Efficacy and safety of baricitinib in 446 patients with rheumatoid arthritis: a real-life multicentre study

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Abstract

Objective

Baricitinib, an oral Janus kinase (JAK) 1-2 inhibitor, is currently used along biologic DMARDs (bDMARDs) after the failure of methotrexate (MTX) in rheumatoid arthritis (RA). We investigated the efficacy and safety of baricitinib in real life.

Methods

We prospectively enrolled 446 RA patients treated with baricitinib from 11 Italian centres. Patients were evaluated at baseline and after 3, 6, and 12 months. They were arrayed based on previous treatments as bDMARD-naïve and bDMARD-insufficient responders (IR) after the failure or intolerance to bDMARDs. A sub-analysis differentiated the effects of methotrexate (MTX) and the use of oral glucocorticoids (OGC).

Results

Our cohort included 150 (34%) bDMARD-naïve and 296 (66%) bDMARD-IR patients, with 217 (49%) using baricitinib as monotherapy. Considering DAS-28-CRP as the primary outcome, at 3 and 6 months, 114/314 (36%) and 149/289 (51.6%) patients achieved remission, while those in low disease activity (LDA) were 62/314 (20%) and 46/289 (15.9%), respectively; finally at 12 months 81/126 (64%) were in remission and 21/126 (17%) in LDA. At all-timepoints up to 12 months, bDMARDs-naïve patients demonstrated a better clinical response, independently of MTX. A significant reduction in the OGC dose was observed at 3 and 12 months in all groups. The serum positivity for both rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA) conferred a lower risk of stopping baricitinib due to inefficacy. Fifty-eight (13%) patients discontinued baricitinib due to adverse events, including thrombotic events and herpes zoster reactivation.

Conclusion

Real-life data confirm the efficacy and safety profiles of baricitinib in patients with RA and provide evidence that drug survival is higher in bDMARDs-naïve and seropositive patients.

Key words

small molecule, Janus kinase, real-world, rheumatoid arthritis, glucocorticoid

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Introduction

In recent years, the therapeutic approach to rheumatoid arthritis (RA) has progressively evolved towards an earlier and more personalised use of disease-modifying anti-rheumatic drugs (DMARDs) with the aim of achieving remission or low disease activity (LDA) and preventing joint damage based on a treat-to-target strategy (1-3).

Two Janus kinase (JAK) inhibitors, baricitinib and tofacitinib, have been recently approved for RA and represent an emerging class of targeted synthetic DMARDs (tsDMARDs). Current recommendations place them at the same level of biologic DMARDs (bDMARDs) after the failure of conventional synthetic DMARDs (csDMARDs), mostly methotrexate (MTX). Baricitinib is an oral tsDMARD that reversibly inhibits JAK1 and JAK2 which represent the intracellular signaling pathways of various cytokines, colony-stimulating factors and hormones involved in the pathogenesis of RA (4). Baricitinib has been available in Europe since 2018 based on the efficacy and the safety profiles inactive RA after csDMARD or bDMARD failure, as reported in randomised clinical trials (RCTs) (5-7) and on its superiority *versus* adalimumab combined with methotrexate (MTX) in csDMARD-insufficient responder (IR) patients (8). Unlike tofacitinib, which has been previously available in several countries (9), there is no data on the use of baricitinib in real life.

We present herein the first real-world cohort of patients with RA treated with baricitinib.

Materials and methods

In this prospective observational study, we included 446 patients, from 11 Italian rheumatology centers, affected by active RA and treated with baricitinib (4 mg/die) between June 2018 and November 2019.

