

ORIGINAL RESEARCH

Efficacy and drug persistence of
baricitinib monotherapy is similar to
combination therapy in patients with
active RA: a prospective
observational study

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ABSTRACT

Background Baricitinib (BARI) is approved for the treatment of rheumatoid arthritis (RA) after failure of conventional synthetic and biologic disease modifying anti-rheumatic drugs (cs/bDMARDs) in combination with methotrexate (MTX) or as monotherapy. However, real-world data are scarce regarding efficacy and drug persistence for BARI monotherapy (BARI-mono) versus its combination with MTX (BARI-combo).

Objective To evaluate efficacy and drug persistence of BARI-mono compared with BARI-combo in routine clinical practice

Methods Patients with RA who were switched to BARI were included in a prospective, monocentric cohort. Demographics, clinical outcomes, adverse events and medication were prospectively recorded every 3 months. Clinical efficacy was measured by DAS-28 ESR while drug persistence was measured as the time on drug. We estimated least-square mean DAS-28 scores over time using linear mixed effects models including time-group interactions. Kaplan-Meier method was used to estimate BARI survival and probability of remission over time.

Results 139 patients (98 women; aged 58.4 (12.8) years; mean disease duration of 9.7 years) were included between 2017 and 2021. 46 patients received BARI-combo, 93 patients received BARI-mono. Mean DAS-28 ESR were not significantly but only numerically different between both groups at baseline and multiple timepoints over follow-up. DAS-28 ESR remission was attained at least once upto 48 weeks in 62% and 51% patients in BARI-combo versus BARI-mono group (log-rank $p=0.64$). Drug persistence was high (69 vs 67% at 48 weeks and 62% vs 56% at 96 weeks) and similar in BARI-combo-treated and BARI-mono-treated patients. b/ts DMARD naïve patients had lower mean DAS-28 scores over the follow-up and attained DAS-28 ESR remission earlier than patients with inadequate response to b/ts DMARDs ($p=0.11$). BARI was discontinued in 11/139 patients (7.9%) due to adverse effects.

Conclusion In routine practice, BARI is effective as monotherapy in case of MTX intolerance with overall high drug persistence rates. No new safety signals were observed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In clinical trials, baricitinib (BARI) is an effective and safe treatment option for patients with active rheumatoid arthritis. However, scarce routine clinical practice data have been generated comparing mono and combination therapy with methotrexate (MTX).

WHAT THIS STUDY ADDS

Bari in combination with MTX probably adds a marginal benefit compared with Bari monotherapy in disease activity therefore baricitinib monotherapy is a viable option in routine practice with similar retention rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

For patients who do not tolerate MTX, BARI is an effective drug when used as monotherapy in routine practice.

INTRODUCTION

Rheumatoid arthritis (RA) is a severe inflammatory joint disease and may lead to damage and disability.¹ RA is characterised by specific signature cytokines, TNF- α and IL-6, which orchestrate the disease process and can be therapeutically inhibited by respective cytokine inhibitors² and for example require Janus kinases (JAK) for its action. The use of JAK inhibitors (JAKi) has been recognised as particularly effective in RA patients, allowing to achieve low disease activity (LDA) or even remission in a substantial number of patients. The efficacy of the JAKi baricitinib has been studied as monotherapy and as combination therapy with MTX in patients with active RA in randomised controlled trials^{3–6}. In a randomised controlled trial conducted by Fleischmann *et al*, BARI monotherapy

provided equivalent ACR responses in comparison to BARI in combination with MTX. The combination was better at preventing radiographic progression, suggesting the combination as the preferable option. RA-BEYOND, a long-term extension study that recruited from RA-BEGIN demonstrated that many patients with RA responded to BARI monotherapy especially when they switched from MTX monotherapy. MTX, added to BARI contributed to an improved efficacy especially in patients with RA in whom disease was not adequately controlled with the initial therapy.⁷

