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Original article

Effectiveness of baricitinib and tofacitinib compared with bDMARDs in RA: results from a cohort study using nationwide Swedish register data

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Abstract

Objectives. To describe the use of baricitinib and tofacitinib by Swedish RA patients and to compare their effectiveness with that of biologic DMARDs (bDMARDs).

Methods. RA patients who initiated baricitinib ($n = 1420$), tofacitinib ($n = 316$), abatacept ($n = 1050$), IL-6 inhibitors (IL-6is; $n = 849$), rituximab ($n = 1101$) or TNF inhibitors (TNFis; $n = 6036$) between January 2017 and November 2019 were followed for a minimum of 1 year using data from several linked Swedish national registers. Proportions reaching a good EULAR 28-joint DAS (DAS28) response, HAQ Disability Index (HAQ-DI) improvement >0.2 units and Clinical Disease Activity Index (CDAI) remission were compared at 1 year, imputing discontinued treatments as 'non-response'. Additionally, we compared drug retention and changes in DAS28, HAQ-DI and CDAI from baseline to 3 months after treatment initiation.

Results. On average, baricitinib, and particularly tofacitinib, were initiated as later lines of therapy and more frequently as monotherapy compared with rituximab and TNFi. Adjusted 1 year response proportions were consistently lower on TNFi compared with baricitinib, with differences of −4.3 percentage points (95% CI −8.7, 0.1) for good EULAR response, −9.9 (−14.4 to −5.4) for HAQ-DI improvement and −6.0 (−9.8 to −2.2) for CDAI remission. Comparisons with non-TNFi bDMARDs also favoured baricitinib, but not consistently. Treatment responses for tofacitinib were only marginally lower than those for baricitinib and generally similar to those of bDMARDs, with precision limited by low power. Comparisons of drug retention and changes in disease activity from baseline to 3 months supported the 1 year findings.

Conclusions. Baricitinib and tofacitinib showed at least equivalent effectiveness compared with bDMARDs after exploring several different effectiveness measures.

Key words: rheumatoid arthritis, effectiveness, biologics, Janus kinase inhibitors, baricitinib, tofacitinib

CLINICAL SCIENCE

Rheumatology key messages

- Baricitinib showed higher treatment retention and overall equivalent or better treatment responses compared with bDMARDs.
- Treatment retention for tofacitinib was lower than for baricitinib, but treatment responses were not significantly different from those of bDMARDs or baricitinib.

Introduction

Since their European Union approval in 2017, the synthetic Janus kinase inhibitors (JAKis) baricitinib and tofacitinib have become common treatment options for

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RA. Indeed, baricitinib is currently the third most frequently initiated targeted DMARD in Sweden, second only to the TNF inhibitors (TNFis) etanercept and adalimumab. Current RA treatment guidelines rank JAKis alongside biologics as options for patients who failed initial conventional synthetic DMARDs (csDMARDs) [1, 2], but their oral administration [3] may explain their relative popularity despite certain safety concerns, including venous thromboembolisms, major cardiovascular events and malignancies [4–6].

Clinical trials have demonstrated superior efficacy of tofacitinib and baricitinib to MTX in monotherapy among DMARD-naïve patients and to placebo among patients who failed initial csDMARDs or TNFis [7–16]. Notably, trials also found efficacy superior to adalimumab for baricitinib and upadacitinib, but not for tofacitinib [13, 16–18]. It remains unclear if the efficacy of JAKis is similarly higher compared with other biologic DMARDs (bDMARDs) and if any such superiority translates to a clinically meaningful increased effectiveness when used in clinical practice.

Real-world evidence on JAKis is primarily available for tofacitinib, from countries where it was introduced earlier. Although generally reporting similar effectiveness between tofacitinib and bDMARDs [19, 20], two large studies have suggested improved drug persistence on tofacitinib compared with TNFis, at least after failure of a first bDMARD [21, 22]. Real-world evidence remains limited for baricitinib, which so far has mainly been compared with tofacitinib in small studies with limited ability to control for confounding [23–25].

To fill this knowledge gap, we aimed to provide a robustly adjusted head-to-head real-world effectiveness comparison of baricitinib, tofacitinib and each class of bDMARDs.

Patients and methods

Data sources

This cohort study employed person-level data prospectively collected in the Swedish Rheumatology Quality Register (SRQ) linked to other Swedish national registers via the personal identity number of each patient [26, 27]. Data on baseline RA characteristics, longitudinal clinical measurements and initiation/discontinuation of bDMARDs or JAKis were extracted from the SRQ. Data on other treatments (co-medication, medication history, etc.) were extracted from the Prescribed Drugs Register, covering dispensations from community pharmacies. Disease history and time in hospital were identified in the National Patient Register, covering inpatient and specialized outpatient care since 2001, and in the Swedish Cancer Register. Demographic data were provided by registers at Statistics Sweden.

Study population

All RA patients who initiated any JAKi or bDMARD, regardless of prior treatment, between January 2017 and November 2019, as identified in the SRQ, were included. Follow-up data were available for all patients until February 2021.

Treatments

Patients contributed to six treatment cohorts corresponding to the initiated index treatments: tofacitinib, baricitinib, abatacept, IL-6 inhibitors (IL-6is; tocilizumab and sarilumab), rituximab and TNFis (etanercept, adalimumab, infliximab, certolizumab pegol and golimumab). Treatment episodes were identified in the SRQ. One patient could participate with several sequential episodes. However, consecutive episodes on the same drug were merged if restarted within 90 days of a previous stop (270 days for rituximab).

In supplementary analyses, co-treatment with csDMARDs and exposure to each individual drug were explored. Co-treatment with csDMARDs was identified as at least one prescription within a window spanning from 180 days before to 30 days after index treatment initiation (Supplementary Tables S1 and S2, available at *Rheumatology* online).

Outcomes

Follow-up for each treatment episode started at the index treatment initiation (i.e. baseline).

