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Clinical science

A retrospective observational study of effectiveness of sequential biologic and targeted synthetic DMARDs in psoriatic arthritis in the UK

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Abstract

Objectives: Evidence evaluating effectiveness of biologic and targeted synthetic DMARDs (b/tsDMARDs) in adults with PsA after exposure to three or more b/tsDMARDs is lacking. We aimed to evaluate response to sequential lines of b/tsDMARDs.

Methods: In this multicentre retrospective observational study, 22 hospitals submitted data from routine clinic appointments of patients with PsA treated with b/tsDMARDs. Purposive sampling obtained a study population exposed to advanced lines of therapy. Effectiveness outcome measures (Psoriatic Arthritis Response Criteria [PsARC]/tender joint count [TJC]/swollen joint count [SJC]) at baseline and first follow-up (12–16 weeks) for each line were recorded. Odds of achieving PsARC in 2nd/3rd line were compared with 4th+ line.

Results: Four hundred and thirty-seven participants (163 male, 274 female) and 1459 treatment courses were included: 430 1st line, 633 2nd/3rd line and 396 4th+ line. The adjusted odds ratio (95% CI) for achieving PsARC in 1st line *vs* 2nd/3rd line was 1.91 (1.40, 2.60) and 4th+ line *vs* 2nd/3rd line was 1.13 (0.84, 1.55). There was no significant difference in change from baseline TJC/SJC between 2nd/3rd and 4th+ lines.

Conclusion: In this cohort the highest chance of a positive PsARC response was to 1st line b/tsDMARD: twice the chance of response *vs* 2nd/3rd line. The chance of a positive PsARC response to 4th+ lines of b/tsDMARD was not significantly different from 2nd/3rd lines after adjustment. This indicates that patients in a UK cohort can continue to have a meaningful response to later lines of treatment. This is the first available evidence of response to later lines of b/tsDMARD treatment in PsA.

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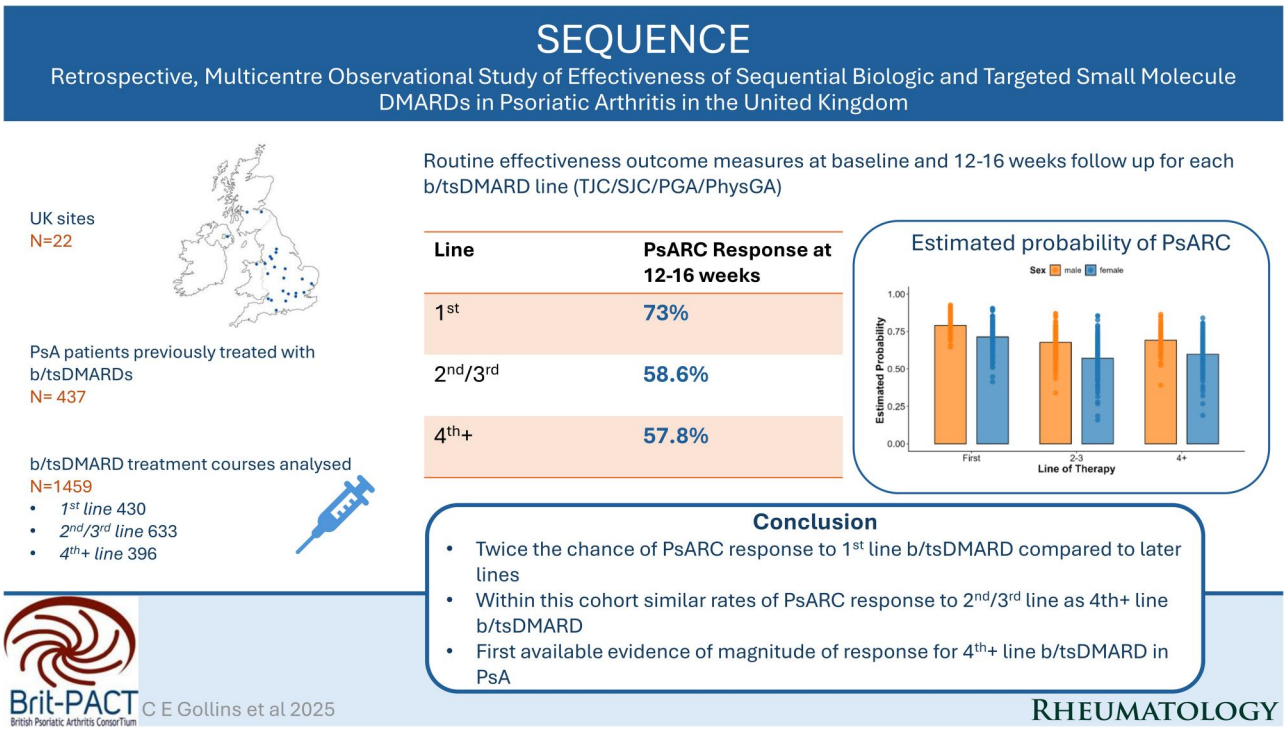
Graphical abstract



Keywords: psoriatic arthritis, bDMARD, tsDMARD, biologic, inflammatory arthritis, 4th line

Rheumatology key messages

- 1st line b/tsDMARD was twice as likely to lead to a positive PsARC response versus 2nd/3rd line in this cohort.
- PsARC response to b/tsDMARD therapy did not appear to diminish after 2nd line to 4th line plus in this cohort.

Introduction

The treatment landscape for psoriatic arthritis (PsA) significantly changed with the introduction of biologic and targeted synthetic DMARDs (b/tsDMARDs) [1], providing more opportunities for tight disease control, reduced joint damage and an improved quality of life [2, 3]. However, the newer therapeutic options are not a panacea; 48% of patients stop their first b/tsDMARD within 2 years, most commonly due to inefficacy [4, 5].

