RHEUMATOLOGY

Rheumatology 2019;58:1367–1377
doi:10.1093/rheumatology/key433
Advance Access publication 21 January 2019

Original article

Comparative effectiveness of abatacept, rituximab, tocilizumab and TNFi biologics in RA: results from the nationwide Swedish register

Thomas Frisell[1], Mats Dehlin[2], Daniela Di Giuseppe [1], Nils Feltelius[3], Carl Turesson[4,5] and Johan Askling[1] on behalf of the ARTIS Study Group*

Abstract

Objectives. Current guidelines rank abatacept, rituximab, tocilizumab and TNF-inhibitors (TNFi) as having equal effectiveness for the treatment of RA, at least as second line therapies. These recommendations are mainly based on meta-analysis of randomized controlled trials, with few direct drug–drug comparisons. Our objective was to compare the real-world absolute and relative effectiveness among RA patients starting any of the available biologic DMARDs (bDMARDs).

Methods. We used the Swedish Rheumatology Register to identify patients with RA initiating TNFi, rituximab, abatacept or tocilizumab in 2010–2016 as first bDMARD ($n = 9333$), or after switch from TNFi as first bDMARD ($n = 3941$). National Swedish registers provided additional covariates and censoring events. Effectiveness was assessed 3 and 12 months after treatment start, as the proportion remaining on therapy and with EULAR Good Response, HAQ improvement >0.2, zero swollen/tender joints and CDAI remission. Adjusted differences were estimated with multivariable linear regression.

Results. Patients starting non-TNFi (*vs* TNFi) as first bDMARD had a higher proportion remaining on drug and reaching most response outcomes as first bDMARD (1-year EULAR Good Response/HAQ improvement: TNFi 24.9/25.4%, rituximab 28.6/37.2%, abatacept 31.9/33.7%, tocilizumab 50.9/43.1%). After switch from a first TNFi, rituximab and tocilizumab, but not abatacept, were associated with significantly better response measures than TNFi (1-year EULAR Good Response/HAQ improvement: TNFi 11.6/16.1%, rituximab 24.8/33.2%, abatacept 13.1/17.5%, tocilizumab 34.1/29.4%). Differences remained significant after adjusting for potential confounders.

Conclusion. Treatment outcomes among RA patients treated in Swedish clinical practice are in line with a superior effectiveness of non-TNFi bDMARDs, in particular tocilizumab and rituximab, compared with TNFi.

Key words: rheumatoid arthritis, effectiveness, treatment outcome, biologics, anti-TNF, rituximab, abatacept, tocilizumab

Rheumatology key messages

- In Swedish clinical practice, receiving non-TNFi (*vs* TNFi) biologics predicted better treatment response in RA.
- Observed response was highest for tocilizumab and rituximab, both as first and second biologic.
- Better treatment outcome was found despite channelling of more severe patients to non-TNFi biologics.

Introduction

Recent EULAR and ACR treatment guidelines for RA have expanded the options for first targeted synthetic or biologic DMARD (bDMARD). Besides TNF-inhibitors (TNFi), recommendations now include abatacept, tocilizumab, rituximab and Janus Kinase-inhibitors, ranking them as comparable in overall safety and efficacy [1–4]. Similarly, in the choice of a second bDMARD, following failure of a first, both TNF-inhibition and other modes of action are currently considered viable alternatives, in principle regardless of the reason for discontinuation [2, 3].

[1]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, [2]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Göteborg, [3]Medical Products Agency, Uppsala, [4]Rheumatology, Department of Clinical Sciences, Lund University and [5]Department of Rheumatology, Skåne University Hospital, Malmö, Sweden

Submitted 10 August 2018; accepted 3 December 2018

*See acknowledgements section for a list of the ARTIS Study Group.

Correspondence to: Thomas Frisell, Clinical Epidemiology Division, Eugeniahemmet T2, Karolinska University Hospital, Stokcholm 171 76, Sweden. E-mail: Thomas.Frisell@ki.se

CLINICAL SCIENCE

Although several randomized controlled trials (RCTs) have included head-to-head comparisons of bDMARDs with different modes of action [5–9], they have been limited by small sample sizes, and have targeted narrow treatment situations (e.g. monotherapy, without methotrexate [5]). Thus, current treatment guidelines mostly rely on evidence from cross-RCT meta-analyses, where recent Cochrane reviews found no significant difference in efficacy or safety between the groups of TNFi *vs* non-TNFi bDMARDs, either as first bDMARD [10] or after bDMARD failure [11]. This may, however, reflect the restricted treatment context of RCTs, a lack of power to detect clinically relevant differences, or inability to account for study heterogeneity.

