Evaluation of discontinuation for adverse events of JAK inhibitors and bDMARDs in an international collaboration of rheumatoid arthritis registers (the 'JAK-pot' study)

Aymon, Romain; Mongin, Denis; Bergstra, Sytske Anne; Choquette, Denis; Codreanu, Catalin; De Cock, Diederik; Dreyer, Lene; Elkayam, Ori; Huschek, Doreen; Hyrich, Kimme L; Iannone, Florenzo; Inanc, Nevsun; Kearsley-Fleet, Lianne; Koca, Suleyman Serdar; Kvien, Tore K; Leeb, Burkhard F; Lukina, Galina; Nordström, Dan C; Pavelka, Karel; Pombo-Suarez, Manuel; Rodrigues, Ana; Rotar, Ziga; Strangfeld, Anja; Verschueren, Patrick; Westermann, Rasmus; Zavada, Jakub; Courvoisier, Delphine Sophie; Finckh, Axel; Lauper, Kim

Published in:
Annals of the Rheumatic Diseases

DOI (link to publication from Publisher):
10.1136/ard-2023-224670

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

OPEN ACCESS

EPIDEMIOLOGICAL SCIENCE

Evaluation of discontinuation for adverse events of JAK inhibitors and bDMARDs in an international collaboration of rheumatoid arthritis registers (the 'JAK-pot' study)

Romain Aymon ,[1] Denis Mongin ,[1] Sytske Anne Bergstra ,[2] Denis Choquette,[3] Catalin Codreanu,[4] Diederik De Cock,[5] Lene Dreyer,[6] Ori Elkayam,[7] Doreen Huschek,[8] Kimme L Hyrich ,[9,10] Florenzo Iannone ,[11] Nevsun Inanc ,[12] Lianne Kearsley-Fleet ,[9] Suleyman Serdar KOCA,[13] Tore K Kvien,[14] Burkhard F Leeb,[15] Galina Lukina,[16] Dan C Nordström,[17] Karel Pavelka,[18] Manuel Pombo-Suarez ,[19] Ana Rodrigues,[20] Ziga Rotar,[21] Anja Strangfeld ,[8] Patrick Verschueren ,[22] Rasmus Westermann,[6] Jakub Zavada,[18] Delphine Sophie Courvoisier ,[23] Axel Finckh ,[23] Kim Lauper [23]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2023-224670).

For numbered affiliations see end of article.

Correspondence to
Romain Aymon, Rheumatology Division, Geneva University Hospitals, Geneve, Genève, Switzerland;
romain.aymon@hcuge.ch

Received 6 July 2023
Accepted 24 November 2023
Published Online First 8 December 2023

To cite: Aymon R, Mongin D, Bergstra SA, *et al*. *Ann Rheum Dis* 2024;**83**:421–428.

ABSTRACT

Background In a clinical trial setting, patients with rheumatoid arthritis (RA) taking the Janus kinase inhibitor (JAKi) tofacitinib demonstrated higher adverse events rates compared with those taking the tumour necrosis factor inhibitors (TNFi) adalimumab or etanercept.

Objective Compare treatment discontinuations for adverse events (AEs) among second-line therapies in an international real-world RA population.

Methods Patients initiating JAKi, TNFi or a biological with another mode of action (OMA) from 17 registers participating in the 'JAK-pot' collaboration were included. The primary outcome was the rate of treatment discontinuation due to AEs. We used unadjusted and adjusted cause-specific Cox proportional hazard models to compare treatment discontinuations for AEs among treatment groups by class, but also evaluating separately the specific type of JAKi.

Results Of the 46 913 treatment courses included, 12 523 were JAKi (43% baricitinib, 40% tofacitinib, 15% upadacitinib, 2% filgotinib), 23 391 TNFi and 10 999 OMA. The adjusted cause-specific hazard rate of treatment discontinuation for AEs was similar for TNFi versus JAKi (1.00, 95% CI 0.92 to 1.10) and higher for OMA versus JAKi (1.11, 95% CI 1.01 to 1.23), lower with TNFi compared with tofacitinib (0.81, 95% CI 0.71 to 0.90), but higher for TNFi versus baricitinib (1.15, 95% CI 1.01 to 1.30) and lower for TNFi versus JAKi in patients 65 or older with at least one cardiovascular risk factor (0.79, 95% CI 0.65 to 0.97).

Conclusion While JAKi overall were not associated with more treatment discontinuations for AEs, subgroup analyses suggest varying patterns with specific JAKi, such as tofacitinib, compared with TNFi. However, these observations should be interpreted cautiously, given the observational study design.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A clinical trial has shown higher adverse event rates in patients with rheumatoid arthritis (RA) taking the Janus kinase inhibitor (JAKi) tofacitinib compared with those taking the tumour necrosis factor inhibitors (TNFi) adalimumab or etanercept.

⇒ Discrepancies between observational studies and clinical trial results have left uncertainties around the safety profile of JAKi in real-world scenarios.

WHAT THIS STUDY ADDS

⇒ This extensive real-world study involving 17 registers and over 46 000 treatment courses found no overall increased incidence of treatment discontinuation due to adverse events with JAKi. However, a higher discontinuation rate was observed with tofacitinib, and among patients aged 65 years and older, indicating potential variations in safety profiles among JAK inhibitors and for patients at higher risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may inform clinical decision-making and policy guidelines for second-line therapy in RA, drawing attention to the importance of individual patient characteristics, including age and cardiovascular risk factors, when considering JAKi treatment.

⇒ However, it is essential to view these findings as preliminary, especially given the relatively short-term nature of our safety events. This underscores the need for further investigation into potential variations in safety profiles among different JAK inhibitors, particularly when examining specific adverse events.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that causes inflammation in the joints, leading to pain, stiffness and joint deformities. The primary objective of RA treatment is to reduce inflammation, preserve joint function and improve quality of life. If initial conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, are ineffective or not tolerated by patients, biological DMARDs (bDMARDs) or targeted-synthetic DMARDs (tsDMARDs) are important treatment options. The most recent second-line treatment options for RA are the synthetic small molecules called Janus kinase inhibitors (JAKi). Currently, five JAKis are available for the treatment of RA: baricitinib, filgotinib, peficitinib (in Japan only), tofacitinib and upadacitinib.[1] JAKi have demonstrated superior efficacy over placebo or csDMARDs, and some have even demonstrated superiority over adalimumab or abatacept in specific outcomes.[2 3] However, an open-label post-marketing safety randomised controlled trial, the ORAL-surveillance study,[4] has raised concerns of an increased risk of malignancies and major adverse cardiovascular events, with tofacitinib compared with tumour necrosis factor inhibitors (TNFi), in patients with RA with particular risk factors. Considering these results, the use of JAKi has been restricted by health authorities worldwide.