Use of b/tsDMARDs for PsA has increased over time, but drug persistence has significantly reduced, with switching from one drug to another occurring at lower disease activity levels in more recent years [6]. Inevitably this has increased the frequency of patients stopping, switching and cycling treatments and so being prescribed multiple sequential lines of b/tsDMARDs. The change in pattern of use of b/tsDMARDs is due to factors including the introduction of novel b/tsDMARD therapeutic classes. There has also been a move towards a treat-to-target approach [7], which encourages tighter disease control and may promote more frequent switches in treatment to achieve the target.

A recent systematic literature review [8] synthesized the evidence on response to b/tsDMARD therapy beyond first line, finding a reduction in effectiveness after 1st line b/tsDMARD, but that data beyond 3rd line is lacking. Other studies have shown a reduction in persistence associated with effectiveness beyond 1st line [5, 9]. A monocentre pilot analysis however indicated that a positive clinical response is possible up to 6th+ line treatment [10]; a Psoriatic Arthritis Response Criteria (PsARC) response was achieved in 51%, 40%, 75% and 66% of 3rd to 6th+ line b/tsDMARD, respectively.

Healthcare systems, even in high performing economies, are resource limited and required to prioritise effective care for patients. PsA is associated with high healthcare costs primarily driven by hospitalizations and medication costs [11]. The lack of available data on effectiveness in later lines of b/tsDMARD for PsA may have led to restrictions in permitted lines of these advanced therapies [12]. Biosimilars have dramatically changed the cost landscape of b/tsDMARDs. As biosimilars are largely now used in early lines of therapy, the cost implications of switching to later lines are potentially more significant.

We set out to evaluate the primary clinical response to sequential lines of b/tsDMARD therapy in PsA, focusing on effectiveness of later line treatments where there is a current

dearth of evidence. Long-term follow-up from clinical trials and prospective observational data have shown that primary response recorded at first follow-up (12–16 weeks) is often maintained long term [13–15]. To ensure feasibility of the study, we focused on primary response.

Methods

Study design

The SEQUENCE study was a retrospective UK-wide multicentre observational study undertaken to assess the response to sequential lines of b/tsDMARD treatment in adults with PsA.

Rheumatology departments across the UK were eligible to submit data if they treated adult patients with PsA using advanced therapies (b/tsDMARDs). Recruitment of sites was achieved via the British Psoriatic Arthritis Consortium (BritPACT) and British Society for Rheumatology networks. Recruitment was open from February to October 2023. Twenty-six sites were recruited across the UK, of which 22 submitted data (18 England, 2 Scotland, 1 Northern Ireland, 1 Wales).

Data submission was open from April to November 2023. Retrospective case note data obtained through normal patient care in Rheumatology clinics were submitted by each site. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bath [16, 17]. All patient data submitted were fully anonymous to the research analysts. Development of the objectives of the study and the data collection tool were undertaken in conjunction with a patient research partner (M.B.).

Purposive sampling was used to obtain a study population exposed to advanced lines of therapy and to meet the sample size criteria. At each site, patients were eligible for participation if they had been treated with between one and 10 b/tsDMARDs for PsA, with changes in therapy principally driven by peripheral arthritis. Participants were selected by each site as the most recent five patients to start each line of treatment at that site, and who had a minimum dataset available (for each line of treatment: start date, stop date, drug, line of therapy and for most recent line of treatment: PsARC response at first follow-up [12–16 weeks]).

Data collected included demographic data (age, sex, ethnicity, comorbidities) and PsA variables (age at diagnosis, predominant subtype, previous DMARDs). For each line of b/tsDMARD treatment, time on drug and concurrent DMARDs were recorded, as well as outcome measures at baseline and first follow-up appointment, typically 12–16 weeks after initiation of a b/tsDMARD. Outcome measures collected where available were tender joint count (TJC) out of 68, swollen joint count (SJC) out of 66, patient global assessment, physician global assessment, Health Assessment Questionnaire (HAQ), Dermatology Life Quality Index (DLQI), Psoriasis Area Severity Index (PASI), psoriasis body surface area percentage (BSA%) and Psoriatic Arthritis Impact of Disease Score (PSAID). At follow-up for each line of treatment, achievement of PsARC was recorded as either achieved or not achieved.

Study size

A sample size calculation was undertaken based on a pilot cohort study which indicated that PsARC response to 1st to 6th+ line therapy was 73%, 50%, 51%, 40%, 75% and 66%, respectively [10]. The sample size was based on a non-inferiority comparison of the proportion of patients who achieve a PsARC response to 2nd/3rd line therapy (mean 50.5%) *vs* 4th and subsequent lines (mean 60.3%). At 5% significance, 80% power, assuming 50% PsARC in both groups, and a non-inferiority limit of 10%, a sample size of 310 treatment courses per group (2nd/3rd line and 4th+ line) was required. One hundred and seventy-five first line treatment courses were also collected for comparison. Therefore, the total sample size of treatment courses was 795.

Data and statistical methods

Data from all lines of treatment were included in the analysis to evaluate the proportion of patients achieving PsARC across different lines of b/tsDMARDs. Data from the same patient could therefore be used in different analysis groups, i.e. if a participant had been treated with four lines of b/tsDMARD, their data would be included in the 1st, 2nd/3rd and 4th+ line groups. The primary response variable was the binary PsARC outcome. Explanatory variables included the line of therapy (categorized as 1st, 2nd/3rd or 4th+ line), baseline TJC/SJC (categorized into 0, 1, 2–4, 5–9, 10–19 and 20+), age (10-year bands), disease duration (2-year bands), sex and a binary indicator of concurrent conventional synthetic DMARD (csDMARD) use.

