

RETENTION RATE OF UPADACITINIB THERAPY IN RHEUMATOID ARTHRITIS: RESULTS OF A LARGE ITALIAN MULTICENTER REAL-WORLD STUDY

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Abstract. Background. Upadacitinib (UPA) is an oral Janus kinase inhibitor (JAKi) recently approved for the rheumatoid arthritis (RA) treatment. Although registrational studies have demonstrated the efficacy of UPA in RA, data on the long-term retention rate of this drug are still lacking. **Objective:** The objective of the study was to evaluate the real-world retention rate of UPA in patients with RA, analyze possible reasons for treatment discontinuation, and attempt to identify independent factors possibly associated with persistence of UPA treatment. **Methods:** We conducted a multicenter retrospective observational study of patients with RA referred to tertiary rheumatology hospitals in Italy. One-hundred-eleven consecutive patients who received UPA in different lines of treatment were enrolled. Clinical history, previous treatments, and RA disease activity at baseline were recorded. The retention rate of UPA was assessed by Kaplan-Meier curve study. Cox proportional regression analysis was also performed to study the effect of independent factors on UPA therapy retention rate including age, sex, smoking habit, presence of anti-citrullinated protein antibody (ACPA)/rheumatoid factor (RF), disease duration, disease activity, line of treatment and concomitant treatments. **Results:** Analysis of demographic data revealed an M:F ratio of 28:83, a median age of 58 years with an interquartile Range (IQR) of 50-65 years, and a median disease duration 78 months (IQR: 40-167). The median observation period was 6.0 months (IQR 3.2-10.0). Most patients were on monotherapy or receiving concomitant steroids (55.0% and 58.6%, respectively). The UPA retention rate at 6 and 12 months was 90.4% and 74.7%, respectively. Reasons for treatment discontinuation included lack of efficacy (8/19), lost efficacy

(6/19), infections (3/19) and cancer onset (2/19). Other factors affecting the rate of UPA maintenance were duration of illness and RA seropositivity. **Conclusion:** The high retention rate of UPA indirectly suggests the good efficacy and acceptable safety profile of this drug in RA therapy. From our study data, we conclude that UPA could be an appropriate choice in most patients with RA, even after failure of previous lines of treatment. We also found that the drug had a higher retention rate in patients with seropositive RA than in their seronegative counterparts.

Key words: retention rate; upadacitinib, rheumatoid arthritis, JAK inhibitors

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune and systemic inflammatory disease that affects the joints causing pain, swelling and progressive damage [1]. Without any therapies RA can cause significant deformity with loss of functionality, disability and worsening of the overall quality of life [1]. Conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), and in particular methotrexate (MTX), have long been the pillars of rheumatoid arthritis treatment [2]. In the last 20 years, biologic agents have expanded the clinical armamentarium but unfortunately, only 40–50% of patients achieve disease remission and therefore the need for alternative treatments became crucial [3]. Janus activated kinases (JAKs) are a family of intra-cellular tyrosine kinases that mediates the downstream signals of multiple cytokines and growth factors involved in the pathogenesis of several inflammatory conditions including RA [4]. The JAK family is composed of 4 members: JAK1, JAK2, JAK3, and receptor tyrosine kinase 2 [4]. Currently, European Medication Agency (EMA) and Food and Drugs administration (FDA) have approved 4 JAK inhibitors (JAKis) for the treatment of RA: tofacitinib (TOFA), a selective inhibitor of JAK1 and JAK3, baricitinib (BARI) a selective inhibitor of JAK1 and JAK2, upadacitinib (UPA) and filgotinib (FILGO) that preferentially target the activity of JAK1 over the other molecules [4, 5]. UPA is an oral JAK inhibitor that has been evaluated in a global phase 3 program that included six randomized trials in patients with moderately to severely active RA [6–12]. Five trials [7–11] were performed in patients with an inadequate response to MTX or other DMARDs. In four trials [7–10], UPA was evaluated in combination with MTX/csDMARD background therapy. Another study evaluated UPA as monotherapy in patients with inadequate response to MTX [11]. The most recent published study included MTX-naïve patients treated with UPA as a standalone regimen [12]. In a recent dedicated safety randomized study involving patients with RA, it was observed that those treated with tofacitinib had higher occurrence

