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Original Article

Clinical science

Characteristics of patients initiating treatment with baricitinib and outcomes at follow-up: analysis of BSRBR-RA Registry data

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Abstract

Objectives: To describe selected baseline characteristics, continuation with baricitinib and disease activity over time in patients initiating treatment with baricitinib in a UK real-world rheumatology setting.

Methods: Baseline and follow-up data were analysed from baricitinib-treated patients newly recruited to the British Society for Rheumatology Biologics Registry–RA (BSRBR-RA) baricitinib cohort between 1 January 2018 and 31 March 2020. The primary objective was to evaluate continuation of baricitinib treatment in patients with at least one follow-up. Analyses were performed using the full baricitinib cohort, overall and by patient subgroup: biologic DMARD (bDMARD)/targeted synthetic (ts)DMARD-naive *vs* -experienced, baricitinib 4 *vs* 2 mg, age ≥65 *vs* <65 years, monotherapy *vs* combination therapy and male *vs* female.

Results: At baseline, the study cohort ($n = 561$) was 76.5% female, mean age 60.0 years, had longstanding (mean 13.1 years) and severe RA, and 54.0% had previously received a bDMARD/tsDMARD. Of 265 and 110 patients completing the 6- and 12-month follow-ups with available data, 77.7 and 69.1% remained on baricitinib at each time, respectively. In all Kaplan–Meier analyses, >60% of patients remained on baricitinib at 540 days. Continuation of baricitinib therapy differed between some subgroup pairs (bDMARD/tsDMARD naive/experienced, baricitinib 2 mg/4 mg). Disease activity was lower at both follow-ups than at baseline, overall and in all subgroups.

Conclusion: In the early years of real-world baricitinib use in the UK, a high proportion of patients continued with treatment at both 6 and 12 months, at which times disease activity was lower than at baseline.

Keywords: baricitinib, Janus kinase inhibitor, observational study, RA, real-world, registry

Rheumatology key messages

- Most patients initiating baricitinib were female, had longstanding and severe rheumatoid arthritis and were bDMARD-experienced.
- A high proportion of patients continued treatment at both 6 (77.7%) and 12 (69.1%) months.
- Disease activity was lower overall and by subgroup at 6 and 12 months *vs* baseline.

Introduction

The targeted synthetic DMARD (tsDMARD) baricitinib is a once-daily oral selective Janus kinase (JAK)-1 and JAK2 inhibitor that was approved in Europe in 2017 for the treatment of moderate-to-severe active RA at a standard dose of 4 mg once daily alone or in combination with methotrexate in adults who have responded inadequately to or are intolerant to one or more DMARDs; a dose of 2 mg once daily is appropriate for selected patients and may be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering [1].

In 2017, the UK National Institute for Health and Care Excellence included baricitinib in its pathways and recommendations for the treatment of RA [2]. Specifically, baricitinib is recommended for use with methotrexate or, if methotrexate is contraindicated/not tolerated, as monotherapy for patients

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with a DAS for 28-joint count (DAS28) of >5.1 and either an inadequate response to a combination of conventional synthetic DMARDS (csDMARDs) or an inadequate response or contraindication/intolerance to other DMARDs, including rituximab. Treatment with baricitinib can only be continued if there is a moderate response, measured using European Alliance of Associations for Rheumatology (EULAR) criteria, at 6 months after starting therapy; after an initial response, treatment should be withdrawn if at least a moderate EULAR response is not maintained. In 2020, baricitinib was additionally approved for the treatment of moderate-to-severe atopic dermatitis.

The British Society for Rheumatology Biologics Registry–Rheumatoid Arthritis (BSRBR-RA) was established in 2001 to study the safety of biologic DMARDs (bDMARDs) used in routine clinical care in patients with RA in the UK and has regularly been expanded to incorporate new treatments, including tsDMARDS. Patients enrolled in the registry are followed up at 6-monthly intervals for the first 3 years and annually thereafter.

The aim of this study was therefore to report real-world experience of early use of baricitinib; this analysis describes selected baseline characteristics, continuation with baricitinib and disease activity over time in patients enrolled in the BSRBR-RA registry initiating treatment with baricitinib.

Methods

Study design

This observational study analysed baseline and follow-up data, when available, from patients receiving baricitinib who were recruited to the BSRBR-RA registry. The current analysis builds on a previous study performed using an earlier baricitinib dataset from the registry [3, 4].

Eligible baricitinib-treated patients were registered to the BSRBR-RA baricitinib cohort (either newly registered to the BSRBR-RA or re-registered after switching from another product in the registry). Characteristics of patients at the time of baricitinib initiation were submitted no later than 6 months after the start of therapy and included demographics and DAS28. Follow-up forms capturing clinical data recorded from regular clinic visits were completed every 6 months from the date of baricitinib initiation to record changes in therapy and post-baseline outcomes in the BSRBR-RA registry. Because the follow-ups were not scheduled study visits, it is possible that follow-up information is missing for some patients.