All statistical analyses were performed using R. Logistic generalized estimating equations (GEEs) were employed, utilizing the R package 'gee' to account for repeated observations within individuals. An exchangeable correlation structure was specified, assuming equal correlation among all pairs of observations within a given patient. A complete case analysis was conducted for model fitting, including only patients with available data for all explanatory variables at each line of therapy. This approach is valid under the assumption that data are missing at random, which is reasonable in this case given that missingness was likely due to differences in clinical practice and data collection systems.

To assess the likelihood of achieving PsARC across different lines of therapy, crude and adjusted odds ratios (ORs) with 95% CI were estimated using logistic GEEs with 2nd/3rd line as the reference level. Crude models adjusted only for repeated measures (Supplementary Data S1), while adjusted models accounted for sex, age, disease duration, baseline joint counts and concurrent csDMARD use. If PsARC data were missing for a treatment course, but the episode of treatment lasted >6 months, an assumption was made that PsARC had been achieved. To evaluate magnitude of response, using TJC/SJC as continuous measures, comparing 1st and 4th+ lines to 2nd/3rd line b/tsDMARDs, a linear GEE with the change in TJC (follow-up TJC minus baseline TJC) and change in SJC (follow-up SJC minus baseline SJC) set to be continuous response variables was fit, while adjusting for the same repeated measures described above.

The probability of achieving PsARC for a 'typical' patient, stratified by reason for stopping first line of therapy, was estimated by the logistic GEE with the interaction term included.

Baseline characteristics of all participants were evaluated quantitatively. Drug retention was defined as the time spent on drug from baseline until discontinuation (from any cause) and was calculated using the Kaplan–Meier method. Sankey plots were developed to assess the sequencing of b/tsDMARDs over time, separated into two plots. The timepoint used to separate the two plots was the median timepoint of initiation of first line b/tsDMARD (January 2017).

Ethical approval was given by the Social Science Research Ethics Committee at the University of Bath (EP 23 007).

Results

Demographics and PsA background

The number of included participants was 437 (163 male, 274 female) (Table 1); 1459 treatment courses were included in the analysis: 430 1st line, 633 2nd/3rd line and 396 4th+ line (Table 2). Missing data are included in Table 2.

The five subtypes of PsA were represented in the cohort, but polyarticular was the most frequent (354; 81%). The age range of participants was 24–85 years (mean 53.7 years). Age at diagnosis ranged from 10 to 80 years (mean 41.2 years). Ninety-six percent of patients had a previous exposure to a csDMARD before starting a b/tsDMARD, with 74.8% treated with a concurrent csDMARD at any point during b/tsDMARD treatment. In all lines, mean BMI was either overweight or obese (Supplementary Table S1). The most common comorbidities in the cohort were hypertension 24%, depression 13.5% and diabetes 12.8% (Table 1).

Effectiveness outcome measures

The adjusted odds ratio (95% CI) for achieving PsARC comparing 1st line to 2nd/3rd line was 1.91 (1.40, 2.60) and comparing 4th+ line to 2nd/3rd line was 1.13 (0.84, 1.55). First line treatment was associated with significantly better PsARC response rates compared with 2nd/3rd line, while the difference between 2nd/3rd and 4th+ lines remained small after adjustment. The estimated probability of achieving PsARC at each line of therapy is shown in Fig. 1.

The adjusted odds ratios (95% CI) of achieving PsARC for 1st to 6th+ line compared with 2nd line were 1.84 (1.30, 2.59), 0.90 (0.61, 1.31), 1.14 (0.74, 1.75), 0.98 (0.55, 1.72) and 1.04 (0.60, 1.81), respectively. The odds of achieving PsARC were significantly higher in 1st line compared with 2nd line, indicating better treatment response to 1st line of therapy. For subsequent lines (3rd lines+), the odds of achieving PsARC were not significantly different from 2nd line, suggesting a relatively stable response across later lines of treatment (Fig. 2).

The change in total TJC comparing 1st and 4th+ lines to 2nd/3rd line estimated 1st line to have a greater reduction in total TJC compared with 2nd/3rd lines, while the difference in TJC reduction was non-significant when comparing 4th+ lines with 2nd/3rd lines (Supplementary Fig. S1). Change in total SJC comparing 1st and 4th+ lines to 2nd/3rd lines was −0.92 (−1.63, −0.20) and −0.21 (−0.97, 0.54), respectively. This indicated first line b/tsDMARD led to a significantly greater reduction in SJC compared with 2nd/3rd lines, while there was no significant difference in the SJC change between 2nd/3rd lines and 4th+ lines. Mean baseline TJC in each line of treatment ranged from 15.9 to 24.9, and mean SJC in each line of treatment ranged from 4.5 to 8.1 (Table 2).

The percentage of missing data was too high to permit analysis of other recorded outcome measures: HAQ/DLQI/PASI/BSA% and PsAID.

Reason for stopping prior line of therapy

There was an increased chance of achieving PsARC in 2nd+ lines if 1st line was stopped due to adverse effects or 'Other'. 'Other reasons' for stopping included patient choice, patient non-compliance and family planning (Fig. 3). Stopping first line due to primary inefficacy or 'multiple' reasons led to a lower chance of achieving PsARC in later lines. There was a significantly higher chance of achieving PsARC in any later line when stopping first line due to adverse effects when compared with primary inefficacy (odds ratio 2.28 [1.25, 4.16]) but this was not significant for any other stopping reason.

There was no difference in the probability of a positive PsARC in 4th+ *vs* 2nd/3rd lines based on reason for stopping first line b/tsDMARD, apart from adverse effects, which had a higher chance of achieving PsARC in 4th+ lines compared with 2nd/3rd lines.

