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Evolution of Janus Kinase inhibitors (JAKi) prescriptions since 2015 in an international collaboration of rheumatoid arthritis registers (the 'JAK-pot' study): effect of regulatory warnings

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ABSTRACT

Background: Janus kinase inhibitors (JAKi) are effective for treating rheumatoid arthritis (RA), but post-marketing safety concerns have triggered regulatory warnings and updated guidelines. The impact of these communications on real-world prescribing remains unclear.
Objectives: To assess the impact of major regulatory safety warnings on the initiation, discontinuation, and switching patterns of JAKi in RA patients, using data from 12 national registries.
Methods: This observational study analyzed 55,365 treatment courses (12559 JAKi and 42806 other bDMARDs) from 40,019 adult RA patients between 2015 and 2024. Segmented regression models examined trends around eight major regulatory events. Logistic generalized estimating equations (GEE), adjusted for demographic, disease, and treatment variables, were used. Sensitivity and subgroup analyses, including at-risk populations (age ≥65 with cardiovascular risk factors), were conducted.
Results: JAKi use rose from <1 % in 2015 to >20 % by 2024, with slowdowns after the 2019 FDA and 2022 EMA warnings. Initiation trends significantly slowed after the first FDA warning and the publication of increased risks for MACE and cancer in early 2021, primarily affecting tofacitinib. Discontinuations surged following the EMA's 2022 warning, again mainly affecting tofacitinib. Upadacitinib initiations also declined, and discontinuations increased after the publication of the ORAL Surveillance trial. Baricitinib use appeared to be less impacted by the safety signals, while filgotinib use steadily increased. Among the at-risk population, the rate of JAKi discontinuation significantly rose after the 2019 EMA warning.
Conclusions: Regulatory safety communications significantly influenced real-world JAKi prescribing patterns. Tofacitinib was most affected through both declines in initiation and increases in discontinuation.

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Introduction

Janus kinase inhibitors (JAKi) are an important part of the therapeutic arsenal available for rheumatoid arthritis (RA) and other rheumatic diseases. Tofacitinib was the first JAKi approved by the U.S. Food and Drug Administration (FDA) for the treatment of RA in 2012[1]. Since then, three additional members of the JAKi family, baricitinib, upadacitinib, filgotinib, differing by binding modes and selectivity for JAK isoforms, have been approved for RA treatment[2]. JAKi all claim a rapid onset of action, convenience of oral delivery, and robust efficacy data, at least comparable to other biologic disease-modifying antirheumatic drugs (bDMARDs)[3–8]

Since the approval of JAKi, important safety concerns have emerged [9,10]. The FDA-mandated post-marketing phase IIIb–IV study, the ORAL Surveillance trial, conducted in patients with RA>50 years of age with at least one cardiovascular risk factor demonstrated a higher rate of major adverse cardiovascular events (MACE) and malignancies in patients treated with tofacitinib compared to those treated with TNF-inhibitors (TNFi), especially pronounced in patients aged ≥65 years[11] The results of the Oral Surveillance trial prompted the regulatory authorities to update the recommendations for the utilization of JAKi. In 2021, The FDA extrapolated the Oral Surveillance findings beyond tofacitinib to all approved JAKi and restricted the use of this class of drugs to patients with RA only after TNFi failure and after a careful evaluation of the benefit-risk ratio[13]. EMA initially cautioned against the use of tofacitinib for patients at risk defined by age≥ 65 years, current or past long-time smokers, or with other cardiovascular or malignancy risk factors, unless no other alternative available. In 2023, EMA extended the warning identified for tofacitinib to all JAKi[14]. Consistently, 2022 updated European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of RA stated that pertinent risk factors must be taken into account prior to initiation of JAKi treatment[15].

The impact of the regulatory safety alert for JAKI is expected to influence clinical decisions related to prescribing new JAKi and possible discontinuation of JAKi in patients-at-risk for adverse events. Two studies evaluated the impact of the EMA safety warning on a real-life practice[16,17]. An Italian multicenter study found that the first two EMA safety warnings negatively affected the use of JAKi in RA but at the same time promoted a shift toward the use of more selective JAKi[16]. A UK-based nationwide study found a decrease in prescribing tofacitinib and baricitinib for all the approved indications, which did not extend to more selective JAKi compounds[17]. Yet, there is a gap of real-world data regarding JAKi prescription patterns following the safety update in different countries. In this aspect, registries serve as an important source of information reflecting the trends of therapeutics use in clinical practice. Therefore, the objective of this study was to investigate how the main safety warnings affected the international prescription trends of JAKi for RA treatment. We studied temporal shifts in the rates of JAKi initiation, discontinuation, and switching before and after FDA and EMA safety warnings, utilizing a substantial dataset from (mainly) European registries.

Methods

Patient sample

The JAK-pot collaboration is an observational study led by investigators to explore the clinical profiles of patients with RA receiving treatment with JAKi and bDMARDs [18–21]. This analysis focused on treatment courses in adult patients aged 18 and older who started treatment with either JAKi or bDMARDs. Patients were eligible to contribute data across multiple treatment courses, whether within the same drug class or across different therapies.

Data on individual treatment courses were supplied by 12 national registries up to November 2024: ATTRA (Czechia), BIOBADASER (Spain), BIOREG (Austria), Biorx.si (Slovenia), GISEA (Italy), NORDMARD (Norway), REUMA.PT (Portugal), RHUMADATA (Canada), ROB-FIN (Finland), RRBR (Romania), SCQM (Switzerland), and UCRCR (Greece). The different JAKi drugs were not always available at the same time for each country, and a detailed year of market introduction is presented in Table 1.

