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Efficacy, retention, and safety of baricitinib in real-life: HUR-BIO monocentric experience

Baricitinibin gerçek hayattaki etkinliği, kalıcılığı ve güvenliği: HÜR-BİO tek merkezli deneyimi

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Abstract

Objective: This study evaluates the effectiveness, retention rate and safety of baricitinib, including a comparison between baricitinib and a tumour necrosis factor inhibitor (adalimumab) in a real-life cohort of patients with rheumatoid arthritis (RA).

Methods: RA patients from the Hacettepe University Biological Prospective Database who received at least one dose of baricitinib or adalimumab between June 2020 and January 2023 were analyzed. Drug survival analysis included patients with at least one dose, while efficacy and safety analyses required at least one follow-up visit. Adverse events, major adverse cardiovascular events (MACE), malignancies, and medication adherence were assessed. The European Alliance of Associations for Rheumatology (EULAR) response classified patients as either good responders or non-responders.

Results: A total of 280 patients (86 baricitinib, 194 adalimumab) were included, with a mean age of 52.4 (±13.6) years; 77.5% were female. Baricitinib significantly improved disease activity parameters. High patient global assessment [odds ratio (OR): 1.05 (95% confidence interval (CI): 1.02-1.09)] predicted a good response, while RF positivity [OR: 7.66 (95% CI: 1.46-40.07)] indicated a poor response. MACE occurred in 2 patients (2.5%) on baricitinib and in 4 patients (2.5%) on adalimumab, with rates of 15.3 and 9.1 per 1000 patient-years, respectively (p=0.20).

Conclusion: Baricitinib improved disease activity parameters and a high patient global assessment predicted a good EULAR response. MACE incidence was comparable to that with adalimumab.

Keywords: Rheumatoid arthritis, baricitinib, real life, major adverse cardiovascular events, adverse events

Özet

Amaç: Bu çalışma, romatoid artrit (RA) hastalarının gerçek yaşam koşullarında tedavisinde barisitinibin güvenliliğini, etkililiğini ve tedavide kalıcılığını değerlendirmek; barisitinib içinde ve bir tümör nekroz faktörü inhibitörü (adalimumab) ile karşılaştırmayı amaçlamaktadır.

Yöntem: Haziran 2020 ile Ocak 2023 arasında en az bir doz barisitinib veya adalimumab alan Hacettepe Üniversitesi Biyolojik Prospektif Veritabanı'ndan RA hastaları analiz edildi. İlaç sağkalımı analizi en az bir doz baricitinib ve adalimumab alan hastaları içerirken, etkililik ve güvenlilik analizleri için en az bir takip viziti bulunması gerekiyordu. Advers olaylar, majör olumsuz kardiyovasküler olaylar (MACE), maligniteler ve ilaca uyum değerlendirildi. Avrupa Romatoloji Dernekleri Birliği (EULAR) yanıtı, iyi yanıt verenler veya yanıt vermeyenler olarak sınıflandırdı.

Bulgular: Toplam 280 hasta (86 barisitinib, 194 adalimumab) çalışmaya dahil edildi; ortalama yaş 52,4 (±13,6) yıl olup hastaların %77,5'i kadındı. Barisitinib, hastalık aktivitesi parametrelerini anlamlı düzeyde iyileştirdi. Yüksek hasta global değerlendirmesi iyi yanıtı öngördü [risk oranı (OR): 0,95 (%95 güven aralığı (GA): 0,92-0,98)], RF pozitifliği ise kötü yanıtı işaret etti [OR: 7,66 (%95 GA: 1,46-40,07)]. MACE, barisitinib kullanan 2 hastada (%2,5) ve adalimumab kullanan 4 hastada (%2,5) görüldü; oranlar sırasıyla 1000 hasta-yıl başına 15,3 ve 9,1 idi (p=0,20).

Sonuç: Barisitinib tedavisi hastalık aktivitesi göstergelerinde düzelme sağladı ve yüksek hasta global değerlendirmesi iyi EULAR yanıtının öngördürücüsüydü. MACE sıklığı adalimumab ile benzerdi.

Anahtar Kelimeler: Romatoid artrit, baricitinib, gerçek yaşam, majör kardiyak olaylar, advers olaylar

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent joint deterioration and additional symptoms, often leading to long-term disability and increased mortality.[1] The primary goal in treating RA is to achieve and maintain either remission or low disease activity (LDA) in all patients.[2]

Targeted therapies, such as biologic disease modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), have led to significant advances in the treatment of RA. These agents have significantly improved treatment effectiveness and increased the likelihood of achieving treatment goals that are often not achievable with traditional synthetic DMARDs (csDMARDs).[3]

Baricitinib, an oral selective inhibitor of Janus kinase inhibitors 1 (JAK1) and JAK2 with lower affinity for JAK3 and tyrosine kinase 2, received approval from the European Medicines Agency (EMA) in February 2017 and from the Food and Drug Administration (FDA) in May 2018 for the treatment of RA. The effectiveness and safety of baricitinib have been assessed in clinical trials, both as monotherapy and in combination with methotrexate, for patients with active RA. The importance of real-life evidence in complementing clinical study data is well recognized, as it provides valuable information. In numerous real-world studies, treatment with baricitinib has been shown to significantly improve disease activity, leading to remission or LDA in many patients. Additionally, it has displayed high persistence rates and comparable or better survival rates compared to tumour necrosis factor (TNF) inhibitors and other bDMARDs.[4] The incidence of opportunistic infections, herpes zoster (HZ), and nonmelanoma skin cancer was higher with JAK inhibitors than with TNF inhibitors. In the last randomized controlled trial (RCT), the odds of major adverse cardiovascular events (MACE) and cancer were higher in the tofacitinib group than in the TNF-inhibitor group, and this effect was interpreted as class-specific.[5] On the other hand, in the most extensive real-life cohort study comparing patients initiating JAK inhibitors versus adalimumab, the risks of MACEs and venous thromboembolisms did not differ significantly between groups.[6]

Given geographic and racial differences, no real-world data on baricitinib in the Turkish population are yet available, and differences in MACE outcomes exist between RCTs and real-world studies. This study aims to evaluate the effectiveness, retention rate and safety of baricitinib, including intra-baricitinib comparisons and comparisons to a TNF inhibitor in real-life settings in patients with RA.