Table 1. Baseline demographics and disease characteristics of all participants and participants stratified by the maximum line of b/tsDMARD treatment

	All participants	1st line	2nd/3rd line	4th+ line
Participants per max line (*n*)	437	64	173	200
Age, mean (S.D.), years	53.7 (12.6)	52.3 (13.8)	54.4 (12.7)	53.5 (12.1)
Female, *n* (%)	274 (62.7)	30 (46.9)	110 (63.6)	134 (67)
Age at PsA diagnosis, mean (S.D.), years	41.2 (13.5)	41.7 (13.5)	42.7 (13.7)	39.7 (13.1)
Age at first b/tsDMARD, mean (S.D.), years	46.5 (12.8)	48.2 (13.8)	48.1 (12.8)	44.5 (12.2)
BMI, earliest available, mean (S.D.)	29.5 (7.1)	29.7 (5.8)	30.1 (6.8)	29 (8.2)
csDMARD exposure, *n* (%)				
Previous exposure (any)	419 (96)	59 (92.2)	165 (95.4)	195 (97.5)
Concurrent exposure (any line)	327 (74.8)	37 (57.8)	104 (60.1)	137 (68.5)
MTX exposure (any line)	232 (53.1)	26 (40.6)	72 (41.6)	103 (51.5)
PsA subtype, *n* (%)				
Polyarticular	354 (81)	46 (71.9)	140 (80.9)	168 (84)
Oligoarticular	32 (7.3)	8 (12.5)	16 (9.2)	8 (4)
Axial	27 (6.2)	5 (7.8)	12 (6.9)	10 (5)
Distal	20 (4.6)	2 (3.1)	4 (2.3)	14 (7)
Arthritis mutilans	4 (0.9)	3 (4.7)	1 (0.6)	0
Comorbidities, *n* (%)				
Depression	59 (13.5)	12 (18.8)	17 (9.8)	30 (15)
Diabetes mellitus	56 (12.8)	8 (12.5)	24 (13.9)	24 (12)
Hypertension	105 (24)	17 (26.6)	32 (18.5)	56 (28)
Fibromyalgia	39 (8.9)	6 (9.3)	7 (4)	26 (13)
Ischaemic heart disease	21 (4.8)	3 (4.7)	7 (4)	11 (5.5)

Baseline equates to the time of data input. PsA subtypes (phenotypes) are based on the Moll–Wright classification [39]. csDMARD: conventional synthetic DMARD; max: maximum; MTX: methotrexate.

Table 2. Effectiveness endpoints at 12–16 weeks of all treatment courses analysed, stratified by b/tsDMARD line

	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Treatment courses total, *n*	430	363	270	194	94	55	29	14	8	2
Baseline TCJ, mean (95% CI)[a]	17.3 (15.9, 18.6)	14.9 (13.4, 16.4)	15.9 (14.2, 17.6)	18.7 (16.7, 20.7)	21.1 (17.6, 24.6)	21.8 (16.9, 26.7)	24.9 (17.4, 32.4)	23.8	22.4	22
Missing baseline TJC, *n* (%)	32 (7.4)	61 (16.8)	41 (15.2)	27 (13.9)	19 (20.2)	11 (20)	6 (20.7)	3 (21.4)	0	0
FU TCJ, mean (95% CI)[a]	8.7 (7.5, 9.9)	9.9 (8.6, 11.2)	10.7 (9.2, 12.2)	11.4 (9.6, 13.2)	12.7 (9.2, 16.1)	15.7 (10.8, 20.7)	17 (10.2, 23.8)	13.8	5.7	8
Missing FU TJC, *n* (%)	49 (11.4)	49 (13.5)	43 (15.9)	35 (18)	22 (23.4)	12 (21.8)	6 (20.7)	2 (14.3)	2 (25)	0
Baseline SCJ, mean (95% CI)[a]	8.1 (7.5, 8.7)	6.7 (6, 7.4)	7 (6.2, 7.7)	8.1 (7, 9.2)	7.7 (6.3, 9.2)	6.4 (5, 7.9)	6.2 (3.9, 8.5)	6.7	6.9	4.5
Missing baseline SJC, *n* (%)	34 (7.9)	63 (17.4)	42 (15.6)	32 (16.5)	19 (20.2)	12 (21.8)	7 (24.1)	3 (21.4)	0	0
FU SCJ, mean (95% CI)[a]	3.3 (2.8, 3.8)	3.7 (3.2, 4.2)	3.9 (3.3, 4.5)	3.5 (2.8, 4.1)	3.8 (2.7, 4.9)	3.1 (1.8, 4.4)	5.8 (2.7, 8.9)	5.3	2.3	3.5
Missing FU SJC, *n* (%)	53 (12.3)	51 (14)	41 (15.2)	35 (18)	21 (22.3)	14 (25.5)	6 (20.7)	1 (7.1)	1 (12.5)	0
Concurrent csDMARD, *n* (%)	276 (64.2)	200 (55.1)	138 (51.1)	101 (52.1)	52 (55.3)	29 (52.7)	11 (37.9)	6 (42.9)	3 (37.5)	0
Concurrent MTX, *n* (%)	201(46.7)	136 (37.5)	85 (31.4)	64 (33)	36 (38.3)	19 (34.5)	6 (20.7)	4 (28.6)	2 (25)	0
Concurrent SSZ, *n* (%)	71 (16.5)	41 (11.3)	26 (9.6)	14 (7.2)	6 (6.4)	4 (7.3)	1 (3.4)	1 (7.1)	1 (12.5)	0
Concurrent LFM, *n* (%)	42 (9.8)	28 (7.7)	23 (8.5)	17 (8.8)	7 (7.4)	4 (7.3)	3 (10.3)	1 (7.1)	1 (12.5)	0
Concurrent ciclosporin, *n* (%)	2 (0.5)	1 (0.3)	0	0	0	0	0	0	0	0
Other concurrent csDMARD[b], *n* (%)	0	16 (4.4)	17 (6.3)	14 (7.2)	7 (7.4)	4 (7.3)	1 (3.4)	1 (7.1)	0	0
PsARC response, *n* (%)	314 (73)	216 (59.5)	155 (57.4)	118 (60.8)	54 (57.4)	31 (56.4)	10 (34.5)	7 (50)	7 (87.5)	2 (100)
Assumed PsARC, *n* (%)[c]	16 (3.7)	26 (7.2)	20 (7.4)	19 (9.8)	8 (8.5)	10 (18.2)	2 (6.9)	2 (14.3)	0	0
Missing PsARC, *n* (%)[d]	3 (0.7)	10 (2.8)	9 (3.3)	11 (5.7)	1 (1.1)	3 (5.5)	3 (10.3)	1 (7.1)	1 (12.5)	0

