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# 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.

### 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.

## INTRODUCTION

Janus kinase inhibitors (JAKi) are oral targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) used frequently as second-line 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 | Rheumatoid arthritis | Spondyloarthritis | | | All patients |
|---|---|---|---|---|---|
| | | Psoriatic arthritis | Axial SpA | All 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) | 1673 (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) |
| MØA | 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) |
| MØA | 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 | Rheumatoid arthritis | Spondyloarthritis | | | All patients |
|---|---|---|---|---|---|
| | | 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 (68.1) | 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 erythrosedimentation rate; GC, glucocorticoid; JAKi, Janus kinase inhibitor; MØA, 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 | | | TNFi | JAKi | | |
| **Total exposure time (years)** | 6432.3 | 3165.1 | | | 10 302.9 | 375.8 | | |
| **Type of adverse event** | **IR (95% CI)** | **IR (95% CI)** | **Crude IRR (95% CI)** | **Adjusted IRR (95% CI)** | **IR (95% CI)** | **IR (95% CI)** | **Crude IRR (95% CI)** | **Adjusted IRR (95% CI)** |
| Mortality* | 4.4 (3.0 to 6.3) | 6.0 (3.8 to 9.4) | 1.4 (0.8 to 2.5)<br>P=0.28 | 1.2 (0.7 to 2.3)<br>P=0.55 | 1.4 (0.8 to 2.3) | 2.7 (0.4 to 18.9) | 2.0 (0.3 to 14.9)<br>P=0.52 | 0.7 (0.1 to 5.7)<br>P=0.69 |
| Malignancies* | 19.9 (16.7 to 23.7) | 19.9 (15.5 to 25.5) | 1.0 (0.7 to 1.4)<br>P=0.99 | 0.9 (0.6 to 1.2)<br>P=0.43 | 13.4 (11.3 to 15.8) | 10.6 (4.0 to 28.4) | 0.8 (0.3 to 2.2)<br>P=0.65 | 0.9 (0.3 to 2.5)<br>P=0.83 |
| All infections | 221.8 (210.6 to 233.7) | 280.9 (263.0 to 300.0) | 1.3 (1.2 to 1.4)<br>**P<0.001** | 1.1 (1.0 to 1.3)<br>**P=0.005** | 170.5 (162.7 to 178.7) | 250.1 (204.4 to 306.2) | 1.5 (1.2 to 1.8)<br>**P<0.001** | 1.2 (1.0 to 1.5)<br>P=0.078 |
| Serious infections | 30.9 (26.9 to 35.5) | 49.3 (42.1 to 57.7) | 1.6 (1.3 to 2.0)<br>**P<0.001** | 1.1 (0.9 to 1.4)<br>P=0.37 | 18.8 (16.4 to 21.7) | 18.6 (8.9 to 39.1) | 1.0 (0.5 to 2.1)<br>P=0.98 | 0.7 (0.3 to 1.4)<br>P=0.28 |
| Herpes zoster | 8.7 (6.7 to 11.3) | 18.6 (14.4 to 24.1) | 2.1 (1.5 to 3.1)<br>**P<0.001** | 2.2 (1.5 to 3.3)<br>**P<0.001** | 4.8 (3.6 to 6.3) | 10.6 (4.0 to 28.4) | 2.2 (0.8 to 6.2)<br>P=0.12 | 1.6 (0.5 to 4.7)<br>P=0.41 |
| Tuberculosis | 1.4 (0.7 to 2.7) | 0.3 (0.0 to 2.2) | 0.2 (0.0 to 1.8)<br>P=0.16 | 0.2 (0.0 to 1.4)<br>P=0.10 | 0.3 (0.1 to 0.9) | 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)<br>**P=0.008** | 1.1 (0.7 to 1.6)<br>P=0.71 | 8.3 (6.7 to 10.2) | 8.0 (2.6 to 24.8) | 1.0 (0.3 to 3.1)<br>P=0.96 | 0.9 (0.3 to 3.0)<br>P=0.89 |
| Thrombotic/vascular | 11.6 (9.6 to 14.1) | 17.2 (11.6 to 25.5) | 1.4 (1.0 to 2.1)<br>P=0.052 | 1.3 (0.9 to 2.0)<br>P=0.16 | 7.5 (6.0 to 9.3) | 8.0 (2.6 to 24.8) | 1.1 (0.3 to 3.4)<br>P=0.91 | 0.9 (0.3 to 2.9)<br>P=0.83 |
| Pulmonary | 30.2 (26.2 to 34.7) | 38.9 (32.6 to 46.4) | 1.3 (1.0 to 1.6)<br>**P=0.028** | 1.1 (0.9 to 1.4)<br>P=0.39 | 22.0 (19.3 to 25.1) | 29.3 (16.2 to 52.9) | 1.3 (0.7 to 2.4)<br>P=0.36 | 1.5 (0.8 to 2.8)<br>P=0.28 |
| Gastrointestinal | 31.2 (27.2 to 35.9) | 50.6 (43.3 to 59.0) | 1.6 (1.3 to 2.0)<br>**P<0.001** | 1.5 (1.2 to 1.8)<br>**P=0.001** | 39.0 (35.4 to 43.0) | 55.9 (36.4 to 85.7) | 1.4 (0.9 to 2.2)<br>P=0.11 | 1.3 (0.8 to 2.1)<br>P=0.28 |
| Gastrointestinal perforation | 2.5 (1.5 to 4.1) | 3.8 (2.2 to 6.7) | 1.5 (0.7 to 3.2)<br>P=0.27 | 1.1 (0.5 to 2.4)<br>P=0.90 | 1.8 (1.2 1 to 2.8) | 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).

