ORIGINAL PAPER

Effectiveness and safety profile of tofacitinib and baricitinib in rheumatoid arthritis patients: results from a 24-month real-life prospective study in Southern-Italy

M. Tasso,[1] N. Bertolini[1], E. Mostacciuolo[1], S. Passavanti[1], J.M.E. Luppino[1], A. Del Puente[1], R. Peluso[1], F. Santelli[2], R. Scarpa[1], L. Costa[1], F. Caso[1]

[1]Rheumatology Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; [2]Department of Political Science, University of Naples Federico II, Naples, Italy

SUMMARY

The primary objectives of the study were to evaluate the efficacy and safety of tofacitinib and baricitinib up to 24 months of follow-up in patients with rheumatoid arthritis (RA) treated in Southern Italy.

Patients' data, activity index, and clinimetric scores were collected at baseline (T0), six (T6), twelve (T12), and twenty-four (T24) months following treatment initiation. At six, twelve, and twenty-four months, adverse events and treatment cessation were also recorded.

Sixty-eight patients (mean age: 62.2±10.9 years; mean RA duration: 15±9.6 years) were enrolled over a period of 12 weeks. At baseline, twenty-four patients (35.3%) were treated with tofacitinib, and forty-four patients (64.7%) were treated with baricitinib. The baseline mean disease activity was moderate as measured by DAS28-ESR (5.0±1.0), DAS 28 CRP (4.69±0.94), and SDAI (26.87±10.73) score.

Before beginning JAKinhibs therapy, thirty-two patients (61.8%) were taking bDMARDs, while the remaining thirty-six (38.2%) were bDMARDs-naïve.

The 24-month retention rate for JAKinhibs was 91.1%. Six months after beginning treatment with JAKinhibs, a statistically significant improvement was observed in all evaluated activity indices and clinimetric scores. Improvement was confirmed during the 12- and 24-month follow-up evaluations. The positive correlation between baseline-T6 SDAI delta and discontinuation of JAKinhibs (p=0.02) suggests that RA worsening in the first six months may be a predictor of therapy withdrawal.

Patients with RA responded favorably to tofacitinib and baricitinib in this prospective, real-world study from a single center in Southern Italy. Efficacy was observed despite an underlying persistent and treatment-resistant disease.

Key words: *Rheumatoid arthritis, tofacitinib, baricitinib, JAK inhibitors.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a multisystemic inflammatory disease affecting small and large joints as well as other tissues (1). Reversing the underlying inflammatory processes is the primary therapeutic objective in order to prevent articular damage or its progression and maximize physical function. Disease control necessitates of a strategic approach based on evaluation of activity by DAS-28 and SDAI or CDAI (2, 3).

The Janus kinase-signal transduction and activation of transcription (JAK-STAT) pathway has been identified as a central mediator of rheumatoid inflammation (4-6). Tofacitinib (5 mg twice daily) and baricitinib (4 mg daily) are approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment, with or without methotrexate (MTX), of moderate to severe active RA in adult patients who have inadequately responded to or cannot tolerate one or more DMARDs (7, 8). Both the European League Against Rheumatism (EULAR) and the American Col-

Corresponding author:
Raffaele Scarpa
Rheumatology Research Unit,
Department of Clinical Medicine and Surgery,
University of Naples Federico II
Via Pansini, 5 - 80131 Naples, Italy
E-mail: rscarpa@unina.it

lege of Rheumatology (ACR) recommend JAK inhibitors (JAKinhibs) as second- and third-line treatments for RA (9, 10). Randomized controlled trials (RCTs) involving JAKinhibs for the treatment of RA patients who are methotrexate (MTX) naive or have an inadequate response to MTX and bDMARDs, have demonstrated favorable outcomes (4-6). In a series of phase II and phase III RCTs, the efficacy and safety of tofacitinib and baricitinib, alone or in combination with methotrexate (MTX), have been extensively evaluated, demonstrating the sustained efficacy and safety profile of these small-molecule oral agents, administered either as monotherapy or in combination with csDMARDs (11, 12).

Extensive observational research on JAKinhibs in RA is expanding, and a substantial amount of data from real-world clinical settings is now accessible. Several of these data are limited to a 12-month follow-up period (13-18).

Consequently, the primary objectives of the present study were to assess the efficacy, as measured by DAS-28 and SDAI, and safety of tofacitinib and baricitinib during a of follow-up up to 24 months in patients with RA treated in a real-world setting in Southern Italy.