Patient and public involvement

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

Safety event and timeline considered

In the present study, we investigated the potential effect of 8 regulatory events related to the safety warnings on prescribing JAKi for patients with RA:

- **FDA first safety warning (26 February 2019)**: The first safety announcement by the FDA highlighted an increased risk of blood clots in the lungs and death associated with tofacitinib,[22] followed one month later by the first safety announcement by the EMA (20 March 2019)[23].
- **FDA Boxed Warning (26 July 2019)**: FDA strengthened the safety alert by issuing a boxed warning, further underscoring the risks associated with tofacitinib[13]
- **EMA Confirmation of Caution (November 2019)**: EMA confirmed its cautionary stance on prescribing tofacitinib, particularly for patients at high risk of blood clots[24]
- **Safety trials first results (27 January 2021)**: The initial results from the safety trials found an increased risk of serious heart-related problems and cancer[25]
- **FDA warning (1st November 2021)**: The FDA issued a broader safety warning regarding increased risks of serious heart-related events, cancer, blood clots, and death for JAKi[26]
- **ORAL Surveillance presentation at the ACR Conference (05 November 2021)** [27–30]
- **ORAL Surveillance Publication (27 January 2022).** [11]
- **EMA Recommendations** for Specific Patient Groups **(28 October 2022)**: EMA recommended avoiding JAKi for specific patient groups, including individuals aged 65 years or older, those at increased risk of cardiovascular events (such as heart attack or stroke), long-term smokers, and those at elevated cancer risk[31]

Statistical analysis

In the first descriptive approach, we calculated the percentage of patients on each type of treatment for each day. The overall time trend of JAKi use and the distribution by specific JAKi type were then modeled as

Table 1
Calendar year of market introduction of the four JAKi studied for the 12 countries contributing to the JAK-pot data used for this study.

Drug Country	tofacitinib	baricitinib	upadacitinib	filgotinib
Austria	2017	2017	2020	2021
Canada	2014	2018	2020	
Czechia	2018	2019	2020	2021
Finland	2018	2017	2020	
Greece	2018	2018	2020	
Italy	2018	2018	2020	2021
Norway	2017	2017	2020	2021
Portugal	2017	2017	2020	2021
Romania	2017	2018	2020	2021
Slovenia	2018	2017	2020	2021
Spain	2017	2017	2020	2021
Switzerland	2013	2017	2020	

piecewise linear trends. Knots for these trends were estimated using segmented modelling[32]: 4 knots when considering the prescription of all all JAKi together, tofacitinib and baricitinib, and 2 knots when considering prescription of upadacitinib and filgotinib.

To investigate the impact of the safety warnings on the rate of JAKi start or discontinuation, for each event of interest, we separately modeled both JAKi initiation and discontinuation as a two-piece linear time trend within 8-month time windows centered on the event. In a sensitivity analysis, this time interval varied from 6 months to 10 months.

In more detail, a logistic generalized estimating equation (GEE) with robust standard errors was used, clustered by patient. Two binary outcomes were considered: starting JAKi as a dichotomic (yes/no) variable for each treatment course to study JAKi initiation and stopping JAKi as a dichotomic (yes/no) variable among patients under JAKi treatment to study JAKi discontinuation. We used a Gaussian distribution to obtain the percentage of positive outcomes instead of the odds, an acceptable model because of the robust standard errors[33].

The change of temporal evolution around the events was assessed using segmented regression, where the change in the time evolution of the initiation or discontinuation rate after the event was the main exposure. The regression was adjusted for the following covariates:

- baseline patient characteristics: age, sex, body mass index, ever smoker, and country.
- baseline disease activity: Health Assessment Questionnaire Disability Index (HAQ-DI), C-reactive protein (CRP), CDAI, and DAS28 (DAS28ESR when available, DAS28CRP if not).
- treatment and disease characteristics: disease duration, seropositivity (defined as a positive rheumatoid factor or anti-CCP), concomitant glucocorticoids (presence/absence), number of previous bDMARDs (operationalised as 0, 1, 2 or 3 and more), and concomitant csDMARDs (operationalized as none; methotrexate; other csDMARDs without methotrexate; methotrexate and at least one other csDMARDs).

To examine whether regulatory events had differential effects among at-risk populations, we conducted an additional analysis incorporating an interaction term between the piecewise time exposures and a binary indicator of patients' risk status. Patients were defined as "at-risk" if they were $\geq$ 65 years old and had at least one cardiovascular risk factor (e.g., hypertension, hyperlipidemia, diabetes, smoking history, or a history of stroke or myocardial infarction). Cardiovascular risk factors were identified based on both reported comorbidities and recorded adverse events available in the JAK-POT register. Missing covariate data were addressed using multiple imputations with chained equations (50 samples, 5 iterations, predictive mean matching algorithm), with all covariates included in the imputation model. Estimates were pooled using Rubin's rule[34].

Results

Study population

The study cohort, derived from the JAK-pot collaboration dataset, included 40,019 patients who accounted for 55,365 treatment courses initiated since early 2015 (Table 2). Overall, 27,985 (50.5 %) of these courses were subsequently discontinued. The patient population was predominantly females (79.9 %), with a mean age of 57.6 years at treatment initiation, and seropositive (77.0 %). A total of 8,840 patients (17.6 %) were considered "at-risk" at treatment baseline, this share being slightly lower for patients starting JAKi compared to other bDMARDs (see Table 1). The share of at-risk patient decreased with time among JAKi treated patients, with clear decline after the safety trial first result and the EMA recommendations, while it tended to increase for other treatments (see supplementary figure 1). Patients initiating JAKi

Table 2
Patients characteristics for all patients in the JAK-pot collaboration since 2015.

