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Original article

Effectiveness of sequential biologic and targeted disease modifying anti-rheumatic drugs for rheumatoid arthritis

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Abstract

Objectives. Whether patients with RA benefit from repeated trials of biologic or targeted synthetic DMARDs (b/tsDMARDs) after three or more attempts is unknown. We aimed to describe treatment outcomes in each line of b/tsDMARD therapy.

Methods. Using data from the British Society for Rheumatology Biologics Register for RA from 2001 to 2020, change to a new b/tsDMARD (except biosimilar switches) was defined as a new line of therapy. Treatment outcomes were compared across lines of therapy, including DAS28 remission (≤2.6), low disease activity (LDA, ≤3.2) at 6 months and median time to drug discontinuation. Multiple imputation was used for missing data.

Results. A total of 22 934 individuals starting a first b/tsDMARD were included (mean age 56 years, 76% female), among whom 10 823 commenced a second-line drug, 5056 third, 2128 fourth, 767 fifth and 292 sixth. Most (71%) had sufficient data for DAS28-derived outcome analyses. TNF inhibitors were the most common first-line drug, but choice of subsequent-line drugs changed over time. Seventeen percent achieved DAS28 remission following first-line, 13% second and 8–13% with third through sixth. LDA was achieved in 29% of first-line, 23% second, 17–22% through to the sixth. Patients stayed on first-line therapy for a median of 2.6 years, ranging from 1.0–1.4 years for lines two to six.

Conclusion. Many patients will eventually benefit after repeated trials of b/tsDMARD. Further research to improve treatment selection are needed to prevent prolonged trial and error approaches in some patients.

Key words: RA, difficult to treat, switching, effectiveness, biologics, DMARDs

CLINICAL SCIENCE

Rheumatology key messages

- The practice of cycling through sequential high-cost biologic/targeted synthetic DMARDs (b/tsDMARDs) in RA has changed over time.
- Treatment response and time on drug were comparable across the third to sixth lines of therapy.
- Patients who do not respond to initial b/tsDMARDs are able to benefit from further treatment.

Introduction

Biologic and targeted synthetic DMARDs (b/tsDMARDs) have greatly improved the management of RA and transformed the lives of countless patients, but up to a quarter do not respond to their first b/tsDMARD (according to EULAR response definition) [1] and require additional trials of treatment. Up to 10% of all RA patients have persistently active or progressive disease despite two or more b/tsDMARDs with different

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mechanisms of action [2–4]. This may be due to immunologically refractory disease or, for example, adverse reactions, non-adherence and comorbidities [4, 5].

Despite advances towards personalized medicine, the prevailing approach to finding an effective drug is still mostly through trial and error. Cycling through sequential therapies is not only suboptimal for timely disease control, but has implications for quality of life, work productivity and irreversible damage. The evidence to support trialling ever more (e.g. beyond three) lines of therapy is lacking, making it difficult to weigh against risk of adverse events, yet the opportunities for this continues to increase as more b/tsDMARDs, with different mechanisms of action, are approved. In the absence of such evidence, many healthcare providers or systems, implicitly or explicitly, limit the number of trials of high-cost b/tsDMARDs that any individual patient may have [6, 7].

Are patients with 'difficult-to-treat' [2] arthritis able to benefit from further trials of b/tsDMARDs? Generating real-world evidence to answer this question is challenging when there are restrictions to the number of b/tsDMARDs that patients can have. The lack of randomized controlled trials and management guidelines in this area further adds to the problem. *Post hoc* analysis of one trial suggested that participants were able to benefit from therapy beyond the third line; results showed no statistically different response (baricitinib *vs* placebo ACR20 at 12 weeks) between participants who tried <3 (odds ratio 2.0; 95% CI 1.2, 3.3) or ≥ 3 prior bDMARDs (odds ratio 4.6; 95% CI 1.5, 14.0) [8]. The aim of this analysis was to describe treatment outcomes with each sequential line of therapy in patients with RA receiving b/tsDMARDs.