of major adverse cardiovascular events (MACEs) and an increased incidence of cancer compared to patients treated with Tumor Necrosis Factor alpha inhibitors (TNFis) [13]. Although registries did not completely confirm the above results [14, 15], these data prompted the FDA and EMA to issue a warning regarding the use of tofacitinib in RA, further extended to all JAKis assuming a similar effect among these classes of molecules. To date, UPA efficacy and safety data are derived exclusively from registry trials, and information from daily practice are still limited [16–18]. The primary aim of our retrospective study was to evaluate the retention rate as an index of drug effectiveness and safety of UPA in a real-world population affected by RA. Secondary objectives were to analyze the reasons for discontinuation of UPA treatment and to identify possible predictors of treatment persistence.

METHODS

This retrospective study was designed to evaluate the retention rate of UPA in RA patients and it is a project of the BIRRA study (Biologics Retention Rate Assessment) [19]. The study was conducted according to the Declaration of Helsinki, and it was approved by the local Ethics Committee (the main is the Comitato Etico dell'Area Vasta Emilia Nord, protocol code 34,713, approved on 28 August 2019) [19]. Patients with confirmed diagnosis of RA according with EULAR 2010 criteria who received UPA were enrolled from 23 Italian rheumatological referral centers. Clinical history, treatment history and RA disease activity at baseline were recorded. The following baseline data were also recorded for each included patient: general characteristics (age, sex, body mass index – BMI), smoking habit, disease duration, positivity for rheumatoid factor – RF, anti-citrullinated protein antibody – ACPA positivity, swollen and tender joint count – SJC and TJC, ESR, CRP, patient Visual Analogue Scale, disease activity, line of treatment, concomitant csDMARDs use, concomitant steroids use, steroids dose (PDN-Eq), prior bDMARDs use, prior tsDMARDs use, and con-

comitant relevant disease. Disease activity was assessed in all patients by calculating both the DAS28-ESR and DAS28-CRP [20, 21]. The relevant comorbidities considered were diabetes, dyslipidemia, history of major adverse cardiovascular events (MACE), cancer, and arterial hypertension. The patient cohort was followed for 12 months, from December 2022 to December 2023.

Statistical Analysis

All continuous variables were reported as median and interquartile range (IQR). Categorical data were expressed as number and percentage. Retention rate at 6 and 12 months was estimated by Kaplan-Meier curve study. Cox regression analysis was used to identify factors associated with UPA retention rate; these included age, sex, smoke habit, BMI, ACPA/RF presence, disease duration, DAS28-ESR, line of treatment, concomitant csDMARD treatment, concomitant steroid treatment and relevant comorbidities. For each comorbidity, we calculated the hazard ratio (HR) and the corresponding 95% confidence interval (CI). A p-value ≤ 0.05 was considered statistically significant. All statistical analyses were two-tailed and were performed using the online statistical software Jamovi (version 2.3, www.jamovi.org).

RESULTS

This study included a total of 111 patients. Table 1 shows their demographic and clinical characteristics at baseline. Most patients were seropositive for RF and/or ACPA (80/111, 72%). The median observation period was 6.0 months (IQR 3.2-10.0). The observation period lasted 8-12 months per patient. Among the study participants, 88/111 (79%) had received at least one previous biologic DMARD (bDMARD), and nearly half of the patients (55/111; 49.6%) had one or more significant comorbidities. UPA retention rates at 6 and 12 months were 90.4% and 74.7%, respectively (Fig. 1). Reasons for treatment discontinuation were lack of efficacy (8/19), loss of efficacy (6/19), infection (3/19), and tumor occurrence (2/19). No thromboembolic events occurred during the observation period. No episodes of herpes zoster were observed. According to Cox regression analysis, the presence of RF and/or ACPA in serum (HR 0.06 CI 0.01-0.50; $p = 0.009$) and disease duration (HR 1.01 CI 1.00-1.02; $p = 0.022$) had a statistically significant influence on the risk of treatment discontinuation (Fig. 2).

