

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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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-2022-222835>).

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Some of the data contained in this manuscript have been previously presented in one abstract: Pombo-Suarez M, Sanchez-Piedra C, Gomez-Reino J et al. Effectiveness of cycling JAKi compared to switching to bDMARD in patients who failed a first JAKi in an international collaboration of registries of rheumatoid arthritis patients (the JAK-pot study). *Arthritis Rheumatol* 2021;73 (suppl. 10).

Published Online First
13 September 2022



► <http://dx.doi.org/10.1136/ard-2022-223071>



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To cite: Pombo-Suarez M, Sanchez-Piedra C, Gómez-Reino J, et al. *Ann Rheum Dis* 2023;**82**:175–181.

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.

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)

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.

recommendations places the use of JAKi at the same level as the biologic disease-modifying antirheumatic 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 trial⁴ 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)
Age, mean (SD)	359	57.44 (12.73)	1587	55.20 (12.43)
Disease duration in years, mean (SD)	251	14.46 (9.50)	1200	12.94 (9.39)
Seropositive, RF or ACPA, n (%)	305	226 (74.1)	1352	915 (67.7)
Number of previous bDMARDs, median (IQR)	347	3.0 (1.0–4.0)	1570	2.0 (1.0–3.0)
First JAKi, n (%)	365		1635	
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	
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)
Tobacco use ever, n (%)	240	73 (30.4)	1063	375 (35.3)
Comorbidities, n (%)	330	140 (42.4)	1456	549 (37.7)
Concomitant glucocorticoids, n (%)	324	171 (52.8)	1274	687 (53.9)
Concomitant csDMARD, n (%)	365	127 (34.8)	1635	749 (45.8)
CDAI, mean (SD)	151	24.35 (13.24)	802	23.42 (12.96)
HAQ-DI, mean (SD)	136	1.39 (0.66)	709	1.27 (0.70)

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.

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.

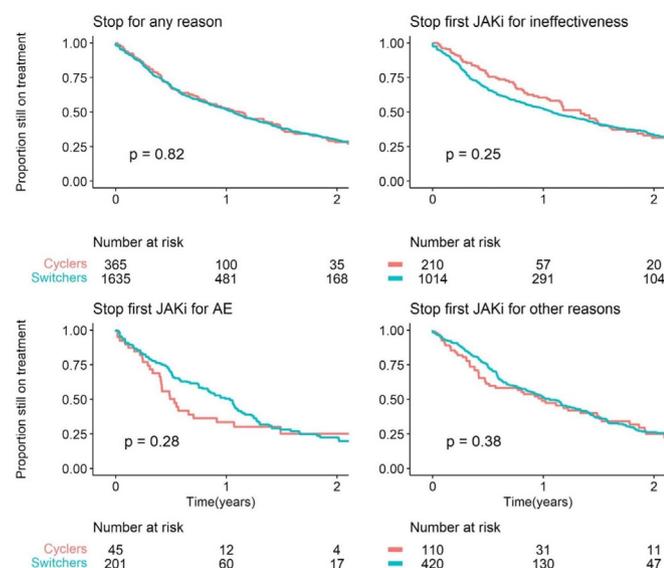


Figure 1 Kaplan-Meier curves of overall discontinuation and by reason for stopping the first JAKi. AE, adverse event; JAKi, Janus kinase inhibitor.

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.