Drug retention

Drug retention was defined as the proportion of patients remaining on treatment over time. If earlier than the recorded discontinuation date, the start of the next bDMARD or targeted synthetic DMARD (tsDMARD) was considered the discontinuation date. Follow-up was censored at death, emigration from Sweden, discontinuation due to pregnancy or at the end of available data. Patients who discontinued treatment due to remission were considered on-treatment until the start of a new b/tsDMARD.

Treatment response at 3 months

Changes from baseline in the 28-joint DAS using ESR (DAS28-ESR), HAQ Disability Index (HAQ-DI) and Clinical Disease Activity Index (CDAI) were evaluated using the available measurements closest to 90 days after index treatment initiation, within a window from 60 to 185 days after index treatment initiation. Treatments discontinued before this window were excluded from the 3-month analysis. Baseline measurements were taken within a window from 90 days before to 30 days after index treatment initiation (see Supplementary Table S1, available at *Rheumatology* online for details).

Treatment response at 1 year

Three binary response measures were assessed using the available measurements closest to 1 year after index treatment initiation, within a window from 275 to 455 days after index treatment initiation. The three measures were EULAR DAS-28 good (*vs* moderate or no) response (evaluation DAS28-ESR $\leq$3.2 units and a decrease in DAS28-ESR $>$1.2 units at evaluation compared with baseline) [28], HAQ-DI improvement (a

decrease in HAQ-DI >0.2 at evaluation compared with baseline) and CDAI remission (a CDAI ≤2.8 at evaluation).

To avoid selection bias, patients who discontinued treatment before the chosen evaluation date within the specified evaluation window were kept in the analysis as 'non-responders'. Patients who died, emigrated or stopped treatment due to pregnancy before the 1 year evaluation (∼1%, equally distributed between treatment arms) were excluded from this analysis.

Covariates

Confounding bias was accounted for by including in the outcome models baseline covariates considered to influence treatment selection [29] and to predict drug retention and treatment response. The list of baseline variables comprises demographic characteristics, RA parameters (such as duration or severity), line of b/tsDMARD therapy (first, second, third or later b/tsDMARD), indicators for previous use of csDMARDs, TNFi or non-TNFi b/tsDMARDs, co-medication with csDMARDs, NSAIDs and glucocorticoids, disease history and general health indicators (such as smoking status or the number of treatments used and days spent in hospital). Detailed definitions can be found in Supplementary Table S1, available at *Rheumatology* online. Continuous covariates were modelled as quadratic polynomials.

Statistical methods

Contrasts between treatments, adjusted for baseline confounders, were estimated as differences in 3 month disease activity/disability changes and in 1 year treatment response proportions using separate multiple linear regression models with robust standard errors for each outcome [30]. Drug retention was plotted for each treatment using the Kaplan–Meier estimator and compared between treatments using proportional hazards Cox regression. Missing outcome and covariate values were imputed 25 times using fully conditional specification multiple imputation (amount of missing data in Supplementary Table S3, available at *Rheumatology* online). Each incomplete variable was imputed conditionally on all the other variables included in the analysis (using the same transformations) plus on-drug indicators to preserve associations between variables and achieve conditional random missingness. Separate imputation processes were used for analyses where exposure was classified differently, where data was stratified, and for survival analysis, where the outcome was included as an event indicator plus cumulative hazard [31]. Non-responder imputation was applied before multiple imputation. Treatment effect estimates and corresponding standard errors were calculated from each imputed data set and pooled using Rubin's rules.

Data management and analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The study was approved by the Ethical Review Board in Stockholm (DNR: 2016/1986-32). In accordance with Swedish law, participant consent was not necessary for this register-based study with pseudonymized data.

Results

Description of study population

Baseline population characteristics are described in Table 1. A total of 8006 patients contributed with 10 772 treatment episodes: 1420 initiated baricitinib, 316 tofacitinib, 1050 abatacept, 849 tocilizumab or sarilumab, 1101 rituximab and 6036 different TNFi. Approximately 18% of patients participated in more than one treatment cohort. Patients were on average 59 years old and 79% were female. Differences in demographic characteristics between treatment groups were not large. The order of therapy lines showed that TNFis were mainly used as first or second b/tsDMARDs, followed closely by rituximab, while abatacept and IL-6is were more frequently used as third line or later. Among the JAKis, baricitinib was more frequently used as second- or third-line therapy, while tofacitinib was used as a later line. The main csDMARD co-treatment used was MTX. Co-treatment with MTX was less frequent for JAKis, with 45% on baricitinib and 37% on tofacitinib, compared with an average of 59% for bDMARDs. The average RA disease activity was slightly higher at JAKi initiation than at TNFi initiation and comparable to disease activity at initiation of non-TNFi bDMARDs. Baseline disease activity was missing for ∼40% of observations. Patients suffering comorbid conditions were generally channelled towards abatacept or rituximab and away from TNFis, with JAKis intermediate.

Drug retention

The crude Kaplan–Meier drug retention curves (Fig. 1), crude proportions of patients remaining on treatment at 1 year and crude drug discontinuation hazard ratios (Table 2 with baricitinib as the reference and Supplementary Table S4, available at *Rheumatology* online, with tofacitinib as the reference) show the highest drug retention over follow-up for rituximab, followed by baricitinib, other bDMARDs and lastly tofacitinib.

After confounding adjustment, drug retention remained significantly higher for baricitinib compared with tofacitinib, abatacept, IL-6is and TNFis (Table 2), while being similar between tofacitinib, IL-6is and TNFis (Supplementary Table S4, available at *Rheumatology* online).

Reasons for treatment discontinuation are presented in Supplementary Table S5 (available at *Rheumatology* online); lack of effect was the most frequently recorded reason for stopping treatment, followed by adverse events. Tofacitinib and IL-6is were more frequently stopped for safety reasons compared with alternatives.