Table 1. Baseline characteristics. (*) Data missing in 14 patients (**) Data missing in 29 patients

Characteristics		Value
N		111
M:F		28:83
Age, median [IQR] yrs		58 [50-65]
Smokers, n (%) (*)	Yes	16 (16.5)
	Former	17 (17.5)
	No	64 (66.0)
Body Mass Index, median [IQR] kg/m ² (**)		24.7 [22.4-27.7]
Disease Duration, median [IQR], months		78 [40-167]
RF positivity, n (%)		72 (64.9)
ACPA positivity, n (%)		68 (61.3)
SJC, median [IQR]		4 [2-8]
TJC, median [IQR]		8 [5-11]
ESR, median [IQR], mm/h		32 [20-53]
CRP, median [IQR], mg/dl		1.2 [0.5-3.1]
VAS Patient (0-100), median [IQR]		70 [50-80]
DAS28 (ESR), median [IQR]		5.5 [4.9-5.9]
DAS28 (CRP), median [IQR]		5.0 [4.4-5.5]
Line of treatment, [IQR]		3 [2-4]
Concomitant csDMARDs use, n (%)	MTX	40 (36.0)
	LFN	3 (2.7)
	SSZ	1 (0.9)
	HQC	5 (4.5)
	CyA	1 (0.9)
Concomitant steroids use, n (%)		65 (58.6)
Steroids dose (PDN-Eq), median, mg/die		5 [5-6]
Prior bDMARDs use, n (%)	TNFi	80 (72.0)
	IL6i	23 (20.7)
	IL1i	3 (2.7)
	CD20i	6 (5.4)
	CD80i	23 (21.6)
Prior tsDMARDs use, n (%)	Baricitinib	9 (8.1)
	Tofacitinib	2 (1.8)
Concomitant relevant disease, n (%)	Diabetes	12 (10.8)
	Hypercholesterolemia	23 (20.7)
	MACE	5 (4.5)
	Arterial Hypertension	34 (30.6)
	Cancer	5 (4.5)

Acronyms: RF, Rheumatoid Factor; ACPA, Anti-Citrullinated Proteins Antibodies; SJC, swollen joints count; TJC, tender joints count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein, VAS, Visual Analogic Scale; DAS28, Disease Activity Score 28; csDMARD, conventional synthetic modified antirheumatic drugs; PDN-Eq, prednisone equivalent, bDMARD, biological modified antirheumatic drugs; tsDMARD, target synthetic modified antirheumatic drugs. TNFi, TNF inhibitors; IL-6i, IL-6 inhibitors; IL-1i, IL-1 inhibitors, CD20i, CD20 inhibitors, CD80i, CD80inhibitors; MACE, Major Adverse Cardiovascular Events.