The objective of this study was to assess and compare the overall tolerability and safety of JAKi, TNFi and bDMARDs with other modes of action (OMA), by evaluating treatment discontinuations for adverse events (AEs) in a real-world population. In light of the ORAL-surveillance findings, a secondary objective was to explore whether the observed effects are attributable to the entire JAKi class or are specific to tofacitinib.

METHODS

Patient and public involvement

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

Patient sample

The JAK-pot register collaboration conducted an investigator-initiated observational study aiming at evaluating clinical aspects of JAKi and bDMARDs in RA.[5 6] Patients with a clinical diagnosis of RA and starting treatment with a JAKi, a TNFi or a bDMARD-OMA were included. Treatment courses of interest initiated before the first JAKi was commercially available in each participating country were excluded from the analysis to avoid confounding by time-trends. Rituximab was not included as the time to discontinuation is difficult to assess. Patients could contribute to multiple treatment courses. This study included patients from the following 17 registers, which all provided individual treatment course-level data: ATTRA from the Czech Republic, ARBITER from Russia, BIOBADASER from Spain, BIOREG from Austria, BioRx.si from Slovenia, BSRBR-RA from the UK, GISEA from Italy, I-RECORD from Israel, METEOR from the Netherlands, NOR-DMARD from Norway, RABBIT from Germany, REUMA.PT from Portugal, RHUMADATA from Canada, ROB-FIN from Finland, RRBR from Romania, SCQM from Switzerland, TURKBIO from Turkey.

Exposure of interest

The exposure of interest was the type of treatment course: JAKi (baricitinib, filgotinib, tofacitinib or upadacitinib), TNFi (adalimumab, certolizumab, etanercept, golimumab or infliximab) or bDMARD-OMA (abatacept, sarilumab or tocilizumab).

Time point definitions

Each treatment course was defined as the time between treatment initiation (baseline), and treatment discontinuation, start of a new treatment, end of participation in the register or the end of the study period (November 2022), whichever came first. The end of the study period was set at an earlier date for some registers who could not provide their most recent data (see online supplemental material).

Study outcomes

The primary outcome was the rate of treatment discontinuation due to AE, as decided by treating clinician, compared across treatment groups. Each treatment course was linked to a single reason for discontinuation. When several reasons were provided the order of precedence was (1) AEs, (2) others and (3) ineffectiveness.

Covariates of interest

Baseline covariates were chosen a priori based on clinical knowledge and literature. They included patient, disease and treatment characteristics, namely gender, age, body mass index, tobacco smoking (ever/never), disease activity (Clinical Disease Activity Index (CDAI) or Disease Activity Score 28 if CDAI was unavailable), disease duration, seropositivity (rheumatoid factors and/or anti-citrullinated protein antibody), number of previously used bDMARDs/tsDMARDs (0, 1, 2, ≥3), concomitant csDMARDs treatment (none; methotrexate; other csDMARDs without methotrexate; methotrexate and at least one other csDMARDs), concomitant glucocorticoids (presence/absence), functional status (Health Assessment Questionnaire Disability Index) and C reactive protein. Because AEs are significantly influenced by comorbidities, we further adjusted for pre-existing interstitial lung disease, cardiovascular disease, infections, malignancies, diabetes, depression, hypertension and hyperlipidaemia. The comorbidity variables were dichotomised to represent the presence or absence of a specific condition at treatment baseline. This approach was taken to adapt to data granularity and harmonise data from different registers, making our pooled analysis feasible.

Statistical methods

The results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology recommendations.[7] Baseline disease and patient characteristics by treatment groups are summarised using counts and percentages for categorical variables, mean and SD for continuous variables. The number of treatment courses with valid values (non-missing) are provided. Raw incidence rates were plotted using the crude non-parametric cumulative incidence functions of treatment cessation for AE in JAKi, TNFi and bDMARD-OMA patients. We used unadjusted and adjusted (for baseline confounders, as described above) cause-specific Cox proportional hazard models,[8] considering stopping for ineffectiveness or other reasons as competing events, to compare treatment discontinuations for AE between treatment groups. Treatment discontinuation associated with each treatment group was compared using HR estimates, with JAKi as the reference level. Multiple treatment courses from the same patient were included if the individual had received more than one second-line treatment during the study period. To account for this within-patient correlation, we incorporated a cluster term for the patient identity in the cause-specific Cox model, in order to obtain robust SEs.