Eligible patients had to be ≥18 years old and fulfill the American College of Rheumatology (ACR) 2010 revised criteria for RA (10). For the purpose of the analysis, patients were divided according to the bDMARD-naïve or bDMARD-IR status and the concomitant use of MTX. The baseline characteristics of the four groups are illustrated in Table I. RA activity data, including 28-joint Disease Activity Score (DAS28-CRP) and Clinical Disease Activity Index (CDAI), were collected at baseline and after 3 and 6 months, while for a smaller group of patients data were available also at 12 months (Supplementary Tables S1-S2). The primary endpoint was the assessment of disease activity changes after 3, 6 and 12 months in all patients. Both DAS28-CRP and CDAI were used to assess remission (<2.6 for DAS28 and≤2.8 for CDAI); low disease activity (LDA; ≥2.6 and ≤3.2 for DAS28; >2.8 and ≤10 for CDAI); moderate disease activity (MDA; >3.2 and ≤5.1 for DAS28 and >10 and ≤22 for CDAI); high disease activity HDA; >5.1 for DAS28; >22 for CDAI) according to the EUropean League Against Rheumatisms (EULAR)/ACR collaborative recommendations (11). All patients reported articular pain by using a visual analogue scale (VAS pain) at each visit and considering the following extremes: "no pain at all" as score of 0 and "worst imaginable pain" as score of 100. Concomitant therapies were registered for each patient at every visit, including the MTX dose and changes in OGC use during baricitinib treatment (Table II). A secondary analysis of our population aimed to evaluate the safety of the drug and all significant adverse events were recorded; other secondary endpoints included the description of VAS pain trend and the report of rates of OGC discontinuation, both indirect indices of the drug efficacy in controlling disease activity.

Statistical analysis

Different subgroups were compared using the Wilcoxon, the Mann-Whitney and the Pearson's Chi-square tests as appropriate; to evaluate the drug retention rate we performed a Kaplan Meyer time to event analysis, univariate analysis was used to select variable to assess multivariate Cox proportional hazard models (cut-off used $p<0.25$). All analyses were two-tailed and performed using STATA for Macintosh (Stata Corp. College Station, TX); p-values <0.05 were considered as statistically significant.

Table I. Baseline characteristics of patients with RA receiving baricitinib.