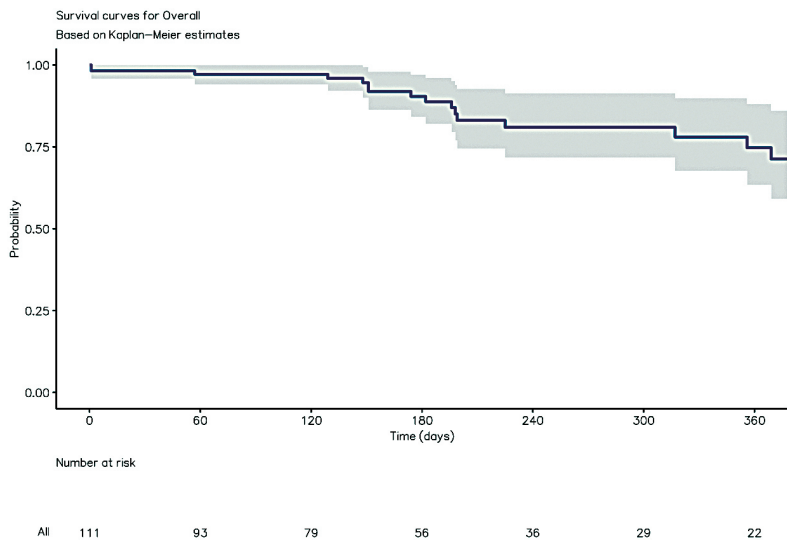


Fig. 1. Upadacitinib retention rate

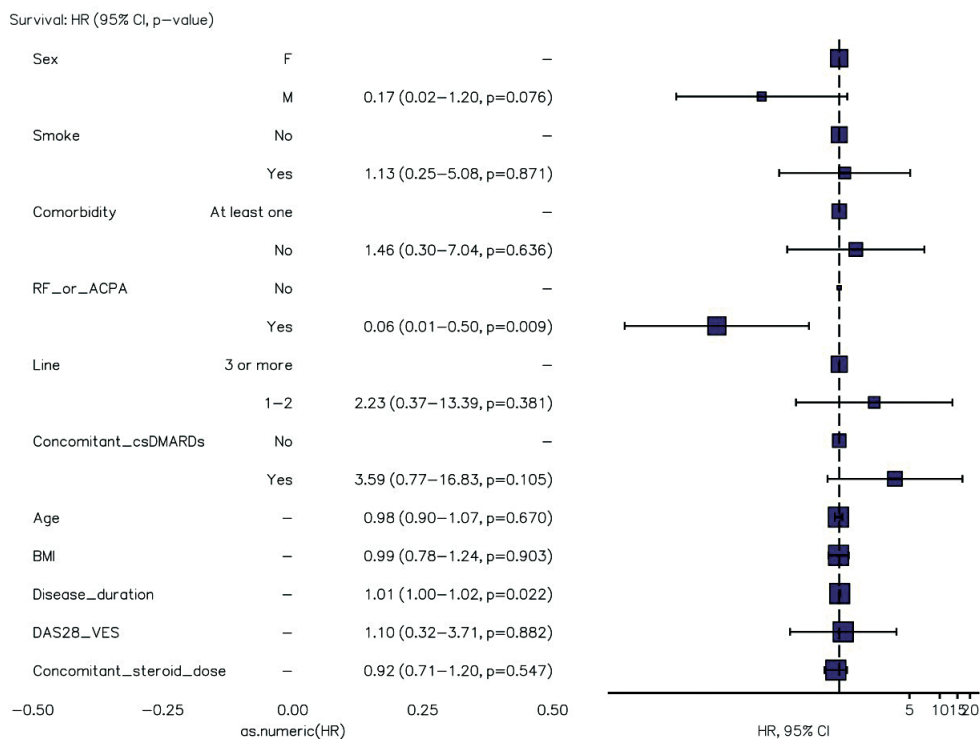


Fig. 2. Forest plot of the risk factors for UPA discontinuation

Discussion

For the first time, we presented data on the real-world retention rate and safety of UPA in an Italian population of patients with RA. In this study, we reported that UPA retention rate at 6, 12 months was 90.4% and 74.7%, respectively. UPA, an oral JAKi selectively targeting JAK1, has been evaluated in the SELECT program which consist in six randomized trials in patients with moderately to severely active RA [7-11]; these patient cohorts are

different from the Italian population as the majority of patients were recruited from America and Eastern Europe, which typically have distinct lifestyles and therapeutic approaches compared to Italians. Furthermore, in registry studies, the average methotrexate dosage exceeded 17 mg, and the steroid dosage was also above 6 mg. Additionally, a greater proportion of patients tested positive for RF or ACPA, were younger, and both the duration of RA and disease activity were higher in comparison to our patient population [7-12]. Considering real