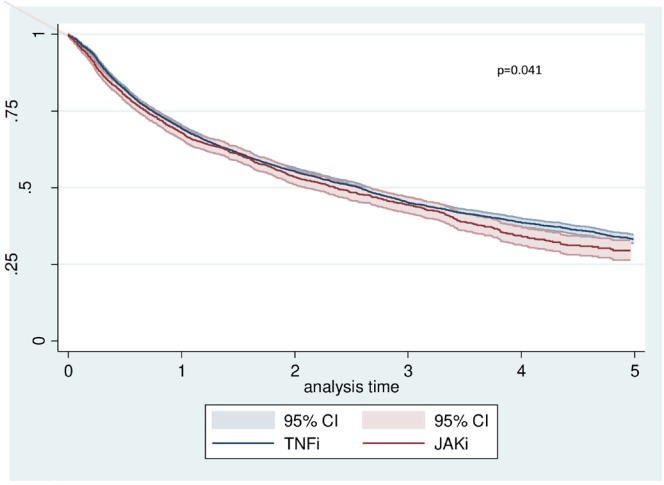


**Figure 1** Kaplan-Meier drug persistence curves by treatment, all patients. JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor.

## 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 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 | | |
|---|---|---|---|---|---|---|---|
| | Retention rate (%) | 95% CI | Retention rate (%) | 95% CI | Retention rate (%) | 95% CI | P value |
| 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** | | | | | | | |
| 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.

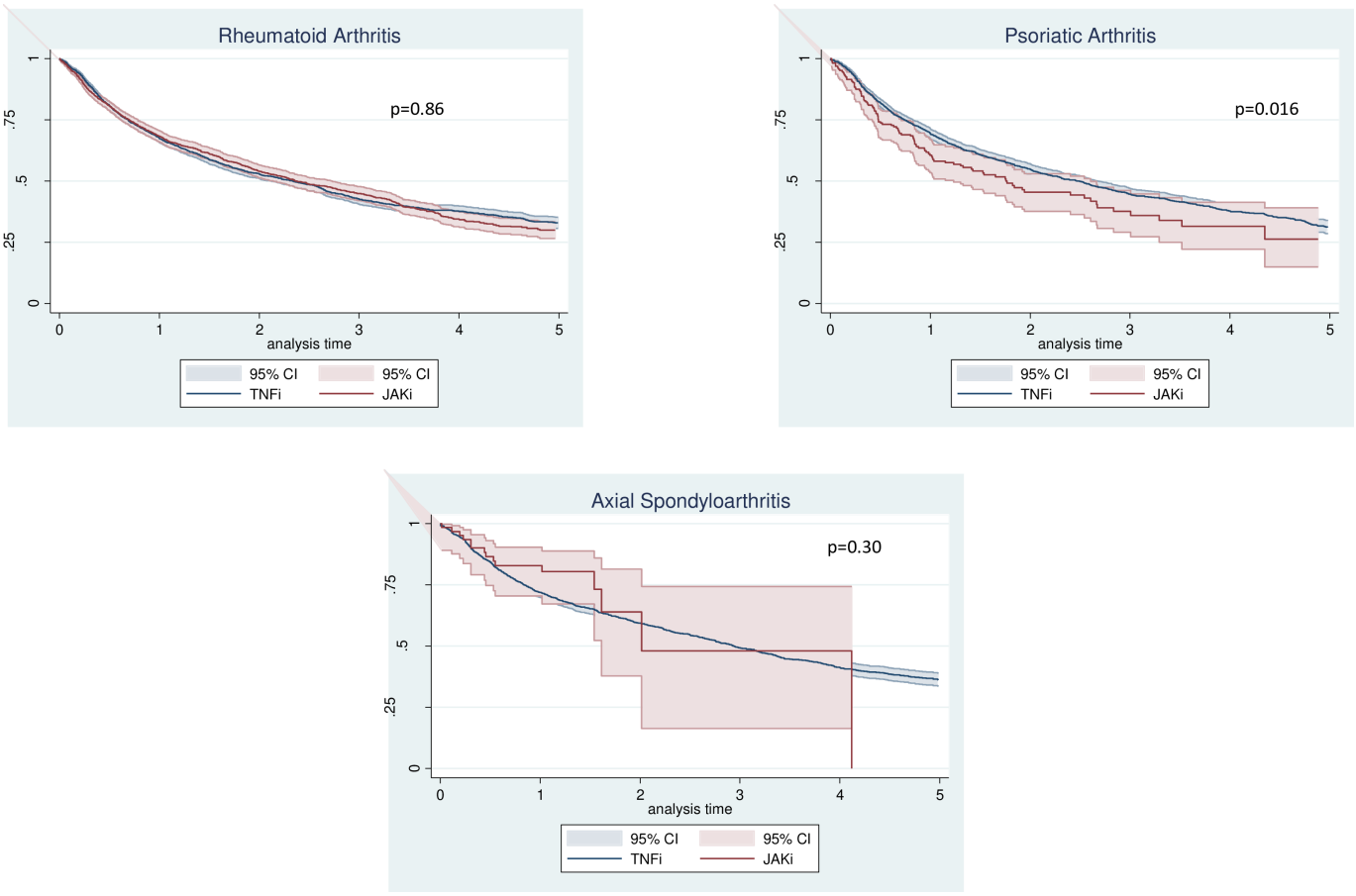


**Figure 2** Kaplan-Meier drug persistence curves by treatment, stratified by disease. JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor.

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] upadacitinib[32] 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 tofacitinib[36] because of its earlier market release. Our data are consistent with this finding

**Table 4** Cox proportional hazards regression models for drug discontinuation

| | | Bivariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **Reference** | **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.[3738] 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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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Consent obtained directly from patient(s)

**Ethics approval** This study involves human participants and was approved by the Hospital Clinic of Barcelona Ethics Committee (approval code: FER-ADA-2015-01). All procedures and materials complied with the International Conference on Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki and with Spanish regulations on data protection and research. Participants gave informed consent to participate in the study before taking part.