The current analyses include data from baseline and the 6-month (follow-up 1) and 12-month (follow-up 2) follow-ups of patients starting baricitinib; these data were obtained from a routine annual dataset shared with Eli Lilly and Company as part of a contractual agreement between the British Society for Rheumatology (BSR) and Eli Lilly and Company. The analyses were independent of the BSR and the academic team who run the BSRBR-RA at the University of Manchester, who had no involvement in the planning or analyses of data or preparation of the manuscript. No calculations of sample size were performed as the study sample was determined by the number of eligible patients enrolled in the BSRBR-RA registry at the time of database lock on 31 March 2020.

This BSRBR-RA study was approved by the North West Multicentre Research Ethics Committee (MREC) on 1 December 2000, reference 00/8/053. Written informed consent was obtained from the subjects (or their legally authorized representative) at entry to the BSRBR-RA. The original consent to be involved in the BSRBR-RA observational study covers the current analyses. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good pharmacoepidemiology practices and applicable laws and regulations of the UK.

Population

Data from patients initiating baricitinib and registered in the BSRBR-RA baricitinib cohort between 1 January 2018 and 31 March 2020 were included in this analysis. To be eligible for the current analysis, patients were required to be aged ≥18 years at the time of baricitinib initiation and to have received at least one dose of baricitinib 2 or 4 mg for the treatment of RA [fulfilled American College of Rheumatology (ACR) classification criteria at the time of registration or were diagnosed with RA by a consultant rheumatologist]. Other baricitinib-specific UK treatment eligibility requirements were assumed to have been met.

Analyses

Primary objective

The primary objective of this analysis was to evaluate continuation of baricitinib treatment. The drug was considered to be discontinued when a stop date was recorded in the BSRBR-RA, with no new start date recorded within the following 28 days. The probability of patients continuing baricitinib over time was determined using Kaplan–Meier analysis. Kaplan–Meier plots up to 540 days were created using all available data on baricitinib start and stop dates, with censoring at date of last follow-up recorded before 31 March 2020 or date of death, whichever was earliest. Transition to an off-label dose of baricitinib (not 2 or 4 mg) was considered as discontinuation; however, treatment interruptions of ≤28 days were permitted. Baricitinib continuation was also summarized as the number (percentage) of patients remaining on baricitinib at follow-up clinic visits.

Secondary objectives

Patient demographics and characteristics, as well as disease characteristics, at the time of baricitinib initiation were reported descriptively. Findings were recorded as number (percentage) for categorical variables and mean (S.D.) and median [interquartile range (IQR)] for continuous variables.

Reasons for baricitinib discontinuation were recorded when available and were classified as lack of efficacy, adverse event (including death) or other (all other reasons). The study dataset did not include data on specific adverse events.

At follow-up, mean (S.D.) and median (IQR) DAS28 using ESR (DAS28-ESR) and the number (percentage) of patients in each DAS28-ESR category [remission <2.6, low disease activity (LDA) >2.6 to ≤3.2, moderate disease activity (MDA) >3.2 to ≤5.1 and high disease activity (HDA) >5.1] were reported for those completing follow-up with available DAS28-ESR data and who had not discontinued baricitinib prior to the follow-up.

Data analysis

Analyses were performed using the full baricitinib cohort and five patient subgroups: (i) monotherapy *vs* combination

therapy; (ii) bDMARD/tsDMARD-naive (prior csDMARD only) *vs* bDMARD/tsDMARD-experienced (i.e. prior exposure to at least one bDMARD/tsDMARD: yes *vs* no); (iii) baricitinib 2 *vs* 4 mg; (iv) male *vs* female; and (v) age ≥65 *vs* <65 years. For the assessment of baricitinib continuation and DAS28-ESR post-baseline, patients were required to have at least one follow-up report after the report of baricitinib initiation; for other objectives, all patients were eligible. All analyses were descriptive, and no statistical testing was performed.

If information on age and/or the dose of baricitinib was missing at baseline, patients were excluded from the analysis. For calculations involving dates, the day and month of birth and diagnosis of RA was assumed to be 30 June for all patients (only year was captured in the database) and date of death was assumed to be the 15th of the month (only month and year were captured in the database). If the dates of the 6- or 12-month follow-up were missing, they were imputed for the purposes of censoring in the Kaplan–Meier analyses as start date plus 6 or 12 months, respectively.

Results

Baseline data were available from 561 patients in the baricitinib cohort who met study eligibility requirements; of these, 272 had completed at least one follow-up.

Population and disease characteristics

The overall baricitinib population had a mean age of 60.0 years and mean RA duration of 13.1 years (Table 1). More than half (60.6%) were taking baricitinib with a csDMARD and 54.0% had received prior bDMARD/tsDMARD therapy. The majority of patients were female (76.5%), overweight (BMI ≥25.0 kg/m^2 [5]) and treated with baricitinib 4 mg. More than half of patients were current (13.8%) or past (39.0%) smokers. Mean (SD) and median (IQR) baseline DAS28-ESR values were 5.7 (1.2) and 5.7 (5.2–6.4), respectively. Overall, 77.6% of patients had HDA, 18.6% had MDA, 1.4% had LDA and 2.3% were in remission.

