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Upadacitinib in Rheumatoid Arthritis After Prior TNF Inhibitor Failure: A 12-Month Multicenter Real-World Study

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ABSTRACT

Objective: Patients with rheumatoid arthritis who do not achieve an adequate response to tumor necrosis factor inhibitors remain difficult to manage in routine clinical practice. Data from daily clinical care regarding selective JAK1 inhibition in this setting are limited. This study aimed to evaluate the 12-month effectiveness and safety of upadacitinib in Turkish patients with rheumatoid arthritis and previous tumor necrosis factor inhibitor failure.

Materials and Methods: This retrospective multicenter study included adult patients with rheumatoid arthritis treated at two tertiary rheumatology centers who initiated upadacitinib at a dose of 15 mg/day after the failure of at least one tumor necrosis factor inhibitor. Disease activity, inflammatory markers, and functional status were assessed at baseline and at 3, 6, and 12 months using validated composite indices and patient-reported outcome measures. Changes over time were analyzed using repeated-measures statistical methods. Safety outcomes were collected from routine clinical follow-up records.

Results: Forty patients were included in the analysis, with a mean age of 48.4 years, and 62.5% were female. Consistent improvements were observed across disease activity measures throughout follow-up. At month 12, ACR20/50/70 response rates reached 87.5%, 77.5%, and 40.0%, respectively. Additionally, 45.0% of patients achieved low disease activity or remission according to the SDAI. Functional status improved in parallel with reductions in inflammatory and clinical parameters. No serious adverse events were observed during the 12-month follow-up, while the reported adverse events were mild.

Conclusion: Upadacitinib demonstrated sustained effectiveness and acceptable tolerability in patients with rheumatoid arthritis who had previously failed tumor necrosis factor inhibitor therapy in routine clinical practice.

Keywords: Janus kinase inhibitors, real-world evidence, rheumatoid arthritis, TNF inhibitor failure, upadacitinib.

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INTRODUCTION

Rheumatoid arthritis (RA) is a long-standing immune-mediated inflammatory condition characterized by persistent joint inflammation, progressive structural damage, and loss of

physical function, affecting an estimated 0.5–1% of the global population.[1] National epidemiological data from Türkiye similarly indicate a prevalence of 0.41–0.56%, with a gradual increase reported over the past decade.[2] This pattern has been linked to better recognition of the disease, wider availability of specialist care, and demographic shifts in the adult population.

Therapeutic approaches to RA have progressed considerably with the development of tumor necrosis factor inhibitors (TNFi), a major class of biologic disease-modifying antirheumatic drugs (bDMARDs). However, roughly 30–40% of patients either do not achieve an adequate response or experience diminished effectiveness over time, underscoring the continued need for additional therapeutic approaches.[3,4] The clinical expression of RA varies widely and is shaped by genetic, environmental, and immunologic influences. These differences lead to diverse treatment responses across populations, including those living in Türkiye.

The advent of targeted synthetic DMARDs (tsDMARDs) has expanded RA treatment options because these agents, including Janus kinase (JAK) inhibitors, offer effective oral therapy by modulating multiple cytokine signaling pathways. Upadacitinib, a selective JAK1 inhibitor, has shown consistent efficacy in multiple phase 3 randomized controlled trials (RCTs), including SELECT-BEYOND and SELECT-COMPARE, particularly in patients with an inadequate response to bDMARDs.[5,6] In RA, randomized controlled trials remain the primary standard for evaluating the efficacy and safety of emerging therapies, while complementary evidence from routine clinical practice helps place these findings in the context of broader and more heterogeneous patient populations. Observational real-world studies conducted in Germany, Italy, and Japan have reported that patients receiving upadacitinib in routine care experience significant improvements in disease activity and functional status.[7–10] However, treatment outcomes observed in routine practice may differ between regions because of variations in healthcare infrastructure, reimbursement frameworks, and population characteristics, underscoring the value of country-specific evidence.

In Türkiye, the use of upadacitinib has expanded in recent years, facilitated by comprehensive national health insurance coverage and relatively streamlined access to rheumatology services. Nevertheless, delays in diagnosis, advanced disease at presentation, socioeconomic disparities, and variable adherence patterns may influence treatment outcomes, reinforcing the need for localized real-world assessments of JAK1 inhibition in RA.