Materials and Methods

Study Population

In this retrospective longitudinal analysis, we examined RA patients who had received at least one dose of baricitinib between June 2020 and the end of January 2023. These patients were part of the Hacettepe University Biological Prospective Database, established in 2005.[7] All patients met the classification criteria set forth by the American College of Rheumatology (ACR) in 1987 and/or by the European League Against Rheumatism (EULAR/ACR) in 2010.[8,9]

According to Turkish social security and prescription rules, the treating physician should see patients receiving biologic/targeted-synthetic DMARDs every three months. Patients who had taken at least one dose were included in the drug survival analysis, while patients who had at least one follow-up visit were included in the efficacy and safety analysis. Furthermore, all patients were contacted by telephone, regardless of whether they attended follow-up visits, to inquire about any potential drug-related adverse effects, major adverse cardiovascular events (after 60 days of drug exposure), malignancies, and adherence to their prescribed medication regimen. Furthermore, relevant variables for consenting patients were obtained from the National Electronic Health Records.

During this period, baricitinib and adalimumab were prescribed to 86 and 194 patients, respectively; 62 (72.1%) and 142 (73.2%) of these patients had at least one follow-up visit. All patients used the medication as recommended. To assess potential differences in major adverse cardiovascular events and side effects relative to anti-TNFs, a control group comprising 194 RA patients who started adalimumab during the same period (June 2020-January 2023) was used. Adalimumab was selected because it is the most common first-line biologic for RA treatment in our country and because it was used in the RCT evaluating the cardiovascular and cancer risks of tofacitinib. The study, based on real-world data, included patients with a minimum follow-up of 3 months and at least one control visit for effectiveness and drug-retention analyses. The maximum observation time was defined by the duration of the study period, with follow-up visits for both treatments scheduled at approximately 3-month intervals. Informed consent was obtained from all patients. This study was approved by Hacettepe University Ethics Commission (approval number: 2023-02-02, date: 24.01.2023).

Data Collection and Assessments

Demographic Data and Population Characteristics

Sex, age, smoking history, body mass index (BMI), and presence of hypertension, hyperlipidemia, chronic kidney disease, and diabetes mellitus (DM) were recorded. Regarding RA, the following data were collected: disease duration, positivity for rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP), duration of baricitinib treatment, concomitant use of DMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine), and glucocorticoids at the last visit; the baseline and final-visit data on disease activity and functional status parameters. These parameters included erythrocyte

sedimentation rate, C-reactive protein (CRP) concentration, number of tender and swollen joints (28 joints), patient global assessment using a visual analogue scale (PGA-VAS), disease activity score [DAS28- estimated sedimentation rate (ESR)], and health assessment questionnaire-disability index (HAQ-DI).

In the main analyses, patients were categorized according to the following criteria: biologicnaïve versus biologic experienced; baricitinib monotherapy versus baricitinib with concomitant csDMARDs; EULAR good response versus EULAR not-good response (moderate or no response); and baricitinib versus adalimumab.

Assessment of Efficacy

The efficacy analysis included patients who had at least one follow-up visit while receiving baricitinib and who had complete baseline disease activity data. Patients were classified into responders and non-responders at baseline and the last follow-up visit based on DAS28 scores: DAS28 ≤3.2 for responders and DAS28 >3.2 for non-responders.[10] We used the EULAR response criteria to evaluate the efficacy of baricitinib. The patients were divided into three groups: good response (DAS28 improvement from baseline >1.2 and DAS28 at the last visit ≤ 3.2), moderate response (DAS28 improvement from baseline >1.2 and DAS28 at the last visit visit >3.2 or DAS28 improvement from baseline >0.6 to ≤1.2 and DAS28 at last visit ≤5.1) and no response (DAS28 improvement from baseline ≤0.6, regardless of DAS28 at last visit, or DAS28 improvement from baseline >0.6 to ≤1.2 and DAS28 at last visit >5.1).[11] In addition to assessing disease activity, HAQ-DI scores were compared between the first and last visits to analyze the impact of baricitinib on patients' functional status. A minimal clinically significant difference in HAQ-DI scores has been suggested to be 0.22 (calculated for patients with a baseline HAQ-DI >0.5), and previous studies have defined functional remission as HAQ-DI ≤0.5.[12,13]

Assessment of Retention Rate

Patients who received at least one dose of baricitinib were included in the drug retention analysis. For a more accurate calculation of drug retention, patients prescribed baricitinib or adalimumab who neither had a follow-up visit within six months nor were identified in the national database as being prescribed any other biologic therapy were categorized as continuing their respective treatment. Patients who had no follow-up visit for more than six months and who were not prescribed baricitinib by another healthcare provider were categorized as having discontinued baricitinib and adalimumab.