Methods

The British Society for Rheumatology Biologics Register for RA (BSRBR-RA) is a national prospective observational study recruiting adults with physician diagnosed RA since 2001. Details of the study design have been previously published [9]. Data are extracted from the medical record by local rheumatology teams and entered into a study database at baseline (start of registration drug), 6-monthly for the first 3 years, and then annually thereafter. Baseline data included age (at b/tsDMARDs initiation), sex, BMI, smoking status (ever or never), comorbidities, age at diagnosis, RF status and disease activity (DAS28 components). The study recorded treatment exposures (drug name, start and stop dates) and outcomes (disease activity and adverse events) for the following drugs: TNF inhibitors (TNFi): infliximab, etanercept, adalimumab and golimumab; IL-6 inhibitors (IL-6i): tocilizumab and sarilumab; JAK inhibitors (JAKi): tofacitinib, baricitinib and upadacitinib; abatacept (CTLA4 immunoglobulin), rituximab (CD20 antibody) and anakinra (IL-1 inhibitor). We excluded participants who subsequently commenced on a non-RA indication treatment that suggests their diagnosis was revised. Ethical approval was obtained from the UK North West Multicentre Research Ethics Committee (MREC 00/8/53) and all participants provided written informed consent. The current analysis used data cut-off 30 November 2020.

Exposure

The 'exposure' in the current analysis was line of therapy, defined as a treatment course under one drug name from start to stop date. Participants do not need to be registered with the study from their first line drug. For example, if they were registered on the third b/tsDMARD and reported dates when they used the first two, all three drugs would contribute to therapy sequence description. Only drugs at and after registration could contribute to analyses requiring DAS28 assessment.

Change from one named drug to another was considered as two distinct lines of therapy, e.g. etanercept to adalimumab would equate to TNFi as first- and second-line. Re-challenges of the same drug, after using an intervening drug, was counted as a new line; e.g. etanercept to tofacitinib to etanercept would constitute three lines: TNFi, JAKi, then TNFi. Direct switch from bio-original to biosimilar drug brands, or vice versa, was considered the same line, e.g. Enbrel to Benepali was one etanercept course. Restarting the same drug after a pause without intervening therapy was not counted as a new line. Individuals were excluded if their exposure (line of therapy) was indeterminable, e.g. if they joined the study on a non-first-line b/tsDMARD with no prior treatment data available.

For treatment courses without a documented stop date, patients were assumed to have continued treatment until they initiated the subsequent drug, or to have remained on treatment until the end of follow-up if it was their latest treatment; similarly, missing start dates were imputed with the stop date of the prior line of treatment where appropriate.

We decided *a priori* to restrict analyses to lines of therapy with over 100 individuals because imputation models for outcome analyses (see below) failed with smaller samples in prior exploratory analyses.

Outcomes

We assessed effectiveness according to three categories of outcomes: continuous change in DAS28, categorical response definitions and time to treatment discontinuation. First, we examined change in (or 'delta') DAS28 between baseline and 6 months (or the nearest assessment to that date between 1 and 12 months) as a continuous variable, regardless of treatment discontinuation (i.e. intention-to-treat analysis). Baseline DAS28 was take from the baseline assessment for the first-line drug; for all subsequent lines, baseline was defined as the nearest DAS28 to the drug start date within 3 months before and 7 days after.

Second, we analysed categorical response at 6 months: remission (DAS28 $\leq$2.6), low disease activity (LDA, $\leq$3.2), EULAR good (DAS28 $\leq$3.2 and delta $>$1.2), moderate (not good or no response), and no response (DAS28 $>$5.1 and delta $\leq$1.2, or delta $\leq$0.6) [10]. The nearest to month-6 on-drug assessments within 1–12 months were used. Participants who stopped treatment before month-6 were imputed with non-response.

The above two analyses were limited to patient exposures recorded during active BSRBR-RA follow-up. As some patients joined the register at point of starting a second or subsequent line therapy, the details of prior lines of therapy (start and stop dates) would be recorded at registration but not the corresponding DAS28.

Third, we examined time to treatment discontinuation (or 'drug survival'), defined as duration between start and stop dates for each line of therapy. Patients were censored from the analysis at their last follow-up date if still on that drug at that time. Individuals with no follow-up time (e.g. no stop date) were assigned a negligible duration (1 day) so they could contribute to models. Drug survival analysis used all available recorded lines of therapy, i.e. including drugs used prior to study registration. Rituximab infusions were assumed to have a therapeutic duration of 9 months (275 days) from the start date, chosen to reflect the previously reported average time taken for B cell reconstitution to take place [11]. Any pause in treatment of longer than 6 months ($>$12 months for rituximab) was considered as discontinuation. For example, if an individual had multiple courses of the same drug but had prolonged pause between each course, then only the first course would contribute on-drug follow-up time.

Since the increase in number and availability of b/tsDMARDs over time may have influenced management practice and treatment outcomes, we performed stratified analyses with the population split into two: individuals who started their first b/tsDMARD before or after the first day of 2010 (approximately half-way through existing study duration; abbreviated as 2010 henceforth).

