SUPPLEMENTARY DATA

Selection of eligible treatment courses

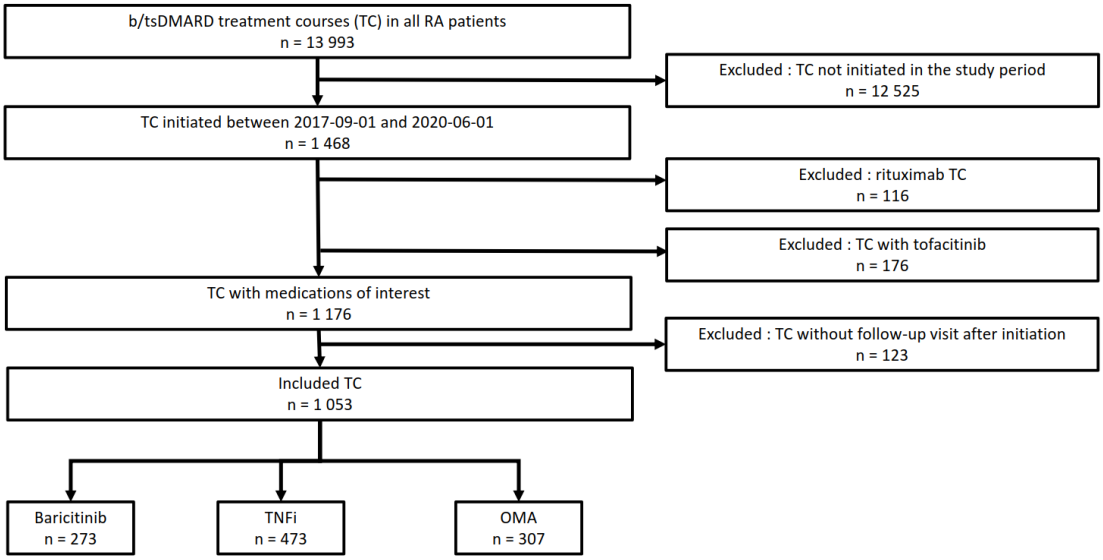

Figure S1 - Selection of eligible treatment courses, SCQM, 2017-2020.

Selection of Treatment courses included in final analysis. TC = Treatment Courses. RA = Rheumatoid Arthritis. bDMARD = biological DMARD. tsDMARD = targeted synthestic DMARD. b/tsDMARD = biological and/or targeted synthetic DMARD. TNFi = TNF inhibitors. OMA = Other Mode of Action bDMARDs.

Notice on TC duration

Due to frequent changes in medication and short study period, it has to be underlined that the median duration of a TC approximates 200 days. The proportion of TC with follow-up data of at least one year is 37% for BARI, 27% for TNFi and 31% for OMA (Figure S2) - i.e. most TC were started less than 12 months before the date of data extraction.

Gilbert BTP, *et al. BMJ Open* 2024; 14:e072300. doi: 10.1136/bmjopen-2023-072300

Notice this % is different from the % of patient still under therapy that we estimate using Kaplan-Meier or Cox model. Indeed, the latter includes a censoring of the lost-to-follow-up patients, hence the denominator is different. As a consequence, this does not contradict the reported “median prescription survival timey”, for instance of 704 days for BARI TCs. The latter is the output estimated by the Kaplan-Meier model, taking censoring into account; it does not imply that actual observations in the dataset have this duration.