Baricitinib Discontinuation and Adverse Events

Analyses of baricitinib discontinuation and adverse events were performed in patients with complete baseline data who had at least one follow-up visit or a final telephone assessment during baricitinib treatment. Adverse events attributable to baricitinib were analyzed for safety, including neutropenia (<1,500/mm^3), leukopenia (<4,000/mm^3), transaminase elevation (alanine aminotransferase >3x upper limit of normal=40 IU/L), changes in lipid profile (assessed in patients with baseline and follow-up values), HZ, infections other than HZ, hepatitis reactivation, tuberculosis, cancer, and major adverse cardiovascular events. Although there are various definitions for MACE, the most commonly used definition in the field of rheumatology includes cardiovascular death (excluding pulmonary embolism), nonfatal myocardial infarction, and nonfatal stroke.[5,14] The incidence rates for MACE and cancer were calculated per 1,000 patient-years.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS statistics version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean (standard deviation) for normally distributed numerical variables, and as median (minimum-maximum) and number and percentage for non-normally distributed numerical variables. The chi-square and Fisher's exact tests were used to compare percentages. Student's t-test and the Mann-Whitney U test were used to analyze the differences between variables according to their distributional patterns.

In the univariate analysis, disease duration, BMI ≥30, positive RF, duration of baricitinib, steroid use at last visit, CRP at first visit, HAQ, patient's VAS, DAS28 CRP, biological naive and baricitinib monotherapy were included in the logistic regression analysis to identify independent predictors of EULAR Responder Index response at the last visit. Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit.

Factors affecting medication adherence and differences in duration were assessed using Kaplan-Meier analysis. Potential factors identified by univariate analyses ($p<0.20$) were subsequently entered into a Cox regression analysis with backward selection to determine independent predictors of baricitinib retention. MACE was estimated per 1,000 patient-years. To compare the rates of major adverse cardiovascular events between patients treated with baricitinib and adalimumab, a Poisson regression model with a log link function was applied. The natural logarithm of follow-up time in person-years was included as an offset variable to account for varying observation periods among participants. The primary predictor was the treatment group, categorized as receiving baricitinib or adalimumab, while additional covariates included smoking status, treatment duration, family history of cardiovascular disease, and treatment-naive status. Goodness-of-fit measures, including the deviance-to-degrees-of-freedom ratio and Pearson

chi-square, were used to assess model adequacy, and rate ratios with 95% confidence intervals were reported for each predictor. Statistical significance was set at $p<0.05$.

Results

Study Population and Patient Characteristics

The study included 280 patients: 86 in the baricitinib group and 194 in the adalimumab group. The mean age was 52.4 (±13.6) years, and 77.5% of patients were female. The mean disease duration was 9.5 (±8.2) years overall, 10.7 (±8.5) years for the baricitinib group, and 8.9 (±8.0) years for the adalimumab group (p=0.09) while the mean disease duration at the time of the first biologic was 5.9 (±7.2) years overall, 6.0 (±7.2) years for baricitinib, and 5.9 (±7.2) years for adalimumab (p=0.91). The proportion of biologic-naive patients was significantly lower in the baricitinib group (30.2%) than in the adalimumab group (55.2%) (p<0.001), suggesting a prevalent inclination towards anti-TNFs as the primary biologic treatment. Interestingly, the baricitinib-treated population had a higher prevalence of smokers than the adalimumab group (51.9% vs. 24.0%). Comorbidities did not differ significantly between groups, but prior percutaneous coronary intervention, hypertension, and chronic kidney disease were more common in the baricitinib group (Table 1). Additionally, treatment-naïve patients in both medication groups were compared, and no significant differences were observed between the groups (Supplementary Table 1).

Baricitinib is utilized more frequently as monotherapy (±GC) than adalimumab (27.9% vs. 20.6%, respectively, p=0.18), although this difference did not achieve statistical significance (Table 2). Supplementary Tables 2 and 3 compare the biologic-naive and biologic-experienced groups, and the baricitinib monotherapy and baricitinib+cs DMARD combined-treatment groups.

Baricitinib Efficacy and Retention Rate

Efficacy

Of the 86 patients prescribed baricitinib, 24 (27.9%) had no control visit data, and 10 (11.6%) were missing first visit data. Therefore, 52 patients (60.5%) with complete baseline and follow-up visit data were included in further analyses to evaluate the drug's effectiveness (Table 3).

Table 1. Comparison of demographic and baseline characteristics between patients receiving baricitinib and adalimumab

	All patients (n=280)	Baricitinib (n=86)	Adalimumab (n=194)	p
Female n (%)	217 (77.5)	68 (79.1)	149 (76.8)	0.67
Age (SD)	52.4 (13.6)	52.5 (13.8)	52.4 (13.5)	0.95
Disease duration, years (SD)	9.5 (8.2)	10.7 (8.5)	8.9 (8.0)	0.09
Disease duration at the time of the first biologic drug: years (SD)	5.9 (7.2)	6.0 (7.2)	5.9 (7.2)	0.91
Biological naive n (%)	133 (47.5)	26 (30.2)	107 (55.2)	**<0.001**
Smoking (%)				
-Never	137/210 (65.2)	39/81 (48.1)	98/129 (76.0)	**<0.001**
-Ex-smoker or active smoker	73/210 (34.8)	42/81 (51.9)	31/129 (24.0)	
BMI (SD)	27.8 (5.4)	27.5 (5.4)	28.0 (5.3)	0.44
BMI ≥30 (%)	68/221 (30.8)	23/81 (28.4)	45/140 (32.1)	0.56
Coronary artery disease (%)	26/242 (10.7)	10/80 (12.5)	16/162 (9.9)	0.53
Early family history of CAD (%)	36/237 (13.4)	7/80 (8.8)	29/157 (18.5)	**0.04**
Percutaneous coronary intervention (%)	24/242 (9.9)	10/80 (12.5)	14/162 (8.6)	0.34
Bypass (%)	6/241 (2.5)	3/80 (3.8)	3/161 (1.9)	0.40
Hypertension (%)	89/241 (36.9)	32/80 (40)	57/161 (35.4)	0.48
Diabetes n (%)	48/241 (19.9)	17/80 (21.3)	31/161 (19.3)	0.71
Hyperlipidemia n (%)	109/225 (48.4)	37/80 (46.3)	72/145 (49.7)	0.62
CKD n (%)	12/240 (5.0)	6/80 (7.5)	6/160 (3.8)	0.22
Infection requiring hospitalization (%)	31/231 (13.4)	11/80 (13.8)	20/151 (13.2)	0.91
History of cancer in first- and second-degree relatives	61/240 (25.4)	13/80 (16.3)	48/160 (30.0)	**0.02**
MACE (%)	6/242 (2.5)	2/80 (2.5)	4/162 (2.5)	1
DVT (%)	4/241 (1.7)	0	4/161 (2.5)	0.30
PTE (%)	5/241 (2.1)	1/80 (1.3)	4/107 (2.5)	0.63