This retrospective multicenter analysis evaluated the 12-month effectiveness and safety of upadacitinib in Turkish patients with RA who had an inadequate response to at least one prior TNFi. The study drew on longitudinal data from two geographically distinct tertiary rheumatology centers, capturing routine care within the Turkish healthcare system. By evaluating these outcomes, the study aimed to generate clinically relevant evidence on the role of selective JAK1 inhibition in patients with treatment-refractory RA.

KEY MESSAGES

- Upadacitinib provided significant and sustained improvements in disease activity, functional outcomes, and patient-reported measures over 12 months in patients with RA and prior TNF inhibitor failure.
- Nearly half of the patients achieved remission or low disease activity, and no serious adverse events were recorded, supporting a favorable safety profile.
- This multicenter study adds real-world evidence from Türkiye, demonstrating that the effectiveness observed in phase 3 trials is maintained in routine clinical practice.

METHODS

This study was designed as a retrospective observational cohort and included patients treated at two tertiary rheumatology centers in Türkiye. Ethical approval was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (November 26, 2024). Subsequent amendments to the study protocol were reviewed and approved by the same committee at its meeting on November 4, 2025 (Meeting No. 20; official decision dated November 10, 2025, No. E-60116787-020-776848). Given that the analysis used only de-identified data obtained from routine clinical practice, individual informed consent was not required.

Eligible patients were adults aged 18 years or older with RA defined according to the 2010 ACR/EULAR classification criteria who commenced upadacitinib at a dose of 15 mg once daily after an insufficient response to at least one TNF inhibitor. The analysis used retrospectively collected data from a multicenter observational setting between October 2023 and November 2024, with information extracted from electronic medical records at baseline and at the 3-, 6-, and 12-month assessments.

Patient identification was performed through systematic screening of electronic medical records at each participating center. All consecutive patients who initiated upadacitinib during the study period were screened for eligibility according to the predefined inclusion and exclusion criteria. The final study cohort consisted of 40 patients, including 20 patients

Table 1. Baseline demographic and clinical characteristics of the study population (n=40)

Variable	Value
Mean age	48.4±11.6
Female patients	25 (62.5%)
Mean BMI	27.6±4.2
Mean disease duration	12.9±6.8
Nonsmokers	21 (52.5%)
RF positivity	23 (57.5%)
Anti-CCP positivity	22 (55.0%)
Mean number of comorbidities	3.3±1.8
Upadacitinib monotherapy	17 (42.5%)
Upadacitinib + DMARD combination therapy	23 (57.5%)

Data are presented as mean±standard deviation or n (%). BMI: Body mass index; RF: Rheumatoid factor; anti-CCP: Anti-cyclic citrullinated peptide antibody; DMARD: Disease-modifying antirheumatic drug.

from each participating center. This distribution was not based on intentional balancing or matching between centers but rather reflected the number of eligible patients with complete longitudinal clinical and laboratory follow-up data available during the study period. Only patients with complete baseline and 3-, 6-, and 12-month clinical and laboratory assessments were included in the final analysis.

Patients were excluded if they had a history of malignancy, active or chronic infections such as hepatitis B, hepatitis C, or tuberculosis, or if upadacitinib was discontinued for nonmedical reasons before the 3-month follow-up assessment. To ensure consistency in the longitudinal repeated-measures analyses, only patients with complete baseline and follow-up data through month 12 were included in the final analysis.

Baseline data collection included demographic variables, body mass index (BMI), smoking status, disease duration, comorbid conditions, serologic status for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, and prior exposure to conventional synthetic or biologic DMARDs. Information on concomitant treatments, including methotrexate, leflunomide, hydroxychloroquine, and systemic corticosteroids, was also recorded (Table 1).

Treatment response was evaluated according to the American College of Rheumatology (ACR) 20%, 50%, and 70% improvement criteria, incorporating proportional changes in joint counts, patient-reported outcomes, global assessments, functional measures, and inflammatory markers (Table 2).

Disease activity was assessed using the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI),

Table 2. ACR response rates at 3, 6, and 12 months

Time point	ACR20, n (%)	ACR50, n (%)	ACR70, n (%)
3 months	27 (67.5)	14 (35.0)	3 (7.5)
6 months	32 (80.0)	28 (70.0)	8 (20.0)
12 months	35 (87.5)	31 (77.5)	16 (40.0)

Data are presented as n (%). ACR: American College of Rheumatology.

and Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP), with remission defined as DAS28-CRP <2.6 and low disease activity as DAS28-CRP <3.2. Functional status was evaluated using the Health Assessment Questionnaire (HAQ). Each visit included documentation of 28-joint tender and swollen joint counts, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values, pain assessed using a visual analog scale (VAS), and patient and physician global assessments (PtGA and PhGA) (Table 3).