Statistics

The primary analyses were descriptive. Delta DAS28 was summarized using means and categorical responses using percentages. Drug survival was described using the Kaplan–Meier estimator (restricted to 10 years because later lines of treatment were unlikely to have had longer follow-up) and median survival time. We did not formally compare estimates statistically across different lines of therapy in the primary analyses, since our aim was to describe actual treatment outcomes.

Multiple imputation was used to account for missing follow-up DAS28 in these real-world data. We imputed 6-month DAS28 using chained equations (30 imputed sets) and regression methods including: age, gender, drug class (TNFi *vs* non-TNFi, due to small numbers in the latter treatment lines), line of therapy, smoking status and RF status, and normal-transformed: BMI, comorbidity count, age at diagnosis, baseline patient global, and baseline swollen and tender joint counts. Imputed DAS28 was used to derive (as 'passive' variables, rather than directly imputing) delta DAS and categorical DAS28 outcomes for each line of therapy.

Patient and disease characteristics may differ across lines of therapy thus limiting comparability. Therefore, we use regression models to adjust for these potential differences as a secondary analysis. We used multivariable linear models for delta DAS28, logistic for remission/LDA, ordinal logistic for EULAR responses, and Cox proportional hazard for time to treatment discontinuation, including the following covariates: line of therapy, baseline DAS28, age, gender, drug class, BMI, comorbidity count, age at diagnosis, smoking status and RF status. The same imputation model from the primary analysis was used to account for missing covariates. Since each individual could have multiple lines of treatment, we used clustered standard error estimation. Analyses were performed using Stata v14 and R v4.0.1.

Results

A total of 22 934 individuals who started a first-line b/tsDMARDs were eligible for description of sequential therapy (selection flow chart shown in supplementary Fig. S1, available at *Rheumatology* online), among whom 10 823 subsequently commenced a second-line drug, 5056 a third, 2128 a fourth, and 767, 292, 92, 25, 8 and 1 were recorded as receiving lines five through ten. Lines seven and above were excluded as numbers were too small for further analyses.

Baseline characteristics of the analysis population for DAS28-based outcomes are shown in Table 1 (missing data described in supplementary Table S2, available at *Rheumatology* online). Characteristics were broadly similar across lines of therapy, except numerical trends for decreasing age at diagnosis and increasing prevalence of one or more comorbidity from line one to six. Disease activity was highest at line one, with numerically lower mean DAS28 and median ESR/CRP from lines two to six. Participants included in the analysis (71%, $n = 16\,235$) were similar in characteristics compared with those excluded due to missing or unavailable baseline DAS28 (supplementary Table S1, available at *Rheumatology* online).

The median length of follow-up time available between start of first therapy and last follow-up date recorded in the BSRBR-RA was 7.4 years (interquartile rage 3.2, 13.0) and ranged from 0 days to 21 years.