BMI: Body mass index, CAD: Coronary artery disease, CKD: Chronic kidney disease, MACE: Major adverse cardiovascular event, DVT: Deep vein thrombosis, PTE: Pulmonary thromboembolism, SD: Standard deviation

Table 2. Comparison of medication use between patients receiving baricitinib and adalimumab				
	All patients (n=280)	**Baricitinib (n=86)**	**Adalimumab (n=194)**	**p**
Duration of biological drug use, months (SD)	**8.0 (8.9)**	**5.8 (5.0)**	**9.1 (9.9)**	**<0.001**
Monotherapy (±GC) (%)	64 (22.9)	24 (27.9)	40 (20.6)	0.18
Last visit (%)				
- Methotrexate	46 (16.4)	17 (19.8)	29 (14.9)	0.31
- Sulfasalazine	4 (1.4)	1 (1.2)	3 (1.5)	1
- Hydroxychloroquine	120 (42.9)	27 (31.4)	93 (47.9)	**0.01**
- Leflunomide	139 (49.6)	38 (44.2)	101 (52.1)	0.22
- Glucocorticoid	219 (78.2)	59 (68.6)	160 (82.5)	**0.009**
Glucocorticoid (%)				
-<5 mg	35 (23.5)	15 (25.4)	39 (24.4)	0.87
-≥5 mg	114 (76.5)	44 (74.6)	121 (75.6)	
GC: Glucocorticoid, SD: Standard deviation				

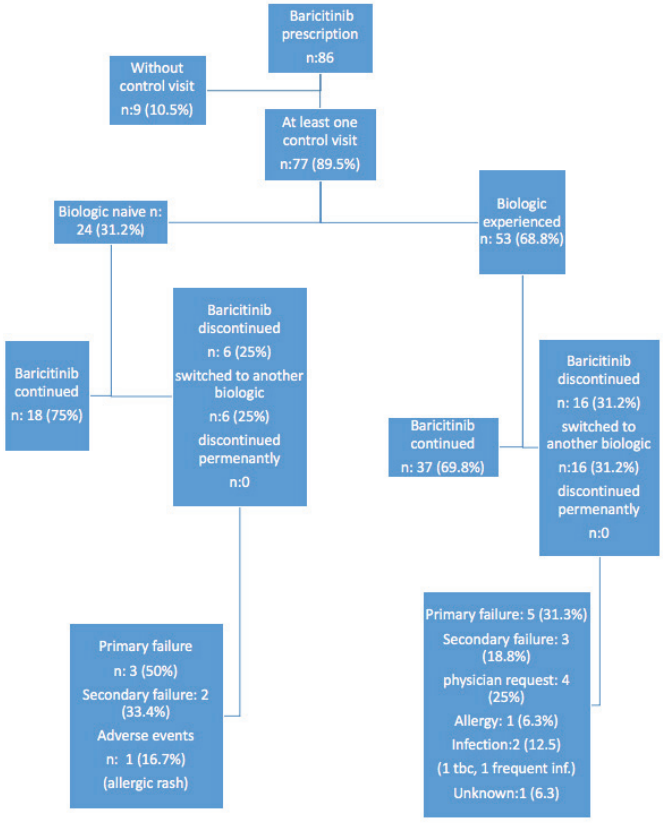

Figure 1. Patient enrollment and discontinuation flowchart

The mean follow-up time for patients who received baricitinib was 5.8 (±5.0) months. Disease activity parameters at baseline and final evaluation were as follows: ESR 30.1 (20) vs. 11.5 (30.0) (p<0.001); CRP 0.9 (1.1) vs. 0.40 (0.6) (p<0.001); DAS28 CRP 4.2 (1.5) vs. 2.7 (2.3) (p<0.001); HAQ 0.91 (0.6) vs. 0.52 (1.3) (p<0.001); SJ 1 (2.0) vs. 0 (0) (p<0.001); TJ 3 (6.0) vs. 0 (3.0) (p<0.001); and P-VAS 60 (30.0) vs. 50 (40.0) (p<0.001). According to the EULAR response index, there was no difference in comorbidities and cs DMARDs between those who responded well and those who did not. Biologic-naive status and use of baricitinib as monotherapy were significantly more common in the good-responder group than in the non-responder group (Table 4).

Predictors of EULAR good response were determined by logistic regression analysis. A high patient global assessment before baricitinib treatment [odds ratio (OR): 1.05 (95% CI: 1.02-1.09)] was associated with a good response, whereas RF positivity [OR: 7.66 (95% CI: 1.46-40.07)] was associated with a poor response (Table 4). Model fit was assessed using the Hosmer-Lemeshow test (p=0.71).

While a significant improvement in DAS 28 CRP was noted in both the baricitinib and adalimumab arms, the EULAR responder index showed that the proportion of good and moderate responses was significantly higher in the adalimumab arm compared to the baricitinib arm (Table 4). At the last visit, no significant differences were observed between baricitinib and adalimumab on disease activity assessment indices, except for the EULAR good response index.