To fill the evidence gaps, several observational studies have compared treatment outcomes in patients with RA treated with specific bDMARDs in clinical practice. Such studies have indicated a better response among patients starting rituximab *vs* TNFi after initial TNFi-failure [12–17], but there is a lack of data on rituximab in first line use. Other studies have reported a greater effect of tocilizumab compared with TNFi both as first bDMARD and after previous TNFi use, when measured with the 28 joint count DAS (DAS28) [18, 19]. It has been suggested that this overestimates the relative effect of tocilizumab, however, because it targets the IL-6 receptor, and DAS28 incorporates the acute phase reactants CRP or ESR, which are under direct influence of IL-6 [20]. Indeed, results have been more inconsistent for response measures that do not incorporate ESR/CRP levels [20–23], and replication studies are needed. Data for abatacept is limited, possibly suggesting a better drug survival than TNFi [24], but similar clinical response after failure of a first TNFi [25]. Comparative effectiveness studies of non-TNFi biologics in RA have often been fairly small, had limited ability to adjust for confounding, and tested a limited set of response measures. Although the clinical reality is a choice between multiple options, most studies, whether observational or randomized, have only compared a single drug pair, and differences in study design and outcome measures make it difficult to extrapolate results across studies.

The objective of this study was therefore to compare treatment outcomes among RA patients treated with any of the available bDMARDs, according to current clinical practice in Sweden during the most recent years. We consider two points of clinical decision-making: first bDMARD initiation and switch to a second bDMARD after failure of an initial TNFi. To extend previous studies, we use a large non-selected sample, all bDMARDs approved for clinical use, and present a range of response measures to avoid bias in favour of any specific drug.

Methods

This cohort study used prospectively collected data on all patients with RA in Sweden who initiated a first or second ever bDMARD therapy during 2010–2016, as recorded in the Swedish Rheumatology Quality register (SRQ) with follow-up data available until 31 January 2018. Covariates and censoring events were added by linking to nationwide Swedish registers. Ethical approval was granted by the Regional Ethical Review Board in Stockholm, waiving the requirement for individual informed consent (DNR: 2016/1986–32).

Data sources

The study database has been described previously [26, 27]. The SRQ is a clinical register with longitudinal data collected at rheumatology visits [28], and an estimated national coverage of bDMARD treatment in RA above 90% [29]. Swedish health care registers provided data on dispensed drugs (the Prescribed Drug Register, coverage virtually complete) [30], all diagnoses recorded in inpatient and non-primary outpatient visits (the Patient Register, positive predictive value 85–95% for diagnoses in inpatient care) [31, 32], and malignancies (the Cancer Register, mandatory registration of morphologically verified malignancies, coverage >95%) [33]. Statistics Sweden's census and taxation registers provided demographic data.

Cohorts

Cohorts were defined by start of therapy between 1 January 2010 and 31 December 2016. Patients were included if they were recorded in the SRQ with a diagnosis of RA and started their first ever bDMARD, and/or if they started a second ever bDMARD within one year of discontinuing a TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) used as first ever bDMARD ('switch from TNFi').

Treatment response

Treatment response was evaluated at 3 months (visit closest to 90 days, between 60 and 183 days) and at 1 year (visit closest to 365, between 275 and 455 days) after treatment initiation. Drug survival was assessed throughout the available follow-up. Because treatment switch is an integral part of the treat-to-target paradigm, restricting the study to those remaining on therapy at 1 year would imply an exclusion of patients responding poorly to their assigned therapy. For this reason, response measures were defined as combined end points: the proportion remaining on therapy *and* with good EULAR response, HAQ improvement >0.2, zero swollen or tender joints (28-joint count) and CDAI remission, defined as CDAI $\leqslant$ 2.8 [13, 34]. Until recently, the SRQ collected physician's global health measure on a 0–4 Likert-type scale instead of the common 0–10 visual analogue scale; these values were multiplied by 2.5 for the CDAI summation.