Patterns of sequential therapy

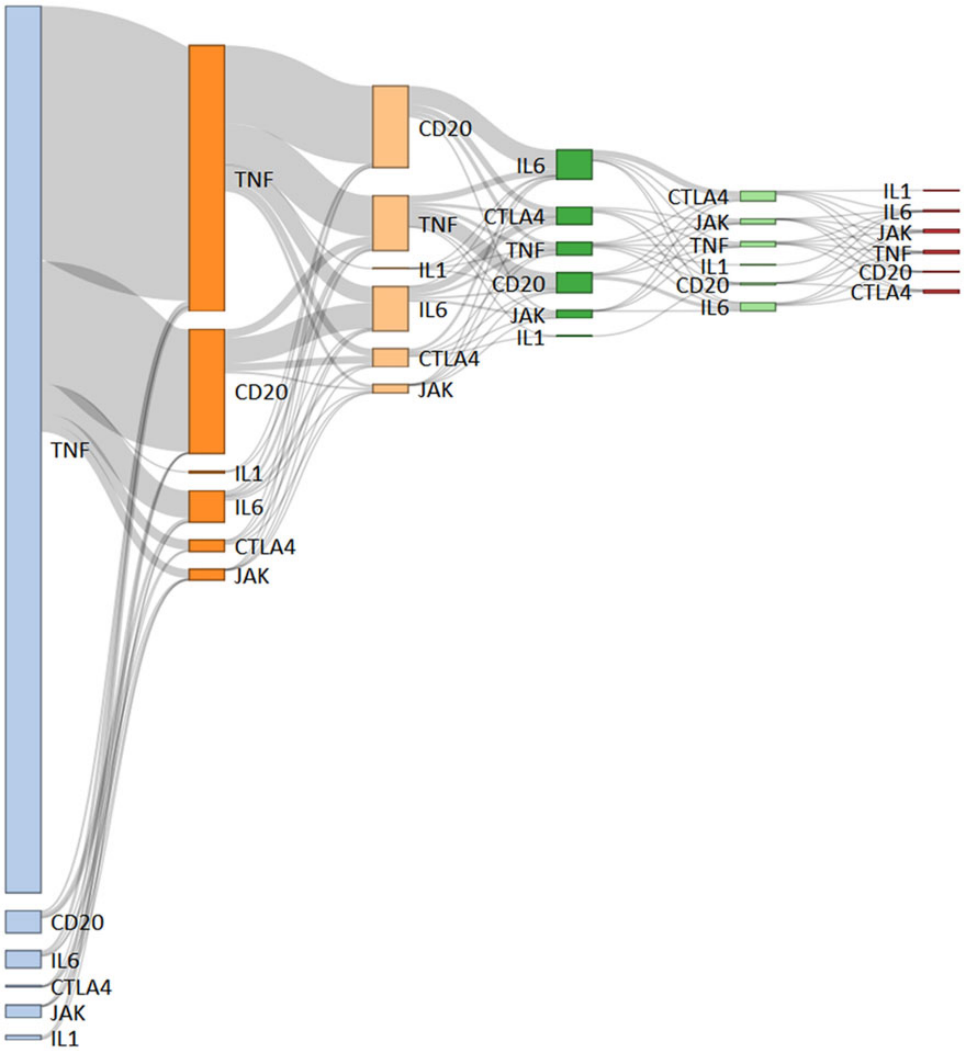
Fig. 1 shows that few individuals in this dataset were recorded as having received a fourth or later line of treatment over their period of follow-up. TNFi was the most frequently used in the first- (94%) and second-line (60%) treatment. The most common third-line treatment

Table 1 Baseline characteristics of the analysis population for DAS28-based outcomes

	Line 1	Line 2	Line 3	Line 4	Line 5	Line 6
N	13 518	4868	2215	915	291	117
Age at drug start date, years, mean (S.D.)	56.5 (12.3)	57.5 (12.3)	58.5 (12.3)	58.0 (12.3)	58.7 (11.8)	58.9 (11.4)
Females, *n* (%)	10 289 (76)	3815 (78)	1780 (80)	748 (82)	234 (80)	88 (75)
RF positive, *n* (%)	8376 (64)	3002 (64)	1359 (64)	562 (64)	195 (69)	69 (62)
Age at diagnosis, years, mean (S.D.)	44.5 (13.7)	44.2 (13.6)	42.9 (13.5)	40.4 (13.4)	40.7 (12.3)	39.6 (11.9)
BMI, mean (S.D.)	27.4 (8.0)	27.7 (8.1)	28.0 (7.0)	28.3 (7.3)	28.1 (6.6)	28.8 (7.8)
At least one comorbidity, *n* (%)	8653 (64)	3215 (66)	1498 (68)	648 (71)	214 (74)	85 (73)
DAS28, mean (S.D.)	6.4 (1.1)	5.7 (1.3)	5.9 (1.3)	5.7 (1.3)	5.6 (1.4)	5.5 (1.3)
Tender joint count, median (IQR)	15 (10, 21)	11 (6, 18)	13 (8, 20)	13 (8, 20)	12 (8, 20)	12 (8, 20)
Swollen joint count, median (IQR)	10 (6, 14)	7 (4, 11)	7 (4, 11)	7 (4, 11)	6 (3, 10)	6 (3, 8)
ESR (mm/h), median (IQR)	37 (21, 60)	32 (16, 56)	32 (16, 57)	26 (11, 48)	22.5 (8, 47)	28 (13, 45)
CRP (mg/l), median (IQR)	24 (9.8, 52)	14 (5, 38)	13.9 (5, 35.5)	11 (5, 32)	9.3 (5, 29)	9.6 (3, 37)
Patient global (mm), median (IQR)	76 (62, 88)	70 (50, 82)	75 (60, 88)	75 (60, 85)	70 (55, 86)	77.5 (68, 90)