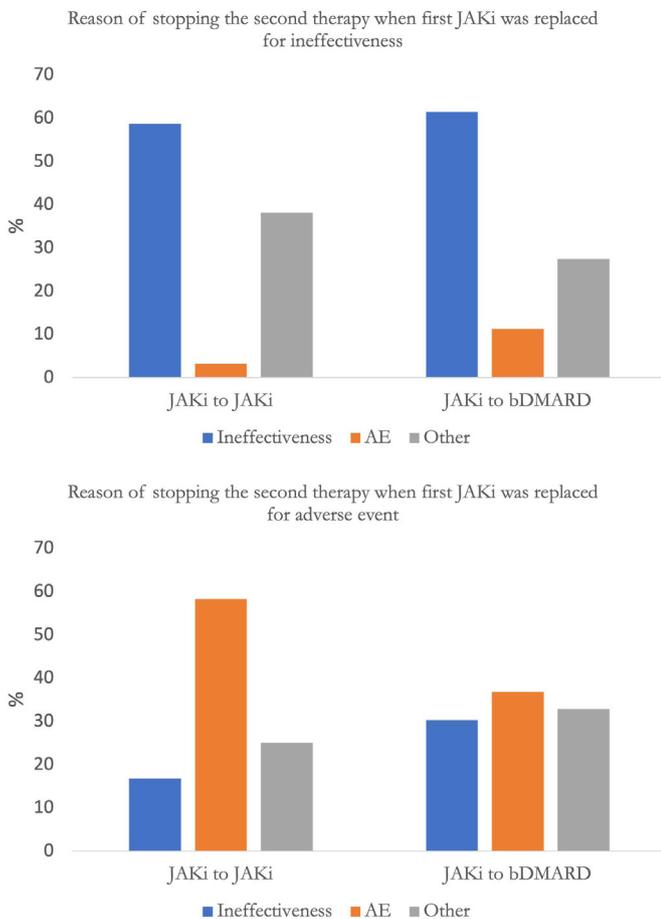


Figure 2 Proportion of patients discontinuing the second treatment for AE or ineffectiveness by reason for stopping the first JAKi. AE, adverse event; bDMARD, biologic disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor.

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.¹²⁶ 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

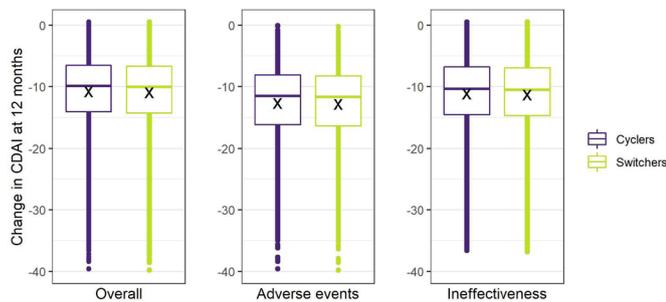


Figure 3 Adjusted change in disease activity overtime, overall and by reason for discontinuing the first JAKi. X indicates the mean. Analyses were adjusted for sex, age, disease duration, seropositivity, number of previously used bDMARDs/tsDMARDs, treatment duration of the first JAKi, concomitant csDMARD 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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Acknowledgements The authors thank all the health professionals and patients who participated in the registers.

Contributors All the authors have provided substantial contribution to the conception or design of the work, the acquisition of the data and the interpretation of data. DSC and CS-P performed the statistical analysis. MP-S, DSC, JG-R and CS-P made 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. MP-S and DSC accept full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The JAK-pot consortium is an investigator-initiated collaboration initially funded by an unrestricted research grant by Pfizer and later also by AbbVie and Galapagos. These companies had no influence on the research questions, results and conclusions. The sponsor did not participate in the collection or analysis of data and did not have access to the data.