Date of treatment discontinuation is recorded in the SRQ by the treating rheumatologist. If earlier than a recorded stop, start of another bDMARD was counted as discontinuation. Switch between originator and biosimilar (same compound) was not considered discontinuation. Patients discontinuing therapy due to remission were considered on therapy until the start of another bDMARD. Censoring events were death, emigration from Sweden and discontinuation due to pregnancy.

Covariates

Covariate selection was informed by a parallel study of channelling to therapy [35]. Briefly, a comprehensive list of clinical, sociodemographic and general health covariates were tested as predictors for treatment assignment, and drug survival and treatment response. The previous study suggested limited potential for confounding from the assessed covariates, but variables were included in the present study if they differed significantly between treatments or were significant predictors of response, with further variables added based on expert opinion. Thus multivariate models were adjusted for age, sex, geographical region, year of treatment start, education level, history of serious infection, recent and non-recent malignancy, diabetes, chronic obstructive lung disease, heart failure, stroke, quintile of days hospitalized and total health care costs, baseline use of methotrexate and corticosteroids, disease duration, RF, DAS28, HAQ disability index, visual analogue scale pain and CRP. Continuous covariates were modelled with linear and quadratic terms. Medical history variables were assessed during the five years just before treatment start, except history of serious infections (one year before start) and of non-recent malignancy (more than five years before).

Statistics

Differences in proportions, adjusted for observed baseline differences, were estimated using linear regression models with Huber–White (robust) standard errors [36]. Survival on drug during the first five years was estimated with Kaplan–Meier plots. Multiple imputation for missing outcome and covariate data were performed to ensure that results were not biased by non-random missingness linked to measured variables. Imputation models included each outcome and all other covariates parametrized as in analysis models, and additionally history of acute coronary syndrome, SLE and IBD, as these were identified as predictors of missing response. Imputed datasets ($n = 25$) were constructed using fully conditional specifications in SAS version 9.4 TS1M4.

Sensitivity analyses

To assess the sensitivity to our definition of treatment discontinuation, we also compared the time to starting another bDMARD. To supplement the imputation models, we performed a complete-case analysis (i.e. restricting each analysis to patients with complete data on necessary covariates), and two extreme imputations: assigning all patients lacking return visits in the evaluation window as good, and poor response, respectively. Further, we estimated response at 1 year, regardless of which therapy patients were on at that point (an intention-to-treat like approach). Finally, main analyses were also made using only etanercept as reference, as etanercept has been associated with better drug survival than other TNFi [37].

Results

The study population included 9333 patients with RA starting a first ever bDMARD, and 3941 starting a bDMARD after having used a TNFi as first bDMARD. Receiving one of the TNFis was most common both as first bDMARD (83%) and at switch from a first TNFi (65%), followed by rituximab (10% and 13%) (Table 1). All available TNFis were in use, but etanercept was most common, 36% of all TNFi as first bDMARD and 39% at switch.

Patients starting TNFi compared with non-TNFi were younger, more well educated, had lower disease activity, and had less often had other medical conditions before treatment start. The largest differences in demographic and medical history variables were in comparison with those starting rituximab, who were more often seropositive and had longer disease duration. Abatacept-initiators were more similar to the TNFi-group overall, while tocilizumab-initiators were most extreme in terms of disease activity but more similar to the TNFi-group in demographics and medical history. At switch from TNFi, cohort differences were smaller, but followed the same pattern.

Treatment outcome: first bDMARD

Few patients (<10%) discontinued therapy before 3 months, but by 1 year 30% had discontinued TNFi; significantly more than among the non-TNFi treated (Table 2). Sequential adjustment for potential confounders revealed no major impact of any individual covariate, and the final adjusted difference in proportion remaining on drug was similar to the crude comparison: ~20 percentage points (pp.) higher on rituximab, and ~10 pp. higher on abatacept and tocilizumab, compared with TNFi. Kaplan–Meier curves suggested that rituximab drug survival remained higher throughout the first five years of therapy, while the drug survival of abatacept coincided with that of TNFi after 2 years and tocilizumab had drug survival intermediate to TNFi and rituximab (Fig. 1A). The increased discontinuation of TNFis was mostly due to more treatment stops with recorded reason 'lack of effect' (Fig. 1B–D).

