particularly infections, herpes zoster and gastrointestinal events. However, these AEs were mild and did not increase mortality. Drug persistence was similar for JAKi and TNFi in patients with RA and axSpA, and only slightly higher for TNFi in patients with PsA. Treatment with JAKi and concomitant use of csDMARDs were associated with a lower risk of discontinuation, although this differed by diagnostic group. The variables increasing the probability of discontinuation were comorbidities, later lines of treatment, glucocorticoids and baseline disease activity, with differences by disease. In patients with PsA, a greater probability of discontinuation was associated with female sex, later lines of treatment and disease activity.

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Supplementary material. Most common adverse events by disease and treatment.

	Rheumatoid arthritis				Spondyloarthritis			
	TNFi		JAKi		TNFi		JAKi	
	n	%	n	%	n	%	n	%
Mortality	28	100	19	100	14	100	1	100
Infections								
Lower respiratory tract	2	7.1	2	10.5	2	14.2	0	0
Endocarditis	1	3.5	0	0	0	0	0	0
Urinary tract	0	0	2	10.5	0	0	0	0
SARS-Cov-19	0	0	3	15.7	0	0	0	0
Cardiovascular								
Myocardial infarction	2	7.1	0	0	1	7.1	0	0
Cerebral ischemia/infarction	0	0	0	0	1	7.1	0	0
Intracerebral hemorrhage	1	3.5	1	5.2	0	0	1	100
Congestive heart failure	1	3.5	1	5.2	1	7.1	0	0
Intestinal ischemia	1	3.5	0	0	1	7.1	0	0
Hypertensive emergency	0	0	0	0	0	0	0	0
Solid tumors								
Lung	4	14.2	0	0	1	7.1	0	0
Colorectal	3	10.7	1	5.2	1	7.1	0	0
Brain	1	3.5	0	0	0	0	0	0
Pancreatic	0	0	0	0	1	7.1	0	0
Bladder	0	0	0	0	0	0	0	0
Chronic kidney disease	1	3.5	0	0	1	7.1	0	0
Respiratory failure	1	3.5	0	0	0	0	0	0
Infections								
Upper respiratory tract	271	18.9	101	11.3	307	17.4	12	12.7
Urinary tract	177	12.4	96	10.7	182	10.3	16	17.2
SARS-Cov-2	148	10.3	99	11.1	220	12.5	13	13.8
Lower respiratory tract	107	7.4	73	8.2	132	7.5	5	5.3
Herpes zoster	99	6.9	99	11.1	92	5.2	11	11.7
Dental abscess	42	2.9	13	1.4	40	2.2	2	2.1
Pneumonia	32	2.2	19	2.1	21	1.1	0	0
Acute gastroenteritis	31	2.1	21	2.3	44	2.5	1	1.0
Acute conjunctivitis	29	2.0	15	1.6	48	2.7	1	1.0
Skin and soft tissues	16	1.1	10	1.1	18	1.0	3	3.1
Serious infections								
SARS-Cov-19	35	17.5	31	19.8	49	25.2	4	57.1
Pneumonia	36	18.0	22	14.1	26	13.4	0	0
Upper respiratory tract	20	10.0	26	16.6	33	17.1	1	14.2
Lower respiratory tract	11	5.5	9	5.7	4	2.0	0	0
Urinary tract	3	1.5	7	4.4	6	3.0	0	0

Osteomyelitis/septic arthritis	11	5.5	4	2.5	1	0.5	0	0
Skin and soft tissues	13	6.5	10	6.4	4	2.0	1	14.2
Bacteremia	3	1.5	1	0.6	5	2.5	0	0
Herpes zoster	4	2.0	2	1.2	3	1.5	0	0
Tuberculosis	3	1.5	1	0.6	1	0.5	0	0
Malignancy								
Basal cell carcinoma	21	16.4	12	19.0	15	10.8	0	0
Lung cancer	9	7.0	7	11.1	3	2.1	0	0
Breast cancer	8	6.2	5	7.9	8	5.7	1	25.0
Urinary tract cancer	7	5.4	2	3.1	4	2.8	0	0
Pancreatic	4	3.1	4	6.3	1	0.7	0	0
Malignant melanoma	5	3.9	0	0	4	2.8	0	0
Squamous cell carcinoma	3	2.3	2	3.1	3	2.1	1	25.0
Multiple myeloma	3	2.3	3	4.7	2	1.4	0	0
Lymphoma	2	1.5	2	3.1	2	1.4	0	0
Colorectal	3	2.3	0	0	4	2.8	0	0
Prostate cancer	1	0.7	1	1.5	4	2.8	0	0
Cardiovascular								
Atrial fibrillation	12	19.0	7	13.7	11	12.9	0	0
Tachyarrhythmia	15	23.8	11	21.5	15	17.6	1	33.3
Chest pain	9	14.2	7	13.7	18	21.1	0	0
Myocardial infarction	7	11.1	3	5.8	11	12.9	1	0
Pericarditis	7	11.1	9	17.6	2	2.3	0	33.3
Heart failure	6	9.5	7	13.7	3	3.5	0	0
Angina pectoris	3	4.7	3	5.8	11	12.9	1	33.3
Lung								
Cold	93	47.9	63	51.2	138	60.7	9	81
Dyspnea	22	11.3	13	10.5	22	9.6	0	0
Cough	7	3.6	6	4.8	2	0.8	0	0
Pulmonary embolism/thrombosis	5	2.5	6	4.8	4	1.7	0	0
Pulmonary fibrosis	3	1.5	0	0	0	0	0	0
Pleural effusion	3	1.5	2	1.6	1	0.4	0	0
Bronchiectasis	0	0	0	0	1	0.4	0	0
Epistaxis	4	2.0	6	4.8	3	1.3	0	0
Interstitial lung disease	4	2.0	4	3.2	2	0.8	0	0
Chronic obstructive lung disease	2	1.0	3	2.4	3	1.3	0	0
Gastrointestinal								
Diarrhea	50	24.8	27	26.8	75	18.6	6	28.5
Abdominal pain	24	11.9	34	21.2	37	9.2	0	0
Oropharyngeal pain	24	11.9	11	6.8	39	9.7	3	14.2
Oral ulcers	15	7.4	8	5.0	17	4.2	1	4.7
Nausea	14	6.9	14	8.7	10	2.4	1	4.7
Vomiting	11	5.4	10	6.2	13	3.2	1	4.7
Crohn disease	1	0.4	0	0	11	2.7	0	0
Gastrointestinal perforations	1	0.4	1	0.6	1	0.2	0	0

TNFi Tumour Necrosis Factor inhibitor, JAKi Janus kinase inhibitors