[a] Baseline equates to the beginning of each treatment course. Confidence intervals computed if sample size is ≥20. [b]Includes hydroxychloroquine and azathioprine. [c]Total assumed PsARC per line, as described in methods: 'If PsARC data was missing for a treatment course, but the episode of treatment lasted >6 months, an assumption was made that PsARC had been achieved'. [d]Missing PsARC % was calculated after inclusion of assumed PsARC in total PsARC response. b/tsDMARD: biologic and targeted synthetic DMARDs; csDMARD: conventional synthetic DMARD; FU: follow up; PsARC, Psoriatic Arthritis Response Criteria; SJC, swollen joint count; TJC: tender joint count.

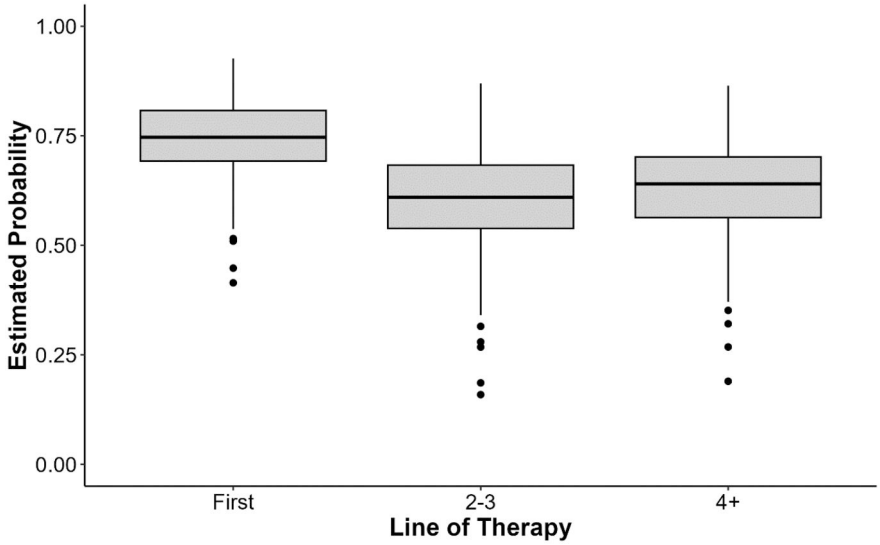


Figure 1. A box and whisker plot summarizing the distribution of the individual estimated probabilities from the adjusted GEE. The lower whisker extends from the 25th percentile to the minimum estimated probability in the dataset, excluding outliers, which are defined as data points >1.5 times the inter-quartile range from the 25th percentile. The outliers are plotted as individual datapoints. The upper whisker extends from the 75th percentile to the maximum value in the dataset. GEE: generalized estimating equation

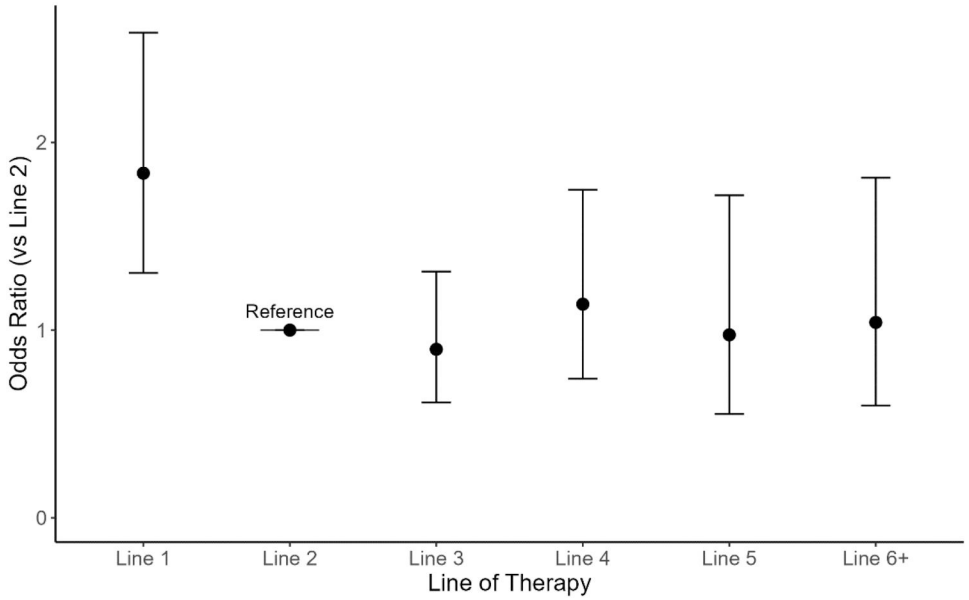


Figure 2. The adjusted odds ratios and 95% CI for achieving PsARC for each line compared with 2nd line b/tsDMARD. b/tsDMARD: biologic and targeted synthetic DMARDs; PsARC, Psoriatic Arthritis Response Criteria

Sequencing of b/tsDMARDs

The sequencing of b/tsDMARDs over time is presented in the Sankey plots in Fig. 4, with Fig. 4A indicative of participants who had initiation of first-line therapy pre-2017 and Fig. 4B of those who initiated b/tsDMARDs from January 2017 onwards. Comparison of the plots highlights an increase in the use of IL-17 inhibitor (IL-17i) earlier in the treatment pathway in participants who started b/tsDMARD treatment post-2017. There is also more variation in mode of action of treatment at 3rd line in those starting b/tsDMARDs post-2017, compared with pre-2017, when TNF inhibitor (TNFi) and IL-17i were predominantly used. The use of TNFi in 3rd line and beyond is reduced in those starting b/tsDMARDs post-2017, with an increase in IL-17i, IL-12/23 inhibitor (IL-12/23i), IL-23 inhibitor (IL-23i) and Janus kinase inhibitor (JAKi). The Sankey plots highlight the infrequent use of phosphodiesterase-4 inhibitor (PDE4i) in this study population.