Clinical response was significantly better for tocilizumab compared with TNFi after 12 months, for all outcome measures, although the difference was markedly higher for DAS28-based measures (27–28 pp.) than for HAQ improvement (17 pp.) and CDAI or joint count remission (12 pp.). The difference *vs* TNFi was smaller but similar at 3 months. Differences were less pronounced at 3 months for rituximab and abatacept, but after 1 year, both groups had better EULAR response and HAQ improvement than the TNFi-group, abatacept also had more joint and CDAI remission. The difference *vs* TNFi was similar among patients remaining on each therapy at 1 year, if overall somewhat attenuated, with rituximab significantly higher only in HAQ improvement, and abatacept in DAS28-outcomes and HAQ improvement (Supplementary Table S1, available at *Rheumatology* online).

Table 1 Patient characteristics at start of bDMARD therapy, among all Swedish RA patients, 2010–2016

	As first bDMARD ($n = 9333$)				At switch from TNFi as first bDMARD ($n = 3941$)			
	TNFi[a]	Rituximab	Abatacept	Tocilizumab	TNFi[b]	Rituximab	Abatacept	Tocilizumab
***n* patients**	7702	938	376	317	2548	528	408	457
Start-year, median (IQR)	2013 (2011–2015)	2013 (2011–2015)	2014 (2012–2015)	2014 (2012–2015)	2013 (2011–2015)	2012 (2011–2014)	2014 (2012–2015)	2013 (2011–2015)
Demographics								
Age at treatment start, mean (S.D.), years	55.3 (14.1)	64.9 (12.6)	60.8 (14.1)	58.1 (14.0)	55.1 (14.2)	60.4 (12.4)	59.0 (13.3)	56.6 (13.6)
Female, %	74.3	71.4	73.7	77.9	76.8	73.3	79.4	76.6
Highest education, %								
9 years or less	22.0	32.8	29.6	24.2	21.8	27.8	26.9	26.5
10 years to 12 years	48.3	43.7	48.0	48.4	47.3	48.7	50.2	46.0
>12 years	29.7	23.5	22.4	27.5	30.9	23.5	22.9	27.5
RA clinical characteristics								
RF positive, %	75.1	88.7	77.4	76.0	75.4	90.1	77.1	80.0
Disease duration, mean (S.D.), years	9.4 (10.0)	13.2 (12.7)	10.0 (11.7)	7.7 (10.5)	11.9 (10.4)	14.3 (11.7)	12.8 (11.1)	10.8 (10.3)
HAQ, mean (S.D.)	1.0 (0.6)	1.2 (0.7)	1.1 (0.7)	1.1 (0.6)	1.1 (0.6)	1.2 (0.6)	1.2 (0.7)	1.2 (0.6)
DAS28, mean (S.D.)	4.7 (1.3)	4.8 (1.3)	4.9 (1.3)	5.1 (1.2)	4.4 (1.4)	4.9 (1.2)	4.8 (1.3)	5.0 (1.3)
Tender joints, 0–28, mean (S.D.)	6.9 (5.7)	6.8 (5.9)	6.7 (5.6)	7.6 (5.9)	5.7 (5.3)	6.5 (5.7)	6.3 (5.2)	7.5 (6.2)
Swollen joints, 0–28, mean (S.D.)	6.2 (4.8)	6.4 (4.9)	6.3 (4.8)	6.4 (5.0)	4.7 (4.6)	5.7 (5.0)	4.9 (4.0)	6.4 (5.1)
Patient global health, mean (S.D.)	54.3 (24.9)	54.1 (24.7)	55.9 (23.9)	56.9 (23.4)	54.0 (25.2)	57.7 (24.9)	58.8 (23.8)	59.1 (24.8)
ESR, mean (S.D.)	24.4 (20.5)	31.1 (22.4)	29.6 (22.9)	32.3 (25.6)	24.8 (21.7)	34.0 (24.7)	28.9 (22.1)	33.0 (25.1)
CRP, mean (S.D.)	15.8 (21.5)	19.0 (22.7)	19.8 (25.5)	22.0 (26.5)	14.5 (22.1)	20.9 (25.0)	17.0 (23.0)	22.9 (28.2)
VAS pain, mean (S.D.)	54.8 (24.8)	53.5 (25.0)	56.7 (24.6)	57.7 (24.4)	53.9 (25.6)	56.7 (25.7)	57.9 (24.0)	59.9 (24.8)
Conc. use of MTX, %	69.9	54.5	54.5	49.0	61.7	63.5	65.5	54.3
Conc. use of non-MTX csDMARD, %	19.0	26.4	20.0	11.9	13.0	13.7	9.6	8.1
Conc. use of oral steroids, %	48.6	59.2	50.3	41.3	45.0	56.0	56.2	51.0
Medical history at treatment start[c]								
Serious infection, %	2.1	6.2	7.4	2.5	3.1	7.6	7.1	4.2
Malignancy, recent, %	1.6	9.9	2.9	3.8	1.6	5.9	2.5	2.4
Malignancy, non-recent, %	3.3	12.2	7.2	4.4	3.1	4.4	3.7	3.1
COPD, %	2.6	15.6	13.6	6.0	3.1	6.8	4.7	3.5
Diabetes mellitus, %	6.1	11.2	11.2	4.7	6.7	9.5	8.8	7.4
Stroke, %	0.9	2.6	2.1	1.3	1.2	2.1	1.5	1.1
Heart failure, %	1.1	6.6	6.4	3.8	0.9	1.9	4.7	2.4
Days hospitalized, mean (S.D.)	5.6 (16.2)	16.2 (49.0)	14.0 (32.1)	7.2 (16.0)	7.0 (15.8)	11.7 (21.9)	8.5 (18.2)	8.9 (18.4)
Health care costs, TSEK, mean (S.D.)	121.9 (134.3)	225.0 (239.0)	230.6 (554.5)	133.4 (136.1)	315.4 (256.1)	371.9 (273.9)	360.2 (273.3)	333.0 (268.2)

