Effectiveness and safety of baricitinib in rheumatoid arthritis: a monocentric, longitudinal, real-life experience

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Abstract

Objective

Baricitinib is a Janus-kinase (JAK) 1/2 inhibitor, approved for the treatment of moderate-to-severe rheumatoid arthritis (RA) patients with inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). We report the first real-life experience with baricitinib in a monocentric cohort of unselected RA patients.

Methods

We enrolled consecutive RA patients starting baricitinib. At baseline and after 4, 12, 24 and 48 weeks we assessed the disease activity by composite indices (SDAI, CDAI and DAS28$_{CRP}$) and ultrasonography, and we recorded any adverse events. The primary endpoint was the percentage of patients achieving SDAI remission at week 4.

Results

We enrolled 59 patients [(F:M = 50:9, median age 58.1 years (IQR 12.8), median disease duration 144 (IQR 150) months] treated with baricitinib in combination with a csDMARD (52.5%) or monotherapy (47.5%) for a median follow-up of 24 weeks (IQR 36). The 12-month drug retention rate was 74%. At weeks 4, 12, 24 and 48 we observed a significant reduction of DAS28, CDAI and SDAI, global health and pain ($p<0.001$ for all). After 4 weeks of treatment, 12% of patients achieved SDAI remission. Concomitant csDMARDs, previous biological DMARDs, gender, seropositivity and BMI did not affect the efficacy of baricitinib. Baricitinib allowed a significant reduction in prednisone dose after 12 and 24 weeks and a rapid and sustained ultrasound improvement. No serious adverse events, serious infections or cardiovascular events were recorded.

Conclusion

Our study confirms the efficacy and safety profile and rapid onset of the effect of baricitinib in RA patients in a real-life setting.

Key words
rheumatoid arthritis, therapy, baricitinib, effectiveness, safety, remission, pain

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Introduction

Janus kinases (JAKs) play a key role in the signalling pathways of many cytokines involved in the pathogenesis of rheumatoid arthritis (RA). The JAK family encompasses 4 cytoplasmic protein tyrosine kinases: JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2). Given their role in cytokines signalling, in the last decade, JAKs emerged as a potential therapeutic target in RA (1, 2). Baricitinib is an oral JAK inhibitor targeting selectively and reversibly JAK1 and JAK2, thus inhibiting the intracellular signal of a broad spectrum of cytokines whose receptors use the JAK1/2. This drug acts as competitive adenosine triphosphate (ATP) antagonist inhibiting the phosphorylation - and activation - of JAKs and the downstream activation of signal transducers and activators of transcription (STATs) pathways. In 2017, the European Medical Agency approved baricitinib 4 mg once a day for the treatment of adults with active RA and an inadequate response or intolerance to conventional synthetic DMARDs (csDMARDs). Baricitinib efficacy and safety profile have been evaluated in an extensive clinical program including 3 phase II, 4 phase III randomised clinical trials (RCTs) and one long term extension study (3-9). Overall, baricitinib showed a significantly greater improvement in efficacy outcomes compared to placebo in patients with inadequate response or intolerance to methotrexate (MTX) or other csDMARDs and to TNF inhibitors (7-9). Moreover, the results of phase III studies demonstrated that baricitinib was superior to MTX in patients naïve to biological DMARDs (bDMARDs) (6, 7). As for the safety profile, the frequency of severe adverse events, including infections, malignancy and cardiovascular events, was similar to that observed with bDMARDs (10, 11).

Although RCTs reduce bias and confounders through randomisation and application of very rigorous inclusion and exclusion criteria, the highly selected patients they include are not usually representative of a real-life context (12). On the other hand, description of routine clinical practice, unaffected by strict criteria, could provide reliable and reproducible information (13, 14). To date, baricitinib efficacy and safety data derive exclusively from RCTs, and information from daily practice are still lacking. To the best of our knowledge, this is the first study describing the effectiveness of baricitinib in a real-life setting, presenting data from an Italian monocentric cohort of unselected RA patients. Notably, the effectiveness of baricitinib was evaluated by using clinimetric and ultrasonographic (US) assessment.

