After JAK inhibitor failure: to cycle or to switch, that is the question - data from the JAK-pot collaboration of registries

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CLINICAL SCIENCE

After JAK inhibitor failure: to cycle or to switch, that is the question – data from the JAK-pot collaboration of registries

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ABSTRACT

Objectives The expanded therapeutic arsenal in rheumatoid arthritis (RA) raises new clinical questions. The objective of this study is to compare the effectiveness of cycling Janus kinase inhibitors (JAKi) with switching to biologic disease-modifying antirheumatic drug (bDMARD) in patients with RA after failure to the first JAKi.

Methods This is a nested cohort study within data pooled from an international collaboration of 17 national registries (JAK-pot collaboration). Data from patients with RA with JAKi treatment failure and who were subsequently treated with either a second JAKi or with a bDMARD were prospectively collected. Differences in drug retention rates after second treatment initiation were assessed by log-rank test and Cox regression analysis adjusting for potential confounders. Change in Clinical Disease Activity Index (CDAI) over time was estimated using a linear regression model, adjusting for confounders.

Results 365 cycling and 1635 switching patients were studied. Cyclers were older and received a higher number of previous bDMARDs. Both strategies showed similar observed retention rates after 2 years of follow-up. However, adjusted analysis revealed that cycling was associated with higher retention (p=0.04). Among cyclers, when the first JAKi was discontinued due to an adverse event (AE), it was more likely that the second JAKi would also be stopped due to an AE. Improvement in CDAI over time was similar in both strategies.

Conclusions After failing the first JAKi, cycling JAKi and switching to a bDMARD appear to have similar effectiveness. Caution is advised if an AE was the reason to stop the first JAKi.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The therapeutic arsenal in rheumatoid arthritis has expanded with the arrival of Janus kinase inhibitors (JAKi).
⇒ In real life, JAKi is being used primarily in patients with treatment failure with biologic disease-modifying antirheumatic drugs (bDMARDs).
⇒ There are no data on the effectiveness of using a JAKi compared with a bDMARD in patients with first JAKi treatment failure.

WHAT THIS STUDY ADDS

⇒ This large observational study, involving 17 registries and 2000 patients who had an inadequate response to or who experienced an adverse event (AE) with the first JAKi, demonstrates that both strategies, cycling to a second JAKi and switching to a bDMARD, appear to have similar effectiveness, achieving a slightly higher retention when cycling JAKi.
⇒ For cyclers, but not for switchers, when the first JAKi was stopped due to an AE, it was more likely that the second treatment would also be stopped due to an AE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This analysis provides clinically meaningful evidence of the efficacy of cycling JAKi and switching to bDMARD after JAKi failure, helping decision making in this increasingly frequent scenario.

INTRODUCTION

With the arrival of new Janus kinase inhibitors (JAKi), with different Janus kinase (JAK) inhibition profiles, there is the possibility of using another JAKi after an inadequate response to the first JAKi in patients with rheumatoid arthritis (RA).

The 2019 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations places the use of JAKi at the same level as the biologic disease-modifying anti-rheumatic drugs (bDMARDs), being used in patients with treatment failure with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and no preference is given to any of these agents.[1] Based on the experience gained with tumour necrosis factor inhibitors (TNFi) and even

more so with the appearance of lower priced biosimilars, TNFi is the disease-modifying antirheumatic drug often used as second line of treatment, after failure with csDMARD. However, only about 60% of patients achieve an American College of Rheumatology 20% improvement criteria and a much larger proportion do not reach remission or a low disease activity; furthermore, a considerable proportion of patients lose their initial response or develop adverse events (AE) over time.[2 3] In this scenario, before the appearance of JAKi, if the first TNFi failed, there was the possibility of cycling to another TNFi or switching to a bDMARD with a different mechanism of action (MOA). The first strategy was shown to be valid based on data from a prospective randomised trial[4] and from different observational studies,[5 6] as was the second alternative, confirmed in placebo-controlled trials.[7–10] The only randomised trial comparing both strategies demonstrated that, among patients with inadequate response to TNFi, change to a bDMARD with a different MOA was more effective than the use of a second TNFi.[11]

The appearance of JAKi increased the degree of complexity. EULAR recommendations state that if a bDMARD or a JAKi has failed, treatment with another bDMARD or JAKi should be considered, pointing out that if TNFi has failed the use of a drug with a different MOA would be preferred over a second TNFi. At the time of elaboration of these recommendations, no data were available regarding studies switching to a bDMARD or cycling JAKi after treatment failure with JAKi.