		TOTAL	bDMARD-naive			bDMARD-IR		
		n=446	Total n=150 (34%)	without MTX n=64 (14%)	with MTX n=86 (19%)	Total n=296 (66%)	without MTX n=153 (34%)	With MTX n=143 (32%)
Demographics	Female	362; 81.2%	111; 74.0%*	51; 79.7%	60; 69.8%	251; 84.8%	132; 86.3%	119; 83.2%
	Age, years	59 (51-67)	56 (49-66)*	57 (50-68)	55 (48-64)	60 (53-68)	60 (54-69)	60 (53-68)
	Disease duration, years	9 (4-16)	4 (1-9)*	5 (1-10)	3.5 (1-9)	12 (7-18)	12 (7-19)	11 (7-18)
Disease features	Early disease (< 1 year)	47; 10.5%	39; 26.0%*	16; 25.0%	23; 26.7%	8; 2.7%	2; 1.3%	6; 4.2%
	Previous bDMARDs	1.9 ± 2.0	0 ± 0	0 ± 0	0 ± 0	2.9 ± 1.8	2.8 ± 1.9	2.9 ± 1.8
	ACPA positive	292; 65.5%	100; 66.7%	38; 59.4%	62; 72.1%	192; 64.9%	90; 62%	102; 76%
	RF positive	304; 68.2%	100; 66.7%	39; 60.9%	61; 70.9%	204; 68.9%	97; 63%	107; 75%**
	Glucocorticoid use	327; 73.3%	109; 72.7%	47; 73.4%	62; 72.1%	218; 73.6%	117; 76%	101; 70%
	Glucocorticoid dose (mg)	5.0 ± 4.7	4.7 ± 4.5	5.1 ± 4.6	4.4 ± 4.4	5.2 ± 4.9	5.4 ± 5.0	4.9 ± 4.7
Clinimetrics	Tender joints	7.6 ± 5.7	7.4 ± 5.5	7.8 ± 5.8	7.0 ± 5.3	7.7 ± 5.8	7.2 ± 5.4	8.1 ± 6.0
	Swollen joints	5.5 ± 4.5	5.2 ± 3.9	5.7 ± 4.0	4.8 ± 3.9	5.6 ± 4.7	5.0 ± 3.7	6.2 ± 5.5
	CRP (mg/L)	13.5 ± 19.4	14.2 ± 16.5	14.4 ± 17.4	14.0 ± 15.8	13.2 ± 20.7	11.9 ± 21.5	14.4 ± 19.8
	Patient GH (0-10)	6.7 ± 2.2	6.8 ± 2.0	6.7 ± 2.0	6.8 ± 2.0	6.6 ± 2.3	6.6 ± 2.3	6.7 ± 2.3
	Physician GH (0-10)	6.1 ± 2.0	6.1 ± 1.8	6.3 ± 2.0	6.0 ± 1.6	6.2 ± 2.2	6.3 ± 2.2	6.0 ± 2.2
	VAS pain (0-100)	67 ± 21	67 ± 19	63 ± 20	69 ± 19	68 ± 22	65 ± 23	71 ± 20
	DAS28	4.67 ± 1.05	4.68 ± 0.99	4.78 ± 1.01	4.61 ± 0.97	4.67 ± 1.08	4.56 ± 1.05	4.79 ± 1.11
	CDAI	25.8 ± 11.1	25.4 ± 9.7	26.4 ± 10.3	24.7 ± 9.2	26.0 ± 11.8	25.1 ± 10.2	26.9 ± 13.2
Comorbidities	Cardiomyopathy	56; 12.5%	13; 8.7%*	9; 14.1%	4; 4.6%	43; 14.5%	29; 19%	14; 10%**
	Hypercholesterolaemia	130; 29.1%	32; 21.3%*	16; 25.0%	16; 18.6%	98; 33.1%	55; 36%	43; 30%
	Hypertension	156; 35.0%	47; 31.3%	22; 34.4%	25; 29.1%	109; 36.8%	60; 39%	49; 35%
	Diabetes	38; 8.5%	7; 4.7%*	3; 4.7%	4; 4.6%	31; 10.5%	16; 11%	15; 11%
	Cancer	27; 6.0%	10; 6.8%	7; 10.9%	3; 3.5%	17; 5.7%	9; 6%	8; 6%
	Latent TB	38; 8.5%	13; 8.7%	3; 4.7%	10; 11.6%	25; 8.4%	11; 7%	14; 10%
	Previous VZV	37; 8.3%	10; 6.8%	5; 7.8%	5; 5.8%	27; 9.1%	13; 10%	14; 13%

Categorical variables are expressed as number (%); continuous variables are expressed as mean ± standard deviation; age and disease duration are expressed as median and interquartile range; *p<0.05 bDMARD-naïve *vs*. bDMARD-IR.
**p<0.05 for baricitinib with methotrexate *vs*. baricitinib without methotrexate.

Table II. Oral glucocorticoid use at 3, 6, and 12 months in patients with RA treated with baricitinib; patients are arrayed based on bDMARD-naïve *vs*. -IR and the concomitant use of MTX.

		Steroid doses (mg/day)				Steroid n. pts			
		Basal (n=446)	3 m (n=345)	6 m (n=284)	12m (n=128)	Basal	3 m	6 m	12 m
All patients		5.0 ± 4.7	2.5 ± 3.1**	2.3 ± 2.9**	1.2 ± 2.1**	327/446; 73.3%	187/345; 54%	138/284; 48%	41/128; 32%
bDMARD-naive	Total	4.7 ± 4.5	1.7 ± 2.3**^	1.2 ± 1.8**^	0.5 ± 1.1**^	109/150; 72.7%	58/124; 46.7%	39/113; 34.5%	13/62; 21.0%
	w/ MTX	4.4 ± 4.4	1.5 ± 2.0**	1.2 ± 1.8**	0.5 ± 1.1**	62/86; 72.1%	34/77; 44.1%	24/67; 35.8%	7/40; 17.5%
	w/o MTX	5.1 ± 4.6	1.9 ± 2.6**	1.2 ± 1.9**	0.7 ± 1.1*	47/64; 73.4%	24/47; 51.1%	15/46; 32.6%	6/22; 27.3%
bDMARD-IR	Total	5.2 ± 4.9	3.0 ± 3.4**	3.0 ± 3.2**	1.9 ± 2.6**	218/296; 73.6%	123/221; 55.7%	99/171; 57.9%	28/66; 42.4%
	w/ MTX	4.9 ± 4.7	2.9 ± 3.4**	2.7 ± 3.0**	1.9 ± 2.5**	101/143; 70.6%	64/114; 56.1%	49/92; 53.3%	16/40; 40.0%
	w/o MTX	5.4 ± 5.0	3.0 ± 3.2**	3.3 ± 3.5**	1.9 ± 2.6*	117/153; 76.5%	65/107; 61%	50/79; 63.3%	12/26; 46.1%