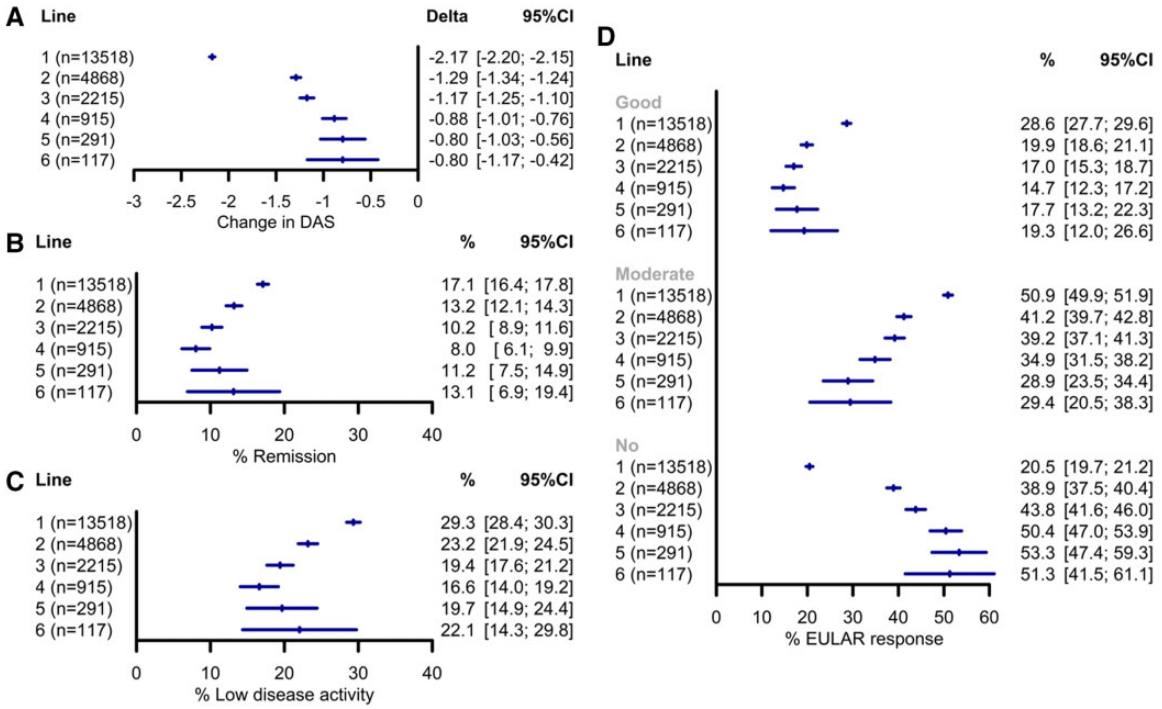
Missing data are quantified in supplementary Table S2, available at *Rheumatology* online. DAS28: 28-joint Disease Activity Score; IQR: interquartile range.

Fig. 1 Pattern of sequential therapy



Each column represents one line of treatment, with length proportional to absolute numbers. TNF, tumour necrosis factor inhibitor; CD20, rituximab is the only example of B cell depletion therapy; CTLA4, abatacept is the sole CTLA4 immunoglobulin; IL6, IL-6 inhibitor; JAK, janus kinase inhibitor; IL1, anakinra is the sole IL-1 inhibitor.

FIG. 2 DAS28-derived outcomes at 6 months across lines of therapy



(**A**) Delta (change in) DAS28, (**B**) remission, (**C**) low disease activity, (**D**) EULAR response.

was rituximab (39%), fourth line IL-6i (33%), fifth line abatacept (32%) and sixth line JAKi (28%). Detailed count of drug class by each line of therapy is shown in supplementary Table S3, available at *Rheumatology* online.

Treatment response

The mean delta DAS28 from baseline to month 6 was –2.17 (95% CI –2.20, –2.15) for the first line b/tsDMARD (Fig. 2A). Delta DAS28 reduced to –1.29 in the second and –1.17 in third line. Fourth to sixth line delta DAS28 were similar (–0.8 to –0.9).

Seventeen percent (95% CI 16%, 18%) of participants on first line b/tsDMARDs achieved remission by month 6 (Fig. 2B). Twenty-nine percent (95% CI 28%, 30%) of individuals on first-line drug achieved low disease activity (Fig. 2C). For remission and low disease activity, the proportion achieving these outcomes reduced linearly from line two through to four.

The proportion of participants achieving good EULAR response was highest among those on first-line drug (29%; 95% CI 28%, 30%), and similar among subsequent lines up to the sixth (range 15% to 20%) (Fig. 2D). EULAR non-response was observed in 21% of the first line, and rose linearly from lines two (39%) to five (53%). Complete case descriptive statistics (without outcome imputation) are presented in supplementary Table S4, available at *Rheumatology* online.