In clinical practice, JAKi is mainly being used in patients who have previously experienced failure to a bDMARD.[12] JAKi has demonstrated efficacy during the clinical development phase in this scenario.[13–16] Nevertheless, in these studies, a proportion of patients had to discontinue JAKi due to lack of efficacy or safety concerns.

One study suggested that patients with an insufficient response to JAKi could achieve clinically meaningful responses when switching to TNFi.[17] On the other hand, available JAKis differ in terms of affinity for the receptor-associated tyrosine kinases of the JAK family. Tofacitinib is a selective inhibitor of JAK1 and JAK3, while baricitinib is a selective inhibitor of JAK1 and JAK2, and upadacitinib and filgotinib inhibit JAK1 selectively.[18] Although there is no evidence that differences in affinity influence response to JAKi, based on previous experience with cycling of TNFi, a second JAKi is often used in case of failure to the first JAKi. There are only limited clinical data to support this strategy; two small observational studies reported that the use of a second JAKi was a safe and effective option after discontinuation of the first JAKi.[19 20]

The objective of this study was to compare the efficacy of a second JAKi versus a bDMARD after failure of the first JAKi. Response and reason for stopping second-line therapies were also examined depending on the reason for stopping the first JAKi. To accomplish this, we used a large international collaboration of cohorts of patients with RA.

METHODS

Patient sample

This is a collaborative observational study of prospectively collected data in 17 national registries within the JAK-pot project (full list of registries and contributing patients in online supplemental table 1). The aim of this collaboration is to carry out studies to evaluate the effectiveness and safety aspects of JAKi and bDMARDs. The first study resulting from this collaboration has recently been published.[21] In this specific nested cohort, we included patients with RA with first JAKi treatment failure who were subsequently being treated with a second JAKi or with a bDMARD. All registries contributed individual patient-level data to this collaborative analysis.

Timepoint definitions and treatment groups

Baseline was defined as the start date of each treatment after failure to the first JAKi. Owing to the non-interventional nature of the study, strict adherence to visit windows was not feasible. To reduce the amount of missing data, baseline characteristics were imputed as the values available in a time window between 2 months prior to baseline date up to 1 day post baseline date. We included only treatment courses initiated after JAKi became commercially available in each country. Each treatment course was defined as starting from the initiation of treatment until treatment stop, end of participation in the register or end of follow-up (November 2021), whichever came first. Reasons for discontinuation were classified as inefficacy, intolerance or other.

Patient and public involvement

Patients and the public were not involved in the design and conduct of the study. There are no specific plans to disseminate the results of the research to study participants or relevant patient community. However, most of the registers disseminate study results to the study participants of their own country.

Exposure of interest

The exposure of interest was the MOA used after first JAKi failure, either another JAKi or a bDMARD.

Study outcomes

The primary outcome was drug retention, which was evaluated in all registries. The secondary outcomes were (1) the reason for stopping the second treatment depending on the reason for discontinuing the first JAKi and (2) Clinical Disease Activity Index (CDAI) evolution over time. CDAI does not include acute phase reactants, making it less sensitive to agents having a strong effect on these inflammation biomarkers,[22 23] and is therefore a more appropriate measure of disease activity than Disease Activity Scale 28.

Covariates of interests

Baseline covariates considered for analysis were selected based on clinical relevance and availability. These covariates were sex, age, disease duration, seropositivity, number of previously used bDMARDs, type of the first JAKi, reason for stopping the first JAKi (lack of efficacy/AE/other), treatment duration of the first JAKi, smoking (ever/never), comorbidity (presence/absence, see online supplemental file 1), concomitant glucocorticoids (presence/absence), csDMARD treatment (yes/no), CDAI and functional status (Health Assessment Questionnaire Activity Index). Patients were classified as seropositive if rheumatoid factor (RF) and/or anticyclic citrullinated peptide antibodies were positive, negative if both were negative, and missing if one was missing and the other was negative, to limit misclassification. In registries with only RF status available, seropositivity was defined as positive if RF was positive, negative if RF was negative and missing if RF was missing.