Retention

Baricitinib retention rate was calculated for the entire study population (n=86; 100%) (Figure 1). The one-year drug survival rate for adalimumab was 61.1%, while that for baricitinib was 54.4% (log-rank test p=0.47). Median retention was 15.1 months for baricitinib and 22.9 months for adalimumab (Figure 2). The median duration of baricitinib treatment was 4.4 (6.3) months [median, interquartile range (IQR)] for biologic-naive patients and 7.5 (6.5) months [med, (IQR)] for biologic experienced patients (p=0.09) (Supplementary Table 1). Survival on baricitinib was significantly higher in biologic-naïve patients compared to biologic-experienced patients [18 (75%) & 37 (69.8%) log rank p=0.02] (Supplementary Figure 1).

Table 3. Clinical and demographic characteristics of patients treated with baricitinib: good vs. non-good responders								
	All patients (n=52)	Good response (n=24)	Non good response (n=28)	p	Multivariate analysis		Final multivariate analysis	
					Adjusted odds ratio (95% CI)	p	Adjusted odds ratio (95% CI)	p
Female n (%)	39 (75.0)	19 (79.2)	20 (71.4)	0.52				
Age (SD)	51.6 (14.0)	51.8 (13.2)	51.2 (15.2)	0.89				
Disease duration, years (SD)	10.4 (6.9)	8.7 (6.3)	11.4 (7.1)	0.15	0.99 (0.88-1.11)	0.90		
Disease duration at the time of the first biologic drug: years (SD)	5.7 (6.0)	5.9 (5.4)	5.1 (6.2)	0.64				
Smoking (%)								
-Never	25/47 (53.2)	12/23 (52.2)	13/24 (54.2)	0.89				
-Ex-smoker or active smoker	22/47 (46.8)	11/23 (47.8)	11/24 (45.8)					
BMI (SD)	26.7 (5.0)	26.7 (4.9)	26.8 (5.1)	0.94				
BMI ≥30 (%)	10/47 (21.3)	4/23 (17.4)	6 (25.0)	0.72				
Hypertension (%)	16/46 (34.8)	9/23 (39.1)	7/23 (30.4)	0.53				
Diabetes n (%)	8/46 (17.4)	2/23(8.7)	6/23 (26.1)	0.24				
Hyperlipidemia n (%)	21/46 (45.7)	11/23 (47.8)	10/23 (43.5)	0.76				
CKD n (%)	4/46 (6.6)	2/23 (8.7)	2/23 (8.7)	1				
Positive RF n (%)	37/50 (74.0)	14/23 (61.0)	23/27 (85.2)	0.05	6.12 (0.89-41.95)	0.06	**7.66 (1.46-40.07)**	**0.01**
Positive CCP n (%)	32/42 (76.2)	14/19 (73.7)	18/23 (78.3)	1				
Duration of baricitinib, months (med, IQR)	5.8 (5.0)	6.8 (4.5)	8.0 (4.3)	0.32				
Last visit (%)								
- Methotrexate	9 (17.3)	4 (16.7)	5 (17.9)	1				
- Salazopyrine	1 (1.9)	0	1 (3.6)	1				
- Hydroxychloroquine	16 (30.8)	5 (20.8)	11 (39.3)	0.15				
- Leflunomide	23 (44.2)	9 (37.5)	14 (50.0)	0.36				
- Glucocorticoid	34 (65.4)	14 (58.3)	20 (71.4)	0.32				
First-visit disease activity								
- ESR (mm/h) (SD)	30.1 (20.0)	29.0 (20.1)	31.0 (19.4)	0.73	1.03 (0.76-1.40)	0.80		
- CRP (mg/dL) (IQR)	0.9 (1.1)	1.27 (0.91)	0.69 (0.98)	**0.05**	0.85 (0.45-1.60)	0.62		
- DAS28 CRP (SD)	4.2 (1.5)	4.7 (1.2)	3.8 (1.7)	**0.04**	0.96 (0.92-1.00)	0.10	**1.05 (1.02-1.09)**	**0.02**
- HAQ (SD)	0.91 (0.6)	0.88 (0.6)	0.94 (0.7)	0.73				
- Swollen joint (IQR)	1 (2.0)	1 (3.0)	0 (2.0)	0.26				
- Tender joint (IQR)	3 (6.0)	3 (5.0)	3 (7.0)	0.15				
- Patient global assessment (VAS) (IQR)	60.0 (30.0)	72.5 (40.0)	50.0 (20.0)	**0.02**				
Last-visit disease activity								
- ESR (IQR)	11.5 (30.0)	7.5 (10.5)	21.0 (40.3)	**<001**				
- CRP (IQR)	0.40 (0.6)	0.34 (0.5)	0.65 (1.2)	**0.07**				
- DAS28 CRP (IQR)	2.7 (2.3)	1.9 (1.4)	3.8 (1.9)	**<001**				
- HAQ (IQR)	0.52 (1.3)	0.05 (0.44)	1.1 (1.01)	**<001**				
- Swollen joint (IQR)	0 (0)	0 (0)	0 (0.8)	**0.03**				
- Tender joint (IQR)	0 (3.0)	0 (0)	2.5 (5.8)	**<001**				
- Patient global assessment (VAS) (IQR)	50 (40.0)	25 (30.0)	50 (30.0)	**0.001**				
DAS28 CRP, last visit (%)								
≤3.2	33 (63.5)	24 (100)	9 (32.1)	**<0.001**				
>3.2	19 (36.5)	0	19 (67.9)					
Biological naive n (%)	18 (34.6)	12 (50.0)	6 (21.4)	**0.03**	2.04 (0.40-10.40)	0.38		
Baricitinib monotherapy (%)	14 (26.9)	10 (41.7)	4 (14.3)	**0.02**	0.42 (0.07-2.32)	0.32		
MACE (%)	2/46 (4.3)	1/23 (4.3)	1/23 (4.3)	1				