Table 1. Baseline characteristics of 561 patients enrolled in the BSRBR-RA baricitinib cohort

Characteristics	BSRBR-RA baricitinib cohort		
	n with non-missing data	Mean (SD)/*n* (%)	Median (IQR)
Age (years)	561	60.0 (12.0)	61.1 (53.0–68.8)
Sex (female)	561	429 (76.5)	
BMI (kg/m^2)	296	28.1 (6.4)	27.0 (23.4–32.0)
BMI category	296		
Underweight (<18.5 kg/m^2)		7 (2.4)	
Normal (18.5–24.9 kg/m^2)		94 (31.8)	
Overweight (≥25.0 kg/m^2)		195 (65.9)	
Rheumatoid factor positive (yes)	432	289 (66.9)	
Smoking category	413		
Current		57 (13.8)	
Ex-smoker		161 (39.0)	
Never smoked		195 (47.2)	
Disease duration (years)	533	13.1 (10.3)	11.0 (5.0–19.0)
Baseline DAS28-ESR	559	5.7 (1.2)	5.7 (5.2–6.4)
DAS28-ESR category	559		
Remission		13 (2.3)	
Low disease activity		8 (1.4)	
Moderate disease activity		104 (18.6)	
High disease activity		434 (77.6)	
Baseline ESR	255	29.7 (24.5)	24.0 (12.0–40.0)
Baseline CRP	269	17.8 (23.9)	24.0 (4.0–22.0)
Baseline HAQ-DI	119	1.7 (0.7)	1.9 (1.4–2.3)
History of	561		
Asthma		75 (13.4)	
COPD		41 (7.3)	
Respiratory disease (asthma/COPD)		107 (19.1)	
Angina		14 (2.5)	
MI		22 (3.9)	
Stroke		10 (1.8)	
CVD (angina or MI or stroke)		38 (6.8)	
Diabetes		45 (8.0)	
Previously treated with biologic (yes)	561	303 (54.0)	
Baricitinib dosing	561		
Dose prescribed 2 mg		83 (14.8)	
Dose prescribed 4 mg		478 (85.2)	
Use with csDMARD (yes)		340 (60.6)	
Use with methotrexate (yes)		237 (42.3)	
Use with steroid (yes)		142 (25.3)	

DAS28-ESR categories: remission (DAS28-ESR <2.6), low disease activity (>2.6 to ≤3.2), moderate disease activity (>3.2 to ≤5.1) and severe/high disease activity (>5.1).
BSRBR-RA: British Society for Rheumatology Biologics Registry–RA; COPD: chronic obstructive pulmonary disease (chronic bronchitis/emphysema); csDMARD: conventional systemic DMARD; CVD: cardiovascular disease; DAS28-ESR: DAS for 28-joint count using ESR; HAQ-DI: HAQ Disability Index; IQR: interquartile range; MI: myocardial infarction.

Numbers of patients were unevenly distributed in the different subgroups considered, as a result of baseline characteristics of the study population, with more patients in the combination therapy *vs* monotherapy, baricitinib 4 *vs* 2 mg, female *vs* male, and younger *vs* older subgroups (Supplementary Tables S1–S5, available at *Rheumatology* online). Review of baseline information between each subgroup pairing showed some differences in patient characteristics; those presenting with an imbalance between the subgroup pairings are identified in Supplementary Tables S1–S5, available at *Rheumatology* online, by use of italics.

Continuation and discontinuation of baricitinib

Kaplan–Meier plots of baricitinib continuation, overall and by subgroup, showed that >60% of patients remained on treatment at 540 days (Fig. 1). Of 265 patients completing the