Randomised controlled trials (RCTs) are essential experiments for causal inference on treatment efficacy and are not aimed at describing the disease course or status in routine practice.^{8–9} For example, patients in routine practice are usually not as active and more commonly suffer from comorbidities in comparison to those included in RCTs.¹⁰ Therefore, results from RCTs need to be corroborated with observational evidence for a comprehensive description and understanding of the disease course under a new treatment¹¹ in order to establish the effectiveness of a treatment in addition to its efficacy. Italian and Spanish multi-centre observational cohorts confirmed the efficacy and safety profile of BARI in bDMARD-naïve RA patients and revealed that drug survival is better in patients with seropositive RA.^{12–13} Analysis from a Swedish registry data revealed that BARI was equally effective compared with other bDMARDs and that BARI was more commonly used as monotherapy compared with rituximab and TNFi.¹⁴ These studies have analysed the efficacy of BARI mono versus BARI combination with overall csDMARDs but detailed observational data comparing BARI monotherapy to an explicit combination with MTX with respect to treatment response and drug survival were not reported. This situation stands in contrast to TNFi in RA, which are recommended in combination with MTX, as it has long been shown that MTX improves the overall response to and persistence with TNFi probably by preventing the development of anti-drug antibodies.^{15–21} To address the question and provide a descriptive account of the disease course under BARI monotherapy in comparison to BARI combination with MTX in a routine practice setting, we prospectively collected data from all patients who newly started treatment with BARI and collected disease activity, adverse event and drug attrition data.

MATERIALS AND METHODS

Patients and assessments

Patients with RA, who initiated BARI treatment due to (1) high disease activity, (2) intolerance to previous b/ts/cs DMARD treatment and (3) their own preference in agreement with their attending physician were included in this prospective, single centre cohort after providing written informed consent (ethics approval 19_18 B). Patients were seen in a specialised university-hospital outpatient centre every 3 months by an experienced rheumatologist.

Baseline data on demographic characteristics and disease status were obtained including disease duration, previous treatments as well as the reason for selecting monotherapy or combination therapy with MTX. Clinical data such as 68 tender joint count (TJC), 66 swollen joint count (SJC), visual analogue scale (VAS) for pain and global disease activity as well as composite indices such as Disease Activity Score-28 (DAS-28 ESR/CRP), Health Assessment Questionnaire (HAQ-DI), Rheumatoid Arthritis Impact of Disease (RAID) and Functional Assessment of Chronic Illness Therapy (FACIT) were recorded. Furthermore, acute phase response was measured by C reactive protein level (CRP) and erythrocyte sedimentation rate (ESR). In addition, autoantibody status (rheumatoid factor, anti-citrullinated protein antibodies) and cholesterol levels were analysed. Adverse events were recorded and reasons for BARI discontinuation were documented.

Patients visited the clinic regularly at 12-week intervals. Cohort follow-up started at the time of BARI initiation and ended on the date of treatment cessation or the last visit at the time of data extraction (2017–2021) if the treatment was ongoing. The primary outcomes of the study were disease activity as measured using DAS-28 ESR and drug persistence defined as time in weeks from treatment onset to termination. We also evaluated time to remission as defined using DAS-28 (ESR) and Boolean remission criteria, the time course of other composite disease activity measurements; DAS-28 CRP, SDAI, CDAI and further indices for function, disease-related quality of life and laboratory assessments.

Statistical analysis

Data analysis was conducted on an ‘as-treated’ population, that is, including data from all visits starting from upto the prior 2 weeks of BARI start date (since not all medication start dates corresponded to visit dates) and upto 4 weeks after BARI stop-date (since not all medication stop dates corresponded to visit dates) or upto the last date of observation if BARI treatment was ongoing. We summarised patient characteristics using means, SD, medians, interquartile ranges for continuous and count variables and percentages for categorical variables.

The time course of DAS-28 scores was analysed using linear mixed effects models, where the treatment group variable (ie, BARI-mono/BARI-combo) and time (weeks) after initiation of BARI were fixed effects and a random intercept was fitted for each patient. Since the course of DAS-28 scores over time is expected to be curvilinear, we used natural splines (ie, restricted cubic splines) to model time. A time–treatment interaction term was also added to the model for the direction and size of between-group differences of DAS-28 over time. To present the results, we used estimated marginal mean values for each group at specific timepoints over 96 weeks and plotted these with their respective 95% CIs. The same approach was used to describe the course of other outcomes over time by fitting separate models for DAS-28 CRP, SDAI, CDAI, tender and SJCs, HAQ-DI, RAID, FACIT, patient global VAS, physician

global VAS, duration of morning stiffness, CRP, ESR, total cholesterol, HDL cholesterol and LDL cholesterol. In these analyses, joint counts, morning stiffness, ESR and CRP were log-transformed and back-transformed to their native scale after estimating the marginal means. Drug survival and remission status over time were analysed using the Kaplan-Meier method. We used the log-rank test for between-group comparisons. We used shift plots to describe changes in laboratory analytes under BARI treatment. No specific procedures were used for missing data. All p values were two tailed and considered significant if <0.05.