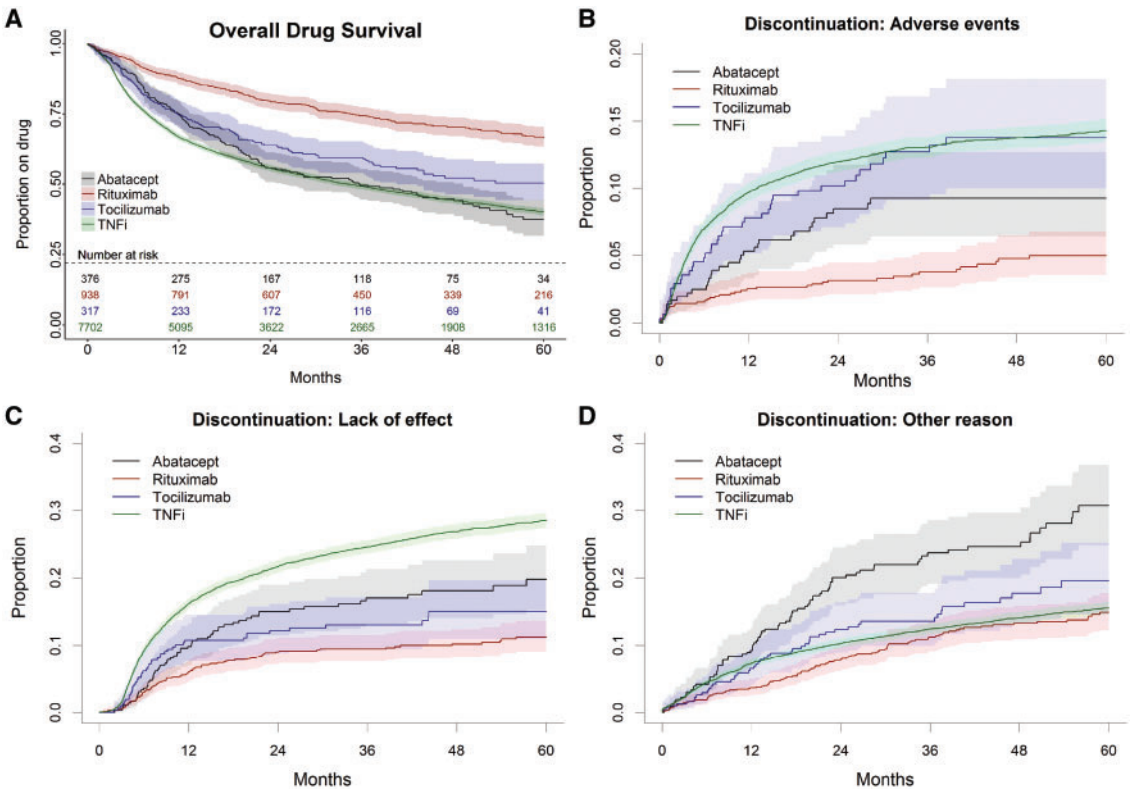
[a]Composed of etanercept (36%), infliximab (24%), adalimumab (16%), certolizumab pegol (14%), golimumab (11%). [b]Composed of etanercept (39%), infliximab (7%), adalimumab (26%), certolizumab pegol (12%), golimumab (17%). [c]Medical history in five years before treatment start, except serious infection (one year before start) and non-recent malignancy (more than five years before). bDMARD: biologic DMARD; csDMARD: conventional syntehtic DMARD; TNFi: TNF-inhibitors; VAS: visual analogue scale; COPD: chronic obstructive lung disease; DAS28: 28 joint count DAS; IQR: Interquartile range; TSEK: thousand SEK.