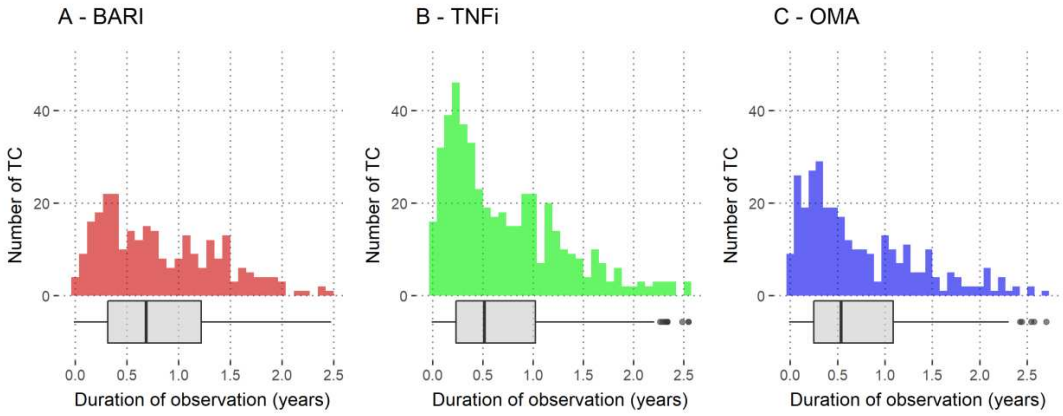

Figure S2: Distribution of the observation time for included TCs, per group, SCQM, 2017-2020. Most of the treatment courses have an actual duration and/or follow-up period of less than one year. TC = Treatment Course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Mode of Action bDMARDs.

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Variable definitions

Below we give additional detail about included covariates:

Age: age in years, at TC initiation. Continuous variable.

Gender: male or female. Categorical variable.

BMI: BMI at TC initiation. Continuous variable.

CDAI score: CDAI score at TC initiation. Continuous variable. If missing, imputed according to procedure described in methods section.

Disease duration: time interval between RA diagnosis date and TC initiation date. Continuous variable, expressed in years, but used in decades in models.

Smoking status: smoking status at TC initiation. Categorical variable (current-, former-, never-smoker).

Concomitant csDMARD: yes/no variable. A concomitant csDMARD was defined as csDMARD prescription ongoing for at least 40% of the duration of the TC. Otherwise, the TC was categorized as monotherapy. csDMARDs included: methotrexate, sulfasalazin, leflunomide, azathioprine and hydroxy-chloroquine, alone or in combination.

Concomitant glucocorticoid: Yes/no variable. Concomitant glucocorticoid usage was defined as having at least one active prescription of glucocorticoid, at any dose, at any timepoint of the TC.

Line of therapy: strictly speaking, this categorical variable is displaying: [*number of previous TC ever* + 1]. 4 or more has been grouped in the same category. Hence, it is considering all data of the SCQM registry, i.e. TCs initiated before our study period are also accounted for as previous therapies.

Seropositivity: yes/no variable. Seropositivity is defined as positivity for anti-citrullinated peptide antibodies and/or rheumatoid factor.

Time to all cause discontinuation

Table S1: Crude treatment discontinuation by group and by reason, SCQM, 2017-2020.

	BARI (TCs = 273; 273 pts)	**TNFi (TCs = 473; 408 pts)**	**OMA (TCs = 307; 289 pts)**
Treatment discontinuation (all causes)	30 %	43 %	35 %
For adverse events	8 %	10 %	10 %
For ineffectiveness	16 %	23 %	17 %
For remission	0 %	1 %	0 %
For other reason	5 %	8 %	7 %

Table S1 legend: % are computed on total number of TCs per group, for the whole study period. BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. TC = Treatment Courses. Pts = Number of patients. Due to rounding, the sum of the percentages of the causes of discontinuation may not correspond exactly to the total treatment discontinuation percentage.

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Cox model output

Table S2 contains the complete output of the two adjusted Cox models used in the main time-to-drug discontinuation analysis.

Table S2: Hazard ratio of drug discontinuation, Cox models, SCQM-RA registry, 2017-2020.