Materials and methods

Patients

We enrolled consecutive patients with RA diagnosed according to 2010 ACR/EULAR classification criteria followed-up at the Arthritis Center, Sapienza University of Rome (15). All patients were candidate to baricitinib 4 mg daily for moderately-to-severely active RA and inadequate response or intolerance to ≥1 csDMARD. The study was approved by the local ethics committee. All patients signed a dedicated informed consent for inclusion in this observational study. The screening for latent tuberculosis, previous Varicella-Zoster and B/C hepatitis virus infections was performed before starting baricitinib. After the baseline visit, all patients returned periodically to the centre to renew their prescription as for local regulation.

At baseline, and then after 4, 12 and 24 weeks of therapy, we collected demographics, height and weight, serological data [erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); Rheumatoid Factor (RF); anti-citrullinated peptides antibodies (ACPA)] and clinical data (number of tender and swollen joints). Disease activity was assessed by Disease Activity Score 28 ($DAS28_{CRP}$), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI).

Remission and low disease activity (LDA) were defined according to DAS28, CDAI and SDAI definitions (16-18).

Moreover, physician's (PhGA) and patient's (PGA) assessment of disease activity and pain were measured by using a visual analogue scale (VAS 0–100 mm).

Ultrasound evaluation

At the same time-points of clinical assessment, US was performed by a 16-year experienced operator, blinded to the clinical evaluation. We applied a multiplanar US grey-scale and power Doppler examination of bilateral I–V metacarpophalangeal, I–V proximal interphalangeal and radiocarpal joints using a MyLab Eight Exp machine (Esaote, Firenze, Italy; linear array transducer 6–18 MHz). According with OMERACT definitions, the presence of synovial effusion, hypertrophy and power Doppler were assessed and scored on a semi-quantitative scale (0=absent, 1=mild, 2=moderate, 3=severe), obtaining a total US score (0–198), representing the joint inflammatory status (19).

Safety profile

At baseline, cell blood count, serum transaminases, creatinine, creatine phosphokinase (CPK) and lipid profile were recorded. These blood tests were repeated at 12 and 24 weeks of follow-up. At each visit, any adverse event was recorded.

Statistical analysis

The primary endpoint of the study was the percentage of patients achieving SDAI remission after 4 weeks of treatment with baricitinib. For the sample size calculation, we assume that a percentage of 3% would have achieved remission after 4 weeks, considering that in RA-BEACON 5% of patients with long-standing RA and inadequate response to TNFi obtained SDAI remission after 12 weeks (9). A sample of 55 patients would have allowed the evaluation of the primary endpoint with a confidence interval of 95% and a margin of error of 5%, considering a drop-out rate of 10%.

Quantitative variables were expressed as median and interquartile range (IQR). Paired non-parametric variables (pre/post comparisons) were compared using the Wilcoxon test and Spearman's tests for correlation. Categorical variables were compared using the χ^2 test. To manage the missing data we used the complete case analysis. All statistical tests were performed at a two-sided significance level of 0.05 with GraphPad Prism v. 7.00 for Mac (GraphPad Software, La Jolla California USA) or SPSS statistical software (SPSS, Chicago, IL, USA).

Results

From February 2018 to December 2019, 59 consecutive RA patients [50F and 9M; median age 58.1(12.8)], attending to the Sapienza Arthritis Center, started treatment with baricitinib. All the enrolled patients were prescribed 4 mg daily. Thirty-one patients (52.5%) took baricitinib in combination with csDMARDs [methotrexate n=26 (83.9%) hydroxychloroquine n=6 (19.4%), leflunomide n=2 (6.5%), sulfasalazine n=3 (9.7%)].

Table I summarises the demographic, clinical and serological features of the enrolled patients at baseline.

Patient's disposition and drug survival rate

Out of 59 patients enrolled, 52 reached 4 weeks of follow-up, 50 and 38 reached the 12- and 24-weeks follow-up visits, respectively. Twenty-three reached the 48-weeks follow-up evaluation. The overall retention rate at this time-point was 74% (Fig. 1). Median drug survival was 24 (IQR 36) weeks.