Table 1 Baseline characteristics by treatment group

	JAKi		TNFi		bDMARDs-OMA	
	BARI (43%), TOFA (40%), UPA (15%), FILGO (2%)		ETA (41%), ADA (28%), CZP (10%), GOLI (8%), INF (7%), unspecified (6%)		TCZ (50%), ABA (36%), SARI (9%), unspecified (5%)	
	N valid	Value	N valid	Value	N valid	Value
N		12 523		23 391		10 999
Treatment duration, years (mean (SD))		1.7 (1.4)		1.8 (1.6)		1.8 (1.7)
Age, years (mean (SD))	12523	58.0 (12.5)	23386	56.3 (13.8)	10997	58.5 (13.0)
Gender (female) (%)	12523	10197 (81.4)	23391	18208 (77.8)	10998	8788 (79.9)
Disease duration, years (mean (SD))	11916	13.5 (10.0)	22190	11.8 (10.0)	10317	13.7 (10.4)
Seropositivity (RF and/or ACPA) (%)	10194	8218 (80.6)	17586	13237 (75.3)	8522	6594 (77.4)
Previous b/ts DMARDs (%)	12115		22162		10487	
0		2813 (23.2)		9815 (44.3)		1995 (19.0)
1		2696 (22.3)		5871 (26.5)		2643 (25.2)
2		2167 (17.9)		3410 (15.4)		2446 (23.3)
3 or more		4439 (36.6)		3066 (13.8)		3403 (32.4)
Concomitant csDMARDs (%)	12292		22545		10643	
MTX		2773 (22.6)		5475 (24.3)		2078 (19.5)
MTX+other		1138 (9.3)		3146 (14.0)		999 (9.4)
None		6504 (52.9)		9936 (44.1)		5754 (54.1)
Other		1877 (15.3)		3988 (17.7)		1812 (17.0)
Concomitant GC (%)	10994	4916 (44.7)	19959	6491 (32.5)	9003	3666 (40.7)
CRP (mg/L) (mean (SD))	9157	12.4 (23.1)	15235	12.4 (23.1)	7101	13.3 (28.9)
CDAI (mean (SD))	3604	25.2 (13.9)	4416	24.1 (13.9)	2044	22.7 (13.9)
DAS 28 (mean (SD))	6291	4.7 (1.6)	9397	4.5 (1.6)	4887	4.5 (1.6)
HAQ (mean (SD))	3860	1.2 (0.7)	6096	1.0 (0.7)	3006	1.2 (0.7)
BMI, kg/m^2 (mean (SD))	12423	27.2 (5.9)	23067	27.4 (6.3)	10926	27.3 (6.0)
Smoking (ever/never)	8674	3054 (35.2)	17052	6198 (36.3)	7383	2658 (36.0)
Past myocardial infarction (%)	6805	134 (2.0)	13043	199 (1.5)	5771	123 (2.1)
Past stroke (%)	6912	73 (1.1)	14624	192 (1.3)	6039	97 (1.6)
Interstitial lung disease (%)	8116	647 (8.0)	13128	840 (6.4)	5950	529 (8.9)
Hypertension (%)	9441	2996 (31.7)	17564	4945 (28.2)	7562	2438 (32.2)
Hyperlipidaemia (%)	7952	1363 (17.1)	12742	1674 (13.1)	5800	1027 (17.7)
Past serious infection (%)	7186	918 (12.8)	11825	1454 (12.3)	5400	847 (15.7)
Current or past malignancy (%)	9316	471 (5.1)	17629	607 (3.4)	7390	396 (5.4)
Diabetes (%)	9003	808 (9.0)	16764	1517 (9.0)	7093	757 (10.7)
Current or past neuropsychiatric disorder (%)	6669	729 (10.9)	10615	923 (8.7)	4474	540 (12.1)

ABA, abatacept; ACPA, anti-citrullinated protein antibody; ADA, adalimumab; BARI, baricitinib; bDMARDs, biological DMARDs; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; csDMARDs, classical synthetic DMARDs; CZP, certolizumab; DAS 28, Disease Activity Score 28; DMARDs, disease-modifying antirheumatic drugs; ETA, etanercept; FILGO, filgotinib; GC, glucocorticoids; GOLI, golimumab; HAQ, Health Assessment Questionnaire; INF, infliximab; JAKi, Janus kinase inhibitors ; MTX, methotrexate; OMA, other modes of action ; RF, rheumatoid factor; SARI, sarilumab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitors; TOFA, tofacitinib; tsDMARDs, targeted synthetic DMARDs; UPA, upadacitinib.

We also used the Fine-Gray subdistribution hazard model,[9] to account for competing risks (stopping for ineffectiveness, pregnancy, remission or other reasons) as a sensitivity analysis. The cause-specific hazard approach focuses on the hazard function for each specific cause separately and treats competing events as censoring events. The cause-specific hazards are more relevant when exploring aetiological inquiries as it quantifies the event rate among individuals at risk of encountering the event of interest (treatment cessation for AE, in this scenario). In contrast, the Fine-Gray method takes competing risks into account when estimating the cumulative incidence function, modelling the subdistribution hazard without treating competing events as censoring events, becoming particularly useful when the objective is predicting an individual's risk. Missing covariates were imputed using multiple imputations with chained equations (50 samples and 25 iterations, predictive mean matching algorithm for continuous variables and logistic and polytomous regression for categorical variables). All baseline covariates were used in the imputation. The outcome variable (reason for discontinuation), an indicator variable (the event of discontinuation) and the untransformed time-to-event were used as predictors in the multiple imputation process but were not imputed.

Subgroup analyses

Randomised controlled trial-cohorts

We considered two subgroup analyses of patients at higher risk of AEs:

- The 'randomised controlled trial (RCT) - duplicate cohort', mimicking the main inclusion criteria of the ORAL surveillance trial,[4] namely patients 50 years or older and with at least one cardiovascular risk factor (hypertension,

Table 2 Discontinuation for adverse events among JAKi, TNFi and OMA patients

	JAKi	TNFi	OMA
Number of treatments	12 523	23 391	10 999
Mean treatment duration, years (SD)	1.7 (1.4)	1.8 (1.6)	1.8 (1.7)
Number of discontinuations for adverse event	899	1387	870
Cause-specific HR			
Unadjusted (95% CI)	Reference	0.80 (0.73 to 0.87)*	1.10 (1.00 to 1.21)
Adjusted (95% CI)	Reference	1.00 (0.92 to 1.10)	1.11 (1.01 to 1.23)*
Fine-Gray subdistribution HR			
Unadjusted (95% CI)	Reference	0.78 (0.72 to 0.85)*	1.07 (0.98 to 1.18)
Adjusted (95% CI)	Reference	0.98 (0.87 to 1.09)	1.08 (0.98 to 1.19)

*P-value ≤ 0.05
JAKi, Janus kinase inhibitors ; OMA, other modes of action ; SD, standard deviation; TNFi, tumour necrosis factor inhibitors.

hyperlipidaemia, diabetes, smoking, prior history of strokes or myocardial infarctions).

- The 'RCT – high cardiovascular disease (CVD) risk cohort', a subset of patients aged ≥65 years with at least one cardiovascular risk factor.

Separate comparison of tofacitinib, baricitinib and other JAKis

To explore signals of AEs reported specifically with tofacitinib, baricitinib and other JAKis, we also analysed them separately, to explore effect modification by the type of JAKi, both in the general cohort and in the higher risk subgroups.

RESULTS

A total of 46 913 treatment courses, started by 33 511 patients, were included: 12 523 on JAKi, 23 391 on TNFi and 10 999 on OMA (table 1). Patients were predominantly women (79%) and seropositive (77%), 57.3 years old on average, with a mean disease duration of 12.7 years. Most of the patients on JAKi were treated with baricitinib (43%), followed by tofacitinib (40%), upadacitinib (15%) and filgotinib (2%). According to routine clinical practice in the participating countries, patients starting a TNFi had shorter disease durations and were more often on their first second-line therapy and less often on monotherapy compared with non-TNFi treatments. Non-TNFi treatments were more often on third-line (or more) therapy, and presented higher counts for some comorbidities, indicating a more refractory disease.