	BARI vs TNFi			**BARI vs OMA**		
	Hazard ratio	**95% CI**	**p**	**Hazard ratio**	**95% CI**	**p**
TNFi (vs baricitinib)	1.76	1.32-2.35	**<0.001**	-	-	-
OMA (vs baricitinib)	-	-	-	1.27	0.93-1.72	0.13
Adjusting variables:						
Age (decades)	1.03	0.92-1.14	0.61	0.98	0.86-1.10	0.69
BMI	1.01	0.98-1.04	0.51	0.98	0.94-1.02	0.31
TC with csDMARD	0.84	0.66-1.09	0.19	1.22	0.90-1.67	0.20
Glucocorticoid usage	1.29	0.93-1.79	0.12	1.86	1.32-2.61	**<0.001**
CDAI score	1.40	1.26-1.56	**<0.001**	1.15	1.03-1.28	**0.01**
Disease duration (decades)	0.95	0.81-1.10	0.46	0.85	0.70-1.03	0.10
Current smoker (vs non-smoker)	1.20	0.86-1.68	0.28	1.09	0.73-1.64	0.66
Ever smoker (vs non-smoker)	1.10	0.79-1.52	0.57	1.38	0.95-2.00	0.09
2nd line therapy (vs 1st)	1.11	0.80-1.53	0.52	1.37	0.81-2.33	0.24
3rd line therapy (vs 1st)	0.98	0.64-1.51	0.93	1.56	0.92-2.64	0.10
4th or later line (vs 1st)	1.06	0.75-1.51	0.73	1.57	0.93-2.63	0.09
Female gender	1.05	0.78-1.42	0.74	1.16	0.81-1.67	0.41
Seropositivity	0.77	0.59-1.01	0.055	0.94	0.67-1.31	0.71

BARI = baricitinib. TNFi = TNF inhibitors. OMA = Other Mode of Action drugs. CI = Confidence Interval. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index.

Figure S3 below gives the exact same information as Table S2:

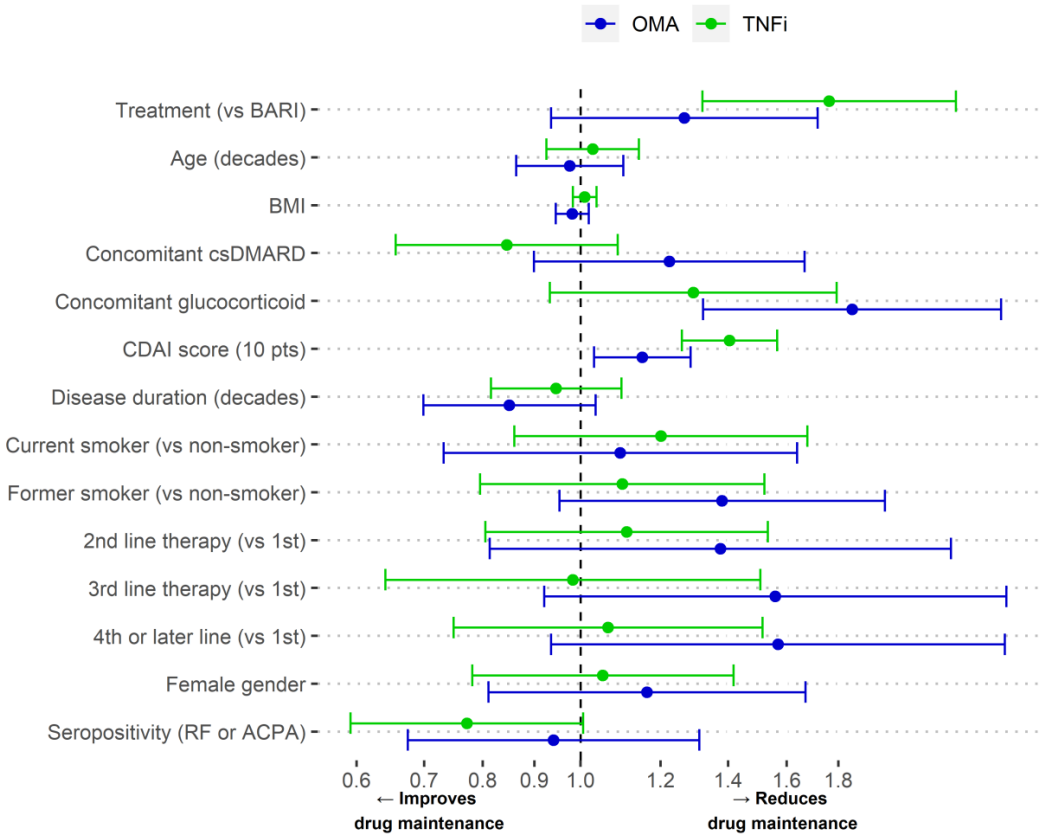

Figure S3: Hazard ratio of drug discontinuation (95% CI).