Two out of 52 patients (3.39%) withdrew for lack of efficacy after 12 weeks. Nine patients stopped baricitinib due to loss of efficacy after a median follow-up of 48 (IQR 24) weeks. Two patients stopped for adverse events after 12 and 24 weeks of treatment and two more patients withdrew for their own decisions. No patients were lost to follow-up.

Achievement of remission or low disease activity

The primary endpoint of the study was met: after 4 weeks of treatment with baricitinib, 12% of patients achieved the SDAI remission, regardless of the baseline disease activity.

Figure 2A shows the percentage of patients achieving remission according to SDAI, CDAI and $DAS28_{CRP}$ during the follow-up. Similarly, the percentage of patients in LDA according to SDAI, CDAI and $DAS28_{CRP}$ increased from week 4 to week 48 (Fig. 2B).

Table I. Baseline demographic, clinical and serological features of 59 enrolled RA patients.

Disease duration (months)*	144	(135)
Rheumatoid Factor positivity, n (%)	48	(81.3)
Anti-cyclic citrullinated peptide positivity, n (%)	50	(84.7)
BMI*	24.53	(5.9)
Disease duration (months)*	144	(135)
Rheumatoid Factor positivity, n (%)	48	(81.3)
Anti-cyclic citrullinated peptide positivity, n (%)	50	(84.7)
Number of previous bDMARDs, n (%)		
0	9	(15.3)
1	12	(20.3)
2	16	(27.1)
3	3	(5.1)
≥ 4	19	(32.2)
Baricitinib monotherapy, n (%)	27	(48.2)
Prednisone daily dose*	5	(7.5)
PGA (0-100 mm)*	70	(30)
PhGA (0-100 mm)*	50	(20)
VAS Pain (0-100 mm)*	75	(25)
TJC*	8	(7)
SJC*	4	(4)
ESR (mm/hour) *	26	(39)
CRP (mg/dL) *	0.61	(1.2)
$DAS\text{-}28_{CRP}$*	4.68	(1.5)
CDAI*	24	(12)
SDAI*	24.6	(14.3)

* Data reported as median (IQR).
BMI: body mass index; RF: Rheumatoid Factor; ACPA: anti-citrullinated peptides antibodies; csDMARDS: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs; PhGA: physician's assessment of disease activity; PGA: patient's assessment of disease activity; TJC: tender joint count; SJC: swollen joint count; DAS28: disease activity score 28; CDAI: clinical disease activity index; SDAI: simplified disease activity index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

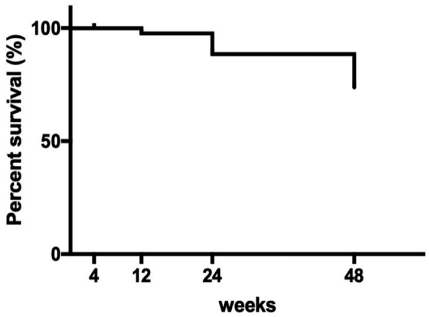


Fig. 1. Drug survival rate during the 48-week follow-up.

Composite indices of disease activity

After 4 weeks of treatment, we observed a significant reduction of $DAS\text{-}28_{CRP}$ compared to baseline (Fig. 3A). Such improvement was maintained at 12, 24 and 48 weeks. We also observed