RESULTS

Demographic characteristics of BARI-treated patients with RA

One hundred thirty-nine patients (98 women/41 men; aged 58.4 (12.8) years; mean disease duration of 9.7 years) were enrolled and analysed in our cohort. Median

follow-up was 53.1 weeks (IQR 23.0–109.3). At the time of cohort entry, mean (SD) DAS-28 CRP was 4.0 (1.3), mean DAS-28 ESR was 4.3 (1.3), mean HAQ was 1.1 (0.7). Ninety-four (67.6%) patients were anti-CCP2 Ab positive. Fifty-five of 139 patients were b/tsDMARD naïve with a similar distribution between the BARI mono (39/93) and BARI-Combo (16/46) (table 1). Ninety-three patients received BARI-mono mainly due to MTX-intolerance. Table 1 provides detailed information on age, sex distribution, antibody status, disease duration and activity, physical function and comorbidities such as diabetes and hypertension. Virtually all characteristics were well balanced between the BARI-mono and BARI-combo arms with the exception of a higher proportion of women as well as a higher proportion of patients with diabetes and hypertension in the BARI-monoarm than in the BARI-combo arm.

Table 1 Baseline characteristics.

N			BARI/all 139	BARI/combo 46	BARI/mono 93
Age (years)		Mean (SD)	58.4 (12.8)	56.2 (14.1)	59.5 (12.0)
Sex	Women	N (%)	98 (70.5)	28 (60.9)	70 (75.3)
	Men	N (%)	41 (29.5)	18 (39.1)	23 (24.7)
Smoking status	Never	N (%)	64 (46.0)	24 (52.2)	40 (43.0)
	Former	N (%)	43 (30.9)	12 (26.1)	31 (33.3)
	Current	N (%)	32 (23.0)	10 (21.7)	22 (23.7)
Anti-CCP2 Ab	Negative	N (%)	45 (32.4)	17 (37.0)	28 (30.1)
	Positive	N (%)	94 (67.6)	29 (63.0)	65 (69.9)
Duration (years)		Mean (SD)	9.7 (8.5)	9.7 (7.5)	9.6 (9.1)
		Median (IQR)	6.9 (3.5–13.8)	7.5 (4.4–13.8)	6.2 (3.0–13.8)
F/U (m)		Mean (SD)	68.9 (53.6)	61.5 (48.9)	72.5 (55.6)
		Median (IQR)	53.1 (23.0–109)	47.6 (21.0–112)	62.3 (23.1–105)
DAS-28 CRP(units)		Mean (SD)	4.0 (1.3)	3.9 (1.3)	4.0 (1.3)
DAS-28 ESR (units)		Mean (SD)	4.3 (1.3)	4.2 (1.3)	4.3 (1.3)
HAQ-DI (units)		Mean (SD)	1.1 (0.7)	1.1 (0.6)	1.2 (0.7)
VAS (global; mm)		Mean (SD)	52.4 (22.9)	51.9 (21.9)	52.6 (23.6)
VAS (physician; mm)		Mean (SD)	50.5 (19.9)	47.9 (23.2)	51.8 (18.0)
TJC		Mean (SD)	6.8 (6.3)	7.0 (7.2)	6.8 (5.9)
SJC		Mean (SD)	4.2 (5.0)	4.1 (6.5)	4.2 (4.2)
VAS pain		Mean (SD)	53.4 (21.5)	50.4 (22.7)	54.9 (20.9)
FACIT		Mean (SD)	30.1 (12.7)	27.6 (14.1)	31.4 (11.9)
RAID		Mean (SD)	5.1 (2.1)	5.3 (2.2)	5.0 (2.1)
HAQ		Mean (SD)	1.1 (0.7)	1.1 (0.6)	1.2 (0.7)
MTX dose at last use		Median (IQR)	15.0 (15.0–20.0)	15.0 (15.0–20.0)	15.0 (15.0–20.0)
History of bDMARD use	b-tsDMARD-naive	N (%)	55 (39.6)	16 (34.8)	39 (41.9)
	b_tsDMARD-IR	N (%)	84 (60.4)	30 (65.2)	54 (58.1)
Diabetes mellitus		N (%)	16 (11.9)	3 (6.5)	13 (14.6)
Hypertension		N (%)	55 (40.7)	15 (32.6)	40 (44.9)