	Overall	Did not start JAKi	Started JAKi	p	Missing (%)
Number of patients	40019	29075	10944		
Number of treatment course	55365	42806	12559		
Patient "at-risk" at baseline (%)	8840 (17.6)	6961 (17.9)	1879 (16.5)	<0.001	9.2
Disease duration in years (mean (SD))	11.4 (9.3)	11.1 (9.3)	12.5 (9.4)	<0.001	6.5
Age in year (mean (SD))	57.6 (12.9)	57.7 (13.1)	57.4 (12.1)	0.026	0.0
Female sex (%)	44261 (79.9)	33946 (79.3)	10315 (82.1)	<0.001	0.0
Ever smoker (%)	13037 (30.2)	10133 (30.2)	2904 (30.1)	0.906	22.0
Body mass index (mean (SD))	26.8 (5.5)	26.8 (5.5)	26.7 (5.6)	0.154	15.5
Treatment (%)				<0.001	0.0
TNFi	25161 (45.4)	25161 (58.8)	0 (0.0)		
JAKi	12559 (22.7)	0 (0.0)	12559 (100.0)		
IL6i	7389 (13.3)	7389 (17.3)	0 (0.0)		
rituximab	5589 (10.1)	5589 (13.1)	0 (0.0)		
abatacept	4513 (8.2)	4513 (10.5)	0 (0.0)		
other	154 (0.3)	154 (0.4)	0 (0.0)		
Previous bDMARDs(%)				<0.001	0.0
0	15816 (28.6)	12611 (29.5)	3205 (25.5)		
1	16468 (29.7)	13578 (31.7)	2890 (23.0)		
2	9779 (17.7)	7274 (17.0)	2505 (19.9)		
3 or more	13302 (24.0)	9343 (21.8)	3959 (31.5)		
Concomitant csDMARD (%)				<0.001	6.0
Methotrexate	15367 (29.5)	12049 (30.0)	3318 (27.7)		
Methotrexate and other	5700 (10.9)	4874 (12.2)	826 (6.9)		
None	19076 (36.6)	13664 (34.1)	5412 (45.3)		
Other without methotrexate	11924 (22.9)	9523 (23.7)	2401 (20.1)		
Glucocorticoid use (%)	22885 (43.1)	17544 (42.9)	5341 (43.8)	0.104	4.2
seropositive (%)	35767 (77.0)	27143 (76.1)	8624 (79.7)	<0.001	16.1
DAS28 (mean (SD))	4.3 (1.7)	4.3 (1.7)	4.6 (1.6)	<0.001	52.5
HAQ (mean (SD))	1.1 (0.7)	1.1 (0.7)	1.2 (0.7)	<0.001	68.4
CDAI (mean (SD))	25.7 (13.6)	25.2 (13.7)	27.1 (13.5)	<0.001	72.8
CRP (mean (SD))	12.1 (23.9)	12.2 (24.6)	11.6 (21.5)	0.010	19.4
Registry (%)				<0.001	0.0
Spain	10322 (18.6)	8369 (19.6)	1953 (15.6)		
Romania	9517 (17.2)	7591 (17.7)	1926 (15.3)		
Italy	7586 (13.7)	5473 (12.8)	2113 (16.8)		
Finland	6253 (11.3)	5390 (12.6)	863 (6.9)		
Czech Republic	4709 (8.5)	2666 (6.2)	2043 (16.3)		
Switzerland	4566 (8.2)	3248 (7.6)	1318 (10.5)		

(*continued on next page*)

Table 2 (*continued*)

	Overall	Did not start JAKi	Started JAKi	p	Missing (%)
Portugal	4355 (7.9)	3647 (8.5)	708 (5.6)		
Austria	2143 (3.9)	1684 (3.9)	459 (3.7)		
Slovenia	2094 (3.8)	1682 (3.9)	412 (3.3)		
Canada	1499 (2.7)	1132 (2.6)	367 (2.9)		
Norway	1335 (2.4)	1172 (2.7)	163 (1.3)		
Greece	986 (1.8)	752 (1.8)	234 (1.9)		

treatment differed from patients starting bDMARDs in several key characteristics: a higher proportion were females (82.1 % versus 79.3 %), they had a longer disease duration (12.5 versus 11.1 years), fewer were biologic-naïve (25.5 % compared to 29.5 %), and they tended to have a slightly higher baseline disease activity. The characteristics of the patient population were comparable across the periods of interest centered around each safety warning event (see Supplementary Table 2 and 3).

JAKi prescription pattern

The proportion of patients on JAKi has increased markedly, from less than 1 % in 2015 to slightly more than 20 % in 2024 (Fig. 1). This growth can be divided into four distinct phases (Fig. 1 and Supplementary Figure 2). From the beginning of 2015 until November 2017, the share of JAKi use rose slowly by 0.6 percentage points (pp) per year. This rate then accelerated significantly to 4.8 pp per year until July 2019, after which it slowed to an increase of 2.6 pp per year. By December 2022, the growth had nearly leveled off with an increase of only 0.6 pp per year.

When counting the total number of JAKi treatments since 2015, baricitinib has accounted for the largest share of JAKi treatments (39.5 %), followed by tofacitinib (28.2 %), upadacitinib (25.6 %), and filgotinib (6.7 %). Over time, the market share of each JAKi treatment has shifted, with tofacitinib dominating until mid-2019, after which baricitinib became the predominant JAKi (Fig. 2). Specifically, tofacitinib's share among all targeted DMARD slowed markedly after June 2019, with its rate of increase falling by 1.7 pp per year to eventually leveling out. This was followed by a second slowdown after October 2020, marking the commencement of a decline in tofacitinib's share (Fig. 2B).