Competing interests MP-S reports personal fees from Janssen, Merck Sharp & Dohme, Novartis and Sanofi Genzyme, outside the submitted work. CS-P has nothing to disclose. JG-R has been a consultant on advisory boards of AbbVie, Bristol Myers Squibb, Hospira, Janssen, Merck Sharp & Dohme, Pfizer, Regeneron, Roche and Sanofi Genzyme, and has received research grants from Pfizer and Roche. KL reports personal fees from Viatrix, Pfizer, Celltrion and Gilead/Galapagos, outside the submitted work. DM has nothing to disclose. FI has received speaker and/or consultancy fees from AbbVie, Galapagos, Janssen, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche and UCB. KP has received fees for lectures and consultations from AbbVie, Pfizer, Merck Sharp & Dohme, UCB, Eli Lilly, SOBI, Roche, Sanofi Genzyme, Celltrion, Viatrix and Novartis. DCN reports speaker and consultancy fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer and UCB. NI reports grants from Roche and Pfizer, and personal fees from AbbVie, Roche, Pfizer, UCB, Novartis, Amgen, Eli Lilly and Merck Sharp & Dohme. CC has received clinical trial expenses from AbbVie, Ewopharma, Eli Lilly, Novartis and Pfizer, and speaker and consultancy fees from AbbVie, Boehringer Ingelheim, Ewopharma, Eli Lilly, Novartis, Pfizer, Sandoz and UCB. KLH has received speaker fees from AbbVie and grants from Pfizer and Bristol Myers Squibb and is also supported by the NIHR Manchester Biomedical Research Centre. DC has received consultant and speaker fees from AbbVie, Amgen, Celgene, Eli Lilly, Fresenius Kabi, Pfizer, Novartis, Sandoz and Tevapharm. AS has received speaker/honoraria from AbbVie, Celltrion, Merck Sharp & Dohme, Roche, Bristol Myers Squibb and Pfizer. BFL has received clinical trial expenses from TRB and Roche, consultancy fees from AbbVie, Amgen, Roche, Merck Sharp & Dohme, Pfizer, Celgene, Grünenthal, Kwizda, Eli Lilly, Novartis and Sandoz, and speaker fees from AbbVie, Roche, Merck Sharp & Dohme, Pfizer, Actiopharma, Boehringer Ingelheim, Kwizda, Celgene, Sandoz, Grünenthal and Eli Lilly. ZR reports speaker and consultancy fees from AbbVie, Amgen, Biogen, Pfizer, Merck Sharp & Dohme, Roche, Novartis, Sanofi Genzyme, Medis, Eli Lilly and Sandoz. AR reports personal fees from Amgen, Pfizer and AstraZeneca, outside the submitted work. EKK reports no competing interests. TKK has received fees for speaking and/or consulting from AbbVie, Amgen, Celltrion, Egis, Eva Pharma, Ewopharma, Gilead, Hikma, Janssen, Mylan, Novartis, Oktal, Pfizer, Sandoz and UCB, and received research funding to Diakonhjemmet Hospital from AbbVie, Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer and UCB. OE has received clinical trial expenses from AbbVie, Pfizer, Novartis, Eli Lilly and Janssen, and speaker fees from AbbVie, Pfizer, Roche, Janssen, Eli Lilly and Novartis. GL has received consultant fees from AbbVie, BIOCAD, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer and R-PHARM. SAB received an ASPIRE grant from Pfizer. AF has received fees for speaking and/or consulting from AbbVie, AstraZeneca, Bristol Myers Squibb, Galapagos, Mylan, Novartis, Pfizer, Sandoz and UCB, and received research funding to Geneva University Hospital from AbbVie, Bristol Myers Squibb, Pfizer and Galapagos. DSC has nothing to disclose.

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, Bristol Myers Squibb, Celltrion, Galapagos, Janssen, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, Samsung, Schering-Plough and UCB). The Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) database is sponsored by public and industrial support (<http://scqm.ch/en/sponsors/>). Clinical work in Czech Republic was partially supported by the project from the Ministry of Health for conceptual development of research organization (MZ00023728023728) (Institute of Rheumatology). 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, Novartis, MSD, Roche, UCB and BMS. The British Society for Rheumatology Biologics Register in 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 HC, Eli Lilly, Pfizer, Samsung Bioepis, Sanofi and Sandoz, and in the past Hospira, MSD, Roche, 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. The BSRBR-RA would like to gratefully acknowledge the support of the National Institute for Health Research through the Local Clinical Research Networks in England (and equivalent organisations in the devolved nations) at participating centres and the BSRBR-RA Control Centre Consortium. Rhumadata is supported by equal unrestricted grants from AbbVie, Amgen, Celgene, Eli Lilly, Fresenius Kabi, Pfizer, Novartis, Sandoz and Tevapharm. The RABBIT register is currently supported by an unconditional grant with equal parts from AbbVie, Amgen, BMS, Celltrion, Fresenius Kabi, Galapagos, Hexal, Lilly, MSD, Viatrix, Pfizer, Roche, Samsung Bioepis, Sanofi-Aventis and UCB. biorx.si has received equal grants from AbbVie, Amgen, Biogen, Pfizer, Merck Sharp & Dohme, Roche, Novartis, Mylan, Sanofi Genzyme, Medis, Eli Lilly, Sandoz and Medis. Reuma.pt has received funding from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis and Pfizer. NOR-DMARD has been supported with research funding to Diakonhjemmet Hospital from AbbVie, Amgen, BMS, MSD, Novartis, Pfizer and UCB.