Table 1 Description of the study population at baseline

Feature	Baricitinib	Tofacitinib	Abatacept	IL-6is	Rituximab	TNFis
Patients, *n*	1420	316	1050	849	1101	6036
Female, *n* (%)	1159 (81.6)	258 (81.6)	832 (79.2)	693 (81.6)	834 (75.7)	4725 (78.3)
Age, years	61 (52–71)	60 (51–69)	63 (53–72)	59 (49–70)	64 (54–73)	58 (47–68)
Country of birth, *n* (%)						
Swedish	1223 (86.1)	279 (88.3)	907 (86.4)	722 (85.0)	912 (82.8)	5141 (85.2)
Scandinavian	67 (4.7)	11 (3.5)	55 (5.2)	47 (5.5)	67 (6.1)	261 (4.3)
Other	130 (9.2)	26 (8.2)	88 (8.4)	80 (9.4)	122 (11.1)	634 (10.5)
Education level (years), *n* (%)						
≤9	290 (20.5)	61 (19.3)	240 (23.0)	158 (18.8)	240 (22.0)	1092 (18.2)
10–12	671 (47.4)	171 (54.1)	483 (46.3)	438 (52.1)	521 (47.8)	2786 (46.5)
>12	456 (32.2)	84 (26.6)	321 (30.7)	244 (29.0)	328 (30.1)	2115 (35.3)
RA						
RA duration, years	13 (7–22)	13 (7–24)	13 (5–22)	10 (5–19)	13 (6–22)	8 (3–16)
RF, *n* (%)	1055 (75.7)	227 (74.2)	800 (78.4)	619 (74.5)	922 (85.4)	4146 (70.0)
DAS28-ESR	4.7 (3.8–5.6)	4.6 (3.9–5.7)	4.8 (3.9–5.6)	4.9 (4.0–5.7)	4.8 (3.9–5.6)	4.4 (3.4–5.2)
HAQ-DI	1.1 (0.8–1.6)	1.3 (0.8–1.8)	1.1 (0.8–1.6)	1.2 (0.8–1.6)	1.1 (0.8–1.8)	0.9 (0.5–1.4)
VAS pain	60 (40–75)	67 (45–80)	63 (42.–77)	65 (45–80)	60 (38–76)	56 (34–73)
CDAI	20 (14–28)	22 (16–30)	21 (15–28)	22 (16–30)	21 (14–29)	18 (12–25)
Joint surgery, *n* (%)	258 (18.2)	66 (20.9)	175 (16.7)	129 (15.2)	183 (16.6)	638 (10.6)
Treatment line	3 (2–5)	5 (3–7)	3 (2–4)	3 (2–4)	2 (1–4)	1 (1–2)
Current MTX, *n* (%)	639 (45.0)	118 (37.3)	520 (49.5)	390 (45.9)	562 (51.0)	3824 (63.4)
Current non-MTX, *n* (%)	292 (20.6)	57 (18.0)	211 (20.1)	142 (16.7)	260 (23.6)	1478 (24.5)
Current GC, *n* (%)	980 (69.0)	236 (74.7)	738 (70.3)	602 (70.9)	845 (76.7)	3876 (64.2)
GC dose, PEQ	7.6 (0–10)	8.3 (0–10)	8.0 (0.0–10)	8.4 (0–10)	8.8 (4–10)	7.2 (0–10)
Current NSAID	345 (30.0)	83 (34.4)	195 (24.7)	187 (27.0)	203 (23.9)	993 (20.8)
General health						
Never smoker *n* (%)	450 (38.8)	116 (40.8)	312 (37.4)	301 (42.8)	318 (35.5)	1929 (43.0)
Ex-smoker *n* (%)	577 (49.7)	133 (46.8)	441 (52.9)	323 (45.9)	471 (52.5)	2009 (44.8)
Current smoker *n* (%)	133 (11.5)	35 (12.3)	81 (9.7)	80 (11.4)	108 (12.0)	551 (12.3)
N ATC codes	11 (7–15)	12 (8–17)	12 (8–16)	10 (7–15)	11 (8–15)	9 (6–13)
Days in hospital	2 (0–8)	2 (0–9)	3 (0–10)	1 (0–7)	3 (0–11)	0 (0–5)
Comorbid conditions, *n* (%)						
Cancer	112 (7.9)	17 (5.4)	99 (9.4)	51 (6.0)	189 (17.2)	372 (6.2)
Diabetes	141 (9.9)	31 (9.8)	135 (12.9)	84 (9.9)	122 (11.1)	532 (8.8)
Acute coronary syndrome	33 (2.3)	6 (1.9)	33 (3.1)	11 (1.3)	30 (2.7)	90 (1.5)
Stroke	26 (1.8)	4 (1.3)	36 (3.4)	19 (2.2)	27 (2.5)	111 (1.8)
Hepatic insufficiency	16 (1.1)	3 (0.9)	17 (1.6)	14 (1.6)	22 (2.0)	66 (1.1)
Renal disease	23 (1.6)	6 (1.9)	23 (2.2)	16 (1.9)	23 (2.1)	80 (1.3)
Obstructive lung disease	67 (4.7)	16 (5.1)	79 (7.5)	30 (3.5)	64 (5.8)	172 (2.8)
Interstitial lung disease	32 (2.3)	7 (2.2)	54 (5.1)	20 (2.4)	69 (6.3)	39 (0.6)
Pain syndromes	109 (7.7)	26 (8.2)	63 (6.0)	69 (8.1)	67 (6.1)	333 (5.5)
Mood disorders	423 (29.8)	104 (32.9)	308 (29.3)	240 (28.3)	349 (31.7)	1582 (26.2)
Severe Infection	78 (5.5)	13 (4.1)	98 (9.3)	21 (2.5)	70 (6.4)	167 (2.8)
Venous thromboembolism	43 (3.0)	13 (4.1)	33 (3.1)	20 (2.4)	37 (3.4)	92 (1.5)

Values are presented as median (IQR) unless stated otherwise. Only observed values (not imputed ones) were used to calculate descriptive statistics. N ATC codes is the number of drug classes (first five characters of ATC code) used within the past year. GC: glucocorticoid; non-MTX: csDMARD other than MTX; PEQ: prednisone equivalent; VAS: visual analogue scale.