BMI: Body mass index, CAD: Coronary artery disease, CKD: Chronic kidney disease, GC: Glucocorticoid, CRP: C-reactive protein, HAQ: The health assessment questionnaire, VAS: Visual analogue scale, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, MACE: Major adverse cardiovascular event, DVT: Deep vein thrombosis, PTE: Pulmonary thromboembolism

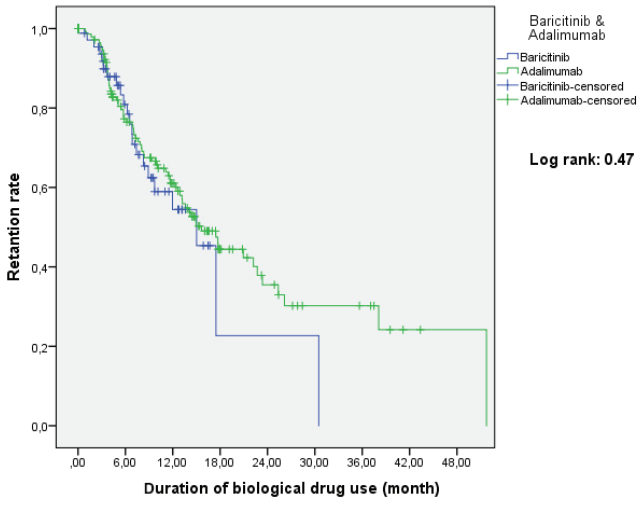

Figure 2. Drug survival rate for adalimumab and baricitinib

Cox regression analysis was performed to evaluate factors associated with survival in patients treated with baricitinib and adalimumab, including disease duration, smoking status, history of cancer in first- and second-degree relatives, HAQ and DAS28 CRP at the first visit, RF positivity, and anti-CCP positivity. We did not identify any significant predictors of improved retention of baricitinib. However, in the adalimumab arm, a higher DAS28 CRP at the first visit [OR: 0.63 (95% CI: 0.41-0.97)] was associated with reduced drug retention.

Adverse Event

Baricitinib was discontinued in 22/77 (28.5%) patients. The primary reason for drug discontinuation in both the biologic-naïve and biologic-experienced groups was treatment failure (Figure 1). In the biologic-naïve group, baricitinib was discontinued in one patient due to an allergic rash. In the biologic-experienced group, one patient experienced an allergic reaction, two patients had infections (tuberculosis and recurrent respiratory and urinary tract infections), four patients discontinued treatment at

Table 4. Comparison of disease activity and response indices between patients receiving baricitinib and adalimumab

	All patients (n=280)	Baricitinib (n=86)	Adalimumab (n=194)	p
First-visit disease activity				
- ESR (mm/h) (SD)	28.7 (21.5)	28.1 (20.2)	29.2 (22.1)	0.72
- CRP (mg/dL) (IQR)	0.9 (1.75)	0.8 (1.3)	1.0 (2.2)	0.23
- DAS28 CRP (SD)	4.4 (1.5)	4.2 (1.5)	4.4 (1.5)	0.37
- HAQ (SD)	1.3 (0.6)	1 (0.6)	1.2 (0.6)	0.07
- Swollen joint (IQR)	0 (2.0)	1 (3.0)	0 (2.0)	0.14
- Tender joint (IQR)	3.0 (7.0)	3.0 (6.0)	3.0 (9.0)	0.62
- Patient global assessment (VAS) (IQR)	70 (30)	60.0 (30.0)	75 (30.0)	0.10
Last-visit disease activity				
- ESR (IQR)	17.5 (31.0)	12.0 (34.0)	19.0 (29.5)	0.06
- CRP (IQR)	0.6 (1.1)	0.5 (0.9)	0.6 (1.2)	0.08
- DAS28 CRP (IQR)	3.6 (2.3)	3.2 (2.7)	3.7 (2.1)	0.21
- HAQ (IQR)	1.1 (1.2)	1.0 (1.4)	1.2 (1.3)	0.27
- Swollen joint (IQR)	0 (1.0)	0 (1.0)	0 (1.0)	0.34
- Tender joint (IQR)	1.0 (5.0)	1.0 (5.0)	1.0 (5.0)	0.94
- Patient global assessment (VAS) (IQR)	57.5 (40.0)	50.0 (50.0)	60.0 (30.0)	0.10
DAS28 CRP, first visit (%)				
≤3.2	50/237 (21.1)	20/76 (26.3)	30/161 (18.6)	0.17
>3.2	187/237 (78.9)	56/76 (73.7)	131/161 (81.4)	
DAS28 CRP, last visit (%)				
≤3.2	74/180 (41.1)	42/83 (50.6)	64/177 (36.2)	**0.02**
>3.2	106/180 (58.9)	41/83 (49.4)	113/177 (73.4)	
EULAR good response index (%)				
Good response	60/159 (37.7)	24 (46.2)	36 (33.6)	**0.03**
Moderate response	30/159 (18.9)	4 (7.7)	26 (24.3)	
Poor response	69/159 (43.4)	24 (46.2)	45 (42.1)	

CRP: C-reactive protein, DAS28: Disease activity score, ESR: Estimated sedimentation rate, EULAR: The European Alliance of Associations for Rheumatology, HAQ: The health assessment questionnaire, IQR: Interquartile range, VAS: Visual analogue scale

Table 5. Comparison of MACE rates between baricitinib and adalimumab in different patient subgroups			
Patient group	**Baricitinib**	**Adalimumab**	**p**
Treatment-naïve patients (events per 1000 patient-years)	25	16.5	0.21
Patients with prior exposure to at least one biologic agent (events per 1000 patients-year)	11	3.8	0.08
Patients without a family history of cardiovascular disease (events per 1000 patients-year)	11.8	7.5	0.41
Non-smokers (events per 1000 patients-year)	17.6	14.1	0.67
MACE: Major adverse cardiovascular event			

the physician's request, and one patient discontinued treatment for unclear reasons. Pulmonary thromboembolism occurred in 1 patient (1.3%) in the baricitinib group and in 3 patients (2.8%) in the adalimumab group. No hepatitis activation was observed in either group; however, HZ was reported in one patient in the adalimumab group but not in the baricitinib group.