BARI = Baricitinib. TNFi = Tumor Necrosis Factors Inhibitors. OMA = Other mode of Action bDMARDs. BMI = Body Mass Index. CDAI = Clinical Disease Activity Index. RF = Rheumatoid Factor. ACPA = Anti-citrullinated Peptides Antibodies.

The corresponding cox-adjusted drug-survival curves are provided below:

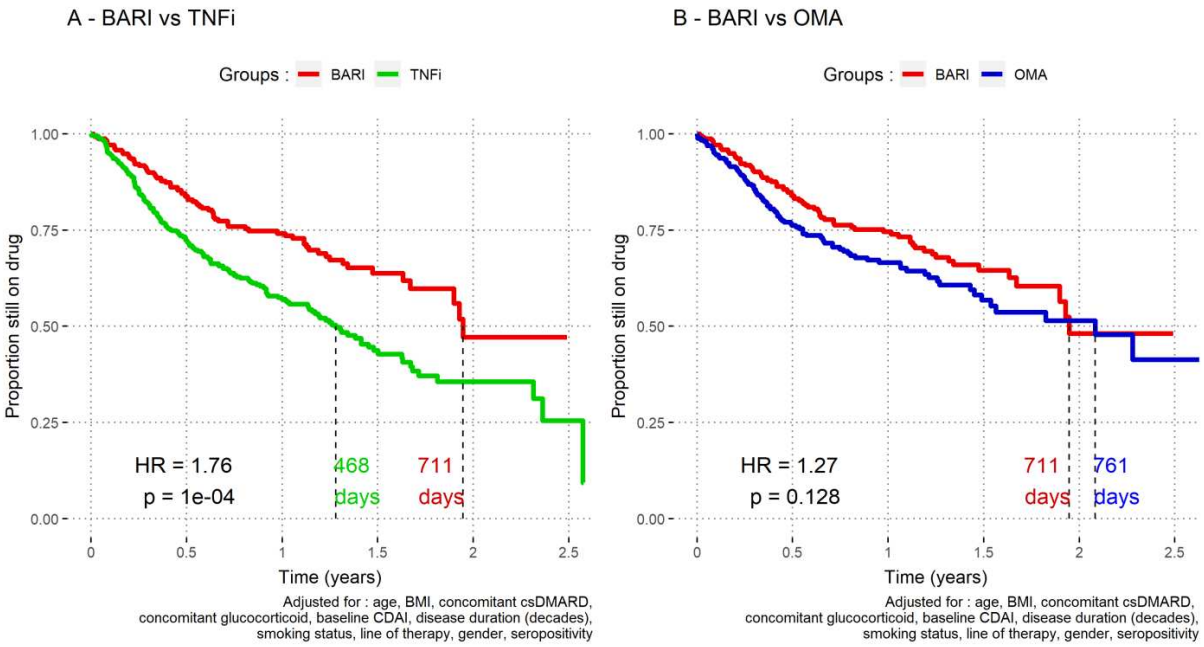

Figure S4: Multivariable Cox model of drug discontinuation by type of treatment, SCQM, 2017-2020.

These curves are merlely the visualisation of Cox models presented in Table S1 and Figure S2.

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action bDMARDs

Models are adjusted for : age, BMI, concomitant csDMARD, concomitant glucocorticoïd, baseline CDAI, disease duration, smoking status, line of therapy, gender, serpostivity.