Baricitinib experienced the steepest rise, increasing at a rate of 2.6 pp per year between October 2017 and the end of 2019. The growth then slowed down to 1.1 pp per year, before starting a slight decrease since the beginning of 2022. For the newer JAKis, upadacitinib and filgotinib, the number of patients on these treatments continued to rise, although the growth rate for upadacitinib also began slowing beginning of 2023.

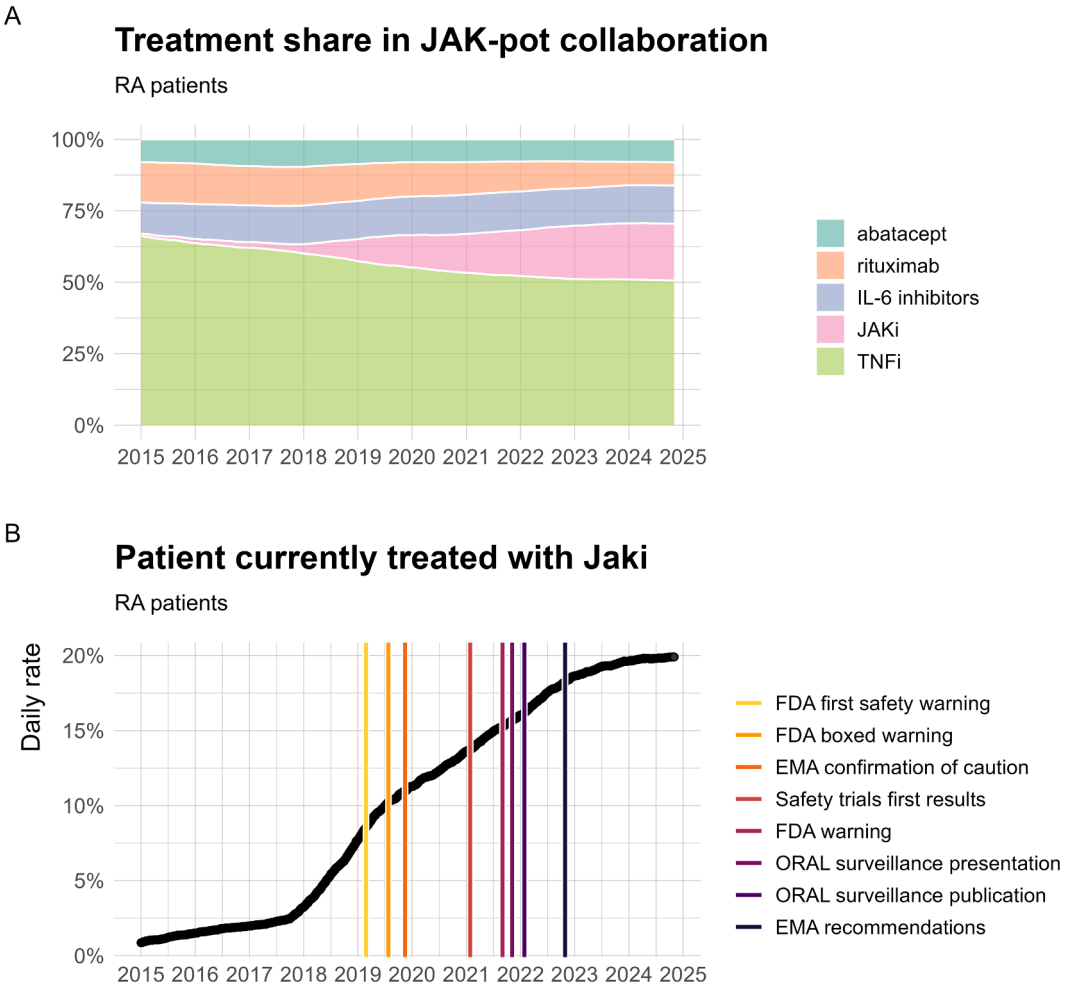

Fig. 1. Temporal evolution of the share of patients under different treatments. Panel A: share of patients under treatment since 2015. B: share of patients under JAK-inhibitor treatment in time, with the different events considered as vertical line.