Statistical methods

Baseline characteristics were analysed using standard descriptive statistics and, as per recommendations,[24] indicated number of patients with valid values by exposure. For all analyses, missing

Table 1 Patient baseline demographics and clinical characteristics

	Valid		Valid		
Female, n (%)	365	311 (85.2)	1635	1324 (81.0)	0.07
Age, mean (SD)	359	57.44 (12.73)	1587	55.20 (12.43)	0.002
Disease duration in years, mean (SD)	251	14.46 (9.50)	1200	12.94 (9.39)	0.02
Seropositive, RF or ACPA, n (%)	305	226 (74.1)	1352	915 (67.7)	0.03
Number of previous bDMARDs, median (IQR)	347	3.0 (1.0–4.0)	1570	2.0 (1.0–3.0)	<0.001
First JAKi, n (%)	365		1635		0.52
Baricitinib		135 (37.0)		609 (37.2)	
Filgotinib		0 (0.0)		1 (0.1)	
Tofacitinib		228 (62.5)		1001 (61.2)	
Upadacitinib		2 (0.5)		24 (1.5)	
Reason for stopping first JAKi, n (%)	365		1635		0.20
Adverse event		45 (12.3)		201 (12.3)	
Lack of efficacy		210 (57.5)		1014 (62.0)	
Other		110 (30.1)		420 (25.7)	
Duration of first JAKi in years, mean (SD)	365	1.34 (1.27)	1635	0.72 (0.74)	<0.001
Tobacco use ever, n (%)	240	73 (30.4)	1063	375 (35.3)	0.18
Comorbidities, n (%)	330	140 (42.4)	1456	549 (37.7)	0.13
Concomitant glucocorticoids, n (%)	324	171 (52.8)	1274	687 (53.9)	0.76
Concomitant csDMARD, n (%)	365	127 (34.8)	1635	749 (45.8)	<0.001
CDAI, mean (SD)	151	24.35 (13.24)	802	23.42 (12.96)	0.42
HAQ-DI, mean (SD)	136	1.39 (0.66)	709	1.27 (0.70)	0.06

ACPA, anticitrullinated peptide antibodies; bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; JAKi, Janus kinase inhibitor; RF, rheumatoid factor.

covariates were imputed using multiple imputations with chained equations (50 samples, predictive mean matching algorithm).

Main outcome

For the primary outcome (drug retention), Kaplan-Meier and Cox regression models were used. The Cox models were adjusted for each covariate (list in the Covariates of interests section).

Secondary outcomes

To examine the association between reasons for stopping the first JAKi and reasons for stopping the subsequent treatment between cycler and switcher groups, we used Fisher's exact test. For disease activity at 1 year, we used a three-step procedure to determine treatment response differences. The frequency of CDAI collection varied between registries; some captured it at every visit, some randomly and some on an annual basis. When no observed CDAI values were present at 1 year, the mean of the values within a 3-month window was used. Values still missing for patients still on drug after 1 year were imputed using the nearest available neighbour.[25] Finally, we estimated change in disease activity by switcher group using linear regression, adjusting for confounders.

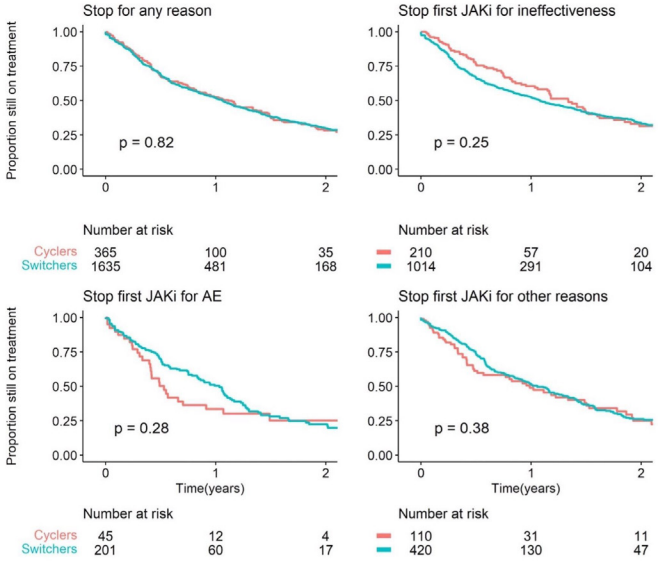

Figure 1 Kaplan-Meier curves of overall discontinuation and by reason for stopping the first JAKi. AE, adverse event; JAKi, Janus kinase inhibitor.