PATIENTS AND METHODS

The Arthritis Outpatients clinic of the Federico II University Hospital in Naples is a large tertiary center that treats over 1500 patients with RA and spondyloarthropathies on bDMARD and tsDMARDs. A prospective database for all RA patients meeting the 2010 ACR-EULAR criteria (19) and receiving JAKinhibs is ongoing. All patients who began therapy between October 2019 and January 2022 (DMCC/02/2021) were enrolled in this study after informed consent; the protocol was approved by the Ethical committee. The study was conducted in accordance with the ethical principles of the Helsinki Declaration and according to the principles of good clinical practice.

Data were collected at baseline (T0) and after 6, 12, and 24 months of treatment (T6, T12, T24). These included age, sex, disease duration, body mass index (BMI), smoking habits, steroid treatment as prednisone equivalent daily steroid dose, current csDMARD use, and history of csDMARDs and bDMARDs exposure.

In addition, at each visit, assessment of disease activity included physician's global assessment of disease activity (PGA), patient's assessment of disease activity (VAS) on a 0-100 mm scale, tender and swollen joint counts on 68 and 66 joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) serological status, disease activity score on 28 joints calculated with C-reactive protein (DAS28-CRP) and with erythrocyte sedimentation rate (DAS28-ESR), and simplified disease activity index (SDAI).

At 6, 12, and 24 months after treatment initiation, adverse events were noted. When patients discontinued therapy, the reasons for JAKinhibs discontinuation were classified as lack of efficacy, adverse event, or loss to follow-up.

Statistical analysis

Continuous data are displayed using the mean and standard deviation (SD). To test the change in the disease activity indices over time, ANOVA and ANCOVA for repeated measures, with Bonferroni post-hoc correction were used.

The retention rates over time were compared using percentages. A p value<0.05 was considered statistically significant. All statistical analyses were conducted using version 4.1.2 of the R software.

RESULTS

Baseline study cohort

Over the course of 12 weeks, 68 patients were enrolled in the study: 54 females (79.5%) and 14 males (20.5%). At baseline, the average age was 62.2±10.9 years, and the average duration of disease was 15±9.6 years. In 39 (57.4%) and 26 (38.2%) patients, respectively, RF and ACPA were positive. The baseline mean disease activity was moderate to severe as measured by DAS28-ESR (5.0±1.0), DAS 28 CRP (4.69±0.94),

and SDAI (26.87±10.73) scores. Twenty-four (35.3%) patients were treated with tofacitinib 5 mg twice daily and 44 (64.7%) were treated with baricitinib 4 mg daily.
At baseline, 38 patients (55.9%), including 9 on tofacitinib and 29 on baricitinib, were receiving combination therapy with one csDMARD. Particularly, 35 were administered MTX, two were administered leflunomide, and one was administered hydroxychloroquine. In addition, 42 (61.8%) patients reported a combined glucocorticoid therapy (mean dosage equivalent to 5 mg±5.58 mg prednisone daily). Before beginning JAKinhibs therapy, 32 patients (61.8%) were taking bDMARDs, while the remaining 36 (38.2%) were bDMARDs-naïve. Table I summarizes the baseline clinical and laboratory characteristics of the study population.

Table I - Baseline clinical and laboratory characteristics of patients.

Number	68
F/M	54/14
Age, years	62.21±10.93
Disease duration, years	15±9.6
Smoking, n (%)	20 (29.4%)
BMI	27.07±4.4
RF, positive	39 (57.4%)
Anti-CCP, positive	26 (38.2%)
Steroids, yes	42 (61.8)
cDMARDs, n (%)	38 (55.9%)
tsDMARDs naïve, n (%)	26 (38.2%)
ESR, mm/h	25.9±19.7
CRP, mg/L	12.4±15.3
DAS28 ESR	5.0±1.0
DAS28 CRP	4.7±0.9
SDAI	26.9±10.7
Tender joint count	8.1±5.1
Swollen joint count	3.1±3.5
Patient's global assessment VAS	7.3±1.8
Physician's global assessment VAS	6.8±1.8

Data are expressed as mean and standard deviation (SD).