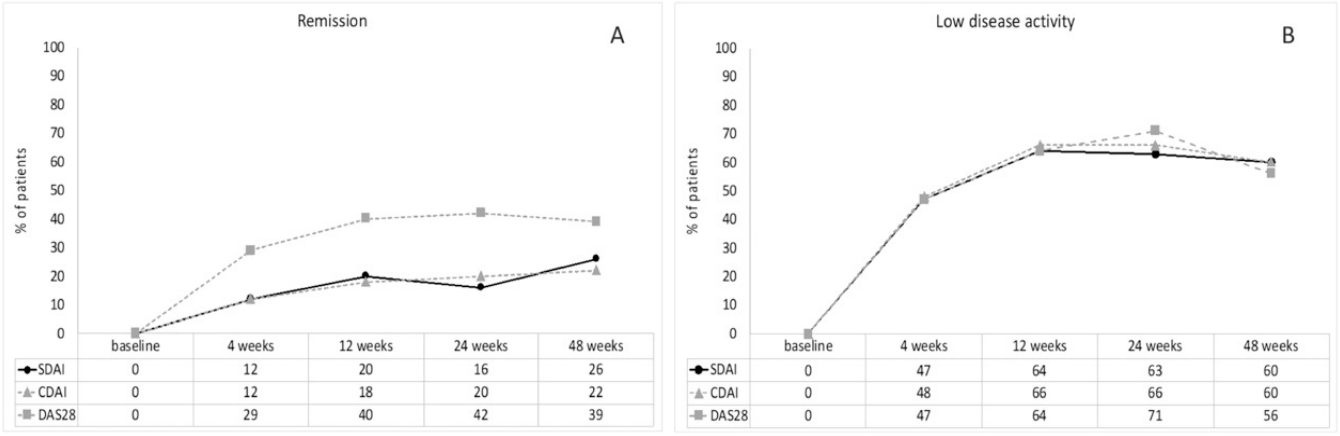
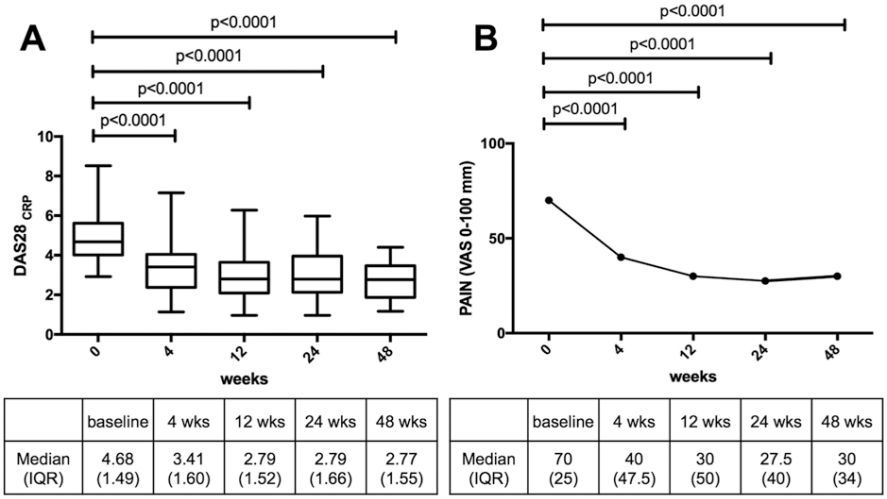


Fig. 2. Percentage of RA patients achieving remission (3A) and low disease activity (3B) according to SDAI, CDAI and DAS28$_{CRP}$.
SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score 28; CRP: C-reactive protein.



	baseline	4 wks	12 wks	24 wks	48 wks
Median (IQR)	4.68 (1.49)	3.41 (1.60)	2.79 (1.52)	2.79 (1.66)	2.77 (1.55)

	baseline	4 wks	12 wks	24 wks	48 wks
Median (IQR)	70 (25)	40 (47.5)	30 (50)	27.5 (40)	30 (34)

	baseline	4 wks	12 wks	24 wks	48 wks
Median (IQR)	50 (20)	15 (28.75)	10 (20)	10 (25)	10 (13.75)

	baseline	4 wks	12 wks	24 wks	48 wks
Median (IQR)	5 (7.5)	5 (7.5)	2.5 (5)	0 (5)	0 (2.5)

Fig. 3. Clinical efficacy endpoints at 4, 12, 24 and 48 weeks of treatment.
DAS28: Disease Activity Score 28; CRP: C-reactive protein; VAS: visual analogue scale; PGA: patient's global assessment; PDN: prednisone; IQR: interquartile range; wks: weeks.