RESULTS

Patient disposition and baseline characteristics

A total of 2000 patients with JAKi treatment failure from 17 countries were collected, of whom 365 were treated with a second JAKi and 1635 switched to a bDMARD (online supplemental table 1).

Compared with patients switching to bDMARD, patients initiating another JAKi were older, had longer disease duration, were more often seropositive, received a higher number of previous bDMARDs and had longer exposure to first JAKi treatment (table 1). Monotherapy was more common among patients switching to another JAKi. Most of the patients received tofacitinib (61.5%) or baricitinib (37.2%) as first JAKi. The use of upadacitinib or filgotinib was limited (1.4%). There was no association between the type of the first JAKi or the reason for discontinuing it and the subsequent decision to cycle a second JAKi or switch to a bDMARD. Measures of disease activity were not different in both groups.

Treatment retention

No crude difference was observed in drug retention between both strategies after 2 years of follow-up (figure 1). Retention

Table 2 Results of Cox regression analysis of treatment retention

	Univariable analysis			Adjusted analysis		
	HR	95% CI	P value	HR	95% CI	P value
JAKi to JAKi (ref: JAKi to bDMARD)	0.93	0.79 to 1.10	0.39	0.82	0.68 to 0.99	0.04
Sex (ref: female)	0.86	0.74 to 1.01	0.07	0.87	0.73 to 1.03	0.11
Age	1.00	1.00 to 1.01	0.20	1.00	1.00 to 1.01	0.27
Disease duration in years	0.99	0.99 to 1.00	0.20	0.99	0.98 to 1.00	0.16
Seropositive, RF or ACPA	1.00	0.85 to 1.17	0.96	0.95	0.81 to 1.11	0.52
≥1 previous bDMARDs (ref: 0)	1.01	0.85 to 1.20	0.88	1.05	0.88 to 1.26	0.55
Treatment duration of first JAKi, years	1.12	1.02 to 1.22	0.02	1.16	1.05 to 1.28	0.003
Concomitant csDMARD	0.73	0.64 to 0.84	<0.001	0.73	0.63 to 0.84	<0.001
GC at baseline	0.98	0.83 to 1.15	0.80	0.98	0.83 to 1.15	0.79
CDAI	1.01	1.00 to 1.01	0.06	1.01	1.00 to 1.02	0.14
HAQ-DI	1.08	0.95 to 1.23	0.22	1.02	0.85 to 1.22	0.85
Tobacco (ref: never)	1.03	0.86 to 1.24	0.73	0.99	0.82 to 1.20	0.95
Any comorbidities	1.05	0.91 to 1.22	0.50	1.01	0.85 to 1.19	0.94

Analyses were adjusted for sex, age, disease duration, seropositivity, number of previously used bDMARDs/tsDMARDs, treatment duration of first JAKi, concomitant csDMARD treatment, concomitant GC, HAQ-DI, baseline disease activity values, smoking and comorbidity.
ACPA, anticitrullinated peptide antibodies; bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GC, glucocorticoid; HAQ-DI, Health Assessment Questionnaire Disability Index; JAKi, Janus kinase inhibitor; ref, reference; RF, rheumatoid factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