Effectiveness and safety evaluation

The drug retention rate at 24 months was 91.1%. Six patients (8.8%) discontinued JAKinhibs during the follow-up period (three patients at 6 months and three patients at 12 months): four for primary failure (one patient in therapy with baricitinib and three with tofacitinib), one for herpes zoster reactivation on baricitinib; one patient was lost at follow-up.
Six months after beginning treatment with JAKinhibs, a statistically significant improvement was observed in all evaluated activity indices and clinimetric scores. Improvement was confirmed during the 12- and 24-month follow-up evaluations (Table II). According to the study's primary endpoint, a statistically significant improvement in the DAS-28-CRP score was observed at T6, T12, and T24 months compared to baseline ($p<0.0001$). Likewise, DAS28-ESR, SDAI, as well as PGA and VAS, were significantly decreased at T6, T12, and T24 months ($p<0.0001$) compared to baseline (Figure 1A-E). At 6 and 12 months, when DAS-28-CRP values were evaluated, 16 out of 68 (23.5%) and 28 out of 65 (43.1%) patients achieved remission, while 8/68 (11.8%) and 8/65

Table II - Improvement of SDAI, DAS-CRP, DAS-ESR, VAS, and PGA at 6-, 12-, and 24-months follow-up visits after JAK-inhibitors treatment start, and comparison between activity indices and clinimetric variables at baseline and at T6, T12 and T24.

	Baseline (mean±SD)	T6 (mean±SD)	T12 (mean±SD)	T24 (mean±SD)	Baseline vs T6 p-value	Baseline vs T12 p-value	Baseline vs T24 p-value
SDAI	26.87±10.73	16.69±10.80	12.53±11.62	9.42±7.01	p<0.005	p<0.005	p<0.005
DAS-CRP	4.69±0.95	3.54±1.34	2.92±1.37	2.73±0.95	p<0.005	p<0.005	p<0.005
DAS-ERP	5.02±1.08	3.79±1.46	3.41±1.56	2.99±0.98	p<0.005	p<0.005	p<0.005
VAS	6.76±1.77	4.61±2.54	3.43±2.65	2.87±2.47	p<0.005	p<0.005	p<0.005
PGA	7.35±1.78	5.23±2.47	4.12±2.83	3.5±2.67	p<0.005	p<0.005	p<0.005

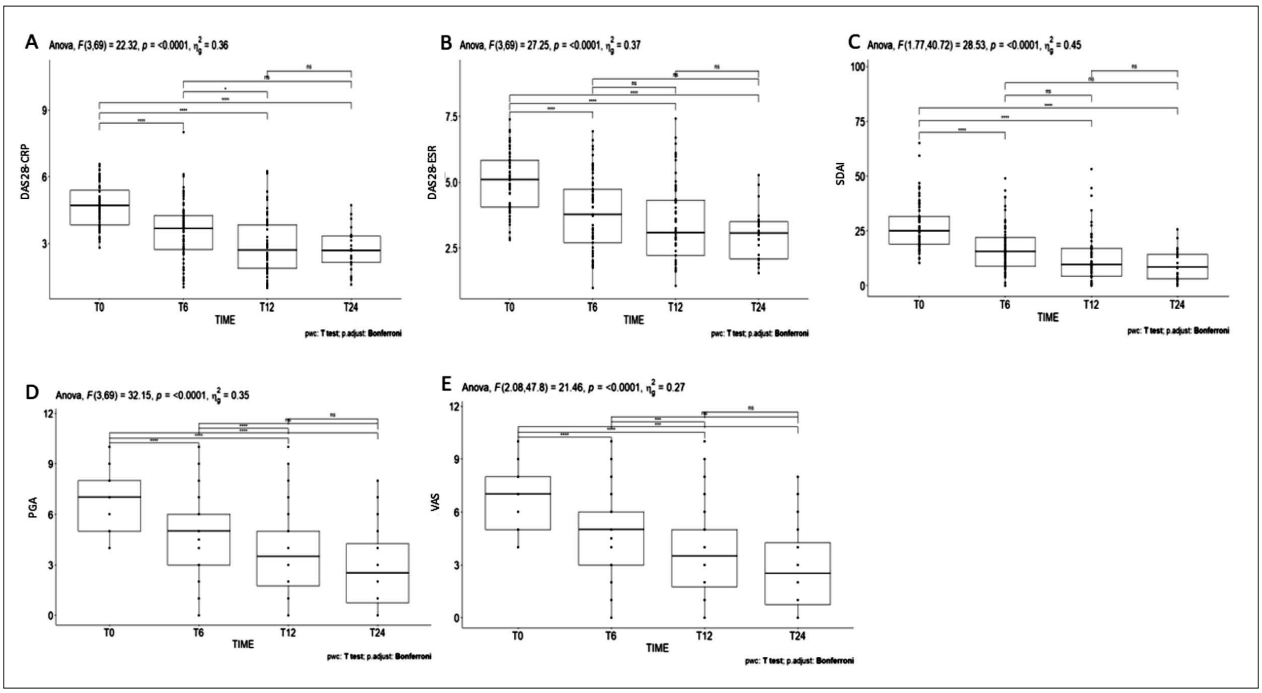

Figure 1 - Tofacitinib and baricitinib effectiveness evaluated by: A) DAS28-CRP; B) DAS28-ESR; C) SDAI; D) VAS-pain; E) PGA.