Sensitivity analysis using AIPTW

As a sensitivity analysis, the main time to drug discontinuation was also performed using "augmented inverse probability of treatment weighting" (AIPTW), including the same covariates. In other words, we combined a propensity score using a logistic regression model and an inverse probability weighted Cox regression. We used the *RiskRegression* package in R, to obtain risk ratios.

Figure S5 represents the absolute risk of treatment discontinuation, for all included timepoints. At one year, the adjusted discontinuation risk in BARI was 19 % lower than in TNFi group (p<0.001) (Figure S5 A), with a risk ratio of 1.76 (95% CI [1.19 – 2.34]; p=0.009). Similarly, at one year, the adjusted treatment discontinuation risk in BARI was 8 % lower than in the OMA group (p=0.06) (Figure S5 B), with a risk ratio of 1.28 (95% [0.91 – 1.65]; p=0.14).

Overall, this sensitivity analysis confirms the findings reported in the main body of the article.

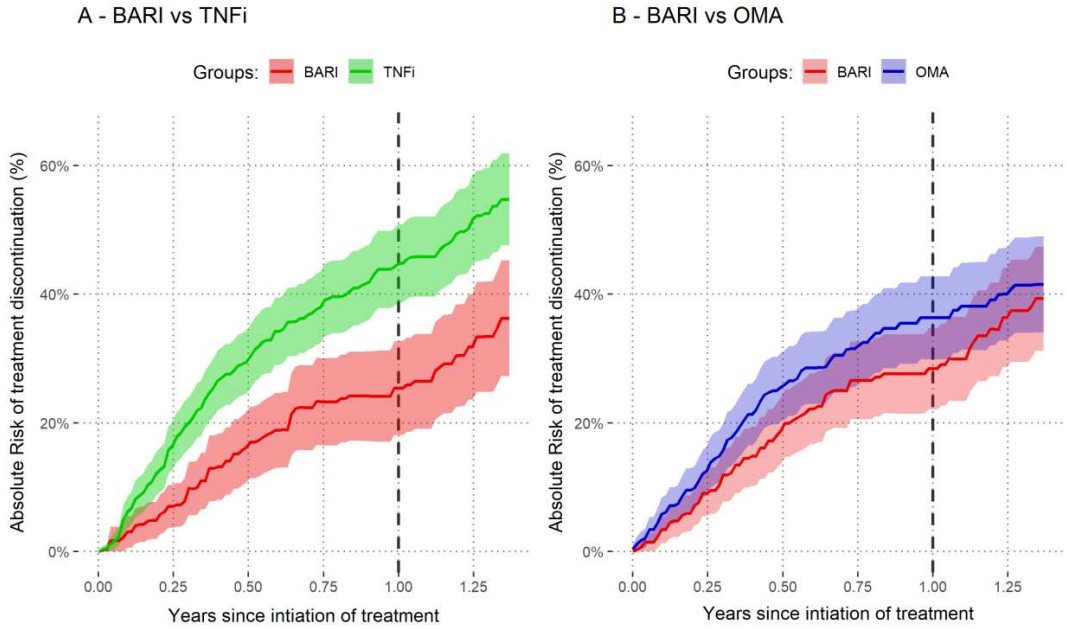

Figure S5: Absolute risk of treatment discontinuation by type of treatment (AIPTW), SCQM, 2017-2020)

BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inihibitors. OMA = Other Modes of Action bDMARDs. AIPTW = Augmtented Inverse Probability of Treatment Weigthning. Adjusted for : age, bmi, concomitant csDMARDs, prednisone usage, baseline CDAI, disease duration, smoking status, line of therapy, gender, seropositivity.

Time to all-cause-discontinuation in b/tsDMARD-naïve patients

Table S3: Baseline characteristics of study population, b/tsDMARD-naïve patients, SCQM-RA registry, 2017-2020.