Major cardiovascular events occurred in 2 patients (2.5%) [1 myocardial infarction, 1 cerebrovascular event in the baricitinib group and 4 patients (2.5%)]. [One patient had both a myocardial infarction and a cerebrovascular event, and three had a cerebrovascular event] in the adalimumab group (Table 1). The median age of these six patients was 60 years (range: 51-78 years). Among the patients with major adverse cardiovascular events, 1 patient presented with hyperlipidemia (HL); 2 patients presented with HL, DM, and hypertension (HT); 1 patient presented with HL, DM, HT, and dysrhythmia; 1 patient presented with DM and HT; and 1 patient presented with HT and deep vein thrombosis. MACE events were recorded at rates of 15.3 and 9.1 per 1,000 patient-years among individuals taking baricitinib and adalimumab, respectively (p=0.2). We separately evaluated MACE rates between the two groups (baricitinib and adalimumab) within the following subgroups: treatment-naive patients; patients with prior exposure to at least one biologic agent; patients without a family history of cardiovascular disease; and non-smokers, and found no statistically significant differences between the groups (Table 5). None of the baseline population characteristics, including treatment group, treatment-naïve status, treatment duration, smoking status, and family history of cardiovascular disease, were significantly associated with the risk of MACE in the multivariate analysis (overall model p=0.93). One patient in the adalimumab group developed renal cell carcinoma within the first year of treatment, while no cancer was detected in the baricitinib group.

Discussion

The study compares the effectiveness, retention rate and safety of baricitinib with adalimumab in treating RA patients in a real-life clinical setting. In addition, this study includes comparisons between biologically naïve and experienced groups, and between baricitinib monotherapy and baricitinib combined with csDMARD treatment groups.

After 6 months of follow-up, significant improvements were observed in disease activity parameters, such as ESR, CRP, DAS, HAQ, patient VAS scores, and swollen and tender joint counts. A high patient global assessment was associated with a good EULAR response. Although both baricitinib and adalimumab showed significant improvement in DAS28 CRP, the EULAR responder index showed a higher proportion of good and moderate responses in the adalimumab arm than in the baricitinib arm. At the last visit, no significant difference was observed between baricitinib and adalimumab in disease activity assessment indices, except for the EULAR good response index. Most studies reported follow-up durations of 24 weeks (6 months), like ours.[4] All JAK inhibitors, including baricitinib, demonstrated non-inferiority or superiority to adalimumab or abatacept.[3,15] In our study, the higher EULAR good-response index in the adalimumab arm may be explained by the adalimumab group being biologic-naïve. Similar discrepancies in the responses of various effectiveness measures have been noted in the relevant literature, including the post-marketing study by Wu et al.[16] on baricitinib in RA (DAS28-CRP and SDAI/CDAI), the Chinese CREDIT study (DAS28-CRP and CDAI), and the RA-BEAM study (DAS28-CRP and SDAI/CDAI). These results highlight the variability in assessing treatment response across scales and the need for careful consideration when interpreting clinical results in RA management.[15-17] In a multicenter study by Guidelli et al.[18], 446 RA patients who were treated with baricitinib were evaluated at baseline and at 3, 6, and 12 months. The cohort consisted of 34% bDMARD-naïve responders and 66% bDMARD-insufficient responders. At 3 and 6 months, 36% and 51.6% of patients achieved remission, while 20% and 15.9% had LDA at those time points, respectively. In the ELECTRA-i study by Benucci et al.[19], baricitinib significantly improved DAS 28, VAS, and HAQ scores, as well as measures of swollen and tender joints, consistent with our study.

RF positivity was an independent predictor of poor treatment response in our cohort (OR: 7.66). This differs from reports showing better responses to rituximab and abatacept in seropositive RA patients. For JAK inhibitors, the evidence is less

consistent: several real-world studies found no clear relationship between RF/anti-CCP positivity and either effectiveness or treatment discontinuation due to lack of effect, and a large claims-based analysis reported similar 1-year effectiveness in seropositive and seronegative patients initiating bDMARDs/JAK inhibitors.[20-22] In contrast, a pooled post hoc analysis of Phase III tofacitinib trials suggested higher ACR responses in anti-CCP+/RF+ patients than in double-seronegative patients.[23] Overall, our findings may reflect differences in patient characteristics, prior treatments, and outcome definitions, and should be confirmed in prospective cohorts.

Adalimumab had a higher one-year drug survival rate (61.1%) than baricitinib (54.4%), with median retention times of 22.9 months and 15.1 months, respectively. Nonetheless, this finding has not reached statistical significance. In contrast, the Australia-wide study by Lieke Scheepers reported a 12-month persistence rate of 61% for baricitinib and 58% for subcutaneous TNF-alpha inhibitors. This discrepancy highlights regional differences in drug persistence and suggests that factors such as patient populations, health practices, and treatment protocols may influence the long-term adherence and effectiveness of these therapies.[24] In our study, biologics-naïve patients had significantly higher baricitinib survival rates than biologics-experienced patients. In the RA-BE-REAL study (baricitinib, n=509), b/tsDMARD-naïve patients had a lower discontinuation rate of baricitinib at 12 months than patients who had received more than two prior b/tsDMARDs.[25]