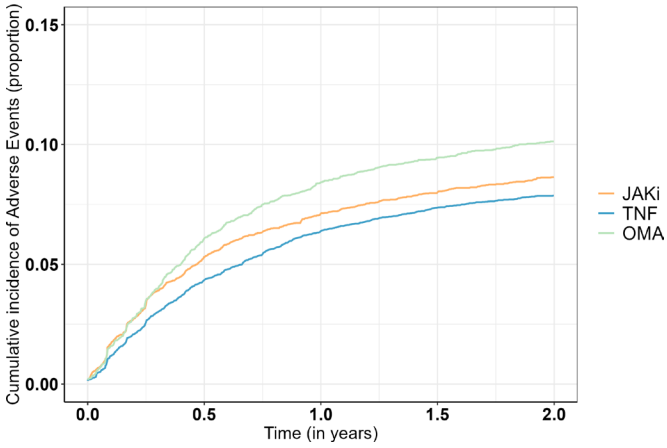

Figure 1 Crude cumulative incidence of stopping for adverse events. JAKi, Janus kinase inhibitors; OMA, biological disease-modifying rheumatic drugs with other modes of action; TNFi, tumour necrosis factor inhibitors

Treatment discontinuation due to AE

During a mean treatment follow-up of 1.9 (SD: 1.6) years, and a mean patient follow-up of 2.9 (SD: 1.9) years, 899 JAKi treatments, 1387 TNFi treatments and 870 OMA treatments were discontinued for an AE (table 2). The crude incidence rate of treatment discontinuation for AEs was 4.3 with JAKi, 3.3 with TNFi and 4.4 with OMA per 100 patient-years of treatment. Crude incidence rates and cause-specific HRs for competing events can be found in the online supplemental table S8. Among patients who stopped their treatment, 47% did so for ineffectiveness or other reasons.

The unadjusted cumulative incidence function (figure 1) showed higher treatment discontinuations for AEs with JAKi compared with TNFi, but lower compared with bDMARDs-OMA. The adjusted cause-specific HR (csHR) of treatment discontinuation for AEs was higher for OMA versus JAKi (csHR 1.11, 95% CI 1.01 to 1.23) and not statistically different for TNFi versus JAKi (csHR 1.00, 95% CI 0.92 to 1.10) (table 2). The significantly higher rate of treatment discontinuations for OMA compared with JAKi is mainly driven by anti-interleukin (IL)-6 medications, whereas abatacept patients have lower treatment discontinuation rates (online supplemental table S7). CsHR for the main analysis and subgroup analysis are shown in figure 2.

The sensitivity analysis using Fine-Gray approach instead of cause-specific Cox demonstrated a similar trend for OMA versus JAKi, although the risk of discontinuation for AEs did not reach statistical significance (subdistribution HR (sHR) 1.08, 95% CI 0.98 to 1.19). No significant difference was found for TNFi versus JAKi (sHR 0.98, 95% CI 0.87 to 1.09) in the discontinuation for AEs. Adjusting for countries did not change the csHRs.

Subgroup analyses

RCT-cohorts

The 'RCT-duplicate cohort' represented 36% of all treatment courses (n=17 146), and crude incidence rates of treatment discontinuations for AEs were comparable to the overall cohort (4.2, 3.2 and 4.5 per 100 patient-years for JAKi, TNFi and OMA, respectively). The results were almost similar to the full cohort (table 3), with a higher csHR for OMA versus JAKi (csHR 1.19, 95% CI 1.03 to 1.39) and no significant differences for TNFi versus JAKi (csHR 0.99, 95% CI 0.86 to 1.14).

In the 'RCT-high CVD risk cohort', the incidence rate of treatment discontinuations for AEs was higher (5.3, 3.4 and 4.9 per 100 patient-years for JAKi, TNFi and OMA, respectively). We no longer found a significant difference in the cause-specific hazard rate of discontinuation for AE between OMA versus JAKi (csHR 1.01, 95% CI 0.82 to 1.25), but the hazard was lower for TNFi versus JAKi (csHR 0.79, 95% CI 0.65 to 0.97).

Separate comparison of tofacitinib, baricitinib and other JAKis

Baseline characteristics of JAKi treatments indicated a more refractory disease for patients on baricitinib and other types of JAKi than patients on tofacitinib (online supplemental table S1).

When exploring effect modification **in the overall cohort** by the type of JAKi, specifically for tofacitinib and baricitinib (table 4), we found some suggestions for an effect modification by type of JAKi. The hazard rate of discontinuation for AE for