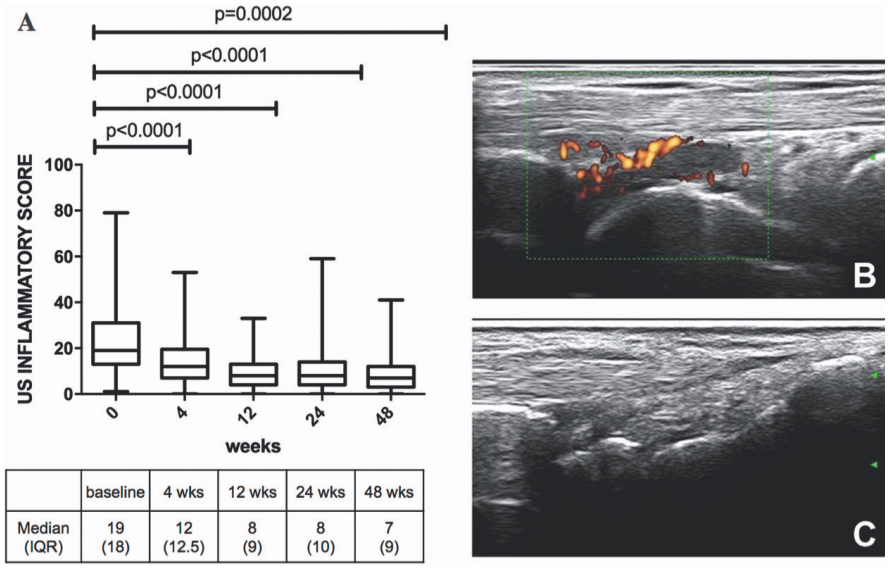
a significant reduction in CDAI and SDAI during the follow up (p<0.0001 at all time-points). At all time-points, we found a significant reduction of the median tender joints count in comparison with baseline [baseline: 8 (IQR 7); 4 wks: 4 (IQR 5); 12 wks: 2 (IQR 4); 24 wks: 1 (IQR 5.5); 48 wks 1 (IQR 4.5) p<0.0001]; the same result was observed for swollen joints count [baseline: 4 (IQR 4); 4 wks: 1 (IQR 3); 12 wks: 0 (IQR 2.25); 24 wks: 0 (IQR 4); 48 wks 0 (IQR 1); p<0.0001 at week 4, 12 and 48 *vs*. baseline; p=0.0005 at week 24 *vs*. baseline].

Moreover, we registered a significant improvement of the patient's disease perception as evaluated by PGA and VAS pain, already after 4 weeks and maintained at follow-up (Fig. 3B-C). Similarly, the physician's disease perception significantly improved: we found a decrease of PhGA from a median baseline value of 50 (IQR 20) to 15 (IQR 29) at week 4, 10 (IQR 20) at week 12, 10 (IQR 25) at week 24 and 10 (IQR 14) at week 48 (p<0.001 for all comparisons).

When stratifying patients according to concomitant csDMARDs treatment (monotherapy *vs*. combination with csDMARDs) or according to previous bDMARDs exposure no difference emerged. Moreover, autoantibody status (RF and ACPA) and BMI did not influence the clinical response.

Ultrasound assessment

At baseline we registered a median US inflammatory score of 19 (IQR 21), significantly correlating with DAS-28$_{CRP}$ (r=0.4; p=0.007), CDAI (r=0.4; p=0.005) and SDAI (r=0.4; p=0.007). During baricitinib treatment, we observed a significant reduction of US score from 12 (IQR 12.5) at 4 weeks (p<0.0001), to 8 (IQR 9) at 12 weeks (p<0.0001), to 8 (IQR 10) at 24 weeks



	baseline	4 wks	12 wks	24 wks	48 wks
Median (IQR)	19 (18)	12 (12.5)	8 (9)	8 (10)	7 (9)

Fig. 4. Ultrasonographic scores at baseline and after 4, 12, 24 and 48 weeks of baricitinib treatment.
A: median inflammatory score change during baricitinib treatment.
B-**C**: representative images showing active synovitis (with power Doppler positivity) at radiocarpal joint at baseline (**B**) and the resolution of the synovitis after 4 weeks of treatment with baricitinib (**C**).
US: ultrasound; wks: weeks; IQR: interquartile range.

(p<0.0001) and 8 (IQR 9) at 48 weeks (p<0.0001) (Fig. 4).

At baseline 31 patients (60.8%) showed positivity for power Doppler in at least one US-assessed joint. This percentage decreased to 29.5% at 4 weeks, to 15.8% at 12 weeks and 22.6% at 24 weeks.