RA: rheumatoid arthritis; bDMARDs: biological DMARDs; n: number; w/o: without; MTX: methotrexate; w: with; IR: insufficient response; m: months; mg: milligrams.
*p<0.01 *vs*. baseline; **p<0.0001 *vs*. baseline (Wilcoxon signed-rank test); ^ p<0.01 n. *vs*. IR (Mann-Whitney U-test).

Results

Demographic, clinimetric, and comorbidity features of the study population at baseline are described in Table I. The majority of the patients were women (81%) with a median age of 59 years (interquartile range- IQR 51-67) and a median disease duration of 9 years (IQR 4–16). Two thirds of RA cases were positive for both RF and ACPA. Patients in the bDMARD-naïve group were significantly younger and with a shorter disease duration compared to bDMARD-IR. Nonetheless, baseline disease activity indices, VAS pain and OGC use did not differ between groups based on previous bDMARD use, while bDMARD-naïve patients had less frequently comorbidities, including cardiovascular disease, hypercholesterolemia, and diabetes. Patients receiving MTX were more frequently seropositive for both RF and ACPA.

DAS28-CRP and CDAI at different timepoints are illustrated in Supplementary Tables S1 and S2, respectively. A reduction in DAS28, CDAI and VAS pain was observed at 3, 6, and 12 months with 36% and 25% of patients reaching remission by 3 months of therapy, using

DAS28-CRP and CDAI, respectively. Despite similar baseline levels, DAS28 and CDAI were significantly lower at all timepoints in the bDMARD-naïve group compared to bDMARD-IR. Importantly, 80/114 (70%) bDMARD-naïve patients reached DAS28-remission or DAS28-LDA at 3 months *versus* 96/200 (48%) of bDMARD-IR; 75/114 (66%) of bDMARD-naïve patients reached CDAI-remission or CDAI-LDA at 3 months *versus* 85/195 (56%) of bDMARD-IR. The use of concomitant MTX was not associated with significant differences in the frequency of remission or LDA in bDMARD-naïve and bDMARD-IR patients. A significant reduction in the OGC dose was observed at 3 and 12 months in all groups, as shown in Figure 1, while OGC doses were lower at all-timepoints in the bDMARD-naïve group (Table II). Of note, compared to the 70% of patients at baseline, only 32% of patients were still taking OGC at 12 months, with significant differences in the bDMARD-naïve and bDMARD-IR groups (21% *vs*. 42%; *p*=0.0093).

At 3, 6, and 12 months, 14/345 (4%), 29/284 (10%), and 31/128 (24%) patients, stopped baricitinib due to inefficacy, respectively. A multivariate regression time to event analysis showed that the hazard ratio (HR) for stopping baricitinib due to inefficacy was significantly lower in patients who were seropositive for both RF and ACPA (HR 0.58, 95% confidence interval -CI- 0.37–0.93; *p*=0.022) or were bDMARD-naïve (HR1.83 95% CI 1.02–3.29; *p*=0.043) (Fig. 2). The number of previous bDMARDs was also significantly associated with baricitinib withdrawal for inefficacy (HR 1.14,95% CI1.02–1.26; *p*=0.013).