Treatment response at 3 months

The proportions of patients who discontinued treatment within 60 days and were excluded from this analysis were baricitinib 6%, tofacitinib 13%, abatacept 6%, IL-6i 8%, rituximab 4% and TNFi 5%. Proportions of missing 3-month changes in RA disease activity and disability were 66% for DAS28-ESR (ranging from 63% for IL-6i to 71% for rituximab), 62% for HAQ-DI (ranging from 59% for IL-6i to 70% for rituximab) and 65% for CDAI (ranging from 60% for IL-6i to 72% for rituximab). On average, all treatments reduced RA disease activity and disability by 3 months compared with baseline. After

Fig. 1 Crude drug retention Kaplan–Meier curves

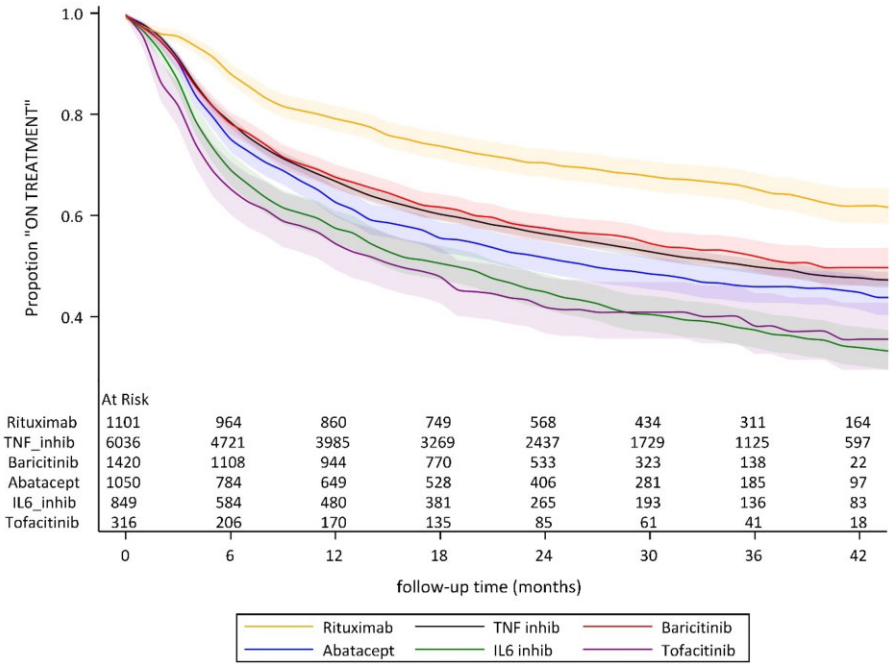


Table 2 Proportions on treatment at 1 year and treatment discontinuation hazard ratios over follow-up

Cohort	Crude % on treatment at 1 year (95% CI)	Crude HR (95% CI)	Adjustment 1, HR (95% CI)	Adjustment 2, HR (95% CI)
Rituximab	79 (77, 82)	0.64 (0.57, 0.73)	0.71 (0.62, 0.81)	0.72 (0.63, 0.82)
Baricitinib	68 (65, 70)	Ref	Ref	Ref
TNFi	67 (66, 68)	1.04 (0.95, 1.13)	1.30 (1.18, 1.42)	1.39 (1.26, 1.53)
Abatacept	63 (60, 66)	1.17 (1.04, 1.31)	1.22 (1.09, 1.37)	1.22 (1.08, 1.37)
IL-6i	57 (54, 61)	1.49 (1.32, 1.67)	1.51 (1.34, 1.69)	1.49 (1.32, 1.68)
Tofacitinib	54 (49, 60)	1.56 (1.32, 1.85)	1.51 (1.28, 1.79)	1.42 (1.20, 1.69)

Adjustment 1 for sex, age, treatment line (three categories). Adjustment 2 for sex, age, origin, clinic region, education level, RA duration, RF, baseline DAS28, HAQ-DI, CDAI and VAS pain, joint surgery, year of treatment start, treatment line (three categories), previous use of csDMARDs, TNFi, non-TNFi DMARDs, co-medication with csDMARDs (MTX, non-MTX), NSAIDs and glucocorticoids, smoking, days in hospital during the last 5 years, number of drugs during the last year and history of cancer, diabetes, heart failure, stroke, acute coronary syndrome, liver or renal disease, respiratory disease, neuropathies, pain syndromes, infections, venous thromboembolism, osteoporosis, anaemia, psoriasis and mood disorders. HR: hazard ratio; VAS: visual analogue scale.

imputation, the crude average changes ranged from −0.91 (95% CI −1.17, −0.66) for tofacitinib to −2.01 (95% CI −2.16, −1.86) for IL-6i for DAS28-ESR, from −0.16 (95% CI −0.24, −0.09) for tofacitinib to −0.25 (95% CI −0.30, −0.20) for rituximab for HAQ-DI and from −9.05 (95% CI −11.02, −7.07 for tofacitinib to −10.56 (95% CI −11.75, −9.38) for IL-6i for CDAI (Fig. 2). After confounding adjustment, IL-6i decreased the DAS28, with 0.81 units (95% CI −0.97, −0.65) more than baricitinib (Fig. 2) and with 0.86 units (95% CI −1.14, −0.57) more than tofacitinib (Supplementary Fig. S1, available at *Rheumatology* online). For baricitinib, results show statistically significant gains in improvement compared with rituximab [0.19 units higher improvement (95% CI 0.05, 0.34)] on the DAS28 scale; abatacept [0.08 units higher improvement (95% CI 0.03, 0.13)], TNFi [0.06 units higher improvement (95% CI 0.02, 0.10)] and IL-6i [0.05 units higher improvement

Fig. 2 Differences between average changes in DAS28-ESR, HAQ-DI and CDAI from baseline to 3 months

DAS28(ESR)