Concomitant glucocorticoid treatment

At baseline, 46 out of 59 patients (78%) were taking concomitant glucocorticoids (GC) at a median dose of 5 (IQR 7.5) mg/day. Interestingly, the percentage of GC-treated patients decreased to74.5% at 4 weeks [median dosage: 5 (IQR 7.5) mg/day], 58.8% at 12 weeks [4.2 (IQR 5)], 44.7% at 24 weeks [0 (IQR 5) mg/day] and 34.8% at week 48 [median dosage: 0 (IQR 2.5) mg/day]. As reported in Fig. 3D, we found a significant decrease in the median GC dose at 12 and 24 weeks compared to baseline (p<0.0001).

Adverse events

Overall, 25.5% of patients reported at least one adverse event; safety issues led to withdrawal only in 2 cases (3.4%): 1 patient stopped after 1 month for grade 3 lymphopenia and another one after 3 months for prolonged gastroenteritis determining the patients wish to withdraw.

The most common haematological change was transient thrombocytosis, observed in six patients (10.2%). Among them, one female patient also presented lymphocytosis, and chronic myeloid leukaemia was diagnosed. Considering the remission of RA at that time, she continued baricitinib and imatinib was started. We observed a slight increase of CPK serum levels (<2UNL) in three patients (5.1%): one of them complained muscle pain, therefore we halved the baricitinib daily dosage with normalisation of CPK value and symptoms improvement within one month.

Table II shows the changes in laboratory parameters during the follow-up.

We recorded one case of mono-metameric Varicella Zoster; of the 51 patients, 4 were vaccinated with Zoster live attenuated vaccine one month before starting baricitinib. One 71-year-old female patient developed a small saphenous vein superficial thrombosis (after 10 days immobilisation); in 2012, when she was taking etanercept, she reported a deep vein thrombosis after a trauma, and she was investigated for acquired and congenital thrombotic risk factors: she was a smoker subject with controlled hypertension and BMI >30. We did not record any serious adverse events.

Discussion

To the best of our knowledge, this is the first report on the effectiveness of baricitinib in a real-life clinical setting, including both clinimetric and imaging assessment. In our cohort of patients, we observed a significant, early and sustained improvement in all the evaluated parameters. These results confirmed the efficacy and safety profile of baricitinib in unselected RA patients

Table II. Laboratory blood test results at baseline and during the follow-up.

Laboratory results	Baseline	12 weeks	p	24 weeks	p	48 weeks	p
Total cholesterol mg/dL	194 (59)	201 (42)	**0.0024**	196 (36)	0.06	193 (42)	0.82
HDL mg/dL	64 (17.5)	69.5 (17.25)	**0.024**	61.5 (14.7)	0.70	68 (24)	0.99
Triglycerides mg/dL	89 (59.5)	87.5 (41.2)	0.92	90 (53.5)	0.67	98 (44)	0.51
Creatinine mg/dL	0.7 (0.21)	0.74 (0.18)	0.88	0.75 (0.13)	0.63	0.78 (0.12)	0.57
CPK mg/dl	56 (57.5)	79 (81)	**0.0177**	89 (74.2)	**0.0002**	79 (51)	**0.0202**
Neutrophils /mm^3	3810 (2491)	3900 (1600)	0.77	3590 (2060)	0.08	4610 (2660)	0.76
Lymphocytes /mm^3	2345 (1097)	2150 (930)	0.32	2000 (970)	**0.0311**	2115 (1115)	0.10
Platelets x10^3/mm^3	278 (127)	324 (115)	**0.0010**	323 (134)	**0.0140**	330 (91)	**0.0391**
Haemoglobin g/dl	12.2 (1.9)	12.4 (1.5)	0.057	11.7 (2)	0.21	12.5 (2.1)	0.84

Data reported as median (IQR)
HDL: high density lipoproteins; CPK: creatine phosphokinase.

resistant to conventional and biological DMARDs. Interestingly, baricitinib induced a very fast improvement in disease activity and pain relief as soon as after 4 weeks.

In addition to the clinical improvement, we confirmed the fast effect of baricitinib also by evaluating, for the first time, the US response. The ultrasonography has a higher sensitivity compared to the physical examination in the assessment of joint inflammatory status. According to the rapid clinical improvement, the US showed a significant reduction of the inflammatory score already after 4 weeks (20).

