

# REAL-WORLD EVALUATION OF JANUS KINASE INHIBITORS IN RHEUMATOID ARTHRITIS: TREATMENT SURVIVAL AND RISK FACTORS FOR DISCONTINUATION

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## Background:

- Janus kinase inhibitors (JAKi) are a new type of medication for rheumatoid arthritis (RA), acting as targeted synthetic DMARDs (tsDMARD), blocking JAKs. Given their role as promising therapeutic agents, understanding their long-term efficacy and safety profile is essential. This study aims to explore the real-world outcomes of JAKi therapy by evaluating the factors influencing JAKi survival and safety.

## Objective:

- To assess the survival of JAKi in RA patients and to identify associated risk factors for treatment discontinuation.
- Secondary objectives included analyzing differences in causes of JAKi discontinuation, mainly inefficacy and adverse events during treatment.

## Methods:

- Data from an observational cohort of RA patients initiating JAKi treatment between 2018 and 2022, with at least a 1-year follow-up, were analyzed. Information, encompassing demographics, clinical details, and laboratory data, was sourced from the RA-Paz database. Disease activity was assessed using DAS28. Patients were classified into two groups according to whether they continued or discontinued treatment, with recorded reasons for discontinuation. Group differences were examined using survival analysis with Kaplan–Meier plots and Cox proportional hazard models.

## Results:

- Among 105 RA patients on JAKi, 43 (41%) discontinued treatment, mainly due to inefficacy (19%) and adverse events (12.4%) (table 1). Table 2 presents patient characteristics based on treatment discontinuation.

Table 1	Patients who discontinued treatment N=43	Inefficacy (n=20)
		Adverse events (N=13):
		-Infections (4 [herpes zoster, respiratory infection and folliculitis])
		-Gastrointestinal complications (2)
		-Headache and dizziness (2)
		-Aphthous ulcers (1)
		-Allergic skin reaction (1)
		-Reticular livedo (1)
		-Weight gain (1)
		-Hematological complications (1).
		High CVR (n=2)
		Loss of follow up (n=4)
		Others (n=4)

Variables	Persistence Treatment (n=62)	Inefficacy (n=20)	Adverse Event (n=13)
Sex (female) n (%)	54 (87.1)	17 (85.0)	12 (92.3)
-Current Age	58.6 (9.3)	51.5 (13.2)	59.0 (15.1)
-Age at diagnosis	41.6 (11.0)	36.9 (11.2)	41.6 (15.4)
-Age at JAKi initiation	58.6 (9.4)	51.4 (13.2)	53.6 (16.9)
Age ≥ 65 years n (%)	15 (24.2)	2 (10.0)	4 (30.8)
Comorbidities*	1 (0-2)	1 (0-2)	1 (0-2)
-Hypertension	19 (30.0)	2 (10.5)	4 (30.8)
-Diabetes Mellitus	11 (17.7)	3 (15.0)	0 (0.0)
-Dyslipidemia	31 (50.0)	9 (45.5)	6 (46.2)
-Heart failure	1 (1.6)	0 (0.0)	0 (0.0)
-Ischemic cardiopathy	3 (4.8)	1 (5.0)	0 (0.0)
-ETEV	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 CVRF	50 (80,6)	14 (70.0)	7 (53.8)
>2 CVRF	13 (20.9)	8 (40.0)	5 (38.5)
JAKi			
Tofacitinib	13 (21.0)	9 (45.0)	6 (46.2)
Baricitinib	24 (38.7)	9 (45.0)	5 (38.5)
Upadacitinib	21 (33.9)	1 (5.0)	1 (7.7)
Filgotinib	4 (6.5)	1(5.0)	1 (7.7)
Time under JAKi treatment (months)*	26.6 (19.7-51.0)	11.5 (7-21.5)	6 (1-14)
Number of previous bDMARD			
-naïve	13 (21.0)	2 (10.0)	4 (30.8)
-≥ 2bDMARD (D2Tpatients)	25 (40.3)	1 (5.0)	2 (15.4)
Monotherapy	16 (25.8)	4 (20.0)	4 (30.8)
Remission at 6 months of iJAK	26 (41.9)	4 (20.0)	4 (30.8)
LDA at 6 months of iJAK	40 (64.5)	8 (40.0)	6 (46.2)
DAS28 at JAKi initiation	4.2 (1.2)	4.4 (1.4)	4.5 (1.1)
HAQ at JAKi initiation	6.5 (2.0-12.0)	9.5 (5.0-14-0)	9.0 (2.5-14.5)
DAS28 6 months	2.9 (1.1)	3.8 (1.3)	2.9 (1.5)
HAQ 6 months	5.5 (0.3-13)	9.5 (6.5-12.0)	8.5 (3.5-9.7)
DeltaDAS28	1.5 (0.9)	1.1 (0.6)	1.6 (0.8)

Quantitative variables are presented as mean (standard deviation), except for those marked with (\*) which are shown as median (range).

- Regarding differences between those who discontinued treatment due to inefficacy or AEs, JAKi survival was shorter in patients with AEs (7.5 months) than in patients with inefficacy (12.0 months) (p<0.01), with no significant differences in baseline characteristics between these groups.
- No significant differences were observed between discontinuation due to AEs and persistence on treatment, except for a higher frequency of cardiovascular risk factors (53.8%, p=0.03) in the former group.
- Comparing patients discontinuing treatment due to inefficacy with persistently treated patients revealed significant differences in current age (51.5 ± 13.2 vs. 58.6 ± 9.3 years, p=0.02), DAS28 at 6 months (3.8 ± 1.3 vs. 2.9 ± 1.1, p<0.01), and age at the start of JAKi therapy (51.4 ± 13.2 vs. 58.6 ± 9.4 years, p=0.02). The discontinuation group showed a younger current age, younger age at JAKi initiation, and a higher DAS28 at 6 months.
- Survival analysis found no differences between naïve and non-naïve patients (p=0.26) or between monotherapy and combined therapy (p=0.31). However, among patients who had tried two or more biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), the survival rate with Janus kinase inhibitors (JAKi) was notably higher (p=0.02)
- Factors associated with treatment survival were identified through Cox analysis. Achieving low disease activity/remission within the first 6 months increased treatment survival odds threefold [HR=2.98, 95%CI (1.17-7.53)], while using JAKi after failing ≥2 bDMARDs increased odds by 13 times [HR=13.04; 95%CI (1.74-99.88)].

## Conclusions:

In our cohort, the discontinuation rate JAKi was 41%, primarily associated with inefficacy. Achieving a better DAS28 at 6 months of starting a JAKi is an independent risk factor for drug persistence over time. Furthermore, these drugs used as the ≥3rd line of treatment exhibit enhanced survival rates.