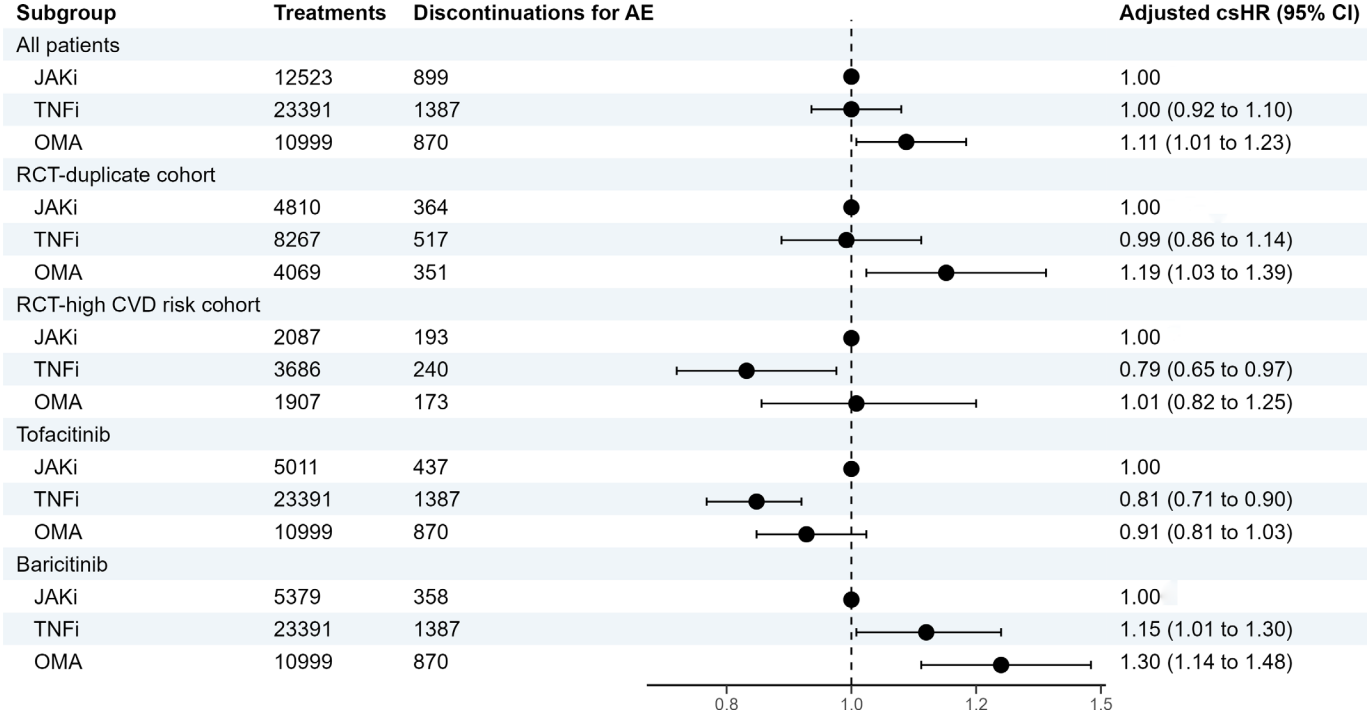

Figure 2 Adjusted cause-specific HRs (csHR) of stopping for AEs for TNFi and OMA against reference JAKi, in the overall cohort and in the different subgroups. AE, adverse event; csHR, cause-specific HR; JAKi, Janus kinase inhibitors; OMA, biological disease-modifying rheumatic drugs with other modes of action; RCT, randomised controlled trial; TNFi, tumour necrosis factor inhibitors.

TNFi was significantly lower compared with tofacitinib (csHR 0.81, 95% CI 0.71 to 0.90), a significant difference which was inversed when comparing TNFi to baricitinib (csHR 1.15, 95% CI 1.01 to 1.30) and other types of JAKi (csHR 1.26, 95% CI 1.02 to 1.55) (online supplemental table S2). Ninety per cent of patients on baricitinib received the 4 mg dose. Similar trends were found in the 'RCT-duplicate cohort' and the 'RCT-high CVD risk cohort' (online supplemental tables S3 and S4). Results remained similar when looking at the time period before ORAL-surveillance results were published (online supplemental table S5).

DISCUSSION

In this large international collaborative study, we did not find an increased incidence of treatment discontinuation due to AEs with JAKi compared with other biological DMARDs in the overall cohort. After adjusting for potential confounders, the incidence and rate of treatment discontinuation for AEs were similar for TNFi versus JAKi, and the range of the CI supports the idea of very similar rates of stopping for AE. The rates of treatment discontinuation for AE tended to be higher with OMA versus JAKi, a difference mainly driven by anti-IL-6 medications. When selecting patients at increased risk for AEs, similar to the inclusion criteria of the ORAL-surveillance trial,[4] the incidence of treatment discontinuation for AEs was higher, but the relative effect sizes between the different treatment groups were similar to the overall group. However, the incidence and the rate of discontinuation for AEs of patients on JAKi was increased compared with TNFi in the 'RCT – high CVD risk cohort' of patients aged 65 years and older. When exploring the possibility of a differential effect between the different types of JAKi, we found a higher rate of discontinuation for AEs with tofacitinib

Table 3 Discontinuation for adverse events among JAKi, TNFi and OMA patients, in the RCT-duplicate cohort and in the RCT—high CVD risk cohort (aged ≥65 years with ≥1 cardiovascular risk factor)

	RCT-duplicate cohort			RCT-high CVD risk cohort		
	JAKi	TNFi	OMA	JAKi	TNFi	OMA
Number of treatments	4810	8267	4069	2087	3686	1907
Mean treatment duration, years (SD)	1.8 (1.4)	1.9 (1.5)	1.9 (1.7)	1.8 (1.4)	1.9 (1.5)	1.8 (1.6)
Number of discontinuations for adverse event	364	517	351	193	240	173
Cause-specific HR						
Unadjusted (95% CI)	Reference	0.81 (0.71 to 0.93)*	1.15 (0.99 to 1.33)	Reference	0.67 (0.56 to 0.82)*	0.98 (0.79 to 1.20)
Adjusted (95% CI)	Reference	0.99 (0.86 to 1.14)	1.19 (1.03 to 1.39)*	Reference	0.79 (0.65 to 0.97)*	1.01 (0.82 to 1.25)
Fine-Gray subdistribution HR						
Unadjusted (95% CI)	Reference	0.78 (0.68 to 0.89)*	1.11 (0.95 to 1.28)	Reference	0.65 (0.54 to 0.79)*	0.95 (0.77 to 1.17)
Adjusted (95% CI)	Reference	0.93 (0.78 to 1.11)	1.23 (1.01 to 1.50)*	Reference	0.72 (0.56 to 0.93)*	0.97 (0.73 to 1.29)

*P-value ≤ 0.05
CVD, cardiovascular disease; JAKi, Janus kinase inhibitors ; OMA, other modes of action ; RCT, randomised controlled trial; TNFi, tumour necrosis factor inhibitors.