Demographics, Disease Activity Score-28 (DAS 28 ESR/CRP), antibody status, follow-up time, disease duration, Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy (FACIT), Rheumatoid Arthritis Impact of Disease (RAID), visual analogue scales (VAS) for pain, global and physician, morning stiffness, 68 tender joint count (TJC) and 66 swollen joint count (SJC) as well as comorbidities are shown for all patients as well as for the monotherapy and combination therapy arm: statistically no significant difference between the groups. The proportion of men and diabetic patients with RA, which are numerically more frequent in the BARI monotherapy arm without statistical significant differences. BARI, baricitinib; bDMARDs, biologic disease modifying anti-rheumatic drugs; RA, rheumatoid arthritis.

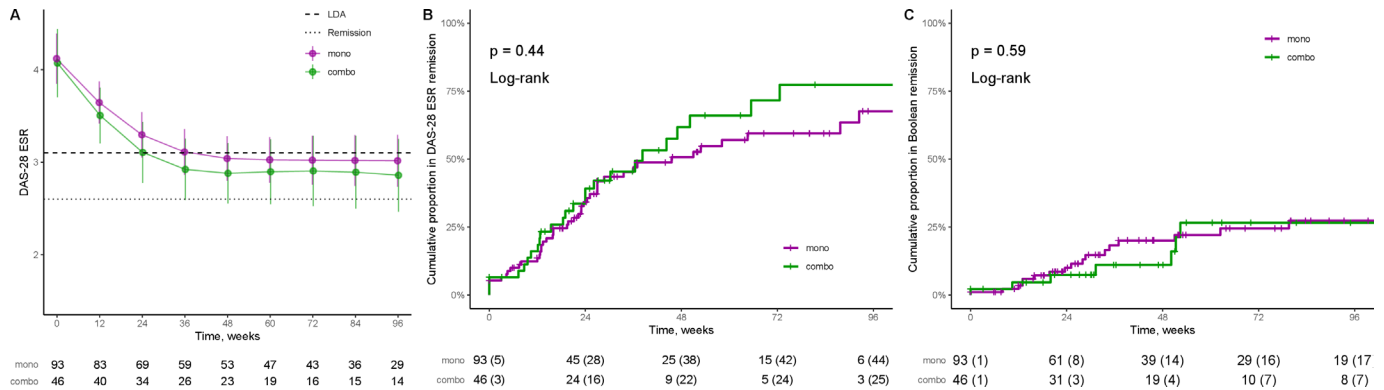


Figure 1 Effects of baricitinib (BARI)-mono and BARI-combo therapy on disease activity measured by Disease Activity Score 28 (DAS-28) erythrocyte sedimentation rate (ESR). DAS-28 based on ESR as well as low disease activity (LDA) and remission are displayed as estimated marginal mean values in (A). No significant but only numerically differences were seen at any time point between patients receiving BARI monotherapy and BARI/MTX (MTX) combination therapy. Kaplan-Meier survival curves are used in (B) and (C) to illustrate time to DAS-28 ESR and Boolean remission. Patients at risk or under follow-up at each time point are presented below the x axes. Error bars indicate 95 CI for each time point.

Similar clinical response to treatment with BARI-mono and BARI-combo

The mean DAS-28 ESR corresponding to moderate disease activity at baseline decreased over time to the range of LDA after 36 weeks of treatment onset and remained stable thereafter in both groups. The mean DAS-28-ESR value was numerically higher in the monotherapy group in comparison to the combination group (figure 1A) but this difference was small (maximal absolute mean difference was 0.31) and not significant at any time point. The cumulative proportion of patients that attained DAS-28 ESR remission at least once (figure 1B) was not different between groups, for example at week 24, 28/93 patients in BARI-mono and 16/46 patients in BARI-combo therapy had achieved DAS 28 ESR remission at least once (figure 1). Almost comparable proportions were achieved for week 48 (figure 1B). Boolean remission was achieved at least once in 17/93 of the patients undergoing BARI monotherapy and 7/46 patients among patients under BARI-combo therapy with comparable cumulative probabilities as seen in figure 1C. The figures for DAS-28CRP, SDAI and CDAI (online supplemental figure 1) were also similar. Overall, b/ts DMARD naïve patients showed a better response to BARI (online supplemental figure 2)

Similar drug survival with BARI-mono and BARI-combo therapy

BARI treatment was discontinued overall in 41 (29.5%) patients as a result of inefficacy and in 11 patients (7.9%) due to adverse events (table 2). Overall drug survival was high over time attributing to 66.5% of the patients at 1 year and 56.4% of the patients at 2 years (figure 2A). BARI-mono and BARI-combo showed an essentially identical drug survival (69% vs 67% at 1 year and 62% vs 56% at 2 years). While drug survival was slightly higher in b/tsDMARD-naïve than b/tsDMARD-IR patients, these differences were not significant (online supplemental figure 2).