Remission and low disease activity according to the SDAI and CDAI were determined using established cutoff thresholds (Supplementary Table 1).

Safety outcomes included all adverse events recorded during routine clinical follow-up. Adverse events were graded as mild, moderate, or severe based on clinical significance, including the need for hospitalization, treatment discontinuation, or additional medical intervention.

Statistical Analysis

Statistical analyses were conducted using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro–Wilk test, with continuous variables reported as mean±SD or median (IQR) and categorical variables as counts and percentages. Descriptive summaries in all tables and analyses followed these distribution-based reporting conventions.

Changes over time in continuous clinical and laboratory measures across the four predefined assessments were examined using the Friedman test for repeated measures. If a significant overall difference was observed, post hoc pairwise analyses were performed using the Wilcoxon signed-rank test, with Bonferroni correction applied to determine which time points accounted for the observed changes.

Changes in categorical response outcomes over time, including ACR20, ACR50, and ACR70 rates, were examined using Cochran's Q test. Pairwise post hoc comparisons were subsequently conducted using McNemar tests with Bonferroni-adjusted significance thresholds.

Table 3. Longitudinal changes in disease activity

Variable	Baseline Median (IQR)	3 months Median (IQR)	6 months Median (IQR)	12 months Median (IQR)	Friedman Test p value
SDAI	41.5 (35.2–59.4)	21.4 (13.4–31.8)	17.7 (10.0–24.0)	11.3 (6.3–18.9)	<0.001
CDAI	29.5 (22.0–40.3)	16.0 (9.0–25.3)	10.0 (6.0–16.0)	6.0 (3.0–10.5)	<0.001
DAS28-CRP	5.13 (4.74–5.97)	4.03 (2.95–4.73)	3.34 (2.62–3.92)	2.76 (1.95–3.40)	<0.001
TJC28	9 (6–12)	4 (2–8)	3 (1–5)	2 (1–4)	<0.001
SJC28	7 (5–9)	3 (1–5)	2 (1–3)	1 (0–2)	<0.001
CRP (mg/L)	21.1 (14.0–29.0)	11.0 (5.3–19.0)	8.3 (4.6–14.5)	7.0 (4.3–10.2)	<0.001
HAQ-DI	1.60 (1.2–1.9)	1.00 (0.8–1.5)	0.85 (0.6–1.2)	0.70 (0.5–0.9)	<0.001
Pain VAS	7.5 (6.5–8.2)	4.0 (4.0–6.0)	3.0 (2.0–4.0)	2.3 (1.5–3.5)	<0.001
PtGA	8.0 (7.0–9.0)	5.0 (3.0–6.0)	3.0 (2.0–4.0)	2.0 (1.0–4.0)	<0.001
PhGA	6.5 (5.8–8.0)	3.5 (3.0–5.0)	3.0 (2.0–4.0)	1.5 (1.0–3.0)	<0.001

Data are presented as median (interquartile range). Longitudinal changes across visits were evaluated using the Friedman test, followed by post hoc Wilcoxon signed-rank analyses with Bonferroni correction. SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; DAS28-CRP: Disease Activity Score in 28 joints using C-reactive protein.

Categorical outcomes were compared using the chi-square test or Fisher's exact test, depending on the expected cell counts. All statistical analyses were two-sided, with a significance threshold of $p<0.05$.

RESULTS

The cohort comprised 40 patients with RA and a prior inadequate response to TNFi (Table 1), with a mean age of 48.4±11.6 years, a mean disease duration of 12.9±6.8 years, and 62.5% being female; the mean comorbidity count was 3.3±1.8, and the mean BMI was 27.6±4.2 kg/m^2. Seropositivity for RF and anti-CCP antibodies was observed in 57.5% and 55.0% of patients, respectively. Upadacitinib was administered as monotherapy in 42.5% of cases and in combination with conventional synthetic DMARDs in 57.5%.