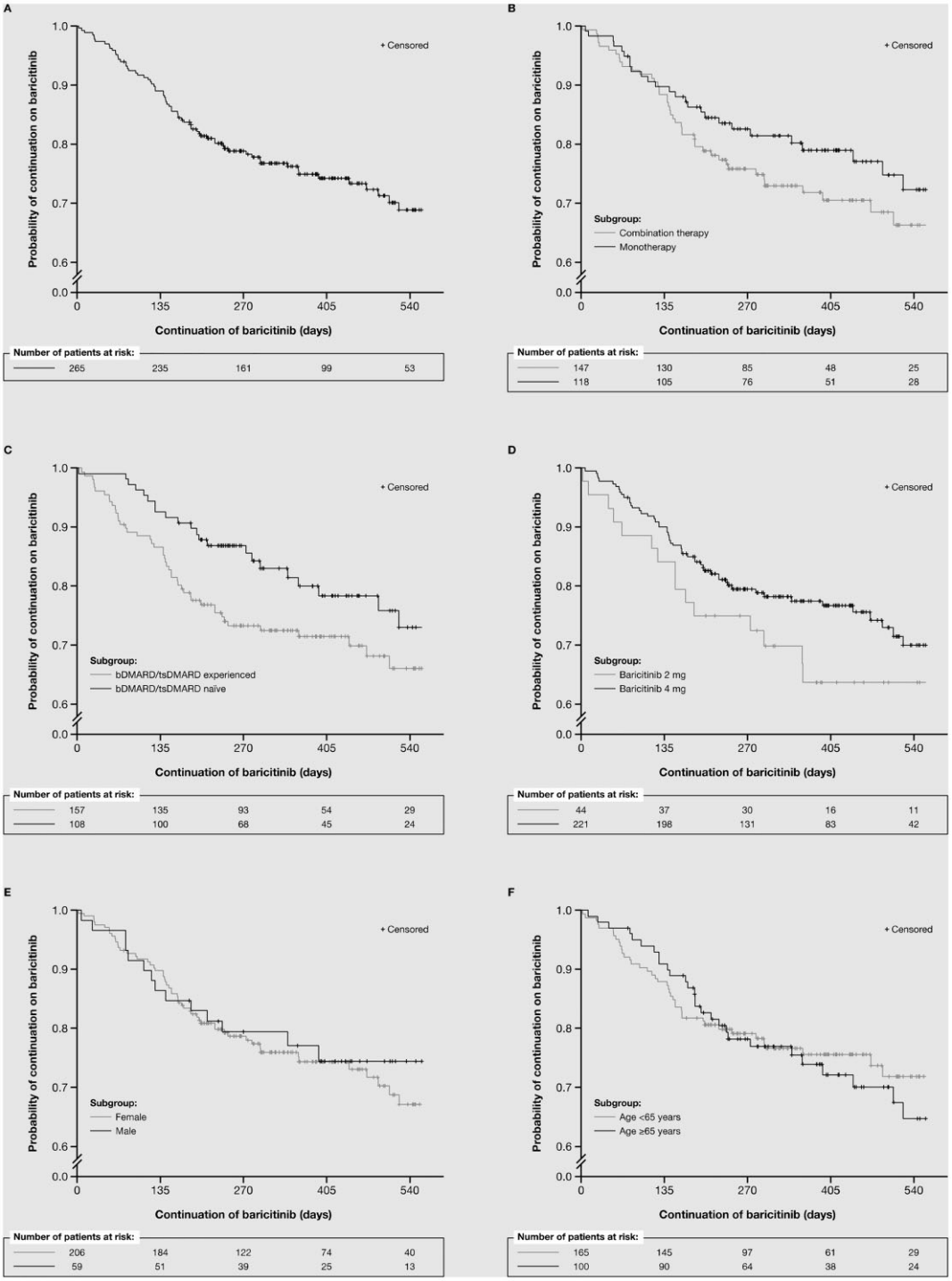

Figure 1. Kaplan–Meier plots of baricitinib survival over time for the overall cohort and patient subgroups. (**A**) Overall population. (**B**) Therapy subgroups (monotherapy *vs* combination therapy). (**C**) Previous therapy subgroups [bDMARD/tsDMARD naive (prior csDMARD only) *vs* bDMARD/tsDMARD experienced]. (**D**) Baricitinib dose subgroups (2 *vs* 4 mg). (**E**) Sex subgroups (male *vs* female). (**F**) Age subgroups (≥65 *vs* <65 years). bDMARD: biologic DMARD; csDMARD: conventional systemic DMARD; pts: patients; tsDMARD: targeted synthetic DMARD

Table 2. Proportion of patients continuing baricitinib at follow-up, for the overall cohort and patient subgroups

Population and subgroups	6-month follow-up		12-month follow-up	
	N	*n* (%)	N	*n* (%)
Overall population	265	206 (77.7)	110	76 (69.1)
Therapy subgroups				
Monotherapy	118	95 (80.5)	47	36 (76.6)
Combination therapy	147	111 (75.5)	63	40 (63.5)
Previous therapy subgroups				
bDMARD/tsDMARD naïve (prior csDMARD only)	108	91 (84.3)	49	36 (73.5)
bDMARD/tsDMARD experienced	157	115 (73.3)	61	40 (65.6)
Baricitinib dose subgroups				
2 mg	44	31 (70.5)	19	10 (52.6)
4 mg	221	175 (79.2)	91	66 (72.5)
Sex subgroups				
Male	59	47 (79.7)	28	21 (75.0)
Female	206	159 (77.2)	82	55 (67.1)
Age subgroups				
≥65 years	100	77 (77.0)	46	29 (63.0)
<65 years	165	129 (78.2)	64	47 (73.4)

For patients completing at least one follow-up.
bDMARD: biologic DMARD; csDMARD: conventional systemic DMARD; N: number of patients with follow-up data; tsDMARD: targeted synthetic DMARD.