	BARI (n = 46)		**TNFi (n = 225)**		**OMA (n = 66)**		**p values**
	n % Otherwise: Mean (SD)						
Patient-Variables		Miss.		Miss.		Miss.	
Female	70 %	0	71 %	1	73 %	1	0.88
Age (years)	57 (15)	0	52 (14)	1	57 (16)	1	<0.01
Disease duration (years)	6 (6)	1	5 (7)	13	7 (9)	2	0.24
CDAI baseline (raw data)	16 (8)	31	18 (10)	135	18 (14)	42	0.77
CDAI baseline (imputed)	12 (7)	0	14 (9)	0	14 (10)	0	0.61
Obesity (BMI > 30)	11 %	13	13 %	58	5 %	27	0.28
Smoking Current Former Never	 28 % 26 % 26 %	9	 18 % 24 % 39 %	42	 14 % 21 % 46 %	13	0.18
Seropositive (ACPA or RF)	80 %	1	69 %	5	76 %	2	0.20
TC variables							
Dose of BARI (4mg)	83 %	0	-	-	-	-	-
TC duration > 12-months	37 %	0	29 %	0	35 %	0	0.48
Concomitant csDMARD	41 %	0	66 %	0	50 %	0	<0.01
Line of Therapy 1st (= bio-naive) 2nd 3rd 4th or later	100 %	0	100 %	0	100 %	0	-
Previous tsDMARD use (non-BARI)	0 %	0	0 %	0	0 %	0	-
Concomitant glucocorticoid (at any time)	13 %	0	20 %	0	17 %	0	0.50
Mean dose of concomitant glucocorticoid (mg)	1 (4)	0	3 (6)	0	2 (6)	0	0.50

Table S3: BARI = baricitinib. TC = Treatment Courses. CDAI = Clinical Disease Activity Index. TNFi = Tumor Necrosis Factor Inhibitors. OMA = bDMARDs with Other Mode of Action. tsDMARD = targeted synthetic DMARDs. ACPA = Anti Citrullinated Peptide Antibodies. RF = Rheumatoid Factor. Miss. = number of missing values. p-values are computed with either Chi^2 or ANOVA.

Response rates – raw CDAI data

Figure S6 shows the crude available values for CDAI scores, by type of treatment and time. Only a minority of CDAI scores were assessed at 0- or 12-month timepoints of TCs (i.e. 680/1053 = 65% were missing for baseline value, and 908/1053 = 86% were missing for exact 12-month value). Future research would certainly benefit having CDAI scores assessed at regular and homogenous time-intervals, based on the initiation date of biological therapies.