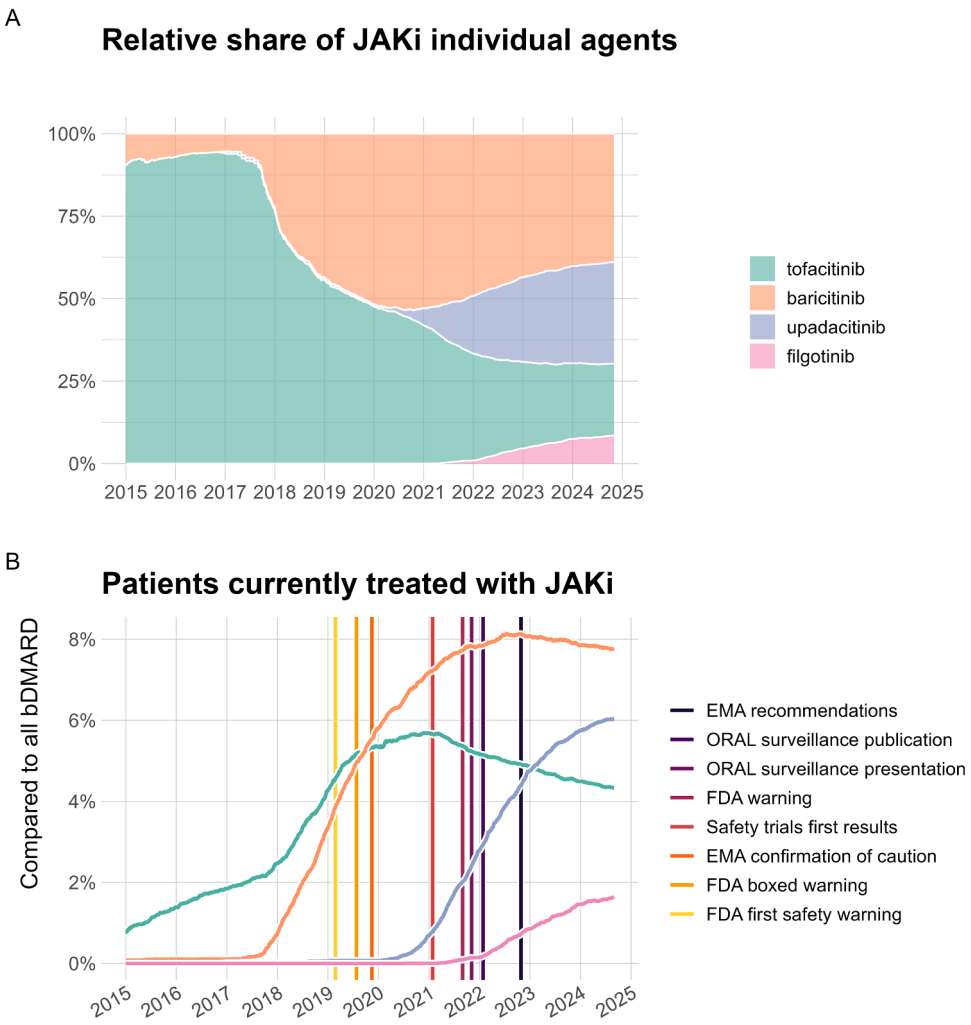

Fig. 2. Evolution in time of the share of patients under different generic Jak-inhibitor treatments. Panel A: share of patients under JAKi treatment since 2015. B: share of patients under Jak-inhibitor generic treatment in time, with the different events considered as vertical line.

JAKi treatment initiations

The monthly rate of JAKi initiation (relative to the initiation of all bDMARDs) among JAK-pot patients showed a clear increase between mid-2017 and the beginning of 2019, reaching approximately 30 % and subsequently fluctuating between 25 % and 35 % (Fig. 3A).

Each linear regression within the 8-month windows centered around regulatory events included between 8,000 and slightly over 9,000 treatment courses, covering around 7,500 unique patients (Supplementary table 3 for full details).

Adjusted regression analyses indicated significant changes in the initiation trend of JAKi following the FDA first safety warning and safety trial's first results. For these two events, the initiation rate [95 % CI] increased before the event by 5.7 pp per year [0.6,10.8] and 11.7 pp [6.6,16.9] pp per year, respectively (Table 3). After the event, the initiation rate evolution declined by 12.4 [3.1, 21.8] and 12.6 [2.9, 22.2] pp per year for the FDA first safety warning and safety trials first results, respectively, resulting in an adjusted post-event decline of -6.7 and -0.9 pp per year, respectively.

Analyzing initiation trends by individual JAKi (see supplementary table 4, and supplementary figures 3 to 6), the decrease in JAKi initiation after the FDA first safety warning was primarily attributable to a decline in tofacitinib initiations, which dropped by -7.5 [0.5, 14.6] pp per year.

Following the safety trial's first results event, both baricitinib and tofacitinib initiation rates showed a similar non-significant decrease of around 3 pp per year.

Notably, while the overall rate of JAKi initiation did not appear to change, upadacitinib showed significant downward shifts in its initiation trend following both the ORAL surveillance presentation at the ACR conference and ORAL surveillance publication events, with decreases of -8.0 pp per year [-15.6, -0.4] and -12.7 pp per year [-20.2,-5.2], respectively.

Changing the time windows around each event of interest to 6 or 10 months did not change the results (Supplementary table 4) and evidenced an additional slowdown of upadacitinib and filgotinib after the EMA recommendations event when considering longer time windows.

When examining the at-risk populations, we found a significant decrease of 17.1 percent point per year in the JAKi initiation rate after the EMA confirmation of caution (Supplementary table 5).

JAKi treatment discontinuations

Examining the monthly rate of discontinuation among the patients on JAKi (Fig. 3B), we observed an overall decline from around 2 % of JAKi users discontinuing treatment each month in 2018 to less than 1 % by 2024. Adjusted piecewise regression around each regulatory event revealed a significant change in discontinuation trends after the EMA recommendations event, where the rate of JAKi discontinuation shifted from a flat trend to an increase of 0.8 pp per year thereafter (Table 3).