No difference in individual disease activity components between BARI-mono and BARI-combo therapy

Tender and swollen joints showed a similar decrease with BARI-mono and BARI-combo therapy (figure 3). Furthermore, responses in VAS pain and VAS global showed no differences in the dynamics and size of the response. Broader instruments like RAID and instruments measuring fatigue (FACIT) also revealed no differences between the two groups. Overall point estimates for mean HAQ were higher including baseline, but this difference was below the clinically meaningful HAQ difference of 0.25.

Laboratory assessments under BARI-mono and BARI-combo therapy

Mean CRP levels were similar with BARI-mono and in BARI-combo over time. Mean ESR values were numerically higher in the monotherapy group than in the combination therapy group, but this difference also existed at the time treatment initiation and persisted over time. (figure 3). A possible explanation for this could be a difference in gender distribution between BARI-mono and BARI-combo. However, the results remained similar after stratifying by gender (not-shown). Total cholesterol and HDL were higher in the BARI-combo group, although there were no significant differences. In 49 patients (of whom 36 in the BARI-combo group), a high LDL level was recorded as an AE, but BARI treatment was continued in all of these patients. Overall, the BARI-mono group had more concomitant diseases: Hence, of the 69 patients with arterial hypertension or type 2 diabetes mellitus, 51 were in the BARI-mono group (72.3%).

Safety

Eleven (7.9%) patients discontinued BARI treatment due to adverse events. (three in combo and eight in mono group). We identified transaminase elevations (3/11), herpes zoster infections (3/11), upper respiratory tract