Survival

Crude drug survival for the SEQUENCE cohort using all treatment courses for all participants included in the cohort, as described in the methods, divided into 1st line, 2nd/3rd line and 4th+ line groups is presented in Supplementary Fig. S2.

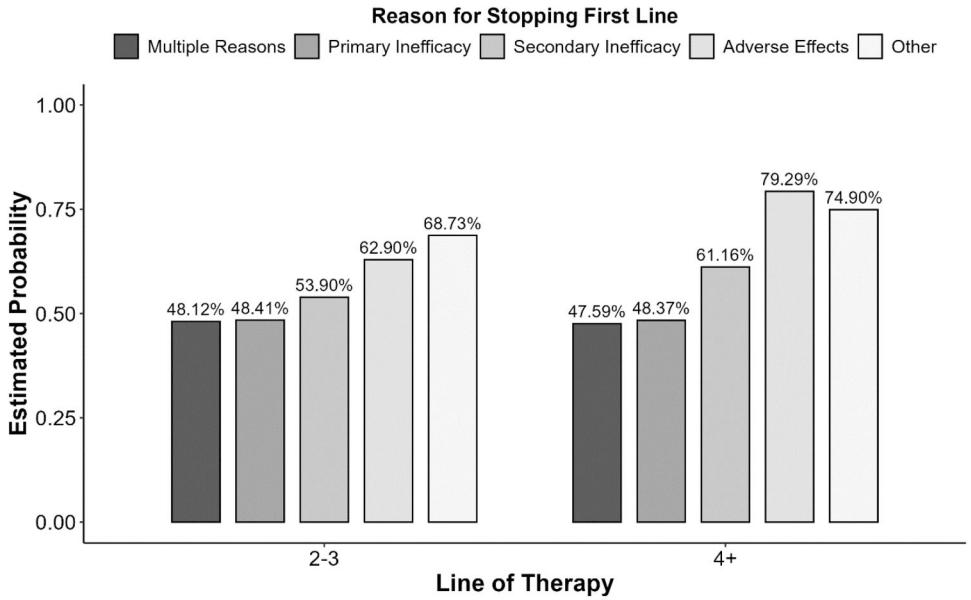


Figure 3. The estimated probability of achieving PsARC for a 'typical' patient at 2nd/3rd lines and 4th+ lines stratified by reason for stopping 1st line, as estimated by the logistic GEE with the interaction term included. GEE: generalized estimating equation; PsARC, Psoriatic Arthritis Response Criteria

Mean drug survival was 30.4, 27.2 and 26.4 months for 1st, 2nd/3rd and 4th+ lines, respectively. At 12 months, 53.9%, 47.6% and 51.8% of participants remained on b/tsDMARD when used 1st, 2nd/3rd and 4th+ line, respectively. At 24 months 38.2%, 33.3% and 37.1% of participants remained on b/tsDMARD when used 1st, 2nd/3rd and 4th+ line, respectively.

Discussion

The adjusted odds of achieving PsARC in 2nd or 3rd line was not significantly different from 4th+ line, which implies there was a similar chance of achieving a PsARC response with all b/tsDMARD lines beyond 1st line, within the SEQUENCE cohort. Our data indicated that the adjusted odds of achieving PsARC in the SEQUENCE cohort were twice as high for 1st line compared with 2nd/3rd line b/tsDMARD.

Our data are consistent with previous studies in finding a significantly improved chance of response in 1st line b/tsDMARD [18–22], compared with subsequent lines. These data may support the clinical notion that the threshold to switch from 1st to 2nd line b/tsDMARD should be maintained at a high level to preserve the potential absolute benefit of 1st line treatment. A lack or loss of response to first line b/tsDMARD could lead to a re-evaluation of concurrent comorbidities that may affect the outcome scores. Decisions to switch subsequent lines appear to have less impact on potential for later PsARC response within this cohort.

These data collected from routine clinical practice provide the first available composite outcome measure of effectiveness in 4th+ line b/tsDMARDs for PsA. There is a growing recognition that there is a population of PsA patients who are 'difficult to treat' (D2T) or complex to manage (C2M), composed of patients with multiple treatment failures [23–25]. International efforts are being made to better understand resistant disease in PsA; D2T centres on resistant inflammatory disease and C2M on comorbidities, associated conditions and residual symptoms despite supressed inflammation. Unified definitions will permit more targeted research for these patients, as has been the case in rheumatoid arthritis [26]. This study adds to the currently limited data on response to later lines of treatment in this under-researched population and provides evidence against limiting the number of lines of b/tsDMARD in the treatment of PsA.

The overall proportion of patients achieving PsARC within the SEQUENCE cohort was comparable to other studies: 73%, 59.5%, 57.4% in 1st, 2nd and 3rd lines, respectively (Table 2). Vieira-Sousa *et al.* reported a 3-month PsARC response of 76% first line and 57% second line TNFi in a prospective national Portuguese registry [18] whereas Krüger *et al.* reported a lower 3-month PsARC response in first, second and third line golimumab of 62.6%, 45.5% and 36.9%, respectively in a post-hoc analysis of a prospective observational study [20]. These two studies, however, only assessed response to TNFi, and so the reduction in effectiveness with subsequent lines of treatment may be caused by diminishing returns from the use of drug with the same mode of action.