world data of UPA, an ongoing study from Australia reported at 12-month persistence rates of 61% for all JAKis (BARI, TOFA, UPA), 62% for tocilizumab, 52% for all TNFis, and 51% for abatacept. The persistence of UPA was 78% and it was superior to BARI (64%), TOFA (54%) and in general JAKis persistence rates were superior to TNFis [22]. Another Italian study reported a retention rate of 95% at 6 months with UPA and 89% at the last follow up (median 7 months, IQR 3-12) in 93 RA patients. Compared with our study, the included patients were younger, with overall less severe disease activity with respect to our population and 88% were on previous treatment with MTX and 52% were treatment naïve to biologic drugs. Conversely, most of the patients enrolled in our study had experienced failure with multiple biologic DMARDs (bDMARDs). It is important to underline that this data provide promising results regarding the retention rate of UPA even in this subgroup of patients [16].

Bergman et al. in a retrospective analysis using data from the Merative and MarketScan Research Databases reported persistence rates of 54.6% for patients on UPA treatment, compared with 49.6%, 48.0%, and 40.1% for adalimumab, TOFA, and BARI at 12 months, respectively [23]. Both studies showed that persistence rates were higher for patients treated with UPA than for those treated with another JAKi or adalimumab. Recently, a study from Japan reported a retention rate at 6 months of 83.0% with UPA, with a 5.7% discontinuation rate due to toxic adverse events and/or lack of efficacy [24]. In a separate study conducted in Japan, the authors examined drug retention rates in two age groups: very elderly patients (≥ 75 years) and elderly patients ($65 \leq \text{years} < 75$). The study reported similar results for both age groups, suggesting that age did not significantly influence the outcomes; moreover, drug retention rate were higher in patients who received reduced or tapered doses of JAKis than in patients being treated with standard dosage [25]. These results suggest that treatment with UPA is effective and that there is less risk of discontinuation, also when compared with TNFis. Another study showed that the probability to maintain TOFA after 12 months was 86.5%; it is worth noting that the patient populations in this study had a longer duration of the disease, with a higher proportion receiving MTX (76.5%) compared to the UPA study (36%), the median line of treatment was two for TOFA instead UPA was prescribed after 3 lines of treatment. This discrepancy suggests that TOFA may have been

prescribed earlier than UPA, probably because it was placed on the market first and did not undergo regulatory changes or oral surveillance studies from the outset [19].

The effects of the ACPA serologic status on the treatment efficacy have been reported in RA [26]. A meta-analysis showed a difference in treatment response between ACPA-positive and ACPA-negative patients treated with abatacept. ACPA-positive patients were 13% more likely to respond to treatment compared to the ACPA-negative patient [27]. Seropositivity for RF or anti-CCP, compared to seronegativity, may be associated with an increased likelihood of certain events, such as cigarette smoking. In our study, UPA showed to have a better retention rate in ACPA-positive patients than in ACPA-negative patients, suggesting that this might be due at least in part to better drug effectiveness in this patient population. These data must be interpreted with caution as we have not considered the methods of laboratory detection and future works are needed to confirm our results. With regard to disease duration, it is known that a longer disease duration may impact outcomes and future therapies [28-30]. In fact, among the patients receiving treatment, there was a response rate of 53% for those with a disease duration under 1 year, 38% for 5-10 years' disease duration, and 35% for patients with a disease duration exceeding 10 years [27], and in addition responsiveness in HAQ scores was inversely associated with mean disease duration in RA [29]. It has been shown previously that rapid introduction of csDMARDs or TNFis in patients with RA results in better disease control than delayed initiation of therapy [28]. These analyses confirm the benefits of early therapeutic intervention.