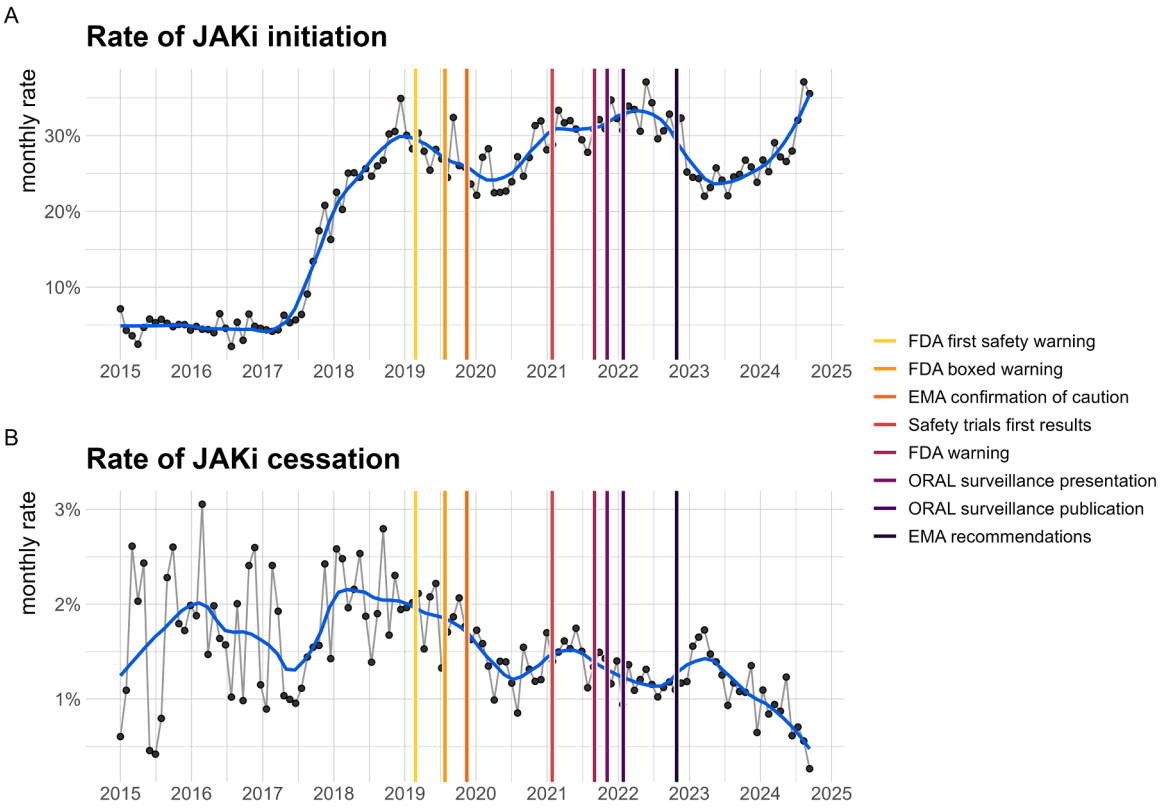

Fig. 3. Time evolution of A: monthly starting rate of Jak-inhibitors (compared to all bDMARD treatments) and B: monthly stopping rate of Jak-inhibitors when compared to all patient under Jak-inhibitors.

Table 3
Regression coefficients of the two-piece linear time regression for the adjusted regression, when considering JAKi initiation as the outcome or JAKi discontinuation as the outcome. Regression coefficients are here percent point of JAKi initiation or JAKi discontinuation per year. 95 % confidence interval are given between brackets, significance is marked with the following codes: *: p value between 0.05 and 0.01, **: p value between 0.01 and 0.001, ***: p value lower than 0.001.

	JAKi initiation		**JAKi discontinuation**	
Safety event	Yearly evolution before (percent points per year)	Change of evolution after (difference of percent points per year)	Yearly evolution before (percent points per year)	Change of evolution after (difference of percent points per year)
FDA first safety warning	5.7 [0.6,10.8]*	-12.4 [-21.8,-3.1]**	0.1 [-0.7,1.0]	-0.4 [-1.9,1.0]
FDA boxed warning	-7.5 [-12.9,-2.1]**	6.4 [-3.3,16.1]	-0.1 [-0.8,0.6]	-0.4 [-1.7,0.8]
EMA confirmation of caution	-3.6 [-8.7,1.6]	-3.8 [-13.0,5.4]	-0.3 [-1.0,0.3]	-0.4 [-1.6,0.7]
Safety trials first results	11.7 [6.6,16.9]***	-12.6 [-22.2,-2.9]*	0.6 [0.1,1.1]*	-0.9 [-1.8,0.1]
FDA warning	1.3 [-4.3,6.8]	1.2 [-8.6,11.1]	-0.5 [-0.9,0.0]	-0.0 [-0.8,0.8]
ORAL surveillance presentation at ACR conference	-0.8 [-6.3,4.8]	4.2 [-5.7,14.1]	-0.6 [-1.0,-0.1]*	0.4 [-0.4,1.3]
ORAL surveillance publication	4.8 [-0.5,10.1]	-7.9 [-17.7,1.9]	-0.4 [-0.8,0.0]	0.2 [-0.5,1.0]
EMA recommendations	-8.8 [-14.0,-3.6]***	-3.3 [-12.3,5.8]	0.1 [-0.2,0.5]	0.7 [0.0,1.4]*

This shift was primarily driven by tofacitinib discontinuations (Supplementary Table 4). Among individual JAKi, the discontinuation rate for upadacitinib increased by 3.1 [0.7, 5.5] pp per year following the ORAL surveillance presentation at the ACR conference (Supplementary Table 4 and supplementary figure 3 to 6).

Sensitivity analyses with alternative time windows (6 or 10 months) yielded similar results, with an additional increase of upadacitinib discontinuation after the EMA recommendations when using a 6- and 10-month window (see Supplementary Table 4).

When examining the at-risk population, we found a significant increase of 1.5 percent point per year of the JAKi discontinuation rate after the EMA confirmation of caution in 2019 (Supplementary Table 6).

Switching between JAKi treatments

In our dataset, 1276 patients switched treatment between two different JAKis. Analysis of monthly switching patterns among different JAKi types (Supplementary Figure 7) indicated that the only noticeable trend was a doubling in the rate of switching from tofacitinib to upadacitinib and baricitinib. This trend emerged in the months subsequent to the early 2021 announcement of an increased risk of MACE and cancer associated with tofacitinib.