Baricitinib was discontinued in 28.5% of patients, primarily due to treatment failure across all groups. In the biologic-naïve and biologic-experienced groups, discontinuations of baricitinib were due to allergic reactions, infections, and other reasons; pulmonary thromboembolism was less frequent with baricitinib whereas HZ occurred only with adalimumab. In RCTs, the most common side effects of baricitinib, in addition to HZ, were upper respiratory tract infections, urinary tract infections, nasopharyngitis, influenza, and gastroenteritis. In contrast to these studies, which reported no cases of tuberculosis in baricitinib-treated patients, our series documented one case.[15,26] However, consistent with the literature, our series does not show a significant increase in risk of severe infection.[3] Although solid cancers associated with baricitinib have been reported in RCTs, no such cases were observed in our series. This can be attributed to the relatively small number of patients and the short follow-up period. In real-world data, similar to those from RCTs and our study, the most commonly observed adverse reactions were HZ, upper respiratory tract infections, and gastroenteritis.[27-31]

MACE events occurred at higher rates in the baricitinib group (15.3 per 1000 patient-years) than in the adalimumab group (9.1 per 1000 patient-years); however, this difference was not statistically significant. Although we reported MACE, malignancy, and thromboembolic events for both treatment groups, the absolute number of events was low. Therefore, these safety results are descriptive, and between-group comparisons should be interpreted with caution due to limited statistical power. The ORALSURV study focused on patients with R who were over 50 years old and had cardiovascular risk factors. They received either tofacitinib or anti-TNF therapy (etanercept or adalimumab, depending on the region). During a median follow-up of 4.0 years, the incidence of MACE was higher with combined doses of tofacitinib (3.4%) than with a TNF inhibitor (2.5); the hazard ratio was 1.33 (95% CI: 0.91-1.94). Although the study only evaluated tofacitinib, the FDA applied the study's results to all JAK inhibitors used to treat immune-mediated inflammatory diseases. As a result, they limited the use of this class of drugs to patients with RA only after TNF inhibitor treatment had failed [5]. On the other hand, in a study by Smolen et al.[32] using the "All-Bari-RA" method, which included 3492 patients over 6637 patient years (PY) and data from six studies comparing 4 mg baricitinib and placebo through week 24, the MACE rate was 0.5/100 PY and did not increase with prolonged exposure to baricitinib compared to placebo. In real-world data from the German RABBIT registry, the incidence of MACE in 1,416 RA patients using baricitinib was 0.49 (0.25 to 0.85). This rate did not increase compared with other JAK inhibitors, anti-TNF therapies, and biologics.[33] In a 24-week study of RA patients in Japan, the MACE rate was found to be 0.38/100 PY.[34] The long-term extension study by Taylor et al.[35] assessing the safety of baricitinib found that the safety data reported in previous studies remained unchanged. Given these data, it seems reasonable to re-evaluate the FDA's generalization of a molecular-based class effect for MACE. MACE incidence appeared slightly higher in our study than reported in the literature, possibly because the patients were >50 years old and had multiple comorbidities.

Study Limitations

Our study has limitations, including a short follow-up period and a small sample size. Given the non-randomized, real-world nature of this cohort, baseline characteristics differed between groups; most notably, the baricitinib arm had a lower proportion of biologic-naïve patients. Such imbalances may have influenced comparative effectiveness and retention; thus, between-group differences should be interpreted with caution, as they may partially reflect confounding by indication, rather than isolated treatment effects. Missing baseline and/or follow-up data led to the exclusion of a subset of baricitinib-treated patients from efficacy analyses. Because missingness cannot be assumed to be completely random in a real-life registry, these results may be affected by selection bias and have limited generalizability. Our database did not contain routine assessments of pain scores, and therefore we were unable to assess the effect of baricitinib on

pain. The single-center study design presented another notable drawback. On the other hand, because of the short duration of the study, the impact on radiological progression was not assessed.

The study's strengths lie in its prospective design and the rigorous, three-monthly patient monitoring mandated by the Turkish healthcare system for prescribing targeted and biological DMARDs. Thus, patient-reported outcomes and laboratory checks are completed without exception.

Conclusion

In conclusion, this study highlights that baricitinib has a similar effectiveness and safety profile to adalimumab in patients with RA. Both drugs effectively reduced disease activity, and no significant difference was observed in the incidence of MACE (Major Adverse Cardiovascular Events) between the two groups. Baricitinib was more frequently used as monotherapy and showed favorable responses, particularly in biologic-naïve patients. These findings suggest that baricitinib is a safe and effective alternative to adalimumab for the management of RA.

Ethics

Ethics Committee Approval: This study was approved by Hacettepe University Ethics Commission (approval number: 2023-02-02, date: 24.01.2023).

Informed Consent: Informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.E., Z.Ö., G.A., G.S.U., E.Ü., B.F.Y., G.S.K.B., B.B., L.K., A.A., Ş.A.B., S.K., İ.E., Concept: M.E., E.B., L.K., İ.E., Design: M.E., E.B., L.K., İ.E., Data Collection and Processing: M.E., İ.Y.İ., E.E.D., Z.Ö., G.A., G.S.U., E.Ü., B.F.Y., G.S.K.B., B.B., A.A., Ş.A.B., S.K., İ.E., Analysis or Interpretation: M.E., L.K., İ.E., Literature Search: M.E., E.Ü., L.K., İ.E., Writing: M.E., E.B., L.K., İ.E.

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Supplementary Tables Link: https://d2v96fxpocvxx.cloudfront.net/7a593d95-86ec-4d2b-8dd3-26b0d0b79ea4/content-images/2190214e-bfdc-41e1-b5e1-7e23b97036ab.pdf

Supplementary Figure 1 Link: https://d2v96fxpocvxx.cloudfront.net/7a593d95-86ec-4d2b-8dd3-26b0d0b79ea4/content-images/1c15ec3a-a9a2-47d1-ba99-74338e97cfb9.pdf

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