Although MTX is the gold standard of treatment according to the EULAR guidelines [31], a significant percentage of patients had to be treated with UPA in combination with steroids. This was because most of them were intolerant to MTX and other csDMARDs or have expressed their unwillingness to take these drugs. The combination with corticosteroids was chosen in these patients because UPA was not sufficient in monotherapy to achieve a remission state or low disease activity, as suggested by the target-to-treat principle indicated by the ACR/EULAR international guidelines [31].

One of the main issues in RA therapy is drug safety. All molecules used for the treatment of RA are designed to reduce inflammation. However, they may also affect the body's immune re-

sponse against pathogens, potentially increasing the risk of infections in these patients. The ORAL post marketing surveillance study revealed safety concerns about JAKis drugs for the possible development of infectious, cardiovascular, and neoplastic diseases. Although it has been criticized for its flawed design [32] the results from this study led to the issuance of black box warnings by the U.S. Food and Drug Administration (FDA) regarding the prescription of these drugs [33]. Following FDA concerns, European Medicines Agency (EMA) issued the recommendations for European Union (EU) countries, including Italy. The committee recommended that these drugs be used only if no suitable therapeutic alternatives are available in subjects aged 65 years and older, subjects at increased risk of major cardiovascular problems, subjects who smoke or have done so for a long time in the past, and subjects at increased risk of cancer. The committee also recommended that JAK inhibitors be used with caution in patients with risk factors for blood clots in the lungs and deep veins other than those listed above (<https://www.ema.europa.eu>). However, it should be emphasized that there is no absolute contraindication to the use of JAKs in the at-risk population, although careful clinical surveillance is necessary in this patient population in the absence of safer alternative treatment options. In our study, patients treated with JAKis with associated conditions, including diabetes, hypertension, or other risk factors for MACE or cancer, had no treatment alternatives and had particularly severe forms of RA, with an estimated favorable ratio between the benefits of treatment and its potential risks. A recent study conducted a pooled analysis of safety in a large number of patients treated with UPA [34]. 4298 patients received UPA 15 mg (RA n = 3209, PsA n = 907 and AS n = 182) and 2125 patients received UPA 30 mg (RA n = 1204 and PsA n = 921). In patients with RA and PsA, the rates of MACE (0.3-0.6 E/100 PY) and VTE (0.2-0.4 E/100 PY) were infrequent and similar between the two different doses of UPA. No MACE and only one VTE event occurred in patients with AS. These data are therefore reassuring regarding the safety of JAKis. Although we did not experience any serious adverse events even in patients with comorbidities, caution in prescribing UPA in these patients is mandatory, and a cardiovascular risk screening for each patient should be performed at the beginning

of prescribing. In any case, failure to achieve low disease activity per se exposes the patient to the risk of cardiovascular disease.

In addition, we did not observe any cases of herpes zoster severe enough to lead to discontinuation of treatment during the follow-up period. A recent meta-analysis suggests that there is a higher risk of herpes zoster in patients with RA who are treated with baricitinib 4 mg QD, peficitinib 100 mg QD, and upadacitinib 30 mg QD compared to placebo. [30].

Lastly, we observed only 2 cases of neoplasia. In a recent metanalysis, the risk of malignancy did not differ significantly between JAKis and placebo or between JAKis and methotrexate with respect to TNFis. However, JAKis associated with a higher incidence of malignancy. Further analysis, after exclusion of patients on ORAL surveillance, suggested a greater percentage of tumors in patients with JAKis compared with TNFis, although this difference was not statistically significant [35]. Therefore, at the moment, the association between malignancy and JAKis is still far from being fully elucidated.