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## REFERENCES

1 Tanaka Y, Luo Y, O'Shea JJ, *et al*. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022;18:133–45.
2 Nash P, Kerschbaumer A, Dörner T, *et al*. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis* 2021;80:71–87.
3 Fragoulis GE, McInnes IB, Siebert S. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology* 2019;58:i43–54.
4 Choy EH. Clinical significance of Janus kinase inhibitor selectivity. *Rheumatology (Oxford)* 2019;58:953–62.
5 Smolen JS, Landewé RBM, Bergstra SA, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82:3–18.
6 Gossec L, Baraliakos X, Kerschbaumer A, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700–12.
7 Ramiro S, Nikiphorou E, Sepriano A, *et al*. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis* 2023;82:19–34.
8 US Food and Drug Administration. Center for drug evaluation and research: NDA 203,214 tofacitinib for rheumatoid arthritis, Addendum to primary clinical review. edited by Department of health and human Services. Silver Spring, MD. CENTER FOR DRUG EVALUATION AND RESEARCH 203214Orig1S000 APPROVAL LETTER. 2012.1–10.
9 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022;386:316–26.
10 European Medicines Agency. Available: https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki
11 Food and Drug Administration. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death
12 Agencia Española de Medicamentos y Productos Sanitarios. Boletín Mensual de la AEMPS Sobre Medicamentos de USO Humano del Mes de Noviembre de 2019. 2019.
13 Elsevier. Available: https://www.elsevier.es/es-revista-revista-espanola-reumatologia-29-pdf-13033456
14 Sanchez-Piedra C, Hernández Miguel MV, Manero J, *et al*. Objetivos y metodología de la fase III de BIOBADASER. *Reumatología Clínica* 2019;15:229–36.
15 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573.
16 Zavada J, Dixon WG, Askling J, *et al*. Launch of a checklist for reporting longitudinal observational drug studies in rheumatology: a EULAR extension of STROBE guidelines based on experience from biologics registries. *Ann Rheum Dis* 2014;73:204102.
17 Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (Meddra). *Drug Saf* 1999;20:109–17.
18 Charlson M, Szatrowski TP, Peterson J, *et al*. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51.
19 Prevoo ML, van 't Hof MA, Kuper HH, *et al*. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
20 Kuriya B, Schieir O, Lin D, *et al*. Thresholds for the 28-joint disease activity score (DAS28) using C-reactive protein are lower compared to DAS28 using Erythrocyte sedimentation rate in early rheumatoid arthritis. *Clin Exp Rheumatol* 2017;35:799–803.
21 Machado PM, Landewé R, Heijde D van der, *et al*. Ankylosing spondylitis disease activity score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis* 2018;77:1539–40.
22 Kwon OC, Park MC. BASDAI cut-off values corresponding to ASDAS cut-off values. *Rheumatology (Oxford)* 2022;61:2369–74.
23 Schoels MM, Aletaha D, Alasti F, *et al*. Disease activity in psoriatic arthritis (PSA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis* 2016;75:811–8.
24 Michelsen B, Sexton J, Smolen JS, *et al*. Can disease activity in patients with psoriatic arthritis be adequately assessed by a modified disease activity index for psoriatic arthritis. *Ann Rheum Dis* 2018;77:1736–41.
25 Dixon WG, Carmona L, Finckh A, *et al*. EULAR points to consider when establishing, analysing and reporting safety data of Biologics registers in rheumatology. *Ann Rheum Dis* 2010;69:1596–602.
26 Barbulescu A, Askling J, Chatzidionysiou K, *et al*. Effectiveness of baricitinib and tofacitinib compared with bDMARDs in RA: results from a cohort study using nationwide Swedish register data. *Rheumatology (Oxford)* 2022;61:3952–62.
27 Egeberg A, Rosenø NAL, Aagaard D, *et al*. Drug survival of biologics and novel immunomodulators for rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, and psoriasis - a nationwide cohort study from the DANBIO and DERMBIO registries. *Semin Arthritis Rheum* 2022;53:151979.