Table 2 Treatment outcome among Swedish RA patients starting a first ever bDMARD 2010–2016

	TNFi	RTX	Diff. *vs* TNFi (95% CI)	ABA	Diff. *vs* TNFi (95% CI)	TCZ	Diff. *vs* TNFi (95% CI)
***n* patients**	7702	938		376		317	
At 3 months							
Proportion still on therapy…	92.1	96.7	6.3 (4.7, 7.9)	94.4	3.9 (1.4, 6.4)	93.4	2.9 (0.0, 5.7)
and EULAR Good Response	37.8	30.1	−1.3 (−6.6, 3.9)	35.6	2.7 (−3.9, 9.3)	65.1	29.5 (23.5, 35.5)
and DAS28 $<$ 2.6	36.0	26.4	−2.4 (−6.6, 1.8)	27.9	−1.2 (−7.0, 4.6)	57.7	28.9 (22.9, 34.8)
and ΔHAQ $<$ -0.2	46.1	44.3	2.6 (−2.7, 7.8)	51.2	6.8 (0.7, 12.9)	60.0	10.8 (4.2, 17.3)
and joint count remission	25.4	21.7	−3.1 (−6.8, 0.6)	19.8	−4.3 (−9.4, 0.8)	30.6	7.3 (1.3, 13.2)
and CDAI $\leqslant$ 2.8	17.6	11.0	−4.9 (−8.0, −1.8)	14.2	−0.9 (−5.3, 3.5)	23.5	7.9 (2.7, 13.0)
At 1 year							
Proportion still on therapy…	69.4	88.3	21.8 (19.1, 24.5)	75.9	9.7 (5.2, 14.2)	76.2	9.7 (4.8, 14.7)
and EULAR Good Response	24.9	28.6	9.8 (5.2, 14.4)	31.9	12.2 (5.1, 19.2)	50.9	27.4 (20.4, 34.3)
and DAS28 $<$ 2.6	25.0	23.1	5.0 (1.2, 8.8)	27.7	9.0 (3.3, 14.8)	48.7	28.0 (21.3, 34.6)
and ΔHAQ $<$ -0.2	25.4	37.2	16.9 (12.5, 21.2)	33.7	12.5 (6.9, 18.1)	43.1	16.6 (9.9, 23.2)
and joint count remission	20.7	22.4	3.6 (−0.0, 7.2)	23.3	5.1 (0.1, 10.2)	31.5	12.3 (6.7, 18.0)
and CDAI $\leqslant$ 2.8	13.9	12.8	1.6 (−1.6, 4.9)	17.0	5.8 (0.9, 10.7)	24.8	11.8 (6.8, 16.8)

Mean differences are compared with TNFi, in multivariable linear regression adjusted for age, sex, year of treatment start, geographical region, education level, history of serious infection, malignancy, COPD, diabetes, stroke, heart failure, total days in hospital and health care costs past five years, baseline use of csDMARDs and corticosteroids, RF, DAS28, HAQ, VAS pain and CRP. Confidence intervals are based on robust (Huber–White) standard errors. bDMARD: biologic DMARD; TNFi: TNF-inhibitors; RTX: rituximab; ABA: abatacept; TCZ: tocilizumab; VAS: visual analogue scale; COPD: chronic obstructive lung disease; DAS28: 28 joint count DAS.

Fig. 1 Five year drug survival on first bDMARD in RA



Overall proportion remaining on drug (**A**), and cumulative proportion discontinuing for specific reasons (**B**–**D**), among Swedish patients with RA initiating treatment during 2010 to 2016. Shaded regions are 95% confidence intervals. bDMARD: biologic DMARD.