Fifty-eight of the 446 patients (13%) stopped baricitinib because of adverse events and were not evenly distributed at 3 (20/314, 6%), 6 (19/289,7%), and 12 (19/126, 15%) months. Our multivariate regression time to event analysis demonstrated that older patients and those who were bDMARD-IR had a higher HR for stopping baricitinib due to an adverse event (HR 1.03, 95% CI 1.01–1.06 for each additional year; *p*=0.008 and HR 1.93, 95% CI1.01–3.67; *p*=0.045, respectively). Of particular interest, among the entire cohort, there were 4 thrombotic events, all in patients younger than 65 (one event occurring in the first 3 months of treatment, 2 in patients with hypercholesterolaemia, in one case associated with hypertension). We also observed 6 cases of Varicella Zoster Virus (VZV) reactivation (3 in patients younger than 65, 3 in the first 3 months of treatment, 2 with multiple localisation, 5 with concomitant OGC, 4 with MTX, 3 in the first 3 months) and 20 non-VZV infections (5 with concomitant OGC and 7 with concomitant MTX) including 7 upper respiratory tract infections, 1 sepsis, 1 hepatitis B virus reactivation. VZV reactivations were significantly associated with OGC therapy (83% *vs*. 25% in the other infections; *p*=0.034 with Yates correction). Non-VZV infections did not occur more frequently in patients concomitantly treated with MTX. Haematological abnormalities were observed in 4 patients with 2 cases of pancytopenia and 2 of neutropenia; none of these patients developed serious infections.

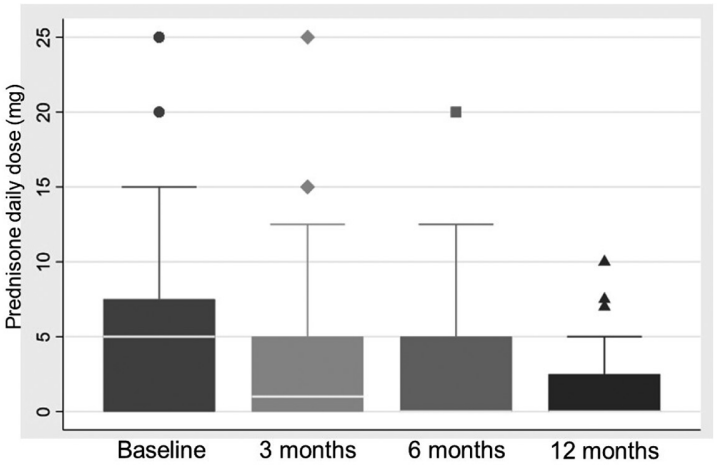

Fig. 1. Oral glucocorticoid dose (expressed as mg/day of prednisone) in patients at baseline, 3, 6, and 12 months of treatment with baricitinib.