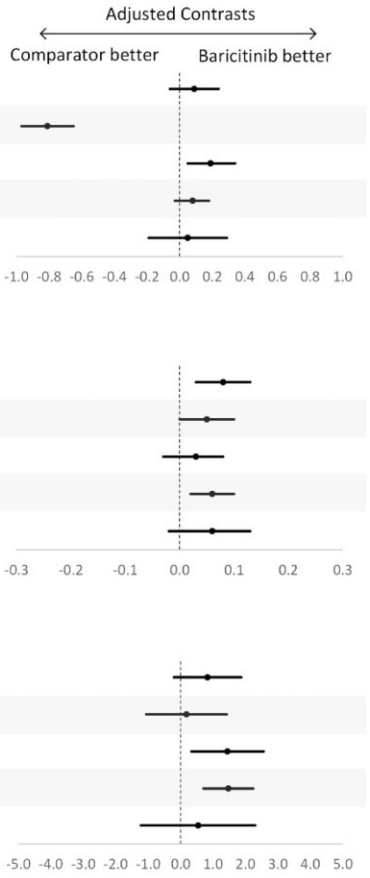
Cohort	N	Baseline Mean	Mean Change	Crude Change Contrast	Adj. Change Contrast
Abatacept	982	4.72 (4.62 to 4.81)	-1.06 (-1.19 to -0.93)	-0.01 (-0.17 to 0.15)	0.09 (-0.06 to 0.24)
IL6 inhib.	774	4.89 (4.78 to 5.00)	-2.01 (-2.16 to -1.86)	-0.96 (-1.14 to -0.78)	-0.81 (-0.97 to -0.65)
Rituximab	1044	4.77 (4.68 to 4.87)	-1.08 (-1.22 to -0.93)	-0.03 (-0.19 to 0.14)	0.19 (0.05 to 0.34)
TNF inhib.	5691	4.34 (4.29 to 4.38)	-1.21 (-1.26 to -1.16)	-0.16 (-0.26 to -0.05)	0.08 (-0.03 to 0.18)
Tofacitinib	271	4.75 (4.56 to 4.94)	-0.91 (-1.17 to -0.66)	0.14 (-0.14 to 0.41)	0.05 (-0.19 to 0.29)
Baricitinib	1325	4.64 (4.55 to 4.72)	-1.05 (-1.14 to -0.96)	Ref	Ref

HAQ-DI

Cohort	N	Baseline Mean	Mean Change	Crude Change Contrast	Adj. Change Contrast
Abatacept	982	1.24 (1.19 to 1.29)	-0.18 (-0.22 to -0.14)	0.05 (-0.01 to 0.11)	0.08 (0.03 to 0.13)
IL6 inhib.	774	1.24 (1.19 to 1.29)	-0.23 (-0.28 to -0.19)	-0.01 (-0.06 to 0.05)	0.05 (-0.00 to 0.10)
Rituximab	1044	1.22 (1.17 to 1.27)	-0.25 (-0.30 to -0.20)	-0.02 (-0.08 to 0.04)	0.03 (-0.03 to 0.08)
TNF inhib.	5691	0.97 (0.95 to 0.99)	-0.21 (-0.23 to -0.20)	0.01 (-0.02 to 0.05)	0.06 (0.02 to 0.10)
Tofacitinib	271	1.27 (1.18 to 1.37)	-0.16 (-0.24 to -0.09)	0.06 (-0.02 to 0.15)	0.06 (-0.02 to 0.13)
Baricitinib	1325	1.20 (1.16 to 1.24)	-0.23 (-0.26 to -0.19)	Ref	Ref

CDAI

Cohort	N	Baseline Mean	Mean Change	Crude Change Contrast	Adj. Change Contrast
Abatacept	982	22.05 (21.23 to 22.87)	-9.26 (-10.27 to -8.25)	0.20 (-1.12 to 1.53)	0.83 (-0.21 to 1.87)
IL6 inhib.	774	23.65 (22.72 to 24.58)	-10.56 (-11.75 to -9.38)	-1.10 (-2.49 to 0.30)	0.18 (-1.06 to 1.42)
Rituximab	1044	22.32 (21.48 to 23.15)	-9.47 (-10.61 to -8.33)	-0.01 (-1.37 to 1.36)	1.44 (0.33 to 2.56)
TNF inhib.	5691	19.73 (19.38 to 20.09)	-9.27 (-9.64 to -8.90)	0.20 (-0.66 to 1.05)	1.47 (0.70 to 2.24)
Tofacitinib	271	23.84 (22.26 to 25.43)	-9.05 (-11.02 to -7.07)	0.42 (-1.70 to 2.54)	0.54 (-1.23 to 2.30)
Baricitinib	1325	21.82 (21.18 to 22.46)	-9.46 (-10.21 to -8.72)	Ref	Ref



Contrasts, calculated as differences from baricitinib, were adjusted for: sex, age, origin, clinic region, education level, RA duration, RF, baseline DAS28-ESR, HAQ-DI, CDAI and VAS pain, joint surgery, year of treatment start, treatment line (three categories), previous use of csDMARDs, TNFi, non-TNFi DMARDs, comedication with csDMARDs (MTX, non-MTX), NSAIDs and glucocorticoids, smoking, days in hospital during the last five years, number of drugs used in the last year, history of cancer, diabetes, heart failure, stroke, acute coronary syndrome, liver or renal disease, respiratory disease, neuropathies, pain syndromes, infections, venous thromboembolism, osteoporosis, anaemia, psoriasis and mood disorders.VAS: visual analogue scale.

(95% CI 0.00, 0.10)] on the HAQ-DI scale; and TNFi [1.47 units higher improvement (95% CI 0.70, 2.24)] and rituximab [1.44 units higher improvement (95% CI 0.33, 2.56)] on the CDAI scale (Fig. 2). For tofacitinib, improvements in DAS28-ESR (except IL-6i), HAQ-DI or CDAI were similar to bDMARDs (Supplementary Fig. S1, available at *Rheumatology* online).