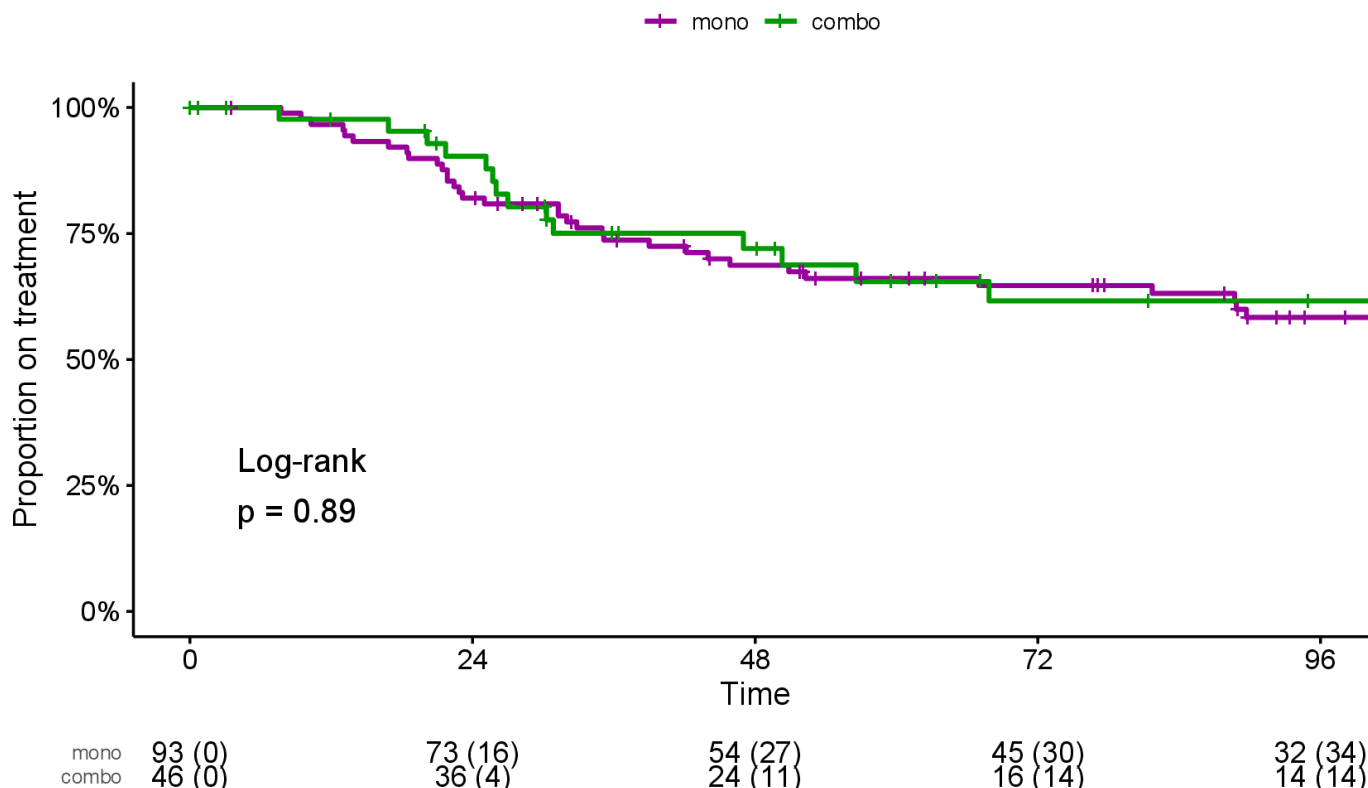


Figure 2 Baricitinib drug survival under baricitinib (BARI)-mono and BARI-combo therapy. Kaplan-Meier curve displays drug survival probability of combo (red) and mono (blue). No significant difference was observed between groups. Numbers at risk for each time point are presented below the x-axis including in brackets the cumulative number of patients who stopped treatment for any reason.

infections (2/11), gastrointestinal complaints (1/11), elevated creatine kinase (CK) levels (1/11) and one report of central venous thrombosis in the right eye (1/11); of note: this event was not considered to be drug associated by the respective treating doctor; however, BARI was switched despite clinical efficacy in our documentation as adverse events that led to discontinuation of BARI. Major adverse cardiovascular events occurred in 13 patients, 9 in the BARI-mono group and 4 in the BARI-combo group. One patient (age 79, previous smoker) in the monotherapy group was diagnosed with metastatic breast cancer after 16 months of treatment with BARI.

Laboratory value of special interest

CK elevation is a known side effect of JAK inhibitor therapy. Shift plots presented in online supplemental figure 3 show the baseline values at the X-axis and the mean of the follow-up values at the Y-axis. The shift plot for CK shows a clear upward shift of CK values during follow-up compared with baseline indicating a constitutive increase of CK under treatment. For LDH, the points seem to be symmetric around perfect correlation except for a few outliers suggesting sporadic increases in LDH values.

Table 2 Reasons for treatment decisions.

(A) Reasons for choosing BARI monotherapy; N (%)				
Not specified	MTX failure	MTX intolerance	Doctor and patient preference	
8 (8.60)	4 (4.3)	70 (75.26)	11(11.82)	
(B) Reasons for BARI discontinuation, N (%)				
	Adverse event	Inefficacy	Not specified	Patient preference
Overall	11 (7.9)	41 (29.5)	3 (2.2)	2 (1.4)
Mono	8 (8.6)	28 (30.1)	2 (2.2)	2 (2.2)

This table reflects the reasons of the treating physicians why a patient was given monotherapy or why treatment with BARI was stopped. Reasons to decide for monotherapy (A) were mainly due to MTX-incompatibility (75.26%), followed by doctor and/or patient preference (11.82%). (B) Reason for treatment withdrawal with BARI was mainly due to inefficacy (29.5%), followed by adverse events (7.9%). BARI, baricitinib; MTX, methotrexate.