Table 3. Reasons for discontinuation of baricitinib in the BSRBR-RA

Reason for discontinuation	*n*	%
6-month follow-up		
Lack of efficacy	14	24.6
Adverse events	36	63.2
Other	7	12.3
12-month follow-up		
Lack of efficacy	8	25.0
Adverse events	20	62.5
Other	4	12.5

A total of 59 patients with at least one recorded follow-up discontinued baricitinib by the 6-month follow-up and 34 patients with at least one recorded follow-up discontinued baricitinib by the 12-month follow-up; two patients had missing data at the 6-month follow-up and two patients had missing data at the 6-month follow-up.
n: number of patients with reported reason.

6-month follow-up, 206 (77.7%) remained on baricitinib at this time. Of 110 patients completing the 12-month follow-up, 76 (69.1%) remained on baricitinib at this time (Table 2). Patients appeared more likely to have continued baricitinib therapy at both the 6- and 12-month follow-ups if they were in the following subgroups: bDMARD/tsDMARD-naïve *vs* -experienced and baricitinib 4 *vs* 2 mg. At the 6-month follow-up, there was little difference in baricitinib continuation between the monotherapy *vs* combination therapy, male *vs* female, and age ≥65 *vs* <65 years subgroups. However, at the 12-month follow-up, patients in the monotherapy, male and younger age subgroups appeared more likely to remain on therapy than those in the combination therapy, female and older age subgroups, respectively, although the numbers of patients in each subgroup at this time were small.

The most common reason for baricitinib discontinuation at both follow-ups was adverse events (about 63% of both the 57 and 32 patients who discontinued and had a reason recorded at the 6- and 12-month follow-up, respectively; Table 3).

Severity of rheumatoid arthritis

Overall, mean (S.D.) and median (IQR) DAS28-ESR scores were lower at the 6-month follow-up [3.3 (1.5) and 3.2 (2.2–4.2), respectively] than at baseline; this pattern was observed in all subgroups (Table 4). Examination of subgroups suggested that, at the 6-month follow-up, mean and median DAS28-ESR scores were lower in bDMARD/tsDMARD-naive *vs* -experienced patients, patients receiving baricitinib 4 *vs* 2 mg, and those aged ≥65 *vs* <65 years (Table 4). The proportions of patients in each DAS28-ESR category supported these findings: overall, 35.4% of patients were in remission, 13.7% had LDA, 37.1% had MDA and 13.7% had HDA (Fig. 2). Notably, at the 6-month follow-up, 44.2 and 28.6% of bDMARD/tsDMARD-naive and -experienced patients, respectively, and 38.4 and 16.7% of patients in the 4 and 2 mg subgroups, respectively, were in remission. Remission rates also appeared to differ according to age and sex at the 6-month follow-up, with males and those aged ≥65 years achieving higher rates than females and those aged <65 years, respectively. There was little difference in DAS28-ESR levels at the 6-month follow-up between the monotherapy and combination therapy subgroups (Table 4, Fig. 2).

Data were available for a total of 52 evaluable patients at the 12-month follow-up; numbers in each subgroup were too small to provide meaningful information and are therefore not presented. For the overall population, mean (S.D.) and median (IQR) DAS28-ESR at the 12-month follow-up were 3.3 (1.3) and 3.3 (2.3–4.0), respectively, and 32.7% of patients were in remission, 13.5% had LDA, 44.2% had MDA and 9.6% had HDA.

Discussion

This observational study used real-world data on the treatment of RA with baricitinib, collected prospectively in the BSRBR-RA registry. These analyses have provided important information about the characteristics and outcomes of patients with RA initiating baricitinib in the UK. The current study covers the early baricitinib post-launch period in the UK and predates the major disruption of UK healthcare services due to the COVID-19 pandemic. The proportions of patients continuing baricitinib at the 6- and 12-month follow-ups were high at 77.7 and 69.1%, respectively. Kaplan–Meier plots indicated that, overall and in all subgroups, >60% of patients remained on therapy at 540 days (~18 months). These findings for an oral therapy are encouraging and appear broadly similar to continuation rates at 1 year reported for a first tumour necrosis factor-α inhibitor or tocilizumab [6, 7] but lower than that reported for rituximab [8] in the BSRBR-RA.

In general, the study cohort of patients initiating treatment with baricitinib was predominantly female, with a mean age of 60.0 years, and had longstanding, pre-treated (with a bDMARD/tsDMARD) RA and HDA. Patients had notable functional disability (mean Health Assessment Questionnaire Disability Index 1.7). Characteristics of the current baricitinib BSRBR-RA cohort were generally similar to those described for other BSRBR-RA bDMARD/tsDMARD cohorts [7–11], reflecting previous access to bDMARD or tsDMARD therapy

Table 4. DAS28-ESR at baseline and the 6-month follow-up after baricitinib initiation, for overall cohort and patient subgroups