Treatment response at 1 year

Proportions of missing 1-year responses were 52% for EULAR response (ranging from 44% for IL-6i to 60% for rituximab), 51% for HAQ-DI improvement (ranging from 43% for IL-6i to 57% for rituximab) and 47% for CDAI remission (ranging from 39% for IL-6i to 51% for rituximab). After imputation, crude 1-year treatment responder proportions ranged from 21.4% (95% CI 13.1, 29.6) for tofacitinib to 33.9% (95% CI 28.5, 39.4) for IL-6i for good EULAR response, from 28.0% (95% CI 23.7, 32.4) for IL-6i to 38.6% (95% CI 34.0, 43.1) for rituximab for HAQ-DI improvement and from 11.1% (95% CI 7.7, 14.5) for rituximab to 16.9% (95% CI 15.3, 18.5) for TNFi for CDAI remission (Fig. 3). After confounding adjustment, good EULAR responder proportions among IL-6i initiators were 8.7 percentage points (pp) higher (95% CI 2.9, 14.4) than among baricitinib initiators (Fig. 3) and 9.7 pp higher (95% CI −0.3, 19.7) than among tofacitinib initiators (Supplementary Fig. S2, available at *Rheumatology* online). Conversely, for TNFi, the good EULAR responder proportion was 4.3 pp lower (95% CI −8.7, 0.1) than for baricitinib. Baricitinib initiators also achieved HAQ-DI improvement more frequently than any alternative except rituximab and CDAI remission more frequently compared with rituximab [−5.5 pp difference (95% CI −10.9, −0.1)] and TNFi [−6.0 pp difference (95% CI −9.8, −2.2)] (Fig. 3). No differences in good

FIG. 3 Differences between proportions of good EULAR responders, HAQ-DI improvements and CDAI remissions at 1 year

Good EULAR response

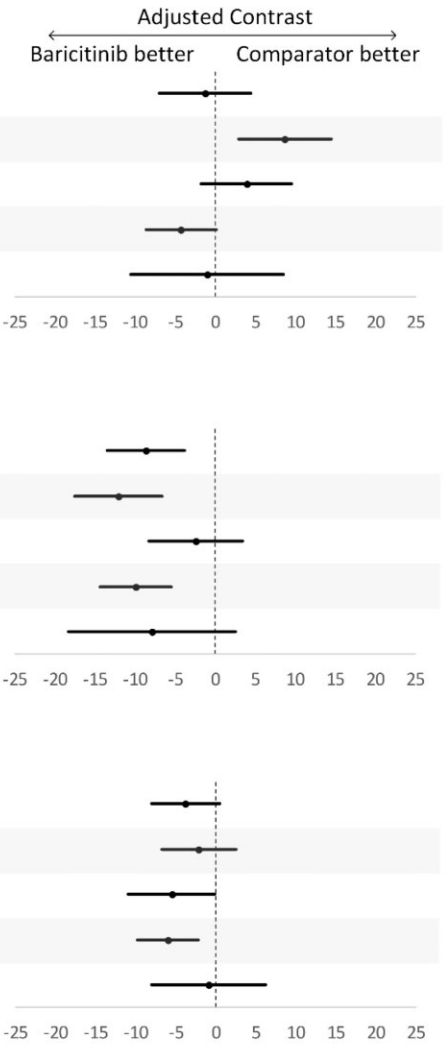
Cohort	*N*	*Crude Proportion*	*Crude Contrast*	*Adj. Contrast*
Abatacept	*1040*	25.0 (20.7 to 29.3)	-0.2 (-6.1 to 5.7)	-1.3 (-7.0 to 4.5)
IL6 inhib.	*838*	33.9 (28.5 to 39.4)	8.8 (3.0 to 14.5)	8.7 (2.9 to 14.4)
Rituximab	*1089*	32.3 (28.1 to 36.4)	7.1 (1.5 to 12.7)	3.9 (-1.8 to 9.6)
TNF ihib.	*5981*	29.6 (27.3 to 31.8)	4.4 (0.4 to 8.4)	-4.3 (-8.7 to 0.1)
Tofacitinib	*313*	21.4 (13.1 to 29.6)	-3.8 (-13.1 to 5.4)	-1.1 (-10.6 to 8.5)
Baricitinib	*1403*	25.2 (21.3 to 29.1)	Ref	Ref

HAQ-DI improvement

Cohort	*N*	*Crude Proportion*	*Crude Contrast*	*Adj. Contrast*
Abatacept	*1040*	30.4 (26.6 to 34.1)	-6.4 (-11.3 to -1.5)	-8.6 (-13.5 to -3.8)
IL6 inhib.	*838*	28.0 (23.7 to 32.4)	-8.7 (-14.2 to -3.2)	-12.1 (-17.5 to -6.6)
Rituximab	*1089*	38.6 (34.0 to 43.1)	1.8 (-4.1 to 7.8)	-2.4 (-8.3 to 3.4)
TNF ihib.	*5981*	32.9 (30.7 to 35.0)	-3.9 (-8.1 to 0.3)	-9.9 (-14.4 to -5.4)
Tofacitinib	*313*	28.2 (18.6 to 37.8)	-8.5 (-19.1 to 2.0)	-7.9 (-18.3 to 2.5)
Baricitinib	*1403*	36.8 (33.4 to 40.2)	Ref	Ref

CDAI remission

Cohort	*N*	*Crude Proportion*	*Crude Contrast*	*Adj. Contrast*
Abatacept	*1040*	11.7 (9.0 to 14.5)	-3.2 (-7.4 to 0.9)	-3.8 (-8.0 to 0.5)
IL6 inhib.	*838*	12.6 (9.0 to 16.2)	-2.4 (-6.8 to 2.1)	-2.1 (-6.7 to 2.5)
Rituximab	*1089*	11.1 (7.7 to 14.5)	-3.8 (-8.9 to 1.2)	-5.5 (-10.9 to -0.1)
TNF ihib.	*5981*	16.9 (15.3 to 18.5)	2.0 (-1.42 to 5.4)	-6.0 (-9.8 to -2.2)
Tofacitinib	*313*	11.2 (5.0 to 17.5)	-3.8 (-11.0 to 3.5)	-0.9 (-8.0 to 6.2)
Baricitinib	*1403*	15.0 (11.7 to 18.3)	Ref	Ref



Contrasts, calculated as differences from baricitinib, were adjusted for: sex, age, origin, clinic region, education level, RA duration, RF, baseline DAS28-ESR, HAQ-DI, CDAI and VAS pain, joint surgery, year of treatment start, treatment line (three categories), previous use of csDMARDs, TNFi, non-TNFi DMARDs, comedication with MTX, non-MTX csDMARDs, NSAIDs and glucocorticoids, smoking, days in hospital during the last 5 years, number of drugs used in the last year and history of cancer, diabetes, heart failure, stroke, acute coronary syndrome, liver or renal disease, respiratory disease, neuropathies, pain syndromes, infections, venous thromboembolism, osteoporosis, anaemia, psoriasis and mood disorders.VAS: visual analogue scale.