Discussion

In this large international collaboration of registries, we found that during 2015–2023 the overall market share of JAKi among second-line therapies increased from 1 % to 20 % and the rate of monthly JAKi discontinuation had decreased from 2 % to less than 1 % per month. The initial steep rise in JAKi initiations decelerated by approximately half from mid-2019 to the end of 2022, before stabilizing. This shift was largely influenced by key events: the initial safety warnings issued by the

FDA and EMA, and the 2021 announcement of the ORAL Surveillance trial findings, which highlighted increased risks of MACE and cancer. Expectedly, prescribing patterns for individual JAKi diverged, with tofacitinib appearing to be the most affected. Specifically, following the first wave of safety warnings, new initiations of tofacitinib—then the predominant JAKi—declined significantly. This was followed by a further reduction in overall prescription after the 2021 safety trials first results about MACE and cancer risks. Concurrently, a notable increase in switching from tofacitinib to other available JAKi, such as baricitinib and upadacitinib, was observed. The change in JAKi prescribing practices following specific EMA communications seemed primarily driven by an increase in tofacitinib discontinuations. Temporal shifts in baricitinib prescribing patterns did not demonstrate a significant association with regulatory events and likely reflected the natural competition between the different available alternative JAKi options. Concerning upadacitinib, a decline in initiation and an increase in discontinuation was observed mainly after the announcement of the ORAL Surveillance trial findings in 2021-2022. The use of filgotinib, which was approved by EMA only in 2020 and thus accounted for the lowest JAKi share, increased during the whole study period. Interestingly, the observed trends did not differ significantly in the high-risk patient population, as defined by the ORAL Surveillance trial. Our findings align with previous studies in other fields of medicine indicating that safety warnings issued by regulatory agencies had an influence on clinical practice[35,36].

Overall, the effects of regulatory safety communications appeared to be more pronounced on JAKi initiation than on treatment discontinuation. While a modest increase in discontinuation was observed following the first EMA warning, subsequent safety signals, including the ORAL Surveillance results and related regulatory actions, were associated with limited additional changes, especially in the overall population. In contrast, initiation rates showed clearer and more sustained decelerations. This pattern suggests that safety warnings may exert a greater influence on treatment choices for new initiations than decisions to discontinue ongoing therapy, where clinicians may balance emerging safety concerns against individual patient benefit and disease control.

The observation of increasing use of JAKi within mainly European countries participating in the JAK-POT collaboration was consistent with real-world data from Canada, reporting increased use of JAKi for all the approved indications through a similar period (2016-2022), at both provincial and national levels[37] In this study, tofacitinib was the most dispensed JAKi during the entire study period, similar to the tofacitinib predominance in our study database until mid-2019. A UK-based nationwide study conducted between 1st January 2019, and 31 August 2023 also found a four-fold increase in prescribing JAKi for all the approved indications within the study period[17] Following EMA safety warnings a significant change in the prescription pattern was observed. In November 2021, the growth rate of tofacitinib prescribing had decelerated significantly, with a further step down after each alert. Baricitinib prescribing trends remained consistent after the initial EMA tofacitinib safety warning, but slowed significantly after the second tofacitinib safety warning, and steeply decreased, after the EMA warning end of October 2022. By contrast, prescriptions of upadacitinib and filgotinib have continued to increase[17]

A multicenter retrospective study from Italy analyzed the impact of the first two safety warnings issued by the EMA in November 2019 and March 2021 on the prescription pattern of JAKi used for treatment of RA (n=864 patients) from July 2019 to 30 June 2022[16]. An overall JAKi prescribing decreased after the safety alerts, with a particular decrease in prescribing tofacitinib and baricitinib, consistently with the pattern observed in our study. Concomitantly, a gradual increase in prescriptions of the selective JAKi, upadacitinib and filgotinib, was observed, especially after March 2021, with a notion that these medications became licensed and available on the market at the later stage compared to the other two. Another Italian monocentric study[38] evaluated the impact of the EMA recommendations on JAKi prescriptions, and found that only a small proportion of patients requested therapy discontinuation due to concerns regulatory recommendations.

A previous study based on the JAK-pot collaboration compared treatment discontinuations for adverse events among second-line therapies up-to November 2022 and found no overall increased incidence of treatment discontinuation due to adverse events with JAKi[20] Remarkably, a higher discontinuation rate was observed with tofacitinib against TNFi among patients aged 65 years and older, indicating potential variations in safety profiles among JAKi and among high-risk patients, or a greater tendency to attribute discontinuations to adverse events with tofacitinib in this age group. The sharp rise in JAKi discontinuations within our at-risk population after the 2019 EMA safety warning is consistent with the adoption of this regulatory advice in clinical practice.

Our study provides a wide overview of prescribing practice, covering 12 countries and more than 35,000 patients with RA since 2015 and reports the first large-scale analysis of the JAKi prescription patterns in relation to 8 regulatory safety warnings. The availability of multiple patient characteristics in our database allowed us to provide an estimation of prescription changes adjusted for patients' characteristic.