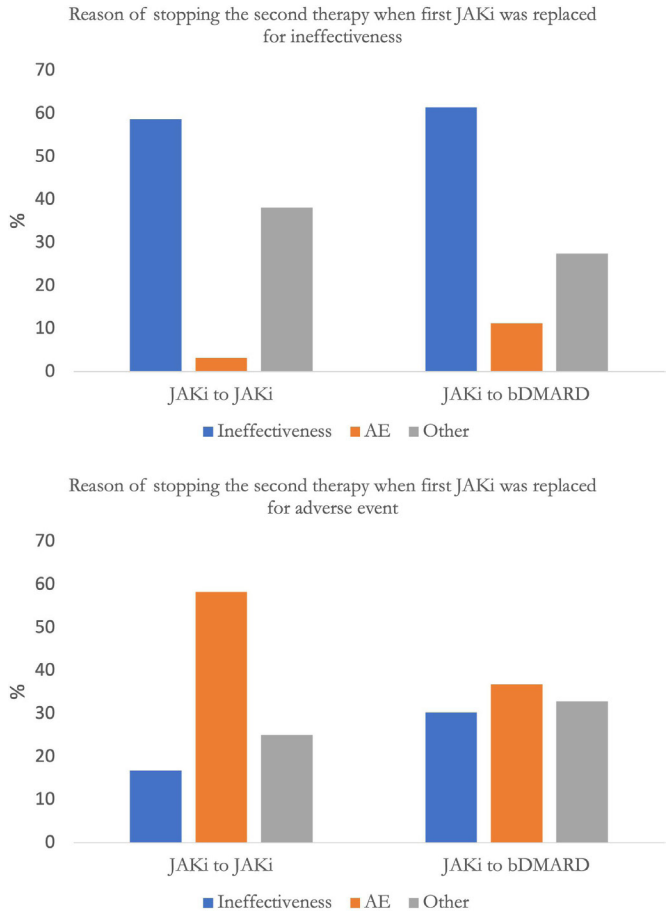

Figure 2 Proportion of patients discontinuing the second treatment for AE or ineffectiveness by reason for stopping the first JAKi. AE, adverse event; bDMARD, biologic disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor.

was also similar when stratifying for reasons for discontinuation of the first JAKi.

In univariable analyses, treatment strategy was not associated with a different retention (table 2). Nevertheless, the adjusted analysis demonstrated that cycling to another JAKi was associated with higher retention compared with the use of a bDMARD, with an HR for withdrawal of 0.82 (95% CI 0.68 to 0.99).

Secondary analysis

The reason for stopping the first treatment was associated with the reason for discontinuing subsequent treatment. When the reason for stopping the first JAKi was lack of efficacy, most of the patients in both treatment groups would also cease for this reason (difference between groups: p=0.59; figure 2). If the first JAKi was discontinued due to an AE and a second JAKi was used, the reason for stopping it would be more likely another AE, whereas if a bDMARD was used more variability was detected (p=0.01).

CDAI improved in a similar way in both groups after 12 months of follow-up. The mean CDAI improvement was 10.8 (95% CI 3.4 to 18.2) for the JAKi switcher group vs 10.4 (95% CI 3.1 to 17.7) for the bDMARD group (p=0.79), with large individual variability (figure 3).

DISCUSSION

There is little clinical evidence to support current recommendations for managing patients with RA after failure to JAKi treatment.[1 26] This large international observational study investigates the optimal therapeutic strategy for patients with RA after failure to the first JAKi. After JAKi discontinuation, the use of JAKi or bDMARD has similar effectiveness in terms of reducing disease activity, yet with slightly higher retention in the adjusted analysis when using a second JAKi.

There was a 4:1 ratio of switchers versus cyclers. This may indicate lack of confidence of physicians in cycling JAKi due to limited evidence. Patients who cycled JAKi were older, had

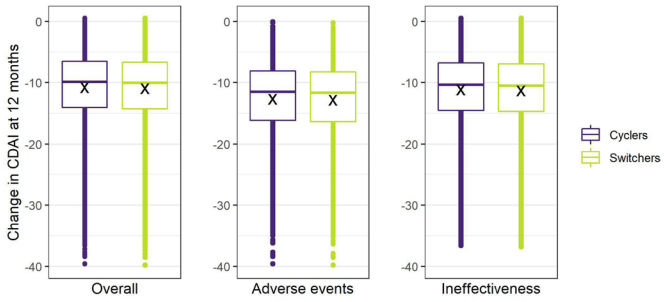

Figure 3 Adjusted change in disease activity overtime, overall and by reason for discontinuing the first JAKi. X indicates the mean. Analyses were adjusted for sex, age, disease duration, seropositivity, number of previously used bDMARDs/tsDMARDs, treatment duration of the first JAKi, concomitant csDMARD treatment, concomitant glucocorticoids, HAQ-DI, baseline disease activity values, smoking and comorbidity. bDMARDs, biologic disease-modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; JAKi, Janus kinase inhibitors; tsDMARD, targeted synthetic disease-modifying antirheumatic drug .