At the first follow-up visit, after 4 weeks of treatment, we detected a significant decrease in all the disease activity indices compared to the baseline evaluation. However, nowadays, the mere reduction of disease activity should not be accepted as a satisfactory response. Indeed, the contemporary treatment of RA, aims at achieving clinical targets: remission or low disease activity (21). Patients with long-standing RA, as those enrolled in our observational study, should be treated at least until a low disease activity is achieved.

Data from randomised clinical trials demonstrated that baricitinib induced remission, as assessed by SDAI, in a percentage of patients ranging from 5% to 17% after 12 weeks of treatment (4, 7, 9). In our cohort we confirmed a similar percentage – around 17% – of clinical remission when using CDAI and SDAI; moreover, by using DAS28, the remission was achieved by more than one third of patients. Overall, our cohort had a long disease duration, exceeding 10 years in most of patients. Therefore, LDA could be considered an acceptable, alternative target. After only 4 weeks, almost a half of the patients achieved the LDA. The clinical improvement was sustained, and more than a half of the patients still taking baricitinib were in LDA after 12 and 24 weeks. When evaluating the single items included in the composite indices, we noticed that the more pronounced factor contributing to the decrease of disease activity was the global health reported by the patients. In parallel, we observed a profound decrease in the pain score that almost halved already after 4 weeks and decreased by 75% at the end of the observation at 6 months. Our results are in line with data from a sub-analysis of RA-BEAM showing a ≥50% pain relief in 48% of patients treated with baricitinib after 4 weeks of follow-up and ≥70% pain relief from baseline in 40% by week 24 (22). Furthermore, in the RA-BEAM, baricitinib started differentiating from placebo just after 1 weeks, and from adalimumab after 4 weeks of treatment (7, 22). In contrast with the rapid reduction of pain, we did not detect an equally significant decrease in acute phase proteins. Therefore, we can speculate that the pain relief is the main driver of the fast response described during the treatment with JAK inhibitors. Again, our results agree with the observation derived from the sub-analysis of the RA-BEAM suggesting that pain relief cannot be solely attribute to the direct effect of baricitinib on inflammation.

The 2016 updated EULAR recommendations for management of RA stated that "short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible" (20). The EULAR task force suggests using GC in combination with conventional synthetic (cs)DMARDs – overlooking the combination of GC with biological and targeted synthetic DMARDs – as a "bridging therapy" until the maximum effect is reached: indeed, the administration of GC could be reduced by using a drug with rapid onset of action, such as baricitinib. Rheumatologists are aware of the potential toxicities associated GC but the "*dirty little secret"* of rheumatology is that prednisone commonly is used often and for periods of >6 months (23). Most of the patients who achieved a sustained remission after the introduction of a bDMARDs continue to take very low doses of prednisone (24). In our cohort, the introduction of baricitinib allowed a rapid decrease of prednisone dose; moreover, the drug also allows stopping the concomitant GC in more than a half of the patients within 6 months.

Other than confirming the effectiveness of baricitinib, the results of our study also suggests its safety profile in unselected patients. Despite the short follow-up does not allow to draw definite conclusion, in our cohort we did not record any serious adverse events, no cardiovascular events or major thromboembolic events, serious infections and any case of death. The only case of haematologic malignancy did not lead to withdrawing baricitinib; moreover, given the short period between the diagnosis and the beginning of the treatment, we cannot rule out the pre-existence of the chronic lymphatic leukaemia.

The main limitation of our study is the small number of subjects evaluated up to 48 weeks and the relatively short-term observation; yet, the cohort was assessed homogeneously by the same rheumatologists during the whole period of observation. Moreover, the safety was evaluated up to 48-weeks, thus limiting the detection of long-term safety issue such as cardiovascular events and malignancy. However, as expected, most of the laboratory changes occurred in the first trimester.

In conclusion, this is the first report confirming the efficacy of baricitinib in a real-life experience; our evaluation of effectiveness was not limited to the clinimetric assessment but also included additional items such as ultrasonography and steroid-sparing effect. The daily practice also confirms the good safety profile of baricitinib.

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