ACR20/50/70 response rates at 3, 6, and 12 months are presented in Table 2 and Figure 1. At the 3-month assessment, 67.5% of patients achieved an ACR20 response, 35.0% achieved an ACR50 response, and 7.5% achieved an ACR70 response. Cochran's Q test demonstrated a significant overall change over time for all three ACR response levels, with a global p value of <0.001. At month 6, ACR20/50/70 response rates increased to 80.0%, 70.0%, and 20.0%, respectively, and further increased to 87.5%, 77.5%, and 40.0% at month 12.

Changes in disease activity measures and patient-reported outcomes over time, from baseline to the 3-, 6-, and 12-month assessments, are presented in Table 3. Friedman testing demonstrated significant improvements over time in the SDAI, CDAI, DAS28-CRP, tender and swollen joint counts, CRP, patient and physician global assessments, and pain VAS, with overall p values of <0.001 for all measures. Post hoc Wilcoxon signed-rank analyses with Bonferroni adjustment confirmed statistically significant reductions at each follow-up visit compared with baseline.

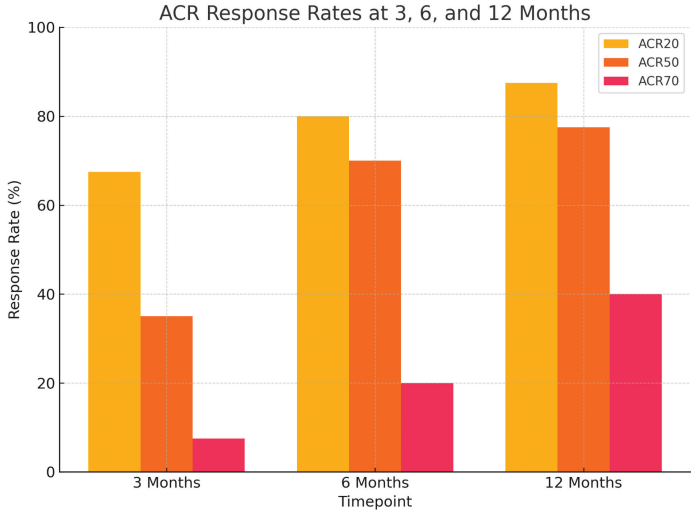

Figure 1. ACR20/50/70 response rates at 3, 6, and 12 months. Bars represent the proportion of patients achieving ACR20, ACR50, and ACR70 responses at each follow up visit.

Functional outcomes improved steadily over the 12-month follow-up. HAQ-DI scores decreased progressively over the 12-month follow-up, indicating improvement in physical function. At the 12-month assessment, 45.0% of patients achieved low disease activity or remission according to the SDAI, while 70.0% achieved the corresponding target according to the CDAI. Rates of remission and low disease

activity defined by the SDAI, CDAI, and DAS28-CRP at each follow-up visit are summarized in Supplementary Table 1.

No serious adverse events occurred during the 12-month follow-up; mild upper respiratory tract infections were reported in four patients (10.0%). Three patients (7.5%) experienced temporary, asymptomatic increases in alanine/aspartate aminotransferase levels to less than two times the upper limit of normal, which resolved without treatment discontinuation. There were no reports of herpes zoster (HZ), venous thromboembolism (VTE), major adverse cardiovascular events (MACE), malignancy, or death.

DISCUSSION

This multicenter retrospective cohort study evaluated the 12-month outcomes of upadacitinib in patients with RA who had a prior inadequate response to TNFi therapy.[11] Improvements across disease activity indices, patient-reported assessments, and functional status indicate that the benefits observed in phase 3 trials are maintained in routine clinical care.[12] The magnitude and trajectory of the clinical response in this cohort underscore the therapeutic value of selective JAK1 inhibition in a population commonly characterized by prolonged disease duration and complex treatment histories.[13]

When the results from our cohort are viewed alongside those of major randomized controlled trials, such as SELECT-BEYOND and SELECT-COMPARE, the early gains in ACR20 responses appear generally comparable to those reported in these studies.[14] While RCTs continue to represent the standard for evaluating efficacy and safety, studies conducted in routine clinical settings provide complementary evidence by capturing outcomes in more diverse and heterogeneous patient populations.[15] The relatively modest ACR50 and ACR70 rates observed at early follow-up visits likely reflect the realities of daily clinical practice, including a higher burden of comorbidities, longer disease duration, and the inclusion of patients who had previously failed multiple biologic therapies.[16] These characteristics are well-recognized factors associated with lower rates of rapid and deep treatment responses in RA.[17] Despite these unfavorable baseline characteristics, ACR20/50/70 response rates increased progressively over the 12-month follow-up, indicating that upadacitinib retains clinically meaningful effectiveness even in treatment-refractory settings.[18] This pattern is consistent with findings from international real-world cohorts reported from Germany, Italy, Japan, and Canada, as well as with systematic evaluations of JAK inhibitor effectiveness in routine practice.[19]