Drug survival

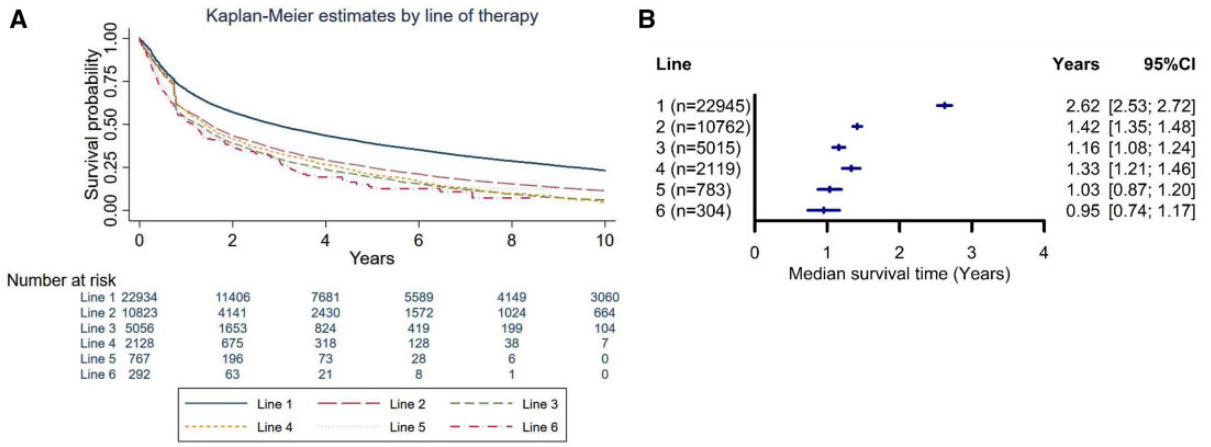
Compared with line one, the probability of discontinuation was higher for lines two to six, for which curves were mostly overlapping (Fig. 3A). At 1 year, the probability of remaining on the first-line drug was 64%, 55% for second line, 49% third, 50% fourth, 44% fifth and 37% sixth (probabilities for years 2–5 are shown in supplementary Table S5, available at *Rheumatology* online). The median time to treatment discontinuation was 2.6 years (95% CI 2.5, 2.7) for first-line treatment, and 1.4 years for the second line (95% CI 1.4, 1.5) (Fig. 3B). Median time to treatment discontinuation for lines three to six was approximately 1 year.

Analyses stratified by year of treatment initiation

The number of participants starting each line of therapy over time is shown in supplementary Fig. S2, available at *Rheumatology* online. The population was divided into individuals who started their first b/tsDMARD before ($n = 13\,933$) and after 2010 ($n = 7430$). Use of non-TNFi drugs generally increased post-2010, with proportionally fewer patients cycling through repeated lines of TNFi (supplementary Fig. S3). For first-line therapy, post-2010 (*vs* pre-2010) participants were generally older and more comorbid, but with lower disease activity (supplementary Table S6).

Delta DAS28 before and after 2010 were similar across lines of treatment; for example, delta for the first

FIG. 3 Time to treatment discontinuation according to line of therapy



line drug was 2.3 in both groups (Fig. 4A). The proportions achieving remission were higher post-2010 across lines one to five, compared with before (Fig. 4B). Similar patterns were observed for low disease activity and EULAR good response (supplementary Fig. S4, available at *Rheumatology* online). Median drug survival was longer pre- than post-2010 across all lines (Fig. 4C).

Secondary analyses

Multivariable models adjusting for differences in baseline characteristics were used to compare outcomes by line of therapy. Delta DAS28 at month 6 reduced incrementally with increasing lines of therapy, as was observed in the unadjusted analysis (supplementary Fig. S5, available at *Rheumatology* online). Analogous results were observed for categorical outcomes. In Cox models using line one as the referent and adjusting for the same covariates, hazard ratios for treatment discontinuation for lines two to six ranged from 1.19 to 1.49 (supplementary Fig. S5).