(12.3%) patients were in low disease activity (LDA); at 24 months, 28/62 (45.2%) patients were in remission and 9/62 (14.5%) were in LDA.

Evaluation of SDAI at 6 and 12 months revealed that 4768 (5.9%) and 12/65 (18.5%) patients achieved remission, whereas those in LDA were 18/68 (26.5%) and 18/65 (27.7%); at 24 months, 12/62 (19.3%) patients achieved remission, whereas those in LDA were 18/62 (29%). At 24 months, 11/38 patients on combined therapy with csDMARD and 25/42 patients on steroids discontinued their respective medications.

Neither sex nor other variables were significant in determining differences in SDAI over time. We did not find statistically significant differences in SDAI, DAS28-ESR, DAS 28-CRP, VAS, and PGA at different times, when patients were categorized according to the following variables: sex, age, disease duration, body mass index (BMI), smoking habits, current treatment with steroid as determined by the prednisone equivalent daily steroid dose, current csDMARD use and history of csDMARDs and bDMARD exposure.

During the 24-month follow-up period, infections were the most common adverse event, occurring in 13 patients (19.1%); three patients tested positive for SARS-CoV-2; urinary tract and upper respiratory tract infections occurred in three and six patients, respectively; therapy was not discontinued in these cases. Herpes zoster reactivation was observed in one baricitinib-treated patient, resulting in treatment discontinuation. During the study, no major cardiovascular adverse events were observed.

Analyzing baseline-T6 SDAI delta, it was found to be positively correlated with discontinuation of JAKinhibs (p=0.02), suggesting that a worsening of the disease in the first six months may be a predictor of therapy discontinuation.

DISCUSSION

This study confirms that tofacitinib and baricitinib, both as monotherapy and in combination with csDMARDs, are effective and safe in a real-world setting for patients with moderate-to-severe RA, leading

to clinical improvement. Specifically, this prospective, real-world study evaluating RA patients treated with tofacitinib and baricitinib at a single center in Southern Italy demonstrated a positive response to these therapies. Efficacy was observed despite the disease being active, persistent, and treatment-resistant at baseline. Despite the small sample size, the results of this study are consistent with those reported in the literature from RCTs and other real-world cohorts demonstrating an improvement in all clinimetric scores and activity indexes in both bDMARD-naïve and failure RA patients (13-18).

According to the literature, we also observed a significant improvement in all activity indexes and clinimetric scores (DAS-28-CRP, DAS28-ESR, SDAI) as well as a significant decrease in pain as measured by VAS, and PGA from the early months of therapy. In fact, at 6 months, more than a quarter of patients treated with tofacitinib and baricitinib achieved remission and LDA. Efficacy was maintained during the 12- and 24-month follow-up visits. Changes in the SDAI over time were not affected by sex or other variables.

Regarding safety, our study reveals that mild adverse events occur during treatment. Twenty percent of enrolled patients experienced mild infections; in only one case (herpes zoster reactivation) was baricitinib therapy temporarily discontinued, resulting in resolution of the infectious disease. Neither deep venous thrombosis/pulmonary embolism nor tuberculous infection reactivation were observed during the study.

Noteworthy, the 24-month drug retention rates were 91.1%. Only six patients (8.8%) discontinued JAKinhibs over the course of the entire follow-up (three patients at 6 months and three patients at 12 months): four for primary failure, one for an adverse event (herpes zoster reactivation), and one patient was lost to follow-up. Moreover, our findings suggest that RA worsening during the first six months of JAKinhibs therapy may be predictive of therapy discontinuation. However, this conclusion may be influenced by factors such as the small number of patients enrolled, their baseline condition, and the use of combined drugs. Therefore, additional research is required to confirm our findings.

This is, to the best of our knowledge, the first study to describe the real-world experience of tofacitinib and baricitinib in Southern Italy, focusing on efficacy, safety, and retention rates.

Significant strengths of the study include a high mean age and a prolonged disease duration, subgroups for which literature data are scarce. The absence of a control group and the small number of enrolled patients are the primary limitations.

Our study addresses the need for additional real-world research in Italy, especially given the widespread use of JAKinhibs-based therapies. In summary, JAKinhibs demonstrate a favorable efficacy and safety profile even during the repeated COVID 19 pandemic waves which occurred during study.

Contributions

Marco Tasso and Nicoletta Bertolini contributed equally to this study; Luisa Costa and Francesco Caso are co-last authors.

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