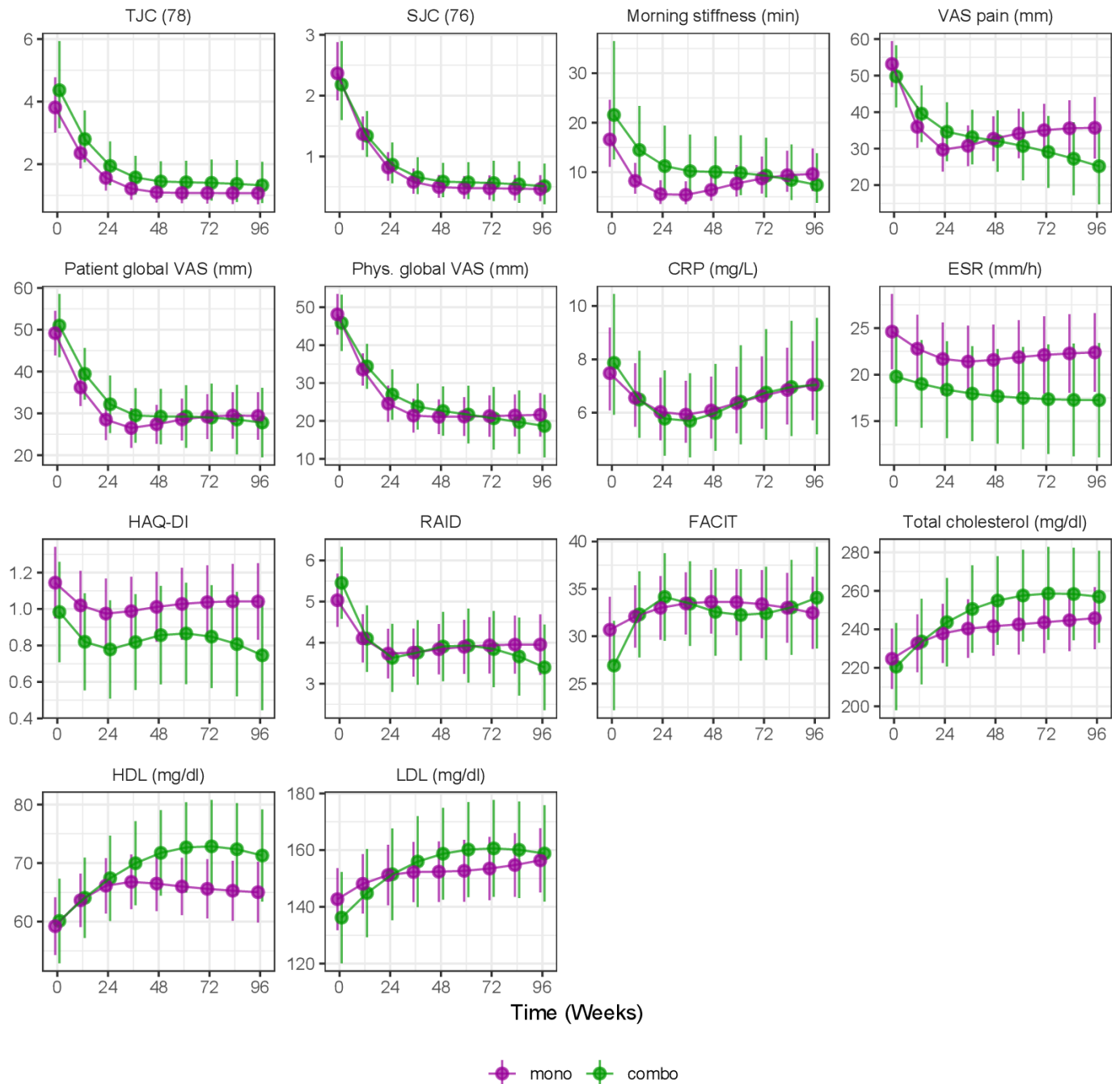


Figure 3 Time course of clinical and laboratory measurements under baricitinib (BARI)-mono and BARI-combo therapy. This figure shows multiple outcome measures for BARI monotherapy (blue) and combination therapy (red) at time points between week 0 and week 96 displayed as estimated marginal mean values. No significant differences were seen for: tender or swollen joint count (TJC 78/SJC 76), morning stiffness in minutes, visual analogue scales (VAS, pain, patient global, physician global) C reactive protein (CRP mg/L), erythrocyte sedimentation rate (ESR) (however a constant but not significant difference was seen), Functional Assessment of Chronic Illness (FACIT), Rheumatoid Arthritis Impact of Disease RAID total cholesterol (mg/dL), high and low density lipoprotein (HDL/LDL in mg/dL). However, at week 96, a significant difference was seen for health-assessment questionnaire (HAQ-DI). Error bars indicate 95 CIs.