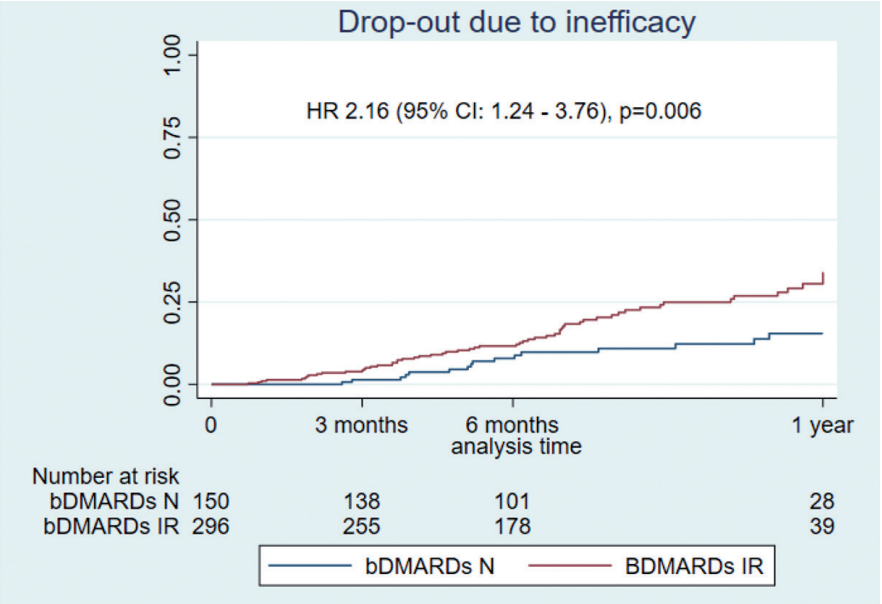

Fig. 2. Baricitinib withdrawal for inefficacy in bDMARD-naive *vs*. bDMARD-IR patients with RA.

Discussion

The availability of new oral drugs targeting the JAK/STAT signaling (12) has significantly contributed to the new treatment landscapes for RA, setting us closer to a personalised approach to the patients. Data from phase III studies,

including a head-to-head superiority study *versus* adalimumab with MTX (5-8) led to the approval of baricitinib. It is the first JAK inhibitor approved in the European Union to treat RA patients who reported treatment failure or intolerance to csDMARDs. To our knowledge there are no current reports on its use in real-life setting.

We reported herein the data from a prospective and multicentric study to evaluate the efficacy and safety of baricitinib, a reversible inhibitor of JAK1 and 2, in a real-world population of Italian RA patients. They were evaluated according to concomitant OGC and MTX use and previous bDMARD therapy. In fact, RCTs reported higher response rates in patients that were bDMARD-naïve, as shown in the RA-BEGIN study which included only these patients (7) or the RA-BEAM head-to-head trial *versus* adalimumab (8). Our data largely support the conclusions that bDMARD-naive patients showed a better clinical response in terms of DAS28-CRP, CDAI, and VAS pain compared to bDMARDs-IR at all-timepoints, independently of MTX concomitant use. The bDMARD-naïve patients also less frequently experienced drug failure with significantly higher retention rates at 12 months. However, we should note that possible confounding factors contributing to this difference include the younger age, a short disease duration and lower rates of comorbidities in the bDMARD-naïve group, despite similar baseline RA disease activity measures. These observations may suggest that an earlier use of baricitinib could be encouraged after the failure of MTX, as supported by the latest EULAR recommendations which include both tsDMARDs and bDMARDs at this time in the disease course (1). These recommendations include disease remission as the target to be sought with treatments. Our data, in agreement with the RA-BEACON study (6), show that 50% and 27% of bDMARD-IR patients achieve remission at 12 months using DAS28-CRP and CDAI, respectively, with worse response rates in patients failing more than one bDMARD, but regardless of the previous bDMARD mechanism of action (13). Since the use of OGC is a major issue in the management of RA, we also focused on the impact of baricitinib on OGC use. We report that more than 50% of patients were not taking OGC within the first 3 months of treatment, particularly if baricitinib was used with MTX, although statistical significance was not achieved. Similar differences were observed when patients were analysed according to the serum positivity for the RF and/or ACPA as the positivity for both was associated with longer drug survival. We observe that this difference was not previously seen in RCTs or *post hoc* pooled analyses (14) and may well support the need for real-life data along RCTs to ascertain the true impact of medical treatments in RA since serum ACPA were for example among the inclusion criteria for the RA-BEAM study (8).

It has been suggested that JAK-inhibitors exert reduce RA-associated pain independent of the effects on inflammation (15), and we indeed report a rapid effect of baricitinib on pain as most patients demonstrate a significant reduction of VAS pain as early as 3 months, with a further improvement at 6 and 12 months (Table III). These results are in accordance with secondary analysis of RCTs in which baricitinib demonstrated a significant efficacy on patients reported outcomes (PROs), with evident improvements since the first weeks of therapy, even in patients in remission or with LDA (16-19). Also in this scenario, bDMARD-naïve patients reported a deeper reduction in pain scores. This could represent a great advance in the management of the disease as a large proportion of patients still experience pain despite an acceptable disease control according to the physician assessment (20).