Upadacitinib treatment was associated with sustained improvements across several disease activity measures, including the SDAI, CDAI, and DAS28-CRP, reflecting a broad therapeutic effect accompanied by parallel reductions in inflammatory markers and clinical joint findings.[11] Improvements in patient-reported outcomes, such as pain and global assessment scores, mirrored these objective changes. Functional outcomes also improved consistently over time, supporting the clinical relevance of the observed reductions in disease activity. Collectively, these improvements across multiple domains resulted in steadily increasing rates of remission and low disease activity, aligning with treat-to-target strategies in RA management. The overall clinical trajectory observed in our cohort closely aligns with real-world findings from multiple European and international settings and complements 1-year outcomes reported in both observational cohorts and extension phases of randomized trial programs evaluating upadacitinib.

With respect to safety, upadacitinib was generally well tolerated throughout the 12-month observation period. No serious adverse events were recorded, and only mild infections and transient elevations in liver transaminase levels were observed. Given the modest sample size, the absence of adverse events of special interest, such as HZ, VTE, MACE, or malignancy, should be interpreted cautiously. Nevertheless, the observed safety profile is broadly consistent with data reported from long-term extension studies and large real-world registries evaluating JAK inhibitors.

An important strength of this study is that it reflects routine clinical practice within the Turkish public healthcare system. Because the participating centers are located in different geographic regions of Türkiye yet operate under a unified national reimbursement and treatment framework, the findings are likely to be representative of everyday rheumatology care at the national level. This study contributes valuable country-specific real-world evidence and helps address a current gap in regional data regarding the use of targeted synthetic disease-modifying antirheumatic drugs.

Several limitations warrant consideration, as the retrospective study design is inherently subject to potential information and selection biases. The absence of a comparator group limits direct comparisons with other biologic or targeted synthetic therapies, and the modest sample size constrains detailed subgroup analyses and the evaluation of infrequent safety events. Additionally, restricting the analysis to patients with complete 12-month follow-up may have introduced selection bias by excluding patients who discontinued treatment or were lost to follow-up earlier. Despite these limitations, the consistency of the findings across validated disease activity measures and the robustness of the repeated-measures analyses support the overall reliability of the observed results. Further clarification of long-term safety and optimal treatment sequencing will require larger prospective and comparative real-world studies with extended follow-up.

CONCLUSION

Across 12 months of follow-up, upadacitinib demonstrated sustained clinical effectiveness and was generally well tolerated in Turkish patients with RA who had an inadequate response to TNFi therapy. These findings add to the real-world evidence supporting upadacitinib in difficult-to-treat RA and are broadly consistent with outcomes reported in controlled clinical trials.

Ethics Committee Approval: Ethical approval was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (November 26, 2024). Subsequent amendments to the study protocol were reviewed and approved by the same committee at its meeting on November 4, 2025 (Meeting No. 20; official decision dated November 10, 2025, No. E-60116787-020-776848).

Informed Consent: Due to the retrospective nature of the study and anonymized data, the requirement for informed consent was waived.

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Supplementary Table 1. Remission and low disease activity rates

Index	3-month remission, n (%)	3-month LDA/ remission, n (%)	6-month remission, n (%)	6-month LDA/ remission, n (%)	12-month remission, n (%)	12-month LDA/ remission, n (%)
DAS28-CRP	5 (12.5)	13 (32.5)	9 (22.5)	20 (50.0)	17 (42.5)	28 (70.0)
SDAI	0 (0.0)	4 (10.0)	0 (0.0)	13 (32.5)	4 (10.0)	18 (45.0)
CDAI	1 (2.5)	11 (27.5)	1 (2.5)	19 (47.5)	6 (15.0)	28 (70.0)

Data are presented as n (%). Remission and low disease activity were defined according to the established cutoff values for each index. LDA: low disease activity; DAS28-CRP: Disease Activity Score in 28 joints using C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.