DISCUSSION

BARI has shown its efficacy in DMARD-naïve RA, MTX inadequate responders and bDMARD inadequate responders in clinical trials both in combination with

MTX or as monotherapy, the latter in DMARD naïve patients.³⁻⁷ Furthermore, long-term extension phases of these clinical trials demonstrated effectiveness and drug persistence for monotherapy as well as combination with MTX with slight benefits for combination therapy.^{5,7} Apart from the RA-BEYOND study results, there is to our knowledge no other published study to date comparing

the efficacy of BARI as monotherapy versus combination therapy with MTX explicitly, while there are data available on combination with csDMARDs.^{13 14} Furthermore, no study from routine practice is available that compared BARI-mono versus BARI-combo therapy in a large cohort.

Our real-world prospective analysis shows a similar time course of disease activity using DAS28 ESR under BARI-mono and BARI-combo therapy with the BARI-combo group being numerically, but not statistically better throughout almost all time points, confirming data from a randomised controlled trial and Swedish Registry data, the latter comparing BARI mono with BARI combination with csDMARDs.^{5 14} Furthermore, we detected similar rates of drug survival between BARI-mono and BARI-combo which is of interest for patients who do not tolerate MTX. The time course of DAS-28-ESR showed similar dynamics in BARI-mono and BARI-combo therapy with again numerically better values for the BARI-combo group, suggesting combination as the preferable treatment option. Furthermore, remission rates were virtually identical with monotherapy and combination therapy. The rapid response on objective signs and symptoms of RA as well as patient-reported outcome measures observed with monotherapy and combination therapy are consistent with the data from clinical trials.^{4 6 7} Causes for a consistent and constant differences in HAQ score between BARI-mono and BARI-combo are most likely due to higher rate of comorbidities in the BARI-mono group (table 1) since a gender-stratified analysis showed similar results. It is well known that patients who did not respond to previous bDMARDs have a lower probability to respond to subsequent treatments. This was confirmed in our cohort, underlining the reliability of our data. We found differences in response rates and time to remission between the subgroups of b/tsDMARD-naïve and b/tsDMARD-IR patients. Nevertheless, a high proportion of b/ts DMARD IR patients responded well with a high drug survival probability leaving BARI as an attractive treatment option in b/tsDMARD IR patients.

No difference in drug survival was seen between BARI-mono and BARI-combo therapy, although a better drug survival could be expected in the combination group as observed with TNFi therapies.^{15–21} Hence, drug survival was comparable among BARI-mono and BARI-combo therapy after 1 and 2 years of treatment. Most of BARI discontinuations were due to inefficacy, much less due to adverse events (ratio 4:1). We found no new safety issues related to BARI; however, this finding needs to be interpreted with caution as the sample size was small. Liver enzyme elevations (>3 times upper normal limit) necessitated withdrawal of BARI in three patients, while moderate elevation in cholesterol levels did not impact treatment. CK elevations were observed but required withdrawal BARI in only one patient with a maximal CK of 918 U/mL. Liver enzyme and CK elevation were reversible after withdrawal of BARI. Three herpes zoster infections occurred, which also lead to treatment withdrawal (3/11).

The strength of this study is the prospective design and observation in routine practice. The limited sample size does not allow any strong conclusions on safety issues as these are uncommon (eg, thrombosis). On the other hand, sample size was fairly good to judge on efficacy, suggesting a numerically but not a statistically significant difference in the efficacy of BARI-mono and BARI-combo therapy in a real-world setting. Since baseline disease activity and other baseline characteristics of the patients undergoing monotherapy and combination treatment were very similar, we did not use any regression adjustment or other analytic procedures against confounding. We therefore cannot exclude confounding due to unobserved variables.

In summary, our prospective, routine practice cohort confirmed data from randomised controlled trials with BARI being effective without revealing new safety issues. This finding attributes to both BARI-mono and BARI-combo therapy. As we did not find any significant differences in efficacy and drug survival between mono- and combination therapy, we think that monotherapy with BARI is an attractive option for patients with RA in the real-world setting if MTX and/or bDMARD treatment fails or is not tolerated.

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Contributors AK, GS, SB, DS, AH and FH collected and controlled the data; AK, SB, KT and GS wrote the manuscript. KT performed statistical analysis; KT, SB and AK prepared the figures. AK is guarantor for this paper.

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Competing interests AK and DS do consultancy work for Eli Lilly regarding a virtual reality application for rheumatology. DS, AK, AH DS received speaker honoraria from AbbVie, Bristol-Myers Squibb, Janssen-Cilag, Eli Lilly, Galapagos, Novartis. GS received speaker honoraria from AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag and Novartis. KT received speaker honoraria and travel support from UCB, CellTrion, Eli Lilly, Gilead Sciences and Novartis.

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