EULAR response, HAQ improvement or CDAI remission between tofacitinib and any bDMARD or baricitinib reached statistical significance, since power was limited by the small tofacitinib group (Supplementary Fig. S2, available at *Rheumatology* online). Nevertheless, numerically higher adjusted response proportions were observed for tofacitinib compared with TNFi on the good EULAR response scale [−3.2 pp difference (95% CI −11.9, 5.4)] compared with IL-6i on the HAQ-DI improvement scale [−4.1 pp difference (95% CI −14.1, 5.8)] and compared with rituximab [−4.6 pp difference (95% CI −11.9, 2.7)] and TNFi [−5.1 pp difference (95% CI −11.5, 1.3)] on the CDAI remission scale.

Supplementary analyses

Co-treatment with csDMARDs

Supplementary Fig. S3 (available at *Rheumatology* online) shows higher response proportions for tofacitinib when used in combination with csDMARDs compared with monotherapy. Lower differences between

csDMARD combination therapy and monotherapy were observed for baricitinib.

Stratifying by co-treatment revealed a similar pattern to the main analysis, but differences between baricitinib and alternatives were more pronounced when comparing monotherapies, and conversely were attenuated for combinations with csDMARDs (Supplementary Figs S4 and S5, available at *Rheumatology* online). Tofacitinib monotherapy appeared inferior to baricitinib monotherapy, however, the two JAKis were equivalent when used combined with a csDMARD.

Supplementary Table S6 (available at *Rheumatology* online) shows that <20% of the patients who initiated monotherapy at baseline according to our definition started csDMARD treatment later during the first year of treatment. The proportion of patients who discontinued baseline csDMARD co-treatment during the same period was ~30% for JAKis and ranged from 10% (TNFi) to 35% (IL-6i) for bDMARDs.

Line of b/tsDMARD therapy

Small sample size combined with the large proportion of missing RA activity measurements resulted in imprecise estimates when restricting to the first line of therapy (b/tsDMARD naïve), offering little indication of any difference between treatments (Supplementary Fig. S6, available at *Rheumatology* online). In the second (Supplementary Fig. S7, available at *Rheumatology* online) and later (Supplementary Fig. S8, available at *Rheumatology* online) lines, the pattern of contrasts was similar to the main results. Tofacitinib was predominantly used as a third or later line and in this stratum achieved similar good EULAR response and CDAI remission proportions as baricitinib, but less HAQ-DI improvement.

Restriction to first treatment in class

Excluding treatment episodes preceded by treatments with drugs from the same b/tsDMARD class yielded virtually identical results to the main analysis after adjustment, although the crude response proportions were much improved for the TNFi group (Supplementary Fig. S9, available at *Rheumatology* online).

Comparison between individual drugs

The comparison between individual drugs (instead of drug classes) supports the main results but shows variations in response for different TNFis (Supplementary Fig. S10, available at *Rheumatology* online).

Restriction to treatments continued for a minimum of 1 year

Excluding treatments stopped within the first year boosted all treatment responses, as expected, since 'non-responder' imputation was no longer applied. Treatments with high discontinuation rates (tofacitinib and IL-6i) were disproportionately advantaged by this restriction. Baricitinib retained its relative advantage to alternatives on the HAQ-DI scale and remained equivalent on good EULAR response and CDAI scales (Supplementary Fig. S11, available at *Rheumatology* online).

Restriction to complete cases (no missing data)

Analysing only complete cases supports the main results where multiple imputation was used. This shows that, conditional on baseline covariates, any potential selection bias from implicitly conditioning the analysis on complete observations may be attenuated (Supplementary Fig. S12, available at *Rheumatology* online).

Discussion

The results of this real-world study suggest that JAKis are overall at least as effective as bDMARDs and that baricitinib may be more effective than TNFis. Our results are broadly in line with evidence from randomized trials. RA-BEAM [16] reported baricitinib superior to adalimumab, while ORAL-STANDARD [13] and ORAL-STRATEGY [18] found similar efficacy of tofacitinib *vs* adalimumab. Consistently, baricitinib was better than TNFis in our study and point estimates for tofacitinib were intermediate between those of baricitinib and TNFis, with no statistically significant difference to either. Moreover, baricitinib showed significantly higher retention compared with tofacitinib or TNFis and was less often stopped due to reported ineffectiveness within the first year compared with any alternative except rituximab. In contrast to the three randomized controlled trials (RCTs), which studied inadequate responders to MTX, the bulk of our results come from patients who have failed at least one b/tsDMARD. We observed relatively lower adjusted response proportions, especially among TNFi initiators, many of whom have used TNFis previously and could be less likely to respond to subsequent TNFis [32]. Nevertheless, a sensitivity analysis restricted to the first b/tsDMARD per class supports the main results despite higher crude response rates for TNFis in this subpopulation compared with the main study population (Supplementary Fig. S9, available at *Rheumatology* online).

Similar to some observational studies, we found comparable discontinuation rates and clinical responses between tofacitinib and TNFis [19, 20, 33], although others have reported higher discontinuation rates for TNFis [22] or for tofacitinib [21]. Three small observational studies have compared baricitinib with tofacitinib. One reported a 6-month CDAI remission for baricitinib of 40% and 30% for tofacitinib [23]. The other two studies found no significant differences between baricitinib and tofacitinib, one reporting CDAI remission rates close to 20% [24, 25]. We observed crude CDAI remission proportions of 15% for baricitinib and 11% for tofacitinib at 1 year (after non-responder imputation), the difference being reduced to 1 pp by adjustment.