PsARC was pragmatically chosen as the primary outcome measure of this study due to the National Institute for Health and Care Excellence specification of achievement of PsARC as the determining factor in ongoing approval and reimbursement for b/tsDMARDs in PsA in England [27]. The individual outcome measures that determine PsARC response (TJC, SJC, patient global assessment and physician global assessment) were therefore more likely to be available for analysis, in comparison with other composite outcome measures. Despite this, due to the observational nature of the data used there was a proportion of missing outcome measure data (Table 2). There are several limitations to the PsARC, which only measures articular disease and has limited ability to discriminate between treatment arms in clinical trials [28].

Within the cohort there was an increasing proportion of women beyond first line. Women have previously been shown to be more likely to switch b/tsDMARDs due to inefficacy and discontinue both first and multiple lines of b/tsDMARDs compared with men [29, 30]. The higher rates

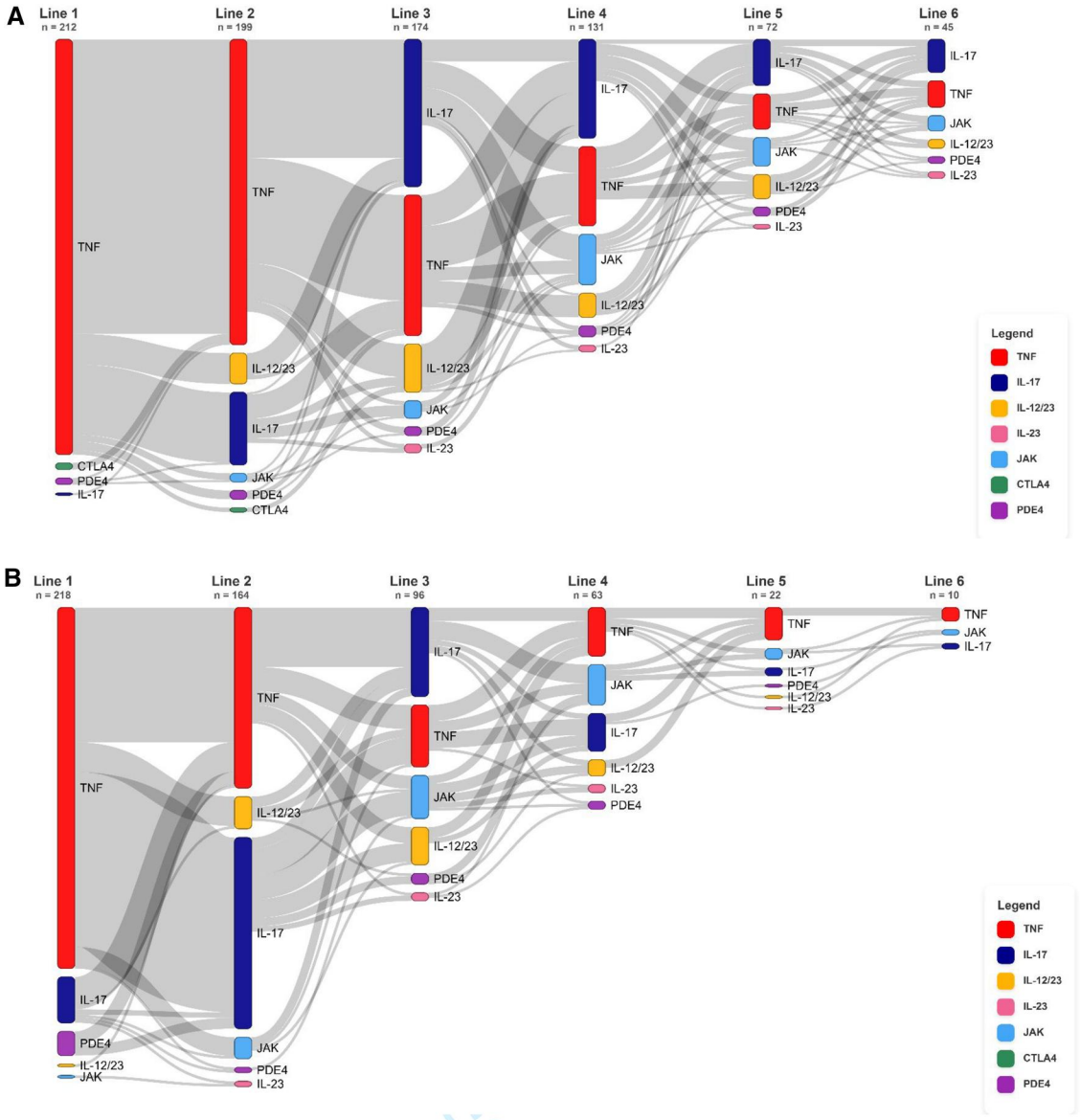


Figure 4. Sequencing of b/tsDMARDs per line of therapy (1st to 6th+). (A) Initiation of 1st line b/tsDMARD pre-January 2017. (B) Initiation of 1st b/tsDMARD January 2017–November 2023. b/tsDMARD: biologic and targeted synthetic DMARDs; CTLA4, cytotoxic T-lymphocyte-associated protein 4 analogue; JAK: Janus kinase inhibitor; PDE4: phosphodiesterase-4 inhibitor

of b/tsDMARD failure in women could have contributed to the higher proportion of females with higher total lines of b/tsDMARD. There is increasing focus on discrepancy of outcomes between men and women in PsA, with recent calls for trial stratification based on sex [31–33]. Although the rate of fibromyalgia within the overall cohort (8.9%) was similar to a recently described real-life US cohort (11%) [34], the rate in the 2nd/3rd line group was noticeably lower at 4%. It is possible that the lower-than-expected rate of fibromyalgia in the 2nd/3rd line group contributed to better treatment outcomes, as it is known that fibromyalgia-related nociceptive pain is associated with elevated disease measures [35]. However, the data were retrospective, without the prospective use of new fibromyalgia criteria, and so there was likely an underdiagnosis of concomitant fibromyalgia within the cohort.