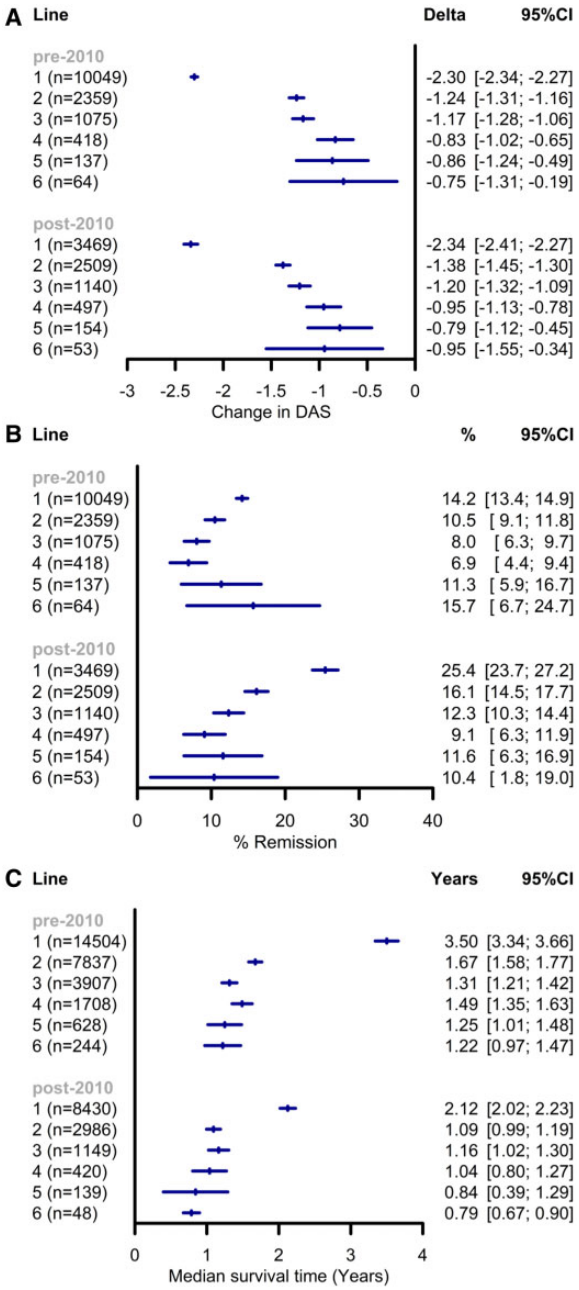
Discussion

This is the first analysis that presents detailed treatment response and drug survival for RA patients who have received multiple (more than three) lines of b/tsDMARD therapy, including some with up to six or more different courses of therapy. Within this large national register, a relatively small proportion of participants received treatment beyond third line. Treatment response and drug survival were the highest for individuals starting their first b/tsDMARD. Improvements in DAS28 were observed across patients starting lines two to six including changes in class of b/tsDMARD, albeit with a lower overall response rate, suggesting that there may be utility in further lines of therapy for many patients despite failure to control disease activity with earlier lines. Approximately 1 in 5 participants on fifth- or sixth-line b/tsDMARD achieved LDA or good EULAR response, and 1 in 10 achieved remission, which were comparable to response observed for third- and even second-line drugs.

Many healthcare providers and systems limit the number of trials of different high-cost b/tsDMARDs for an individual patient. For example, some UK commissioning bodies have set the maximum to four [6, 7]. Very few studies have examined treatment outcomes beyond the third line [12]; such decisions may in part be influenced by earlier evidence that showed linearly reduced effectiveness from first- to third-line TNFi [13]. A trial of i.v. tocilizumab showed similar 6-month ACR20 response when comparing one to three prior TNFi drugs (49%, 50% and 54%, respectively), but differential response when using ACR50 (30%, 31%, 19%) and ACR70 (12%, 15%, 8%) [14]. Discrepancy across outcomes may be due to lack of precision in small later-line groups, as was the case in our study, but may also reflect limitations of using trial outcomes in observational settings (percentage change is problematic when baseline DAS28 differs across comparison groups [15]). For abatacept, 6-month change in DAS28 has previously been shown to be similar for those who had one or two prior TNFi (both –2.1) but lower for three (–1.7); proportions achieving DAS28 low disease activity (25%, 23%, 15%) and remission (16%, 13%, 7%) decreased with more TNFi failures [16]. These earlier trials reflected practice when fewer treatment options were available; cycling through the same drug class, e.g. three lines of TNFi, was rare in our study. In the more recent RA-BEAM trial of baricitinib, ACR20 response did not differ between <3 *vs* ≥ 3 prior bDMARDs at week 12 or 24 [8].

Lack of treatment response can reflect factors other than inflammatory RA disease activity. It is important to note that DAS28 and other composite outcomes include subjective components that can be influenced by comorbidities [17] (e.g. depression or FM) and other factors (e.g. decreased mobility due to joint damage). For example, individuals may not meet the ACR or EULAR

FIG. 4 Treatment outcomes stratified by first treatment start date before and after 2010



response criteria solely due to elevated patient global score, despite having minimal or no inflammatory disease activity (and sometimes despite considering themselves as being in remission) [18].