This study includes several limitations. First, the study is observational, and it has been conducted only in referral centers in Italy, so it may not be extendable to other geographical areas. Second, the relatively short observation period in a long-standing chronic disease such as RA may lead to underestimation of the incidence of adverse events or patient dropout. Third, the proportion of biologic drug treatment-naïve patients with early-stage disease is relatively small: most patients had previously failed at least one bDMARD, and several patients had failed three biological lines, which may influence drug retention rate. Fourth, it should be noted that regulatory restrictions in our country limit the use of JAK in bio-naïve patients and these limitations may introduce a bias, influencing the composition of our patient cohort.

Finally, we had no data regarding steroid reduction, or metabolic effects such as increased triglycerides or possible elevation of creatine kinase.

In conclusion, to the best of our knowledge this is the first real-world study with a relatively extended follow-up period to document the retention rate of UPA, even in patients who have failed multiple treatment lines, and to identify potential predictors of the retention rate for UPA.

Our findings on the retention rate of UPA are consistent with those reported in previous studies and appear to support the idea that this drug could be a viable and safe treatment option in patients with

rheumatoid arthritis, particularly those with seropositive rheumatoid arthritis. Serious adverse events were an uncommon reason of discontinuation. Real-world data published so far have not indicated any particular or previously unrecognized safety concerns, therefore it could be plausible in a future scenario, that JAKis could replace methotrexate, currently the drug of choice for the initial treatment of RA. Further studies with a longer follow up period will better clarify the safety aspects of individual JAKis and more accurately identify individuals with RA at mayor risk for adverse events.

References

1. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. *JAMA* 2018, 320(13):1360-1372.
2. Favalli EG, Biggiongero M, Meroni PL. Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an "anchor" drug? *Autoimmun Rev* 2014, 13(11):1102-1108.
3. Patel JP, Konanur Srinivasa NK, Gande et al. The Role of Biologics in Rheumatoid Arthritis: A Narrative Review. *Cureus* 2023, 15(1):e33293.
4. Schwartz DM, Kanno Y, Villarino A et al. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov* 2017, 17(1):78.
5. Traves PG, Murray B, Campigotto F et al. JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signalling by filgotinib, upadacitinib, tofacitinib and baricitinib. *Ann Rheum Dis* 2021, 80(7):865-875.
6. Sanmarti R, Corominas H. Upadacitinib for Patients with Rheumatoid Arthritis: A Comprehensive Review. *J Clin Med* 2023, 12(5).
7. Burmester GR, Kremer JM, Van den Bosch F et al Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018, 391(10139):2503-2512.
8. Genovese MC, Fleischmann R, Combe B et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* 2018, 391(10139):2513-2524.
9. Fleischmann R, Pangan AL, Song IH et al. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. *Arthritis Rheumatol* 2019, 71(11):1788-1800.
10. Rubbert-Roth A, Enejosa J, Pangan AL et al. Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis. *N Engl J Med* 2020, 383(16):1511-1521.
11. Smolen JS, Pangan AL, Emery P et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet* 2019, 393(10188):2303-2311.
12. van Vollenhoven R, Takeuchi T, Pangan AL et al. Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-Naive Patients With Moderately-to-Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Multicenter, Multi-Country, Randomized, Double-Blind, Active Comparator-Controlled Trial. *Arthritis Rheumatol* 2020, 72(10):1607-1620.
13. Ytterberg SR, Bhatt DL, Connell CA. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. Reply. *N Engl J Med* 2022, 386(18):1768.
14. Khosrow-Khavar F, Desai RJ, Lee H, Lee SB, Kim SC. Tofacitinib and Risk of Malignancy: Results From the Safety of Tofacitinib in Routine Care Patients With Rheumatoid Arthritis (STAR-RA) Study. *Arthritis Rheumatol* 2022, 74(10):1648-1659.
15. Meissner Y, Schafer M, Albrecht K et al. Risk of major adverse cardiovascular events in patients with rheumatoid arthritis treated with conventional synthetic, biologic and targeted synthetic disease-modifying antirheumatic drugs: observational data from the German RABBIT register. *RMD Open* 2023, 9(4).
16. Lanzillotta M, Boffini N, Barone et al. Safety of Janus Kinase Inhibitors: A Real-World Multicenter Retrospective Cohort Study. *J Rheumatol* 2023.
17. Amirdzhanova VN, Karateev AE, Pogozheva EY et al. Are the Goals of Therapy Achievable in Patients with Rheumatoid Arthritis Receiving Upadacitinib in Real Clinical Practice? *Dokl Biochem Biophys* 2023, 511(1):180-186.
18. Kivitz A, Wells AF, Vargas JI et al. Long-Term Efficacy and Safety of Upadacitinib in Patients with Rheumatoid Arthritis: Final Results from the BALANCE-EXTEND Open-Label Extension Study. *Rheumatol Ther* 2023, 10(4):901-915.
19. Paroli M, Becciolini A, Bravi E et al. Long-Term Retention Rate of Tofacitinib in Rheumatoid Arthritis: An Italian Multicenter Retrospective Cohort Study. *Medicina (Kaunas)* 2023, 59(8).
20. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010, 69(9):1580-1588.
21. Aletaha D, Landewe R, Karonitsch T et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Arthritis Rheum* 2008, 59(10):1371-1377.
22. Scheepers L, Yang Y, Chen YL, Jones G. Persistence of Janus-kinase (JAK) inhibitors in rheumatoid arthritis: Australia wide study. *Semin Arthritis Rheum* 2024, 64:152314.
23. Bergman M, Chen N, Thielen R, Zueger P. One-Year Medication Adherence and Persistence in Rheumatoid Arthritis in Clinical Practice: A Retrospective Analysis of Upadacitinib, Adalimumab, Baricitinib, and Tofacitinib. *Adv Ther* 2023, 40(10):4493-4503.
24. Hayashi S, Tachibana S, Maeda T et al. Real-world comparative study of the efficacy of Janus kinase inhibitors in patients with rheumatoid arthritis: the ANSWER cohort study. *Rheumatology (Oxford)* 2023.
25. Temmoku J, Miyata M, Suzuki E et al. Drug Retention Rates of Janus Kinase Inhibitors in Rheumatoid Arthritis Patients with Therapy-Induced Lymphopenia. *J Clin Med* 2023, 12(14).
26. Alemão E, Postema R, Elbez Y et al. Presence of anti-cyclic citrullinated peptide antibodies is associated with better