28 Lauper K, Iudici M, Mongin D, *et al*. Effectiveness of TNF-inhibitors, abatacept, Il6-inhibitors and JAK-inhibitors in 31 846 patients with rheumatoid arthritis in 19 registers from the 'JAK-pot' collaboration. *Ann Rheum Dis* 2022;81:1358–66.
29 Guidelli GM, Viapiana O, Luciano N, *et al*. Efficacy and safety of baricitinib in 446 patients with rheumatoid arthritis: a real-life multicentre study. *Clin Exp Rheumatol* 2021;39:868–73.
30 Cohen SB, Tanaka Y, Mariette X, *et al*. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD Open* 2020;6:e001395.
31 Taylor PC, Takeuchi T, Burmester GR, *et al*. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. *Ann Rheum Dis* 2022;81:335–43.
32 Cohen SB, van Vollenhoven RF, Winthrop KL, *et al*. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis* 2021;80:304–11.
33 Kavanaugh A, Westhovens RR, Winthrop KL, *et al*. Safety and efficacy of filgotinib: up to 4-year results from an open-label extension study of phase II rheumatoid arthritis programs. *J Rheumatol* 2021;48:1230–8.
34 Keeling S, Maksymowych WP. JAK inhibitors, psoriatic arthritis, and axial spondyloarthritis: a critical review of clinical trials. *Expert Rev Clin Immunol* 2021;17:701–15.
35 Burmester GR, Nash P, Sands BE, *et al*. Adverse events of special interest in clinical trials of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and psoriasis with 37 066 patient-years of tofacitinib exposure. *RMD Open* 2021;7:e001595.
36 Álvaro-Gracia JM, García-Llorente JF, Valderrama M, *et al*. Update on the safety profile of tofacitinib in rheumatoid arthritis from clinical trials to real-world studies: a narrative review. *Rheumatol Ther* 2021;8:17–40.
37 Bengtsson K, Forsblad-d'Elia H, Lie E, *et al*. Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. *Arthritis Res Ther* 2017;19:102.
38 Lauper K, Courvoisier DS, Chevallier P, *et al*. Incidence and prevalence of major adverse cardiovascular events in rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. *Arthritis Care Res (Hoboken)* 2018;70:1756–63.
39 Scheepers L, Yang Y, Chen YL, *et al*. Persistence of Janus-kinase (JAK) inhibitors in rheumatoid arthritis: Australia wide study. *Semin Arthritis Rheum* 2024;64:152314.
40 Walsh JA, Cai Q, Lin I, *et al*. Treatment persistence and adherence among patients with psoriatic arthritis who initiated targeted immune modulators in the US: a retrospective cohort study. *Adv Ther* 2021;38:2353–64.
41 Yu CL, Yang CH, Chi CC. Drug survival of biologics in treating ankylosing spondylitis: a systematic review and meta-analysis of real-world evidence. *BioDrugs* 2020;34:669–79.
42 Brahe CH, Ørnbjerg LM, Jacobsson L, *et al*. Retention and response rates in 14 261 PSA patients starting TNF inhibitor treatment—results from 12 countries in Eurospa. *Rheumatology (Oxford)* 2020;59:1640–50.
43 Ikdahl E, Rollefstad S, Kazemi A, *et al*. Non-Steroidal anti-inflammatory drugs and risk of pulmonary embolism in patients with inflammatory joint disease—results from the nationwide Norwegian Cardio-Rheuma registry. *Eur Heart J Cardiovasc Pharmacother* 2024;10:27–34.
44 Ozen G, Pedro S, Michaud K. Major adverse cardiovascular events and mortality with opioids versus NSAIDs initiation in patients with rheumatoid arthritis. *Ann Rheum Dis* 2023;82:1487–94.