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 required.

Ethics approval When required according to local legislation, local ethics committees approved the collection of data in each register. 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.

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Supplementary Methods

Variables in the imputation model

The imputation model included the main exposure (treatments), the outcome and all covariates used in the adjusted cox model (gender, age, disease duration, seropositivity, number of previously used bDMARDs, first JAKi, stop reason of first JAKi, duration of first JAKi, tobacco use, comorbidities, concomitant glucocorticoids, concomitant csDMARDs treatment, HAQ and CDAI).

Comorbidity

We included as a comorbidity: cardiovascular problem, interstitial lung disease, chronic infection, malignancy, metabolic disorder or neuropsychiatric disorder.

Supplementary table 1. Number of patients contributed by each registry

	Total n (%)	JAKi to JAKi n (%)	JAKi to bDMARD n (%)	Date of first entry	Date of last entry
Total	2000 (100)	365 (18.3)	1635 (81.7%)	15-08-2013	08-09-2021
Austria, BIOREG	74 (3.7)	8 (2.2)	66 (4.0)	15-06-2016	13-04-2021
Canada, RHUMADATA	79 (3.95)	9 (2.5)	70 (4.3)	09-09-2014	15-02-2021
Czech Republic, ATTRA	192 (9.6)	40 (11.0)	152 (9.3)	30-08-2017	13-05-2021
Finland, ROB-FIN	154 (7.7)	27 (7.4)	127 (7.8)	18-06-2017	18-09-2020
Germany, RABBIT	77 (3.85)	18 (4.9)	59 (3.6)	21-07-2017	23-12-2019
Italy, GISEA	207 (10.35)	46 (12.6)	161 (9.8)	14-12-2017	08-09-2021
Israel, I-RECORD	17 (0.85)	0 (0.0)	17 (1.0)	15-09-2014	17-03-2019
Netherlands, METEOR	1 (0.05)	0 (0.0)	1 (0.1)	25-10-2017	25-10-2017
Norway, NOR-DMARD	25 (1.25)	2 (0.5)	23 (1.4)	09-10-2017	24-01-2019
Portugal, REUMA.PT	26 (1.3)	2 (0.5)	24 (1.5)	23-07-2018	24-05-2021
Romania, RRBR	124 (6.2)	3 (0.8)	121 (7.4)	26-03-2018	13-04-2021
Russia, ARBITR	8 (0.4)	0 (0.0)	8 (0.5)	22-08-2014	15-02-2019
Slovenia, BIORX.SI	66 (3.3)	15 (4.1)	51 (3.1)	19-09-2017	29-03-2021
Spain, BIOBADASER	276 (13.8)	79 (21.6)	197 (12.0)	02-10-2017	10-05-2021
Switzerland, SCQM	419 (20.95)	90 (24.7)	329 (20.1)	15-08-2013	19-05-2021
Turkey, TURKBIO	138 (6.9)	0 (0.0)	138 (8.4)	15-07-2015	24-09-2020
UK, BSRBR	117 (5.85)	26 (7.1)	91 (5.6)	20-01-2017	18-08-2020

bDMARD, biologic disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor.