



Real-World Effectiveness and Metabolic Effects of Upadacitinib in Rheumatoid Arthritis after Tumor Necrosis Factor Inhibitor Failure

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Abstract

Objectives: To evaluate the real-world effectiveness and laboratory impact of upadacitinib in patients with rheumatoid arthritis (RA) who had an inadequate response to at least one tumor necrosis factor inhibitor (TNFi), with a specific focus on clinical disease activity, inflammatory biomarkers, and metabolic indices.

Methods: This single-center, retrospective, real-world study included 82 patients with RA who initiated upadacitinib (15 mg/day) following TNFi failure. Demographic data, disease characteristics, Disease Activity Score in 28 joints (DAS28-CRP), inflammatory markers (CRP and ESR), hematological indices, liver enzymes, and a comprehensive lipid profile were analyzed. In addition, the triglyceride–glucose (TyG) index and the HDL-to-monocyte ratio were calculated as markers of metabolic and cardiovascular risk. Clinical and laboratory parameters were compared between baseline and Week 12 using paired-sample statistical tests.

Results: At Week 12, the DAS28-CRP score significantly decreased from 5.4 to 2.9 ($p < 0.001$), with 80.5% of patients achieving low disease activity or remission. While total cholesterol, LDL-C, and HDL-C levels increased (all $p < 0.001$), the HDL/monocyte ratio improved significantly by 7.7% ($p = 0.012$). A moderate negative correlation was observed between the change in DAS28-CRP and the change in HDL/monocyte ratio ($\rho = -0.42$, $p = 0.001$). Creatine kinase (CK) levels showed a modest but statistically significant increase (+8.1%, $p = 0.025$); however, values remained within normal reference ranges and were not associated with muscular symptoms or treatment discontinuation. Clinical efficacy was consistent across rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) subgroups. No serious adverse events or treatment discontinuations due to adverse events were observed during the 12-week follow-up period.

Conclusions: In this difficult-to-treat, real-world cohort of TNFi-refractory RA patients, upadacitinib demonstrated rapid and robust clinical effectiveness. Despite the anticipated elevations in lipid parameters, the concomitant increase in HDL cholesterol, the stable TyG index, and the marked suppression of systemic inflammation suggest no evident short-term deterioration in metabolic parameters. However, given the 12-week follow-up duration, these metabolic findings should be considered exploratory and hypothesis-generating rather than definitive regarding cardiovascular or metabolic safety. These results support upadacitinib as an effective therapeutic option for anti-TNF-resistant RA in routine clinical practice.

Keywords: Upadacitinib; Rheumatoid arthritis; Janus kinase inhibitors; Real-world evidence; Lipid paradox; Triglyceride–glucose index

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TNF İnhibitörü Başarısızlığı Sonrası Romatoid Artritte Upadasitinibin Gerçek Yaşam Etkinliği ve Metabolik Etkileri

Öz

Amaç: En az bir tümör nekroz faktörü inhibitörüne (TNFi) yetersiz yanıt veren romatoid artrit (RA) hastalarında upadasitinibin gerçek yaşam koşullarındaki etkinliğini ve laboratuvar etkilerini; özellikle klinik hastalık aktivitesi, inflamatuvar biyobelirteçler ve metabolik göstergeler üzerindeki etkilerini değerlendirmek.

Yöntemler: Bu tek merkezli, retrospektif, gerçek yaşam çalışmasına TNFi başarısızlığı sonrası upadasitinib (15 mg/gün) başlanan 82 RA hastası dahil edildi. Demografik veriler, hastalık özellikleri, 28 eklemde Hastalık Aktivite Skoru (DAS28-CRP), inflamatuvar belirteçler (CRP ve ESR), hematolojik indeksler, karaciğer enzimleri ve kapsamlı lipid profili analiz edildi. Ayrıca metabolik ve kardiyovasküler risk belirteçleri olarak trigliserid-glukoz (TyG) indeksi ve HDL kolesterolün mutlak monosit sayısına oranı olarak tanımlanan HDL/monosit oranı hesaplandı. Klinik ve laboratuvar parametreleri başlangıç ile 12. hafta arasında eşleştirilmiş örneklem istatistiksel testleri kullanılarak karşılaştırıldı.

Bulgular: 12. haftada DAS28-CRP skoru 5,4'ten 2,9'a anlamlı olarak azaldı ($p < 0,001$) ve hastaların %80,5'inde düşük hastalık aktivitesi veya remisyona sağlandı. Toplam kolesterol, LDL-K ve HDL-K düzeylerinde artış gözlenmesine rağmen (tümü $p < 0,001$), HDL/monosit oranı %7,7 oranında anlamlı bir iyileşme gösterdi ($p = 0,012$). DAS28-CRP'deki değişim ile HDL/monosit oranındaki değişim arasında orta düzeyde negatif bir korelasyon saptandı ($\rho = -0,42$; $p = 0,001$). Kreatin kinaz (CK) düzeylerinde %8,1 oranında istatistiksel olarak anlamlı bir artış izlenmiş ($p = 0,025$) olmakla birlikte, bu artış klinik referans aralıkları içinde kalmış ve tedavi kesilmesini gerektirmemiştir. Klinik etkinlik romatoid faktör (RF) ve anti-CCP alt gruplarında tutarlıydı. On iki haftalık takip süresince ciddi advers olay gözlenmemiş ve tedavi kesilmesine yol açan yan etki bildirilmemiştir.

Sonuç: TNFi'ye dirençli, tedavisi zor bu gerçek yaşam RA kohortunda upadasitinib hızlı ve güçlü bir klinik etkinlik göstermiştir. Beklenen lipid parametre artışlarına rağmen, HDL kolesteroldeki eş zamanlı yükselme, TyG indeksinin stabil kalması ve sistemik inflamasyonun belirgin baskılanması kısa dönemde metabolik parametrelerde belirgin bir bozulma olmadığını düşündürmektedir. Bununla birlikte, 12 haftalık takip süresi kardiyovasküler veya metabolik güvenlik açısından kesin çıkarımlar yapmak için yeterli değildir ve bu bulgular kişisel nitelikte değerlendirilmelidir. Bu sonuçlar, anti-TNF'ye dirençli RA hastalarında upadasitinibin etkili bir tedavi seçeneği olduğunu desteklemektedir.

Anahtar kelimeler: Upadasitinib; Romatoid artrit; Janus kinaz inhibitörleri; Gerçek yaşam verileri; Lipid paradoksu; Trigliserid-glukoz indeksi.

INTRODUCTION

Rheumatoid arthritis (RA) is a complex, immune-driven inflammatory disorder defined by persistent synovitis, which can progress to irreversible joint destruction and systemic complications¹. To mitigate long-term structural damage, modern clinical practice utilizes a 'treat-to-target' methodology, aiming for rapid suppression of inflammation to achieve clinical remission². Although conventional synthetic DMARDs (csDMARDs) are the primary intervention, many patients experience secondary failure or inadequate initial response. The prevalence of persistent disease activity following exposure to multiple TNF inhibitors highlights a critical therapeutic gap, necessitating the development of agents that target alternative intracellular signaling pathways³.

JAK pathway modulators have become a primary alternative for RA patients failing to achieve goals with TNF-targeted therapies. The distinct advantage of JAK inhibitors lies in their intracellular mode of action, which differs from the extracellular neutralization used by biologics and allows for convenient oral dosing⁴. Among these, Upadacitinib stands out for its preferential affinity for JAK1, showing significant efficacy in dampening inflammatory responses⁵. High-level evidence from the SELECT program illustrates that this agent can secure stringent disease control and remission in patients with a history of treatment failure⁵. Despite these robust efficacy data, the broader impact of JAK1 selectivity on metabolic profiles and laboratory parameters in daily clinical practice remains an area of ongoing study.

Recent clinical investigations have placed increasing emphasis on the cardiovascular safety profile of JAK inhibitors⁶. Data from the ORAL Surveillance trial evaluating tofacitinib suggested an increased incidence of major adverse cardiovascular events (MACE) and venous thromboembolism in selected high-risk populations⁷. Although these findings were primarily associated with a non-selective (pan-JAK) inhibitor, they underscore the importance of carefully evaluating cardiometabolic parameters in patients receiving selective JAK1 inhibitors such as upadacitinib in routine practice⁸. Importantly, extrapolation of cardiovascular risk across different JAK inhibitors requires caution, and additional real-world data are needed.

The management of systemic inflammation in RA often results in rising serum lipid levels, a phenomenon known as the 'lipid paradox' where decreased lipid concentrations during active disease are actually linked to higher cardiovascular risk⁹. Although the impact of JAK inhibitors on traditional cholesterol levels is documented, there is a lack of comprehensive data regarding their influence on modern cardiometabolic indicators like the TyG index and the HDL-to-monocyte ratio¹⁰. The TyG index serves as an effective proxy for insulin resistance, while the HDL-to-monocyte ratio provides a dual perspective on systemic inflammation and the antioxidant capacity of HDL particles¹¹. Analyzing these specific markers in a real-world setting is essential to clarify the metabolic footprint and vascular safety of selective JAK1 blockade.

This retrospective study evaluates the 12-week real-world effectiveness of upadacitinib in RA patients with prior TNF inhibitor failure. The primary endpoint was the change in DAS28-CRP. In addition to clinical outcomes, the study explores the short-term changes in systemic inflammation, conventional lipid parameters, and metabolic indices including the TyG index

and HDL-to-monocyte ratio. Rather than aiming to establish definitive conclusions regarding cardiovascular safety, this analysis seeks to characterize early laboratory trends and generate hypotheses regarding the metabolic implications of selective JAK1 blockade in a treatment-resistant population.

METHODS

Study Design and Patient Population

This study was conducted at the Rheumatology Outpatient Clinic of the Dicle University Faculty of Medicine using a retrospective cohort design. We systematically reviewed the medical records of adult RA patients who initiated upadacitinib (15 mg/day) after demonstrating inadequate clinical response, loss of response, or intolerance to at least one tumor necrosis factor inhibitor (TNFi), including adalimumab, etanercept, infliximab, golimumab, or certolizumab.

Ethical approval was obtained from the Dicle University Faculty of Medicine Non-Interventional Studies Ethics Committee (Approval No: 6; 24/12/2025). The study was conducted in accordance with the Declaration of Helsinki. Given the retrospective design and use of anonymized data, the requirement for written informed consent was waived by the Ethics Committee.

The participant selection process is summarized in Figure 1. Initially, all RA patients who were switched to upadacitinib following TNFi failure between predefined study dates were screened for eligibility. Patients were included if they had complete clinical and laboratory data available at baseline and at Week 12. Exclusion criteria were applied to ensure data completeness and to minimize confounding clinical conditions that could affect metabolic or inflammatory parameters. The final study cohort consisted of patients meeting all eligibility criteria after systematic screening.

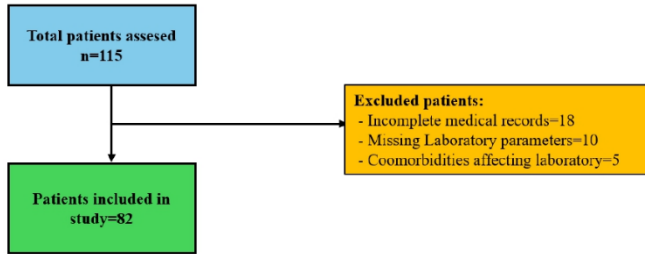


Figure 1. Patient Selection Flowchart for the Upadacitinib Real-World Study in Anti-TNF Resistant Rheumatoid Arthritis.

Inclusion and Exclusion Criteria

Eligible participants were adult patients (≥ 18 years) who fulfilled the 2010 ACR/EULAR classification criteria for rheumatoid arthritis and initiated upadacitinib therapy after documented TNFi failure, with available and complete clinical and laboratory data at both baseline and Week 12. Inclusion additionally required completion of a continuous 12-week course of upadacitinib without interruption unrelated to administrative causes.

To enhance internal validity and ensure patient safety, predefined exclusion criteria were applied. Patients were excluded if they were pregnant or breastfeeding; had active tuberculosis or other serious opportunistic infections; or had severe hepatic impairment (Child–Pugh class C). Individuals with clinically significant baseline cytopenias were also excluded, defined as an absolute neutrophil count < 1000 cells/mm³ or hemoglobin < 8 g/dL. In addition, patients with a documented history of malignancy within the previous five years were not eligible for inclusion.

These criteria were applied during systematic chart review to minimize confounding factors that could independently influence inflammatory or metabolic parameters.

Clinical and Laboratory Assessments

Clinical data, including patient demographics, disease duration, and concomitant medications (including low-dose corticosteroids and conventional synthetic disease-modifying

antirheumatic drugs [csDMARDs]), were retrieved from institutional electronic medical records. The primary outcome measure was the change in Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) from baseline to Week 12. The DAS28-CRP incorporates serum CRP levels, patient global health assessment measured by a visual analogue scale, and the evaluation of tender and swollen joint counts across 28 joints.

Laboratory assessments were conducted using fasting venous blood samples obtained at baseline and Week 12. Hematological parameters, liver enzymes, and inflammatory markers—including erythrocyte sedimentation rate (ESR) and CRP—were recorded.

Metabolic status was evaluated using the triglyceride–glucose (TyG) index and the HDL-to-monocyte ratio. The HDL-to-monocyte ratio (HMR) was calculated by dividing serum HDL cholesterol (mg/dL) by the absolute peripheral blood monocyte count (cells/mm³), reflecting the balance between anti-atherogenic lipid fractions and pro-inflammatory cellular components¹⁰. The TyG index, a surrogate marker of insulin resistance, was calculated using the following formula¹¹:

$$TyG = \ln \left[\frac{\text{Triglycerides (mg/dL)} \times \text{Glucose (mg/dL)}}{2} \right]$$

These metabolic indices were evaluated to explore short-term cardiometabolic trends during therapy rather than to establish definitive cardiovascular risk estimates.

Additionally, serological status—including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies—was recorded to assess the potential influence of autoantibody positivity on clinical and laboratory treatment responses.

Statistical Analysis

Statistical analyses were performed using SPSS software (Version 27.0; IBM Corp., Armonk, NY,

USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test and visual inspection of Q–Q plots. Descriptive statistics are presented as mean \pm standard deviation (SD) for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed data.

For within-group comparisons between baseline and Week 12, the paired-sample t-test was applied for normally distributed variables, while the Wilcoxon signed-rank test was used for non-parametric data. Comparisons between serological subgroups (RF-positive vs. RF-negative and anti-CCP-positive vs. anti-CCP-negative) were performed using the Mann-Whitney U test.

Correlations between changes in clinical and metabolic parameters were assessed using Spearman's rank correlation coefficient. A two-tailed p-value <0.05 was considered statistically significant.

A post-hoc power analysis was conducted using G*Power software (version 3.1.9.7). Based on the observed mean change in DAS28-CRP (primary outcome) and an estimated large effect size (Cohen's $d = 0.85$), the final sample size of 82 patients provided 99% statistical power at an alpha level of 0.05.

RESULTS

Patient Characteristics and Baseline Demographics

The demographic and clinical characteristics of the 82 patients with rheumatoid arthritis (RA) are summarized in Table 1. The mean age of the cohort was 53.0 ± 12.0 years, and 85.4% ($n = 70$) were female. The mean disease duration was 14.1 ± 8.2 years. Baseline serological assessment showed that 84.1% ($n = 69$) of patients were rheumatoid factor (RF) positive and 81.7% ($n = 67$) were anti-cyclic citrullinated peptide (anti-CCP) positive. At

baseline, the mean DAS28-CRP score was 5.93 ± 0.61 . Regarding concomitant therapy, 67.1% ($n = 55$) were receiving low-dose corticosteroids (prednisolone or equivalent). Among conventional synthetic DMARDs (csDMARDs), leflunomide was most frequently used (61.0%, $n = 50$), followed by hydroxychloroquine (29.3%), methotrexate (22.0%), and sulfasalazine (20.7%).

Table 1: Demographic and Clinical Characteristics of the Study Population ($N = 82$)

Variable	Total Patient Group (N = 82)
Age (years)	53.0 ± 12.0 54.0 [46.0–62.0]
Sex, n (%)	
Female	70 (85.4)
Male	12 (14.6)
Disease duration (years)	14.1 ± 8.2 15.0 [8.0–18.0]
Diagnosis, n (%)	
Rheumatoid arthritis	82 (100)
RF positivity, n (%)	69 (84.1)
Anti-CCP positivity, n (%)	67 (81.7)
DAS28 (baseline)	5.93 ± 0.61 5.75 [5.2–8.0]
Concomitant therapies, n (%)	
Methotrexate	18 (22.0)
Sulfasalazine	17 (20.7)
Leflunomide	50 (61.0)
Corticosteroids (Prednisolone / Methylprednisolone)	55 (67.1)
Hydroxychloroquine	24 (29.3)

Data are presented as mean \pm standard deviation, median [interquartile range (IQR)], or number (%). RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; DAS28: Disease Activity Score in 28 joints.

Clinical Effectiveness and Laboratory Dynamics

By Week 12, clinical and laboratory parameters showed changes summarized in Table 2. The DAS28-CRP decreased from a median of 5.4 to 2.9 ($p < 0.001$, Cohen's $d = 0.85$). Median CRP levels decreased by 57.1% ($p < 0.001$) and ESR decreased by 26.1% ($p < 0.001$). Hemoglobin increased by 1.5% ($p = 0.003$), while total white blood cell (WBC) counts decreased ($p < 0.001$) and platelet counts decreased ($p = 0.015$); absolute lymphocyte counts remained

unchanged ($p = 0.402$). Metabolic parameters demonstrated increases in total cholesterol, LDL-C, and HDL-C (all $p < 0.001$), whereas triglyceride levels did not change significantly ($p = 0.075$). The HDL-to-monocyte ratio increased by 7.7% ($p = 0.012$), the TyG index

increased modestly ($p = 0.002$), and fasting glucose levels increased ($p < 0.01$). Liver function tests showed decreases in ALT and AST (both $p < 0.01$), and serum albumin and uric acid concentrations increased (both $p < 0.01$). Figure 2 illustrates these changes at Week 12.

Table II: Changes in Clinical, Laboratory, and Metabolic Parameters from Baseline to Week 12

Parameter	Unit	Baseline Median [IQR] (Min–Max)	Week 12 Median [IQR] (Min–Max)	Δ Change (%)	p value
Clinical and inflammatory parameters					
DAS28	Score	5.4 [3.8–6.3] (2.5–7.5)	2.9 [2.4–3.4] (1.7–5.1)	-43.1	<0.001
CRP	mg/L	7.0 [1.2–27.2] (0.2–114.4)	3.0 [0.8–5.0] (0.1–22.0)	-57.1	<0.001
ESR	mm/h	23.0 [15.0–35.0] (4.0–70.0)	17.0 [11.0–21.0] (2.0–43.0)	-26.1	<0.001
Hematologic parameters					
WBC	$\times 10^9/L$	7.8 [6.4–9.0] (4.8–13.4)	7.5 [6.0–8.9] (4.2–13.5)	-3.8	<0.001
Hemoglobin	g/dL	13.5 [12.7–14.2] (10.6–16.5)	13.7 [13.0–14.5] (11.1–16.9)	+1.5	0.003
Lymphocyte count	$\times 10^9/L$	1.9 [1.6–2.2] (1.0–3.4)	1.9 [1.5–2.2] (1.0–3.1)	0.0	0.402
Platelet	$\times 10^9/L$	260.5 [230.0–299.0] (166–400)	255.0 [225.0–290.0] (168–380)	-2.1	0.015
Lipid parameters					
Total cholesterol	mg/dL	190.0 [170.0–208.0]	197.0 [178.0–215.0]	+3.7	<0.001
LDL cholesterol	mg/dL	116.0 [102.0–134.0]	119.0 [107.0–136.0]	+2.6	<0.001
HDL cholesterol	mg/dL	48.0 [43.0–54.0]	51.0 [46.0–58.0]	+6.3	<0.001
Triglycerides	mg/dL	146.0 [117.0–182.0]	140.0 [115.0–175.0]	-4.1	0.075
Fasting glucose	mg/dL	92.0 [88.0–98.0]	94.0 [89.0–100.0]	+2.2	0.002
TyG index	Score	8.82 [8.65–9.08]	8.84 [8.70–9.09]	+0.2	0.002
HDL/Monocyte ratio	–	58.1 [48.7–70.9]	62.6 [50.1–74.3]	+7.7	0.012
Metabolic parameters					
ALT	U/L	17.0 [14.0–24.0] (9–40)	16.0 [13.0–20.0] (8–35)	-5.9	0.007
AST	U/L	18.0 [15.0–21.0] (11–37)	17.0 [14.0–19.0] (11–34)	-5.6	0.003
CK	U/L	92.5 [65.0–142.0] (35–400)	100.0 [75.0–130.0] (40–350)	+8.1	0.025
Albumin	g/dL	4.4 [4.2–4.6] (3.8–5.0)	4.5 [4.3–4.7] (4.0–5.1)	+2.3	<0.001
Uric acid	mg/dL	5.3 [4.6–6.0] (3.4–8.2)	5.5 [4.7–6.2] (3.6–8.5)	+3.8	<0.001

Continuous variables are reported as median [IQR] (min–max). Changes over time were analyzed using the paired non-parametric Wilcoxon signed-rank test. Δ Change (%) indicates relative change from baseline. $p < 0.05$ was considered statistically significant. DAS28, Disease Activity Score 28; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell; CK, creatine kinase; TyG, triglyceride-glucose index.

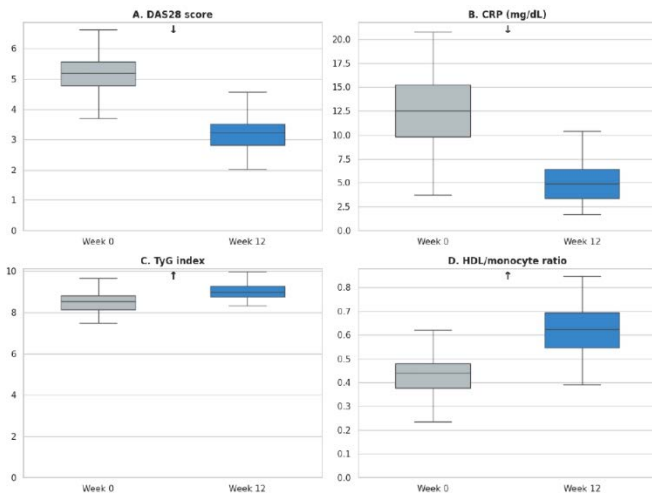


Figure 2. Effects of upadacitinib on clinical and metabolic profiles in patients with rheumatoid arthritis.

Treatment Response by Serological Status

Table III: Comparison of DAS28 Changes According to RF and Anti-CCP Status

Group	n	DAS28 (Baseline) Mean ± SD	DAS28 (Week 12) Mean ± SD	ΔDAS28 Mean ± SD	Within-group p*	Between-group p†
RF positive	69	4.8 ± 1.4	3.0 ± 1.0	1.8 ± 1.2	<0.001	0.675
RF negative	13	4.9 ± 1.6	3.1 ± 1.2	1.8 ± 1.3	<0.001	–
Anti-CCP positive	67	4.9 ± 1.3	3.0 ± 1.0	1.9 ± 1.2	<0.001	0.551
Anti-CCP negative	15	4.7 ± 1.8	2.9 ± 1.3	1.8 ± 1.5	<0.001	–

Data are presented as mean ± standard deviation (SD). ΔDAS28 represents the absolute change in DAS28 from Month 0 to Month 3. *Within-group comparisons were performed using paired tests (Paired t-test or Wilcoxon signed-rank test, depending on data distribution). †Between-group comparisons were performed on ΔDAS28 values (independent t-test or Mann–Whitney U test, depending on data distribution). RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide antibody.

Correlation Between Changes in Disease Activity and Cardiometabolic Indices

Correlation analyses between disease activity and cardiometabolic parameters are summarized in Table 4. A moderate negative correlation was observed between ΔDAS28-CRP and the HDL-to-monocyte ratio ($\rho = -0.42$, $p = 0.001$), whereas the association between ΔDAS28-CRP and the TyG index was positive but not statistically significant ($\rho = 0.18$, $p = 0.095$). Reductions in CRP showed a weak-to-moderate negative correlation with the HDL-to-monocyte ratio ($\rho = -0.35$, $p = 0.005$), while the correlation between ΔCRP and the TyG index

The effect of upadacitinib on clinical outcomes was evaluated according to baseline serological profiles, as summarized in Table 3. Both rheumatoid factor (RF)-positive and RF-negative subgroups showed significant decreases in DAS28-CRP scores at Week 12 compared with baseline (both $p < 0.001$). The mean change in DAS28-CRP was 1.8 ± 1.2 for RF-positive patients and 1.8 ± 1.3 for RF-negative patients ($p = 0.675$). Similarly, anti-cyclic citrullinated peptide (anti-CCP) positive and negative subgroups both demonstrated reductions in DAS28-CRP scores at Week 12 (both $p < 0.001$), with mean changes of 1.9 ± 1.2 and 1.8 ± 1.5 , respectively ($p = 0.551$).

approached borderline significance ($\rho = 0.21$, $p = 0.056$) (Table 4).

Table IV: Correlation Between Changes in Disease Activity and Cardiometabolic Indices

Variable 1 (Δ)	Variable 2 (Δ)	Spearman's ρ	p-value
DAS28-CRP	HDL/Monocyte Ratio	-0.42	0.001
DAS28-CRP	TyG Index	0.18	0.095
CRP	HDL/Monocyte Ratio	-0.35	0.005
CRP	TyG Index	0.21	0.056

Δ indicates change between baseline and follow-up values. Correlations were assessed using Spearman's rank correlation coefficient. Statistical significance was defined as $p < 0.05$.

Disease Activity States at Week 12

At the end of the 12-week follow-up, DAS28-CRP categorical assessment showed that 80.5% of patients (n = 66) achieved either clinical remission or low disease activity (LDA) (Table 5). Among these, 32.9% (n = 27) attained clinical remission (DAS28 ≤ 2.6), while 47.6% (n = 39) achieved LDA (2.6 < DAS28 ≤ 3.2). Moderate disease activity (3.2 < DAS28 ≤ 5.1) was observed in 18.3% of patients (n = 15), and one patient (1.2%) remained in the high disease activity category at Week 12 (Table 5).

Table V: DAS28 (CRP) Categories at Week 12 According to Disease Activity (N=82)

Disease Activity Category	DAS28 Score	Number of Patients (n)	Percentage (%)
Remission	≤ 2.6	27	32.9
Low disease activity	2.6 < DAS28 ≤ 3.2	39	47.6
Moderate disease activity	3.2 < DAS28 ≤ 5.1	15	18.3
High disease activity	> 5.1	1	1.2
Total	–	82	100.0

Disease activity classification was based on DAS28 score. DAS28: 28-joint Disease Activity Score.

DISCUSSION

Following 12 weeks of upadacitinib treatment, this cohort of 82 RA patients—all of whom had previously failed TNFi therapy—demonstrated significant clinical and laboratory improvements¹². The primary outcome was characterized by a 43% decrease in DAS28-CRP levels, with over 80% of the participants achieving the therapeutic goal of either low disease activity or complete remission¹³. Beyond joint health, the data revealed a robust decline in acute-phase reactants (ESR and CRP) and a simultaneous rise in hemoglobin, suggesting that JAK inhibition effectively mitigates the anemia associated with chronic inflammation⁸. Furthermore, an improved HDL-to-monocyte ratio was observed alongside traditional lipid increases, supporting the theory that upadacitinib may exert a protective

influence on systemic cardiometabolic health regardless of the patient's serological status.

The proportion of patients achieving low disease activity or remission at Week 12 was 80.5% in this TNFi-refractory cohort (Table 5). These outcomes are consistent with efficacy data reported in pivotal trials. In the SELECT-NEXT trial, upadacitinib treatment resulted in rapid DAS28-CRP reductions in patients with prior csDMARD exposure¹⁴. Similarly, the SELECT-BEYOND study demonstrated clinical responses in populations previously treated with biologics, including TNFi-experienced patients¹⁵. The response rates observed in this real-world cohort are within the range reported in these trials.

Our data corroborate the results of the SELECT-BEYOND trial, validating upadacitinib as a robust therapeutic alternative for patients who have not responded to traditional biologics¹⁶. A key distinction in our study is the nature of the cohort; our participants exhibited a more diverse clinical profile, characterized by an average disease duration of 14.1 years and a greater prevalence of comorbidities than the restrictive populations typically enrolled in RCTs¹⁷. The fact that clinical goals were met by such a high percentage of patients suggests that the benefits of selective JAK1 inhibition are maintained even in advanced, chronic RA cases managed in daily practice¹⁷.

Our findings regarding metabolic shifts provide further evidence of the 'lipid paradox' inherent in RA, characterized by a rise in serum lipid concentrations as systemic inflammation is successfully mitigated¹⁸. While we observed significant elevations in LDL-C, HDL-C, and total cholesterol over the 12-week study, triglycerides remained stable. Crucially, the concurrent improvement in the HDL-to-monocyte ratio suggests that upadacitinib might do more than just alter lipid volumes; it may actually enhance the anti-inflammatory and antioxidant capacity of HDL particles¹¹. This

implies that despite the increase in absolute lipid levels, the functional cardiovascular profile of these patients may be improving¹¹.

The minimal shift in the triglyceride–glucose (TyG) index suggests that selective JAK1 blockade maintains a state of metabolic neutrality rather than promoting insulin resistance¹⁰. Our observations support the hypothesis that lipid fluctuations associated with agents like upadacitinib and filgotinib actually represent a restoration of lipid homeostasis—specifically the normalization of cholesterol ester transfer protein (CETP) function—once the inflammatory burden is lifted¹⁹. The significant correlation between lower disease activity and better metabolic indicators reinforces the idea that the cardiovascular advantages of profound inflammatory control likely eclipse the potential risks of elevated serum lipids²⁰.

Our data suggest that the advantages of upadacitinib extend into the vascular system, surpassing mere joint-related improvements. We identified a significant moderate inverse relationship between DAS28-CRP fluctuations and the HDL-to-monocyte ratio ($\rho = -0.42$, $p = 0.001$), implying that the most successful clinical responses are paired with enhanced vascular-protective and anti-inflammatory markers²¹. This synergy is reinforced by the negative correlation between CRP shifts and the HDL/monocyte ratio ($\rho = -0.35$, $p = 0.005$). These findings underscore how the burden of systemic inflammation in RA drives both lipid abnormalities and a reduction in antioxidant resilience²¹.