Although statistically significant, the differences we observed between baricitinib and TNFis were small and their clinical significance is debatable. However, our findings were similar to the differences reported in the RA-BEAM trial of baricitinib *vs* adalimumab—1 year CDAI remission 4 pp higher and 1 year HAQ

improvement 10 pp higher for baricitinib compared with adalimumab [16].

Regarding csDMARD combination treatment, baricitinib combinations were not superior to monotherapy, concurring with findings from the RA-BEGIN trial [8]. Conversely, we observed significantly higher good EULAR response and HAQ-DI improvement proportions for tofacitinib in combination *vs* monotherapy, in agreement with ORAL-STRATEGY, [18] but in contrast to two other observational studies [22, 33].

The marked DAS28-ESR reduction observed for tocilizumab is expected considering its strong effect on ESR [34]. Rituximab showed the highest drug retention, which may partially explain its relatively high 1 year response rates, as it was less affected by non-responder imputation. In Supplementary Fig. S11, available at *Rheumatology* online, where only patients who continued treatment for >1 year were kept, rituximab showed comparatively lower response rates. Nonetheless, contrasts with rituximab should be interpreted cautiously since it is notoriously difficult to define its treatment stop, which led to its exclusion from other studies [21, 22]. Moreover, the baseline disease activity measurements for rituximab were made on average 1 week earlier than for the other treatments, while 3-month measurements were made on average 1 week later.

A comparative safety analysis was outside the scope of this study. However, a difference in crude proportions of treatments stopped for safety reasons within the first year after initiation was observed between baricitinib (9.4%) and tofacitinib (14.6%). This deserves further exploring, considering that RCTs showed similar safety profiles between the two JAKis, despite differences in target selectivity [35].

The strengths of our study include the use of registers with national coverage and data collected prospectively and independently of the current research question and the high quality of the SRQ, which contains RA-specific clinical data. Nonetheless, several limitations should be acknowledged.

First, we used non-responder imputation to handle treatment discontinuation in the binary treatment response analyses. Although the main reason for discontinuation within the first year was ineffectiveness, we imputed all discontinuations as 'no response' regardless of the reported reason, thus underestimating the true responder proportions. On the other hand, restricting comparisons to patients on treatment, thus doing well, favours treatments with high discontinuation rates. Despite its relatively lower discontinuation rate, baricitinib remained better or equivalent to alternatives in a sensitivity analysis where only patients continuing treatment for at least 1 year were analysed (Supplementary Fig. S11, available at *Rheumatology* online). Furthermore, the results at 1 year were in line with those at 3 months, where fewer discontinuations had occurred.

Second, disease activity measurements were recorded at de facto clinic visits rather than at fixed time points (baseline, 3 months, 1 year). To reduce the amount of missing data, we collected RA disease activity/disability information from wide windows around baseline and endpoints. Supplementary Figs S13–S15 (available at *Rheumatology* online) show generally overlapping measurement time distributions between treatments, unlikely to bias the comparison between drugs. Despite the wide assessment windows, significant proportions of RA disease activity values were missing. Excluding observations with missing data from the analysis may introduce selection bias if factors influencing missingness also influence treatment assignment and outcome. We used multiple imputation to avoid such selection of complete observations and the resulting bias. However, multiple imputation assumes that, conditional on measured covariates, missingness is independent of the imputed variable and residual bias is possible if unmodelled factors correlated missingness with the imputed variables. Nonetheless, we obtained similar adjusted contrasts when restricting to complete observations.

Third, joint exposure to the index b/tsDMARDs and csDMARDs may be somewhat misclassified. Identifying csDMARD prescriptions within a window extending 180 days before index treatment start leads to potentially classifying some patients who have stopped csDMARD treatment soon before index treatment start as 'co-medicated'. Nevertheless, Supplementary Table S6 (available at *Rheumatology* online) shows that most patients classified as 'co-medicated' continued csDMARD treatment within the first year of follow-up. The classification of treatment as 'monotherapy' is more accurate. Additionally, the prescribed drugs register has excellent coverage for prescriptions dispensed in community pharmacies but does not cover in-hospital drug use. However, most csDMARD treatments should be well covered.

Fourth, each treatment cohort comprises all treatments initiated with the respective drug regardless of dosing regimen. We present a table with the most frequently used doses for each individual drug in Supplementary Table S16, available at *Rheumatology* online.

Finally, although we combined several sources to obtain data on >40 confounding variables, residual confounding remains possible. The line of therapy is a strong confounder since patients at later lines have a less tractable and potentially more severe disease and there was a clear difference in the line of therapy distribution between treatments—with TNFis used mainly as first line and tofacitinib initiated after the third line. We had enough patients initiating each treatment at different lines to allow regression modelling conditional on the line of therapy, but we had little power for analysing each line as a separate stratum. An analysis stratified by the line of therapy generally confirmed the adjusted comparisons. Nonetheless, it is possible that if tofacitinib is used similarly to baricitinib instead of as a last resort alternative, the difference between the two JAKis would be smaller than our results suggest.

In conclusion, we conducted the hitherto largest population-based study comparing RA patients initiating baricitinib, tofacitinib or bDMARDs (as approved in Sweden) and observed a higher treatment retention and overall equivalent or better treatment responses on baricitinib compared with bDMARDs or tofacitinib, with no statistically significant differences between tofacitinib and bDMARDs. Nevertheless, the relative benefits of JAKis should be balanced against comparative safety data, which recently led the US Food and Drug Administration to recommend JAKis only after TNFi failure [36].

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Data availability statement

The individual patient data underlying this article comes entirely from national Swedish registers. According to Swedish law, access to national register data is granted on a restrictive basis and may not be shared without additional specific permissions from the Swedish register-holding authorities.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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