We are aware that safety is a major concern for both tsDMARDs and bDMARDs. An integrated analysis of all RCT patients exposed to baricitinib supported an acceptable overall safety profile, with an incidence of death, serious adverse events including infections, and malignancy comparable to those observed for bDMARDs (21). Despite a low risk of serious infections, JAK-inhibitors are associated with an increased risk of VZV reactivation (9, 22, 23) compared to bDMARDs (24). We report an overall 13% baricitinib withdrawal rate due to adverse events with a higher rate associated with older age and the previous use of bDMARDs. In our cohort 6 patients developed a VZV reactivation, more frequently seen in patients concomitantly treated with OGC, while MTX did not influence this risk. We observed a small number of upper respiratory tract infections without severe complications and only one case of sepsis; also in these cases no correlation with concomitant MTX or was observed and the rates of infection resulted similar across groups. A potential increased risk of thrombotic events has been reported for JAK-inhibitors and a post marketing analysis of baricitinib trials estimated this risk as small (approximately 5 events per

Table III. VAS pain at 3, 6 and 12 months in patients with RA treated with baricitinib; patients are arrayed based on bDMARD-naïve *vs*. -IR and the concomitant use of MTX.

		Mean VAS pain+SD			
		Basal (n= 323)	3 m (n=262)	6 m (n=200)	12m (n=116)
All patients		67 ± 21	38 ± 22**	31 ± 23**	26 ± 24**
bDMARD-naive	Total	67 ± 19	32 ± 19**^	26 ± 23**^	22 ± 22**
	w/MTX	69 ± 19	34 ± 18**	27 ± 23**	20 ± 20**
	w/o MTX	63 ± 20	29 ± 20**	25 ± 23**	24 ± 26**
bDMARD-IR	Total	68 ± 22	41 ± 23**	35 ± 22	31 ± 26**
	w/ MTX	71 ± 20	40 ± 24**	34 ± 21**	30 ± 26**
	w/o MTX	65 ± 23	42 ± 22**	37 ± 23**	32 ± 26*

VAS: visual analogue scale; bDMARDs: biological DMARDs; n: number; w/o: without; MTX: methotrexate; w: with; IR: insufficient response; m: months.
*p<0.01 *vs*. baseline; **p<0.0001 *vs*. baseline (Wilcoxon signed-rank test); ^ p<0.01 n. *vs*. IR (Mann-Whitney U-test).

1000 patient years) and comparable to the risk associated with RA *per se* (approximately 3–7 events per 1000 patient years) (25, 26). In our cohort we observed 4 thrombotic events, all in patients younger than 65 and in 3 cases with coexisting cardiovascular risk factors, cumulatively accounting for 14.7 events per 1000 patient years.

The data on safety highlighted one of the limitations of this study, *i.e.* the short observation period, as only 28% of patients reached the 12-month follow-up visit. We are aware that a prolonged analysis of our results is needed to understand the long-term safety profile of the drug as well as the persistence of the response observed. Another limitation is that our study did not include radiographic evaluations to discriminate the disease progression, particularly in baricitinib monotherapy as RCT data suggested that MTX use influenced most of all the worsening in Sharp score, while the advantages in terms of clinimetrics and PROs were less predominant (7, 27). We cannot conclude that baricitinib is as effective as monotherapy as in combination with MTX and dedicated studies should address this crucial issue since a significant proportion of RA patients are intolerant or manifest contraindications to MTX (28). Third and last, while we included VAS pain in the analysis, we did not register data about other PROs, particularly morning stiffness, fatigue, and quality of life. Despite these limitations, we submit that, to the best of our knowledge, this is the first report of baricitinib efficacy and safety in a large real-life cohort.

We may conclude that our real-life data confirm the efficacy of baricitinib in active RA patients; in particular patients who are bDMARD-naïve or seropositive for both RF and ACPA show a better response, regardless of MTX use, while 50% of patients can withdraw from oral glucocorticoid (OGC) at 12 months. We also register a good safety profile characterised by a possible VZV reactivation in a small number of cases.

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