Conversely, the relationships involving the TyG index were either negligible or reached only marginal significance, implying that significant shifts in insulin sensitivity might necessitate a more prolonged duration of suppressed inflammation²². On the whole, these observations suggest that the metabolic transitions associated with upadacitinib

represent a systematic physiological response to the abatement of inflammation, rather than incidental pharmacological side effects. In the long term, this structured biochemical recovery could play a vital role in reducing the cardiovascular burden for RA patients who have failed prior TNFi therapies²².

The safety data and laboratory findings from our analysis further support the positive clinical profile of upadacitinib in a real-world setting. Specifically, the slight but significant reduction in ALT and AST levels suggests that dampening systemic inflammation may actually mitigate hepatic strain. This stands in contrast to the temporary transaminase increases sometimes associated with non-selective JAK inhibitors²³. Furthermore, the observed rise in hemoglobin levels points toward a resolution of 'anemia of chronic disease.' This improvement likely stems from the suppression of IL-6, which in turn reduces hepcidin synthesis and restores iron homeostasis²³.

In our study, white blood cell and platelet counts showed only minimal fluctuations, with all levels staying within safe clinical limits. This hematologic stability likely reflects the selective JAK1 mechanism, which spares broader hematopoietic pathways more effectively than non-selective JAK inhibitors²⁴. Furthermore, while we noted a minor asymptomatic increase in creatine kinase (CK)—a common observation across the JAK inhibitor class—it had no clinical impact on the cohort²⁴. These results contrast sharply with the safety concerns raised in the ORAL Surveillance trial regarding tofacitinib, such as MACE and venous thromboembolism⁷. Ultimately, our data suggest that upadacitinib offers a robust safety margin across muscular, hepatic, and hematologic parameters, even for high-risk, treatment-experienced patients²⁵.

A primary strength of this investigation is the provision of robust real-world data on upadacitinib's performance in a TNFi-refractory cohort, effectively bridging the

disparity between idealized randomized trials (like the SELECT program) and daily clinical management. Furthermore, the use of composite metabolic indicators—such as the HDL-to-monocyte ratio and the TyG index—offers original perspectives on the cardiovascular safety of selective JAK1 blockade. By examining outcomes according to baseline serology (RF and anti-CCP), this study also provides critical evidence for seronegative RA patients, a demographic that often lacks sufficient representation in major clinical trials.

Several limitations warrant mention. Due to the retrospective nature of this analysis, we cannot establish direct causality, and the potential for information bias from medical records remains a factor. Additionally, while our 12-week observation window effectively captures early therapeutic responses, it may not fully reflect the long-term cardiovascular shifts or gradual changes in insulin sensitivity that could emerge over years. Furthermore, as a single center study with 82 participants, the findings may not be fully representative of broader, more diverse populations. Consequently, large-scale, prospective multicenter investigations are necessary to confirm these observations and to explore the durable metabolic impact of selective JAK1 blockade.

Upadacitinib demonstrates robust clinical potency and metabolic neutrality in a real-world, TNFi-refractory RA population. The observed improvement in vascular-protective markers, such as the HDL-to-monocyte ratio, suggests that its systemic impact extends beyond articular symptom control. Nevertheless, the definitive role of selective JAK1 inhibition in long-term cardiometabolic safety remains to be fully elucidated. Transitioning from this 12-week analysis to larger, multicenter longitudinal studies will be a critical next step in validating these results and ensuring the comprehensive safety of

upadacitinib in the long-term management of difficult-to-treat rheumatoid arthritis.

CONCLUSION

Upadacitinib was associated with reductions in disease activity over 12 weeks in this TNFi-refractory rheumatoid arthritis cohort, with 80.5% of patients achieving low disease activity or remission. Laboratory parameters, including hemoglobin, lipid profiles, HDL-to-monocyte ratio, and the TyG index, showed measured changes without implying direct cardiovascular outcomes. No severe adverse events or treatment-limiting laboratory abnormalities were observed during the 12-week follow-up. These findings provide descriptive real-world evidence on the short-term clinical and biochemical effects of selective JAK1 inhibition. Further prospective, long-term studies are needed to evaluate sustained efficacy and cardiometabolic safety in diverse RA populations.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethical Approval: The study protocol was approved by the Dicle University Medical Faculty Ethics Committee for Noninterventional Studies (Approval No: 6; Date: 24/12/2025).

Conflict of Interest: The authors declared no conflicts of interest.

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