- treatment response to abatacept but not to TNF inhibitors in patients with rheumatoid arthritis: a meta-analysis. *Clin Exp Rheumatol* 2020, 38(3):455-466.
27. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum* 2000, 43(1):22-29.
 28. Aletaha D, Maa JF, Chen S et al. Effect of disease duration and prior disease-modifying antirheumatic drug use on treatment outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2019, 78(12):1609-1615.
 29. Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. *Ann Rheum Dis* 2008, 67(2):238-243.
 30. Xu Q, He L, Yin Y. Risk of herpes zoster associated with JAK inhibitors in immune-mediated inflammatory diseases: a systematic review and network meta-analysis. *Front Pharmacol* 2023, 14:1241954.
 31. Smolen JS, Landewe RBM, Bergstra SA et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023, 82(1):3-18.
 32. Winthrop KL, Cohen SB. Oral surveillance and JAK inhibitor safety: the theory of relativity. *Nat Rev Rheumatol* 2022, 18(5):301-304.
 33. Tokareva K, Reid P, Yang V et al. JAK inhibitors and black box warnings: what is the future for JAK inhibitors? *Expert Rev Clin Immunol* 2023, 19(11):1385-1397.
 34. Charles-Schoeman C, Choy E, McInnes IB et al. MACE and VTE across upadacitinib clinical trial programmes in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. *RMD Open* 2023, 9(4).
 35. Russell MD, Stovin C, Alvey E et al. JAK inhibitors and the risk of malignancy: a meta-analysis across disease indications. *Ann Rheum Dis* 2023, 82(8):1059-1067.

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