Table 4 Discontinuation for adverse events for tofacitinib and baricitinib, against TNFi and OMA patients

	Tofacitinib			Baricitinib		
	Tofacitinib	TNFi	OMA	Baricitinib	TNFi	OMA
Number of treatments	5011	23 391	10 999	5379	23 391	10 999
Mean treatment duration, years (SD)	1.9 (1.7)	1.8 (1.6)	1.8 (1.7)	1.7 (1.3)	1.8 (1.6)	1.8 (1.7)
Number of discontinuations for adverse event	437	1387	870	358	1387	870
Cause-specific HR						
Unadjusted (95% CI)	Reference	0.70 (0.63 to 0.78)*	0.96 (0.86 to 1.08)	Reference	0.88 (0.79 to 0.99)*	1.21 (1.07 to 1.37)*
Adjusted (95% CI)	Reference	0.81 (0.71 to 0.90)*	0.91 (0.81 to 1.03)	Reference	1.15 (1.01 to 1.30)*	1.30 (1.14 to 1.48)*
Fine-Gray subdistribution HR						
Unadjusted (95% CI)	Reference	0.68 (0.61 to 0.76)*	0.93 (0.83 to 1.05)	Reference	0.86 (0.76 to 0.96)*	1.17 (1.04 to 1.33)*
Adjusted (95% CI)	Reference	0.81 (0.70 to 0.93)*	0.96 (0.81 to 1.11)	Reference	1.02 (0.91 to 1.15)	1.30 (1.10 to 1.55)*

*P-value ≤ 0.05
OMA, other modes of action ; TNFi, tumour necrosis factor inhibitors.

compared with TNFi in the overall cohort and in the 'RCT-high CVD risk cohort', a difference that we did not see with the other JAKi. The apparent signal of an elevated rate of treatment discontinuations for AEs with tofacitinib was also increased in the 'RCT-high CVD risk cohort'.

There are several possible explanations for the discrepancy between available observational studies and the ORAL-surveillance trial. First, it is paramount to highlight that our study aims to address a distinct research question. While ORAL-surveillance specifically targets certain AEs, our study is aimed at assessing treatment tolerability. This broader scope encompasses a range of patient experiences, from nuanced feelings of 'not feeling very well' to severe AEs. Consequently, our primary outcome, discontinuation due to AEs, captures a more subjective spectrum of patient reactions than ORAL-surveillance. Second, although we used discontinuation for AEs as our primary outcome, there is always the possibility that the decisions to discontinue therapy is also influenced by other reasons, such as insufficient effectiveness, even though the recorded reason for discontinuation was an AE. Finally, it is possible that the incidence of AEs is only increased in older patients with specific risk factors and not in the overall population. This last explanation is supported by the result of the sensitivity analysis including only patients >65 years and with at least one cardiovascular risk factor. Subgroup analyses of the ORAL surveillance study also suggested similar differential safety results in high-risk groups, such as a history of arteriosclerosis,[10] or a history of tobacco smoking.[11]

It is currently unknown whether the safety signals observed in the ORAL-surveillance study with tofacitinib represent a class effect of the JAKi group or a drug-specific effect of this particular drug. We explored a potential effect modification by type of JAKi and examined tofacitinib, baricitinib and other JAKi separately. Our findings indicate that patients taking tofacitinib were more likely to discontinue treatment due to AEs compared with those taking TNFi. This was not observed with other JAKi, although caution is needed due to limited data on filgotinib and upadacitinib. These results may hint at differences in safety profiles between tofacitinib and other JAKi but should not be considered definitive evidence against a JAKi class-effect. Recent translational research suggested that individual JAKi agents differ in their biological effects on specific immune cells, such as the natural killer cell activation.[12] A recent study from the Swedish ARTIS register[13] did not find any overall differences in discontinuation for AEs between the JAKis tofacitinib and baricitinib and other bDMARDs. However, the study's sample size was limited, with only 170 cases of discontinuation resulting from AEs (114 with baricitinib and 56 with tofacitinib), making it challenging to detect differences if they exist. Subjective factors such as patients' tolerability for AEs can play a significant role in determining treatment discontinuation rates for a particular medication. AEs can vary in severity, and some patients and physicians may be more willing to tolerate mild or moderate AEs if they perceive that the benefits of the medication outweigh the risks, which may have been less the case for tofacitinib than the other JAKi recently, although we should point out that the data collection occurred mostly before the publication of the ORAL-surveillance trial, and results from the analysis did not change when considering data before ORAL-surveillance. The availability of alternative treatments and their accessibility may also vary from country-to-country affecting the decision to change or not the ongoing treatment.

The HR using the Fine-Gray model used for a sensitivity analysis was overall not different from the cause specific Cox hazard model used in the main analysis. In the Fine-Gray model, the cumulative incidence of treatment discontinuation for AEs depends on the hazards of the competing causes, such as ineffectiveness. As there is an increased cause-specific hazard rate for ineffectiveness for TNFi compared with JAKi, the HR for stop for AEs with the Fine-Gray model is less than we would expect if the exposure was not associated with ineffectiveness, and so is smaller than with the cause-specific Cox model.

One of the strengths of this study is the use of several registers from different countries with a large sample size and the possibility to adjust for many covariates, including disease activity and disease and treatment characteristics. In contrast with claims database, disease and treatment registers are also able to incorporate clinical information such as disease activity, function and smoking status. We also used discontinuation for AEs, which is an outcome that is consistently reported among registers and includes not only safety, but also the patients' perceived tolerability. Ineffectiveness being the most common reason for drug discontinuation,[5] accounting for it through a competing risk approach reduces the risk of bias.

The main limitation is the lack of details on the type and seriousness of AEs leading to discontinuation, as this information cannot always be simply linked to the discontinuation of the treatment and is not as consistently reported among the registers. While our results provide an overview of tolerability across treatment groups, the exact nature and severity of AEs leading to discontinuation remains an area that requires further investigation. This absence of details means clinicians must exercise caution when interpreting

these findings in terms of specific safety concerns, such as cardiovascular events or serious infections. Furthermore, drug discontinuation is inherently complex and blends clinical, patient-specific and sometimes socioeconomic variables. Our research highlights some elements, but a comprehensive exploration remains essential for future studies. A second limitation is the absence of randomisation between treatment groups, although we tried to emulate as much as possible a trial, by adjusting for relevant confounding factors, including a wide range of comorbidities known to play a role in the occurrence of AEs, including patients from the start of their treatment, selecting a comparable population, and having a well-defined intervention, follow-up period and outcome. We did not prespecify any direct comparison between OMA and TNFi, so it is not possible to determine if, in addition to having comparable or potentially inferior outcomes to JAKi, OMA could lead to higher discontinuation rates due to AEs when compared with TNFis. Missing data can also present a significant concern, but it was addressed with multiple imputation. The follow-up period is relatively short and may limit our ability to detect long-term AEs or late-onset discontinuations. Finally, misclassification of the cause for drug discontinuation can be a concern. In interpreting our findings, it is essential to acknowledge the potential for physician bias in attributing the reason for drug discontinuation. Physicians might be influenced by pre-existing clinical experiences and knowledge, possibly leading to differential reporting across treatments.