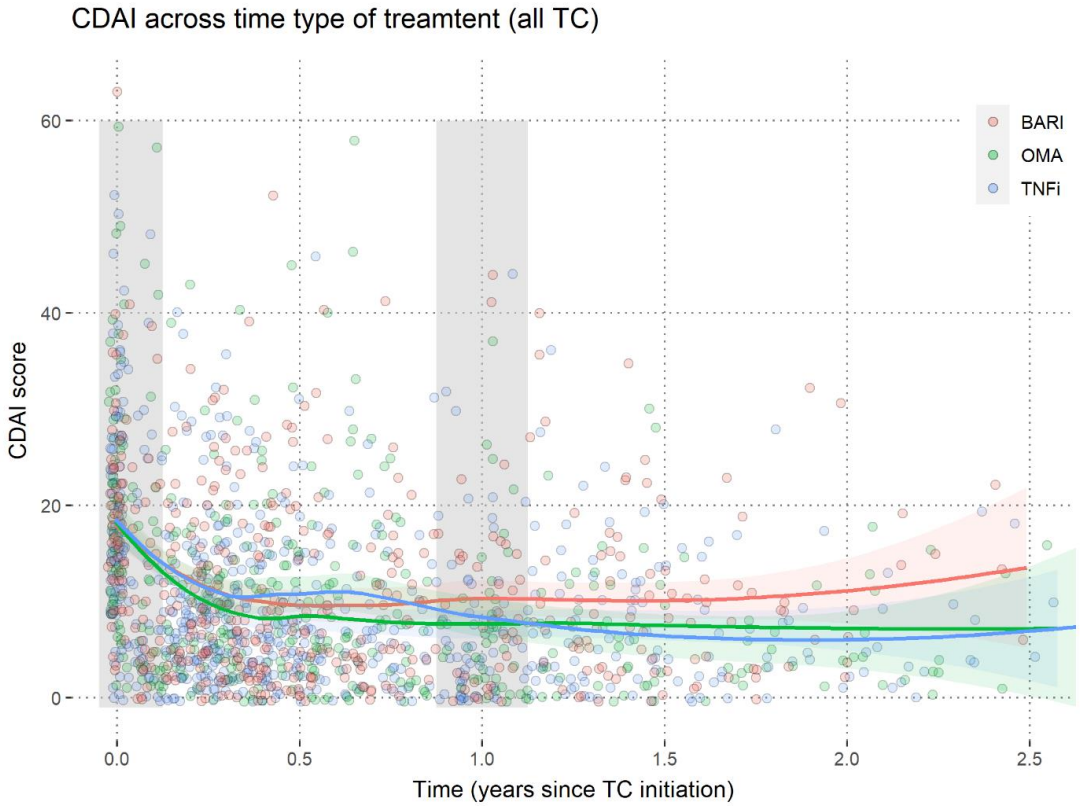

Figure S6: CDAI across time by type of treatment, raw data, SCQM, 2017-2020.

Only a minority of CDAI score were obtained sharp at 0 or 12 months of TCs. CDAI = Clinical Disease Activity Index. TC = Treatment course. BARI = Baricitinib. TNFi = Tumor Necrosis Factor Inhibitors. OMA = Other Modes of Action b/tsDMARDs.

Study size

Based on estimates from similar analyses with tofacitinib (TOFA) performed in this registry, we calculated the number of patients that would be needed to detect a significant decrease in time to all cause-discontinuation of treatment (hazard ratio) between treatment groups using the method described by Schoenfeld and Richter. We assumed a statistical power of 80%, a type I error probability of 0.05, a median BARI retention of 30 months, the inclusion of 3 patients on TNFi for every patient on BARI, an accrual time of 2 years, and additional follow-up of 6 months. We display below the sample size for the BARI group for a range of possible effect sizes ("hazard ratio" between 1.1 and 1.8).

If the true hazard ratio is similar to the one found with TOFA compared to TNFi after a single TNFi failure (HR 1.68), we will need to study 149 patients on BARI and 447 patients on TNFi to be able to reject the null hypothesis that the experimental and control curves are equal with probability (power) of 80%. Pragmatically, we propose to start the analysis of the data only once at least 200 patients on BARI have been included and followed for an average of at least 18 months.

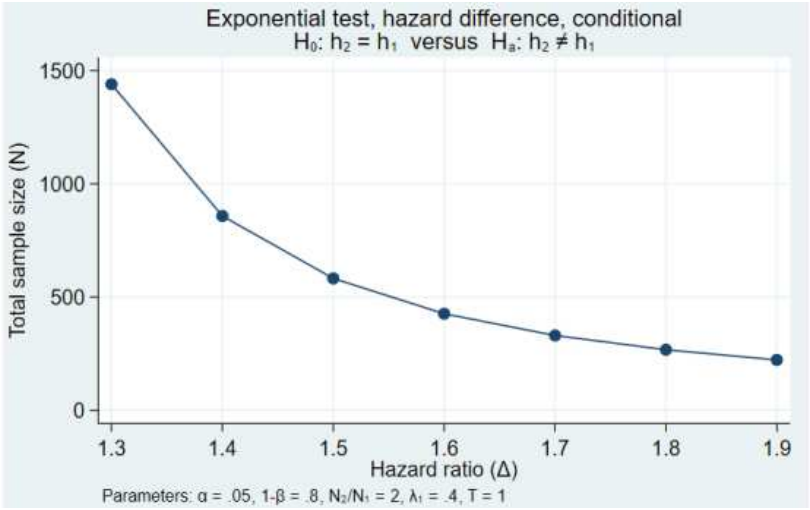

Figure S7: Estimated total sample size for two-sample comparison of survivor functions