Drug persistence is another measure of effectiveness that additionally captures tolerability and aspects of safety (discontinuation due to adverse events). Around two-thirds of participants remained on their first-line drug after 1 year. The probability of drug discontinuation was similar for second- through sixth-line b/tsDMARD. Median drug survival decreased marginally, from 1.4 years in line two to 1.0 years in line six; drug discontinuation was numerically and statistically similar across lines two to six in models adjusting for baseline differences. Assuming staying on treatment reflects its effectiveness (clinicians are unlikely to keep patients on an ineffective drug, while in the UK it is difficult to remain on b/tsDMARD without demonstrable response [19]), these results again suggest patients are able to benefit from and remain on b/tsDMARDs beyond the third line. Median drug survival does not fully portray the fact that some patients have very short follow-up who do not

respond at all, while those who do can have prolonged drug survival.

The most common initial switching was TNFi-to-TNFi. TNFi became less popular as a second line b/tsDMARD, while use of IL-6i and JAKi as second- and third-line drugs increased over time ($<$2010 *vs* $\geq$2010). Median drug survival times were longer pre-2010 than post-2010, suggesting greater opportunities and readiness to switch over time. Nevertheless, the practice of cycling repeatedly through TNFis beyond the third line was still observed after 2010.

Taken together, our findings suggest that patients with RA who have not responded to the first three b/tsDMARDs are able to benefit from further trials of therapy. This evidence supports clinical decisions and funding for trying up to the sixth line. As the number of available b/tsDMARDs increase, more research will be needed to examine the benefit of therapy beyond the sixth line. Randomized controlled trials of patients with 'difficult-to-treat' RA are much needed to compare optimal strategies for sequential therapy.

The key strength of this analysis is use of the large real-world population reflective of routine practice in the UK. Long follow-up within individuals allowed use of multiple advanced-line therapies to be captured and described. There were also limitations. Prescribing practice is confined within national guidelines that may limit generalizability to other healthcare systems; for example, drug survival results will likely differ in settings that do not limit b/tsDMARD cycling. We did not examine treatment response stratified by reason of prior treatment discontinuation, which was in part due to limited sample size in later lines and missing data (e.g. cause not captured for b/tsDMARDs used prior to study registration). Treatment response may differ following discontinuation due to adverse events or loss of effectiveness, although prior studies using the BSRBR-RA suggested that reasons for discontinuation did not differ significantly between first and subsequent lines [3]. A sizeable proportion of participants were excluded from the DAS28 outcome analyses due to missing or unavailable data, but patient characteristics were similar to those included. We used outcome imputation, which improves power with auxiliary variables, but relies on the assumption that missingness can be predicted using observed variables in the imputation model; complete case analysis provided similar conclusions. Participant characteristics differed across lines of therapy that may limit their comparability. Even models adjusting for these differences (i.e. comparing similar patients starting another line of therapy) should be interpreted with caution, since there will likely be important residual confounding. The treatment and retreatment sequences and intervening gaps were highly complex. A number of assumptions and rules had to be made in order to perform this analysis. Although most treatment experiences are represented, there will still be some outliers not captured in this analysis. Lastly, it was not within the scope of the current analysis to explore safety, which would be an interesting area for future study.

In summary, treatment responses to subsequent-line b/tsDMARD therapies are reduced when compared with that observed for first b/tsDMARD at a cohort level but, importantly, good responses were still recorded across all lines of therapy and were similar across third to sixth. Patients who do not respond to their first b/tsDMARDs are still able to benefit from further cycles of treatment, observed out to line six in this analysis, with response and drug persistence comparable to the third- and even second-line drugs. These data also highlight the urgent need for further research to improve upon trial-and-error approaches that many patients have experienced in an attempt to find an effective therapy.

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did not play any role in study design, collection, analysis and interpretation of data, or writing of the manuscript. All relevant information regarding serious adverse events outlined in the manuscript have been reported to the appropriate pharmaceutical company as per the contractual agreements/standard operating procedures.

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Patient and public involvement statement: This study was proposed by and designed with the National Rheumatoid Arthritis Association (NRAS) and refined through collaboration with Ailsa Bosworth from NRAS.

Data availability statement

The data that support the findings of this study are available from the British Society for Rheumatology. Restrictions apply to the availability of these data (see: https://www.rheumatology.org.uk/practice-quality/registers/requesting-registers-data).

Supplementary data

Supplementary data are available at *Rheumatology* online.

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