In conclusion, in this international cohort of patients with RA, patients on JAKi did not demonstrate higher rates of discontinuation for AEs compared with patients on TNFi or bDMARD-OMA in the overall population. However, differences were observed in specific subgroup of patients with older age and cardiovascular risk factors or with different JAKi molecules, with a higher risk of discontinuation of AEs among those with cardiovascular risk factors and older age and with tofacitinib compared with TNFi but not the other JAKi. Treatment discontinuation for AEs comprises a wide range of AEs and includes both the patient perceived intolerability and the physician described safety issues. Our findings suggest that tolerability might differ depending on the subpopulation and possibly the type of JAKi. Further studies are warranted to assess which antirheumatic treatment fits best for which subgroups of patients and if the differences in tolerability by type of JAKi suggested by this study are associated with true differences in safety profile when looking at specific AEs. The conclusions drawn are specific to RA and merit further exploration within the context of other rheumatic and musculoskeletal diseases.

Author affiliations
[1]Rheumatology Division, Geneva University Hospitals, Geneve, Switzerland
[2]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[3]Institut de recherche en Rhumatologie, CHUM, Montreal, Quebec, Canada
[4]Center for Rheumatic Diseases, University of Bucharest, Bucuresti, Romania
[5]Biostatistics and Medical Informatics Research Group, Department of Public Health, Vrije Universiteit Brussel, Brussel, Belgium
[6]Rheumatology, DANBIO, Aalborg University Hospital, Aalborg, North Denmark Region, Denmark
[7]Rheumatology, Tel Aviv University, Tel Aviv, Israel
[8]Programme Area Epidemiology, DRFZ, Berlin, Germany
[9]Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester, UK
[10]Manchester University NHS Foundation Trust, NIHR Manchester Biomedical Research Centre, Manchester, UK
[11]DiMePRe-J -Rheumatology Unit, University of Bari, Bari, Puglia, Italy
[12]Rheumatology, Marmara University School of Medicine, Istanbul, Turkey
[13]Division of Rheumatology, Firat University, Faculty of Medicine, Elazig, Turkey
[14]Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
[15]Austrian registry for Biologics, Biosimilars und targeted synthetic DMARDs (ts-DMARDs) in the treatment of rheumatic diseases, BioReg, Vienna, Austria
[16]V.A.Nasonova Research Institute of Rheumatology, A.S.Loginov Moscow Clinical Scientific Center, Moscow, Russian Federation
[17]Division of Medicine, ROB-FIN, Helsinki University and Helsinki University Hospital, Helsinki, Finland
[18]Rheumatology, Institute of Rheumatology, Praha, Czech Republic
[19]Rheumatology, Hospital Clinico Universitario, Santiago de Compostela, Spain
[20]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa, Lisbon, Portugal
[21]Department of Rheumatology & University of Ljubljana, Faculty of Medicine, University Medical Centre Ljubljana, Ljubljana, Ljubljana, Slovenia
[22]Skeletal Biology and Engineering research Center, KU Leuven, Leuven, Flanders, Belgium
[23]Division of Rheumatology, Geneva University Hospitals, Geneve, Switzerland

Twitter Denis Mongin @denis_mongin, Sytske Anne Bergstra @SytskeAnne, Delphine Sophie Courvoisier @delcourvoisier and Kim Lauper @k_lauper

Acknowledgements The authors thank all the health professionals and patients who participated in the registers.

Contributors All the authors have provided substantial contributions to the conception or design of the work, the acquisition of the data and the interpretation of data. DM performed the data management. RA performed the statistical analysis. RA, KL, DSC and AF wrote the first draft. All the other authors participated in the final drafting of the work or revising it critically for important intellectual content. All authors contributed to the final approval of the version published. RA and KL accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish. RA is the guarantor for this manuscript.

Funding The JAK-pot study has received unrestricted research grant from: AbbVie, Galapagos, Pfizer and Eli Lilly. BIOREG, the Austrian registry for biologicals, biosimilars and tsDMARDs in the treatment of inflammatory rheumatic diseases, is in close partnership with the Austrian Society for Rheumatology and Rehabilitation (ÖGR) and is supported by an unrestricted educational grant from AbbVie, Amgen, Eli Lilly, Fresenius-Kabi, Gilead, Janssen-Cilag, MSD, Pfizer, Sandoz, UCB. Clinical work in Czech Republic was partially supported by the project from the Ministry of Health for conceptual development of research organisation MZ00023728023728 (Institute of Rheumatology). BIOBADASER has received funding from Fundacion Española de Reumatología, the Spanish Medicines and Health Products Agency (Agencia Española del Medicamento y Productos Sanitarios) and equal grants from pharmaceutical companies (AbbVie, BMS, Celltrion, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Regeneron, Roche, Samsung, Schering-Plough and UCB). BioRx.si has received funding for clinical research paid to Društvo za razvoj revmatologije from AbbVie, Roche, Medis, MSD, Biogen, Amgen, Sanofi, Celgene and Pfizer. The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) is funded by a grant from the British Society for Rheumatology (BSR). The BSR currently receives funding from AbbVie, Amgen, Celltrion Healthcare, Eli Lilly, Galapagos, Pfizer, Samsung Bioepis and Sanofi and in the past Hospira, MSD, Roche, Sandoz, SOBI and UCB. This income finances a wholly separate contract between the BSR and The University of Manchester to host the BSRBR-RA. All decisions concerning study design, data capture, analyses, interpretation and publication are made autonomously of any industrial contribution. Members of the BSRBR-RA University of Manchester team, BSR trustees, committee members and staff complete an annual declaration in relation to conflicts of interest. All relevant information regarding serious adverse events outlined in the manuscript have been reported to the appropriate pharmaceutical company as per the contractual agreements/standard operating procedures. DANBIO was partially supported by public and private funding (AbbVie, Biogen, Bristol Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB). NOR-DMARD has been supported with research funding to Diakonhjemmet Hospital from AbbVie, Amgen, BMS, MSD, Novartis, Pfizer and UCB. The German RABBIT registry is currently supported by a joint, unconditional grant from AbbVie, Amgen, BMS, Celltrion, Fresenius Kabi, Galapagos, Hexal, Lilly, MSD, Pfizer, Samsung Bioepis, Sanofi Aventis, VIATRIS SANTE and UCB, and previously by Roche. REUMA. PT is supported by unrestricted grants from AbbVie, Biogen, Celgene, MSD, Roche, Sanofi and Pfizer. ROB-FIN is funded by AbbVie, Hospira, BMS, MSD, Pfizer, Roche and UCB. The Romanian Registry of Rheumatic Diseases (RRBR) uses unrestricted grants from AbbVie, Pfizer, Eli Lilly, Ewopharma, Nopvartis MSD, Roche, UCB, and BMS. Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) database is sponsored by public and industrial support (http://scqm.ch/en/sponsoren/).