Population and subgroups	DAS28-ESR at baseline			DAS28-ESR at the 6-month follow-up		
	N	Mean (S.D.)	Median (IQR)	N	Mean (S.D.)	Median (IQR)
Overall population	559	5.7 (1.2)	5.7 (5.2–6.4)	175	3.3 (1.5)	3.2 (2.2–4.2)
Therapy subgroups						
Monotherapy	221	5.6 (1.3)	5.7 (5.1–6.4)	72	3.3 (1.4)	3.2 (2.2–4.0)
Combination therapy	338	5.7 (1.1)	5.7 (5.2–6.4)	103	3.4 (1.5)	3.3 (2.2–4.3)
Previous therapy subgroups						
bDMARD/tsDMARD naïve (prior csDMARD only)	258	5.6 (1.1)	5.6 (5.2–6.2)	77	3.0 (1.4)	2.7 (2.0–3.7)
bDMARD/tsDMARD experienced	301	5.7 (1.2)	5.7 (5.1–6.5)	98	3.6 (1.4)	3.4 (2.5–4.5)
Baricitinib dose subgroups						
2 mg	82	5.8 (1.1)	5.8 (5.2–6.4)	24	4.0 (1.5)	3.8 (3.0–4.8)
4 mg	477	5.6 (1.2)	5.7 (5.2–6.4)	151	3.3 (1.4)	3.2 (2.1–4.0)
Sex subgroups						
Male	132	5.5 (1.2)	5.5 (5.1–6.3)	42	3.1 (1.5)	3.0 (1.9–4.0)
Female	427	5.7 (1.1)	5.8 (5.2–6.4)	133	3.4 (1.4)	3.3 (2.4–4.3)
Age subgroups						
≥65 years	212	5.8 (1.1)	5.7 (5.2–6.5)	60	3.1 (1.3)	2.9 (2.1–3.9)
<65 years	347	5.6 (1.2)	5.6 (5.1–6.3)	115	3.5 (1.5)	3.4 (2.2–4.4)

Analyses performed in patients completing the 6-month follow-up with available DAS28-ESR data and who had not discontinued baricitinib prior to the follow-up.
bDMARD: biologic DMARD; csDMARD: conventional systemic DMARD; DAS28-ESR: DAS for 28-joint count using ESR; IQR: interquartile range; N: number of patients with follow-up data; tsDMARD: targeted synthetic DMARD.

in the UK at the time baricitinib therapy was initiated in most patients included in this analysis (where treatment with two csDMARDs must have failed and patients must have HDA to be eligible for bDMARD or tsDMARD therapy). A small proportion of patients had LDA or remission (3.7% of the total cohort) at initiation of baricitinib. The reason for this is not known, but we can speculate that this was because patients switched to baricitinib from another treatment as a result of tolerability issues.

Generally, few notable differences in baseline characteristics were identified across the patient subgroups considered, although no formal statistical testing was performed. However, it is worth noting that patients receiving the lower dose of baricitinib (2 mg) were older, had greater functional disability, and were more likely to have a history of asthma and previous bDMARD therapy than those receiving baricitinib 4 mg. This may suggest that clinicians use a lower dose of the drug for patients considered to be older and frailer. In addition, patients with asthma are at increased risk of infection [12], which may have influenced physicians' dosing decisions regarding the use of baricitinib 2 mg. Patients in the bDMARD/tsDMARD-naive subgroup were more likely to be male and have a shorter RA duration, severe RA and higher C-reactive protein (CRP) levels than the bDMARD/tsDMARD-experienced subgroup, suggesting that clinicians are prescribing baricitinib before bDMARDs for selected patients, including males and patients with more severe RA. Patients receiving baricitinib as monotherapy were more likely to have received previous bDMARD therapy, and a greater proportion were receiving concomitant steroid therapy than those in the combination therapy subgroup, suggesting that these former patients may have had unsatisfactory outcomes with or contraindications to previous csDMARD combinations.

The high proportion of patients continuing baricitinib therapy at 6 months (77.7%) is consistent with baricitinib data from a post-marketing surveillance study in Japan (74.4%) [13], a Japanese multicentre biologics registry (the Tsurumai Biologics Communication Registry; 86.5%) [14], the Swiss Clinical Quality Management-RA (SCQM-RA) register (>75%) [15] and the prospective observational study RA-BE-REAL (81.2%) [16]. The most common reason for discontinuation, when one was provided, was adverse events (a limitation of this study is that further details of adverse events were not available for analysis). In contrast, the most common reason for stopping baricitinib in other real-world studies was lack of efficacy [14, 17].