Nevertheless, as any retrospective study and despite our effort to adjust for multiple factors, residual confounding cannot be excluded. Furthermore, our analysis has some limitation. First, it is only able to provide an estimate of changes of prescribing tendency occurring around time events, without being able to test the causality. Prescription patterns can be affected by other factors, such as the introduction of new molecules to the market, drug pricing, or the reimbursement policies, potentially modifying the prescription trends around the considered regulatory events. Second, it considers the time events as independent, while they are different safety regulation concerning the same treatment. Moreover, access to actual sales data could complement our findings by providing a more complete picture of the overall impact of regulatory safety warnings on prescribing behavior. Third, although the data were derived from national registers, they may not be fully representative of the overall RA populations in the participating countries. Registry coverage may be incomplete, and preferential inclusion of patients receiving biologic or newer targeted therapies cannot be excluded; therefore, absolute treatment proportions should be interpreted with caution. While all contributing registers have been established for many years, detailed information on coverage and potential changes in registration practices over time was not uniformly available. Consequently, although our analyses focus on temporal trends rather than absolute estimates, residual bias related to registry coverage cannot be excluded and represents an important limitation.In conclusion, the safety warnings did affect the prescription pattern of JAKi in patients with RA affecting mainly tofacitinib, and to a lesser extent the other JAKi.

Patient and public involvement

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

Ethics approval

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

Study sponsors

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CRediT authorship contribution statement

Denis Mongin: Writing – original draft, Writing – review & editing, Data curation, Methodology, Formal analysis, Visualization, Investigation. **Romain Aymon:** Writing – review & editing, Data curation, Investigation. **Denis Choquette:** Writing – review & editing, Resources, Investigation. **Louis Coupal:** Writing – review & editing, Resources, Investigation. **Catalin Codreanu:** Writing – review & editing, Resources, Investigation. **Florenzo Iannone:** Writing – review & editing, Resources, Investigation. **Sella Provan:** Writing – review & editing, Resources, Investigation. **Tore K. Kvien:** Writing – review & editing, Resources, Investigation. **Ruth Fritsch-Stork:** Writing – review & editing, Resources, Investigation. **Dan Nordström:** Writing – review & editing, Resources, Investigation. **Karel Pavelka:** Writing – review & editing, Resources, Investigation. **Jakub Závada:** Writing – review & editing, Resources, Investigation. **Manuel Pombo-Suarez:** Writing – review & editing, Resources, Investigation. **Lucia Otero-Varela:** Writing – review & editing, Resources, Investigation. **Elsa Sousa:** Writing – review & editing, Resources, Investigation. **Ziga Rotar:** Writing – review & editing, Resources, Investigation. **Prodromos Sidiropoulos:** Writing – review & editing, Resources, Investigation. **Antonios Bertsias:** Writing – review & editing, Resources, Investigation. **Delphine S. Courvoisier:** Writing – review & editing, Resources, Investigation, Methodology, Validation. **Axel Finckh:** Writing – review & editing, Resources, Investigation, Funding acquisition. **Kim Lauper:** Writing – review & editing, Resources, Investigation, Funding acquisition. **Ori Elkayam:** Writing – review & editing, Resources, Investigation, Conceptualization. **Victoria Furer:** Writing – original draft, Writing – review & editing, Resources, Investigation, Conceptualization, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dan Nordström reports speaking and lecture fees from Pfizer and UCB; consulting or advisory fees from Bristol Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer and UCB; and grant funding from Bristol Myers Squibb, MSD and UCB. **Tore K. Kvien** reports speaking and lecture fees from Grünenthal, Janssen and Sandoz; consulting or advisory fees from AbbVie, Gilead, Janssen, Novartis, Pfizer, Sandoz and UCB; and grant funding from AbbVie, Bristol Myers Squibb, Galapagos, Novartis, Pfizer and UCB. **Florenzo Iannone** reports speaking and lecture fees from AbbVie, Alfasigma, Amgen, AstraZeneca, CSL Vifor, GSK, Janssen, Novartis, Eli Lilly and UCB; and consulting or advisory fees from AbbVie, Amgen, AstraZeneca, GSK, Janssen, Eli Lilly and UCB. **Karel Pavelka** reports speaking and lecture fees from AbbVie, Eli Lilly, Sandoz, UCB, Medac and Pfizer. **Jakub Závada** reports speaking and lecture fees from AbbVie, Eli Lilly, Sandoz, Novartis, Egis, UCB, Sanofi, AstraZeneca and Sobi; and consulting or advisory fees from AbbVie, Novartis, AstraZeneca and GSK. **Prodromos Sidiropoulos** reports speaking and lecture fees from AbbVie, Pfizer, Eli Lilly, Novartis and UCB; and grant funding from AbbVie, Pfizer, Eli Lilly, Novartis, UCB, MSD, Roche, Amgen, GSK, Boehringer Ingelheim, AstraZeneca, Janssen, Sandoz and Biocon. **Axel Finckh** reports speaking and lecture fees from AbbVie, Alfasigma, AstraZeneca, Eli Lilly, Pfizer, UCB, Bristol Myers Squibb, Gilead and MSD; and grant funding from AbbVie, Alfasigma, Eli Lilly, Galapagos and Pfizer. **Kim Lauper** reports speaking and lecture fees from AbbVie (paid to the institution); consulting or advisory fees from Pfizer and Novartis (all paid to the institution); and grant funding from AbbVie, Eli Lilly, Galapagos, Pfizer and Alfasigma (all paid to the institution). **Ziga Rotar** reports consulting or advisory fees from AbbVie, Pfizer, Eli Lilly, Sobi, Novartis, AstraZeneca and STADA, reports speaking and lecture fees from AbbVie, Sobi, Pfizer and Eli Lilly; and participation on advisory boards for AbbVie and Sobi. **Catalin Codreanu** reports speaking and lecture fees from AbbVie, Amgen, Boehringer Ingelheim, Ewopharma, Eli Lilly, Novartis, Pfizer, Sandoz, Sobi and STADA; and leadership roles as President of the Romanian Society of Rheumatology and the Romanian Registry of Rheumatic Diseases.The other authors have no conflict of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2026.152946.

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