Competing interests RA has nothing to disclose. DM has nothing to disclose. SAB reports grants from Pfizer outside of this work and speaker fees from Benecke. DC has nothing to disclose. CC reports reports personal fees from AbbVie, Amgen, Boehringer Ingelheim, Ewopharma, Lilly, Novartis, Pfizer outside the submitted work. DDC has nothing to disclose. LD reports contract with BMS outside the present work. OE reports consulting and speaker fees from AbbVie, Pfizer, Eli Lilly, Novartis and Jansen. DH has nothing to disclose. KLH reports grant support from Pfizer and Bristol Myers Squibb and speaking fees from AbbVie. FI reports consulting fees

from AbbVie, Janssen, UCB, Galapagos and speaker fees from AbbVie, Galapagos, Eli Lilly, Pfizer and UCB. NI reports consulting and speaking fees from AbbVie, Novartis, UCB, Eli Lilly, Pfizer and Celltrion. LKF has nothing to disclose. SSK has nothing to disclose. TKK reports grants from AbbVie, BMS, Galapagos, Novartis, Pfizer and UCB, consulting fees from AbbVie, Gilead, Janssen, Novartis, Pfizer, Sandoz, UCB Grünenthal, Sandoz and speaker fees from Grünenthal, Sandoz. BFL reports consulting fees from Eli Lilly, Pfizer and AbbVie, and speaking fees from Sandoz. GL has nothing to disclose. DN reports grants from MSD, consulting fees from BMS, Lilly, Novartis, Pfizer, UCB and speaker fees from Pfizer and UCB. KP reports speaker fees from Novartis, Eli Lilly, Roche, Pfizer, Sobi, AbbVie, Pfizer and MSD. MPS has nothing to disclose. AR reports grants from Amgen, AstraZeneca, Novartis, AbbVie, Pfizer, MSD, Lilly, Boehringer Ingelheim, speaker fees from Amgen, AbbVie and Novartis. ZR reports consulting fees from AbbVie, Pfizer, Janssen, AstraZeneca, Novartis, Boehringer Ingelheim, Eli Lilly and speaker fees from AbbVie, Pfizer, Janssen, AstraZeneca, Novartis, Boehringer Ingelheim, Eli Lilly, SOBI, Lek (Sandoz). AS reports speaker fees from AbbVie, BMC, MSD, Pfizer and Roche. PV reports grants from Pfizer and Galapagos, consulting fees from Galapagos, Gilead, Pfizer, Sidekick Health, speaking fees from Eli Lilly, Galapagos and Roularta. RW has nothing to disclose. JZ reports speaking fees from AbbVie, Sobi, Pfizer and Eli Lilly. DSC reports consulting fees from Medela AG. AF reports grants from AbbVie, Pfizer, Galapagos and Eli Lilly, consulting fees from Eli Lilly, Pfizer, AbbVie, speaker fees from Pfizer, Eli Lilly, AbbVie, MSD and BMS. KL has received consultancy and/or speaker fees from Pfizer, Viatris, Celltrion and Galapagos paid to her institution.

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 Not applicable.

Ethics approval Local ethics committees (when required according to local legislation) approved the collection of data in each participating register, and the Geneva Ethics Committee approved this specific study (CCER 2017-02278, amendment 2).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All the data belong to the registers. Anonymised data can be shared as long as agreements are made with all participating registers.

ORCID iDs
Romain Aymon http://orcid.org/0000-0003-2854-3632
Denis Mongin http://orcid.org/0000-0002-4801-8395
Sytske Anne Bergstra http://orcid.org/0000-0002-7136-5248
Kimme L Hyrich http://orcid.org/0000-0001-8242-9262
Florenzo Iannone http://orcid.org/0000-0003-0474-5344
Nevsun Inanc http://orcid.org/0000-0003-2862-0562
Lianne Kearsley-Fleet http://orcid.org/0000-0003-0377-1575
Manuel Pombo-Suarez http://orcid.org/0000-0002-2524-4883
Anja Strangfeld http://orcid.org/0000-0002-6233-022X
Patrick Verschueren http://orcid.org/0000-0002-0340-3580
Delphine Sophie Courvoisier http://orcid.org/0000-0002-1956-2607
Axel Finckh http://orcid.org/0000-0002-1210-4347
Kim Lauper http://orcid.org/0000-0002-4315-9009

REFERENCES

1 Lauper K, Hyrich KL. How effective are JAK-inhibitors? Perspectives from clinical trials and real-world studies. *Expert Rev Clin Immunol* 2022;18:207–20.
2 Rubbert-Roth A, Enejosa J, Pangan AL, *et al*. Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med* 2020;383:1511–21.
3 Taylor PC, Keystone EC, van der Heijde D, *et al*. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2017;376:652–62.
4 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.
5 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.
6 Pombo-Suarez M, Sanchez-Piedra C, Gómez-Reino J, *et al*. After JAK inhibitor failure: to cycle or to switch, that is the question – data from the JAK-pot collaboration of registries. *Ann Rheum Dis* 2023;82:175–81.
7 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. *J Clin Epidemiol* 2008;61:344–9.
8 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;133:601–9.
9 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
10 Charles-Schoeman C, Buch MH, Dougados M, *et al*. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL surveillance. *Ann Rheum Dis* 2023;82:119–29.
11 Kristensen LE, Danese S, Yndestad A, *et al*. Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL surveillance. *Ann Rheum Dis* 2023;82:901–10.
12 Nocturne G, Pascaud J, Ly B, *et al*. JAK inhibitors alter NK cell functions and may impair immunosurveillance against lymphomagenesis. *Cell Mol Immunol* 2020;17:552–3.
13 Frisell T, Bower H, Morin M, *et al*. Safety of biological and targeted synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis as used in clinical practice: results from the ARTIS programme. *Ann Rheum Dis* 2023;82:601–10.