longer disease duration, received a higher number of previous bDMARDs and had longer exposure to first JAKi treatment. It may be speculated that they had a more complex profile compared with patients switching to a bDMARD. It is possible that the option to cycle JAKi is reserved for more difficult cases and patients who have received more previous treatments and therefore have less therapeutic options. A minority of the patients received JAKi as first line of treatment after failure with csDMARD. A separate analysis to determine the impact of previous treatment on drug retention could not be performed due to insufficient sample size. There was a high prevalence of patients on monotherapy, being more frequent among cyclers. This may reflect current recommendations: in patients who cannot use csDMARD, JAKi and interleukin 6 inhibitors may have some advantages compared with other bDMARDs.[1]

Reports with small sample size support that the use of a second JAKi is a safe and effective option after discontinuation of the first JAKi.[19 20] On the other hand, one study showed clinically meaningful response to bDMARD after failure with JAKi.[17] In our study, even though patients who cycled JAKi were older and received a higher number of previous bDMARDs, no statistical difference in drug retention with both alternatives was detected after 2 years of follow-up when looking at the Kaplan-Meier curves. The adjusted analysis showed that cycling to another JAKi was associated with lower treatment discontinuation. This could be attributed to the fact that JAKi switchers have less therapeutic alternatives, so the clinician maintains the treatment regardless of response. Nonetheless, adjusted CDAI over time evolved in a similar way in both groups, with improvements in both cases. Baseline covariates considered for adjustment are listed in the Methods section and include variables that were significantly different between the two groups, such as the number of previous bDMARDs or the use of concomitant csDMARD.

Due to lack of statistical power, we did not analyse the impact of patient characteristics on drug retention. Nonetheless, we explored prior causes of treatment discontinuation as a possible predictor of response. When the reason for discontinuing the first JAKi was an AE, it was more likely that the second JAKi would also be stopped for the same reason. There was no significant difference in retention between both strategies in patients who discontinued the first JAKi due to AE, although there seems to be a trend during the first year of follow-up where discontinuation was more likely in patients cycling JAKi. Our study was not designed to analyse the specific AE that led to drug discontinuation. For this very interesting topic, more granular data, available in specific registers, will be necessary to determine if specific AE recurs with the use of a second JAKi, with this finding suggestive of a class effect.

This study has several limitations. First, heterogeneity of data coming from different registries could not be assessed due to small sample size contributed by each country. In Europe, there are substantial differences in the use of second-line treatments for RA, regarding access, availability and affordability of these therapies.[27] Second, the primary outcome was overall drug retention since it can be interpreted as a composite measure of effectiveness, safety and tolerability. However, drug retention may also be influenced by other factors such as the number of alternative treatment options available and the characteristics of the patient population.[28] To provide a more complete picture of effectiveness, following EULAR points to consider when analysing and reporting comparative effectiveness research using observational data in rheumatology, a second effectiveness outcome, CDAI, was used.[24] Third, treatment groups were unbalanced, which is a reflection of real-life practice and a common limitation of observational studies. In particular, there may be confounding by indication. Fourth, since upadacitinib and filgotinib have been recently approved, most of the patients received tofacitinib and baricitinib as first JAKi. Due to limited statistical power, we could not assess retention depending on the type of JAKi. In future analysis, it would be interesting to determine if the sequence of use of the different types of JAKi influences the response. Finally, we had to deal with missing data. This is a non-interventional, observational study with a limited follow-up time. To reduce the impact of missing data, baseline characteristics were imputed as the values available in a short time frame, which may increase measurement error. Nonetheless, our results are broadly in agreement with previous reports.[17 19 20]

The main strength of our study relies on the inclusion of a large number of patients being treated in real life, avoiding issues such as low generalisability that occur in randomised control trials.[29]

In conclusion, the results of this study, conducted in real-life conditions reflective of current clinical practice, indicate that, after failing the first JAKi, the use of a second JAKi and switching to a bDMARD have similar effectiveness, while patients who cycled JAKi have a slightly higher retention. However, when the first JAKi is discontinued due to an AE, it is more likely that the second JAKi would also be stopped due to another AE, which may suggest that switching to a bDMARD could be a more reasonable alternative in this scenario.

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