The drug survival rates within the SEQUENCE cohort were lower than have been shown in some previous cohorts. Lindström *et al.* [4] assessed patients in a large Nordic registry, finding one year retention rates of 70%, 64% and 67% in 1st, 2nd and 3rd line adalimumab and 70%, 66% and 60% in 1st, 2nd and 3rd line secukinumab, respectively. This contrasts with the overall drug retention rates of 53.9% and 47.6% at 1 year in 1st and 2nd/3rd line b/tsDMARDs, respectively, within this cohort. At 2 years, the Danish DANBIO registry drug retention rates were 52%, 42% and 40% in 1st, 2nd and 3rd line TNFi, respectively [5], in comparison with lower rates of 38.2%, 33.3% and 37.1% in 1st, 2nd/3rd and 4th+ line SEQUENCE participants, respectively. The US Corrona (now CorEvitas) registry similarly found drug survival at 2 years of 57.3% in 1st line and 48.5% in biologic-experienced patients but did not stratify according to the number of lines of previous b/tsDMARD within the experienced group [36]. The lower drug survival within the SEQUENCE cohort is likely to have been caused by selection bias, as we purposefully selected for patients with multiple

previous treatment failure to ensure we met sample sizes for the later line group. The SEQUENCE cohort is therefore likely not representative of the general PsA population, particularly of patients with fewer lines of treatment.

The Sankey plots in Fig. 4 indicate the changes in sequencing of b/tsDMARDs used in PsA over time within the SEQUENCE cohort. There was a reduction in the proportion of TNFi and increase in IL-17i used as both first- and second-line b/tsDMARDs over time. This was consistent with results from the BIOBADASER Spanish registry in which Sánchez-Piedra *et al.* also found a reduction in the use of TNFi as first line b/tsDMARD [6]. However, although there is an increased use of IL-17i over time, the cheaper biosimilar TNFi remain the most prescribed first line b/tsDMARD. The increasing use of drugs with differing modes of action earlier in a patient's treatment course is due to the approval of new modes of action to treat PsA, inclusion in treatment guidelines and increasing familiarity of clinicians with newer treatments. It is also possible that the wider spectrum of modes of action used in 3rd+ line b/tsDMARD is driven by the limited data in this group of patients [8]. There is no evidence for the use of one mode of action over another at 2nd line or later. Clinicians therefore have less guidance regarding the likely most effective treatment option for their D2T PsA patients. Sensitivity analysis comparing all data from March 2016 onwards (the most recent 55% of the cohort) with the entire cohort showed similar odds ratios for achieving PsARC to the entire cohort, suggesting limited calendar time bias (Supplementary Data S2).

People with PsA report their most important treatment outcome is improvement in symptoms like pain and fatigue, along with improvement in physical function [37, 38]. The possibility of access to later line drugs that may prove effective is therefore of significant importance to D2T patients and their clinicians. The PsARC results in this cohort suggest that a reasonable level of response to later lines of treatment was possible, for example a PsARC response of 57.4% in 5th line and 56.4% in 6th line (Table 2). Further research would be required to generalize these results.

There are several limitations of our current study and considerations to make when interpreting the data. Selection of participants was purposive to include adequate patients with multiple treatment failures to allow for analysis of this D2T population. The selection approach will have generated an inherently more resistant population for analysis, potentially biasing the sample for people less likely to respond to treatment. A further consideration is that we have included data from all lines of treatment an individual has been exposed to, and hence the dataset may be further enriched for a resistant population.

Sensitivity analyses were undertaken to assess the potential for bias derived from this sampling (Supplementary Data S2). Analysis A used data from a single line randomly selected from the highest relevant group per participant. PsARC response to 4th+ line was significantly lower than 2nd/3rd in this analysis, but the response to 2nd/3rd line was likely overestimated due to the exclusion of the data from known resistant patients (4th+ line) from earlier lines. Because of the sampling design, it is likely that within the overall SEQUENCE cohort, the proportion of 4th+ lines analysed (27% of total treatment lines) is higher than would be expected in real clinical practice. The main analysis therefore possibly underestimates the 2nd/3rd line response. Analysis B used data on all available lines of therapy within the resistant population (those with 4th+ lines total) and produced similar results to the main analysis. This suggests that particularly for patients who have failed at least three prior b/tsDMARDs, the short-term treatment response to additional therapies may not be worse, and could even be better, than what they themselves (and others in a similar situation) experienced with their prior, failed treatments.

Patient selection and assignment of treatment are inherent risks for bias in observational studies. Our focus was on short term effectiveness to enable feasibility of the study; long-term outcomes were not assessed within this cohort.

Despite these limitations this study has strengths. The recruitment approach was from routine care across 22 sites from the four nations of the UK, improving the generalizability of the findings. Furthermore, the retrospective approach has allowed evaluation of changing patterns of b/tsDMARD selection for advanced lines of therapy over the last decade.

In conclusion the SEQUENCE study provides the first evidence of PsARC response in a UK cohort in lines of b/tsDMARD beyond third line. Within this cohort, the PsARC response to 4th+ lines of b/tsDMARD was not significantly reduced compared with 2nd/3rd line in participants who had failed at least three b/tsDMARDs. This indicates that patients in a UK cohort can continue to have a meaningful response to later lines of treatment. Further prospective representative studies are required to better understand the effectiveness response in this population of D2T patients.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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