When baricitinib continuation was evaluated by subgroup, it appeared that a smaller proportion of patients continued treatment in the bDMARD/tsDMARD-experienced *vs* -naive subgroup, and the 2 *vs* 4 mg subgroup at the 6- and 12-month follow-ups, and the combination therapy *vs* monotherapy, female *vs* male and older *vs* younger age subgroups at the 12-month follow-up. Similarly, in the SCQM-RA register, combination therapy was associated with reduced continuation on baricitinib, but line of therapy was not [15]. In the Swiss register, the percentage of patients continuing baricitinib at 12 months (>75%) was similar to that in the current analysis (69.1%) and significantly higher than that for patients continuing tumour necrosis factor-α inhibitor therapy (both bDMARD-naive and -experienced) [18]. Analysis of other BSRBR-RA bDMARD/tsDMARD cohorts found that, although bDMARD/tsDMARD-naive patients were more likely to continue with rituximab or tocilizumab than bDMARD/tsDMARD-experienced patients, multivariable analyses or propensity score adjustment to remove confounders no longer showed these differences [7, 8]. At the 6-month follow-up, baricitinib continuation was similar in both age subgroups, and DAS28-ESR scores were actually lower in older than in younger patients, suggesting that age does not need to be a key consideration when selecting patients who may benefit from baricitinib. At the 12-month follow-up, >60% of patients in both age groups remained on baricitinib therapy.

We found that a substantial proportion of patients with RA were receiving baricitinib as monotherapy in the BSRBR-RA

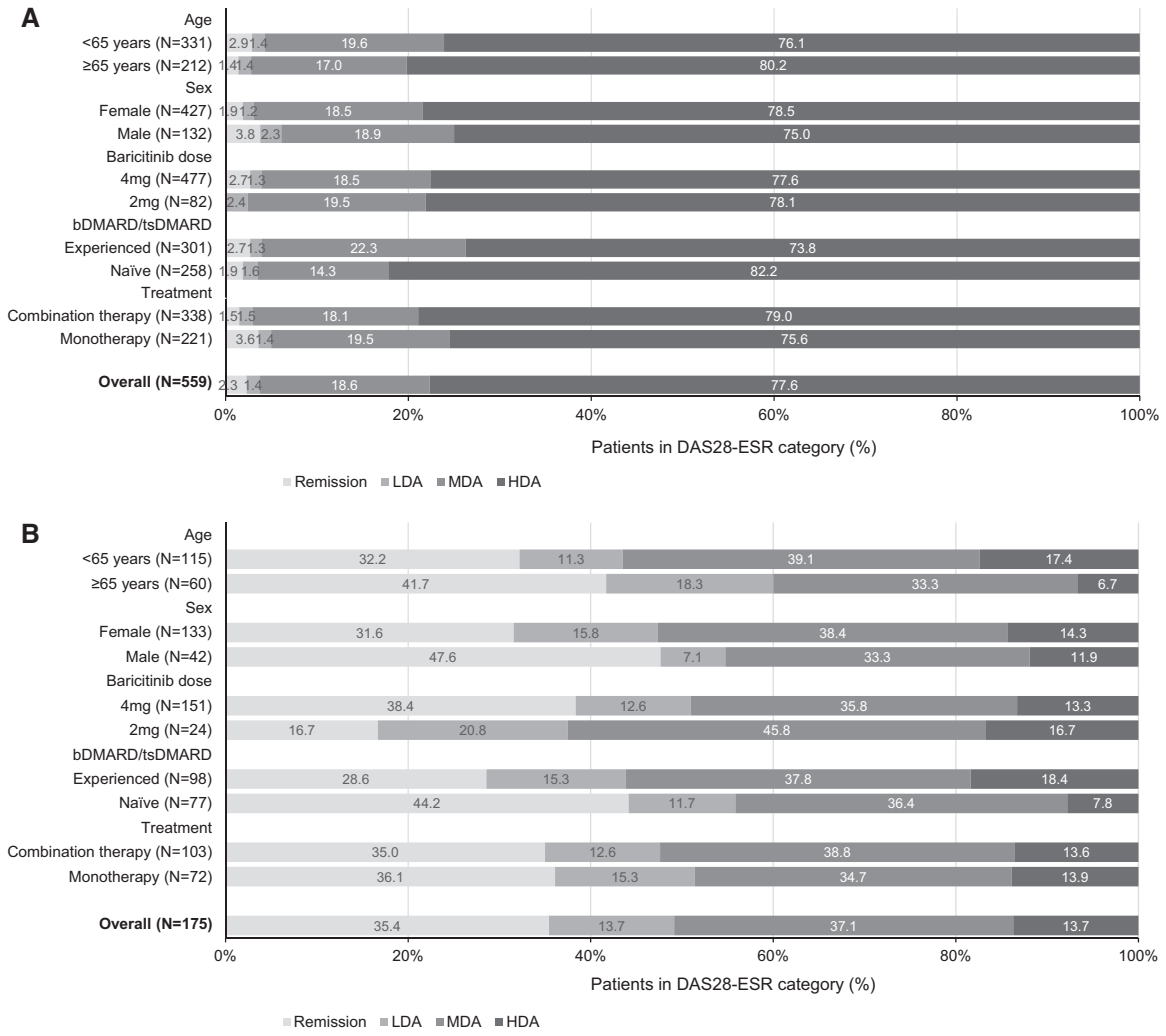

Figure 2. DAS28-ESR at (**A**) baseline and (**B**) the 6-month follow-up after baricitinib initiation. For the overall cohort and patient subgroups (patients completing the 6-month follow-up with available DAS28-ESR data and who had not discontinued baricitinib prior to the follow-up) by DAS28-ESR category: remission (DAS28-ESR <2.6), LDA (>2.6 to ≤3.2), MDA (>3.2 to ≤5.1) and HDA (>5.1). bDMARD: biologic DMARD; csDMARD: conventional systemic DMARD; DAS28-ESR: DAS for 28-joint count using ESR; HDA: high disease activity; LDA: low disease activity; MDA: moderate disease activity; N: number of patients with follow-up data; tsDMARD: targeted synthetic DMARD

cohort (29.8% of the bDMARD/tsDMARD-naive population and 39.4% of the overall population). Data from the 6-month follow-up indicated that disease severity was similar in the baricitinib monotherapy and combination therapy subgroups. Mean DAS28-ESR at the 6-month follow-up was lower than at baseline in the overall population and all subgroups, and the proportions of patients in remission or with LDA at the 6-month follow-up were higher than at baseline. Patients providing data for the 12-month follow-up represent the earliest treated patients who may have had different characteristics to those of patients providing data at baseline and the 6-month follow-up. Nevertheless, at 12 months, mean DAS28-ESR remained low, and the proportions of patients in remission or with LDA remained elevated compared with baseline.

When specific subgroups were considered, sufficient data were available for the 6-month follow-up only. At this time, patients in the bDMARD/tsDMARD-naive and 4 mg subgroups had lower disease activity than the bDMARD/tsDMARD-experienced and 2 mg subgroups, respectively. Analysis of another BSRBR-RA bDMARD/tsDMARD cohort, in which change from baseline in disease activity was evaluated, found a greater difference between baseline and 6-month DAS28 scores in bDMARD/tsDMARD-experienced than -naive patients receiving rituximab therapy; however, adjustment analyses removed the difference [10]. In contrast, multivariable analysis of patients receiving baricitinib enrolled in the Japanese biologics registry revealed that no previous tsDMARD therapy and a lower DAS28-CRP score at baseline, but not concomitant methotrexate therapy, were independently associated with achievement of LDA [14].

Interpretation of the findings of our study must take into consideration the small numbers of patients providing follow-up data for some subgroups, particularly the 2 mg subgroup and all subgroups at the 12-month follow-up (only 110 patients overall completed the second follow-up). Subgroup findings at the 12-month follow-up should therefore be considered exploratory and be treated with caution. However, baricitinib 4 mg has been shown to have greater efficacy than the 2 mg dose [19], with similar tolerability [19–21], potentially explaining the higher rate of continuation and lower follow-up DAS28-ESR with the higher dose. Another potential contributor to these between-dose differences is the

observed differences in baseline characteristics for each subgroup pairing, as already discussed.

The treatment of RA has been transformed by the availability of bDMARDs/tsDMARDs and treat-to-target strategies; however, the currently evolving therapeutic options necessitate high vigilance and carefully conducted studies to assess safety, efficacy and effectiveness [22]. National biologic registers provide valuable information on real-world effectiveness and safety beyond those observed in clinical trials and fill an important gap in the literature, complementing clinical trial data. For example, in common with many registry populations [22], our population differed in some respects from those of clinical trials of baricitinib [19–21, 23, 24].

Nonetheless, all registry data have some limitations, including that allocation of patients to treatment is not randomized, data are often missing, and the type and quality of data collected can vary across registries [22]. Limitations of the current analyses include that outcomes over time could only be reported in patients who had at least one recorded follow-up; although 561 patients started therapy with baricitinib in our study population, only 265 had a recorded first follow-up in the registry. Thus, many of the subgroups considered included only small patient numbers, preventing robust conclusions from being drawn. Additionally, another subgroup analysis was planned [overweight/obese (BMI $\geq$25.0 kg/m^2) *vs* underweight/normal weight (BMI $<$25.0 kg/m^2) [5]], but the numbers of patients providing BMI data were insufficient to allow this. Also, there was notable variability in some baseline characteristics between subgroups. In addition, our continuation estimates may be conservative as we employed the strict requirement that only gaps in baricitinib therapy of $\leq$28 days were allowed. Finally, the study period did not include the time when healthcare provision in the UK was disrupted by the COVID-19 pandemic. Future research might explore the effect of the pandemic on continuation with therapy and DAS28-ESR outcomes; however, missing follow-up data due to cessation of research activities during this period could provide a challenge for data analysis. In addition, it will be interesting to ascertain whether smoking status affects ongoing outcomes in the BSRBR-RA baricitinib cohort.

Conclusion

In the early years of real-world baricitinib use in the UK, a high proportion of patients continued with treatment at both 6 and 12 months, and disease activity was lower at these times than at baseline. It is notable that baricitinib performed well as monotherapy, providing a therapeutic option for patients unable to tolerate csDMARDs.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article were provided to Lilly by the British Society for Rheumatology under licence. Data will be shared upon reasonable request to the corresponding author with the additional permission of the British Society for Rheumatology.

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