Table 3 Treatment outcome among Swedish RA patients starting a bDMARD after initial TNFi 2010–2016

	TNFi	RTX	Diff. *vs* TNFi (95% CI)	ABA	Diff. *vs* TNFi (95% CI)	TCZ	Diff. *vs* TNFi (95% CI)
***n* patients**	2548	528		408		457	
At 3 months							
Proportion still on therapy…	85.2	93.2	8.4 (5.7, 11.1)	90.7	5.7 (2.5, 9.0)	91.2	7.2 (4.1, 10.2)
and EULAR Good Response	18.3	20.6	0.9 (–4.4, 6.2)	14.2	–3.5 (–8.1, 1.1)	51.1	32.4 (26.7, 38.1)
and DAS28 <2.6	22.0	15.2	–1.5 (–6.3, 3.2)	17.3	0.4 (–4.4, 5.3)	43.3	26.5 (21.3, 31.7)
and ΔHAQ <–0.2	29.0	40.4	8.3 (2.7, 13.9)	28.8	–1.9 (–7.8, 4.1)	39.4	5.9 (–0.2, 12.1)
and joint count remission	19.2	17.2	0.1 (–4.3, 4.6)	14.6	–1.9 (–6.5, 2.6)	18.8	3.3 (–1.3, 7.8)
and CDAI ⩽ 2.8	10.5	8.0	–0.7 (–4.2, 2.8)	7.6	–0.5 (–4.6, 3.5)	10.7	2.4 (–1.4, 6.1)
At 1 year							
Proportion still on therapy…	59.2	80.5	21.7 (17.6, 25.8)	65.4	6.6 (1.5, 11.8)	70.3	13.0 (8.3, 17.8)
and EULAR Good Response	11.6	24.8	12.3 (7.4, 17.3)	13.1	2.0 (-2.3, 6.3)	34.1	21.7 (16.6, 26.9)
and DAS28 < 2.6	14.6	20.4	10.4 (6.0, 14.8)	9.7	–1.9 (–5.6, 1.9)	31.3	20.0 (14.4, 25.6)
and ΔHAQ < -0.2	16.1	33.2	15.0 (9.4, 20.7)	17.5	0.8 (–4.8, 6.3)	29.4	10.4 (5.4, 15.3)
and joint count remission	13.6	23.3	11.2 (7.0, 15.5)	13.1	0.6 (–3.7, 5.0)	20.3	9.0 (4.2, 13.8)
and CDAI ⩽ 2.8	7.3	11.2	5.2 (2.0, 8.5)	5.7	–0.9 (–4.0, 2.1)	13.0	6.9 (2.9, 10.9)

Mean differences are compared with TNFi, in multivariable linear regression adjusted for age, sex, year of treatment start, geographical region, education level, history of serious infection, malignancy, COPD, diabetes, stroke, heart failure, total days in hospital and health care costs past five years, baseline use of csDMARDs and corticosteroids, RF, DAS28, HAQ, VAS pain and CRP. Confidence intervals are based on robust (Huber–White) standard errors. bDMARD: biologic DMARD; TNFi: TNF-inhibitors; VAS: visual analogue scale; COPD: chronic obstructive lung disease; DAS28: 28 joint count DAS.

Treatment outcome: switch from TNFi

Table 3 and Fig. 2 summarize treatment outcomes of bDMARDs started after a first TNFi. Compared with when used as first bDMARD, the drug survival was lower for each drug, but the inter-drug differences were similar, with TNFi having lowest drug survival followed by abatacept, tocilizumab and highest drug survival for rituximab. The difference in overall drug survival between abatacept and TNFi seemed more consistent after switch from TNFi, while recorded stop due to lack of effect was now very similar between the two groups, and TNFi had a higher rate of discontinuations due to adverse events (Figs 1 and 2).

Clinical response was overall lower for each drug compared with when used as first bDMARD. Differences between rituximab and TNFi were greater than as first bDMARD, and all reached statistical significance at 1 year, but only HAQ improvement (favoring rituximab) after 3 months. Abatacept was similar to TNFi at both time points. Tocilizumab had the highest proportions with DAS28-based response measures, and similar rate of HAQ improvement, joint count and CDAI remission as rituximab; all differences to TNFi were significant except joint count remission at 3 months. The difference was not driven solely by their higher drug survival, response was also better among patients remaining on rituximab or tocilizumab *vs* TNFi after 1 year (Supplementary Table S1, available at *Rheumatology* online).

Missing data

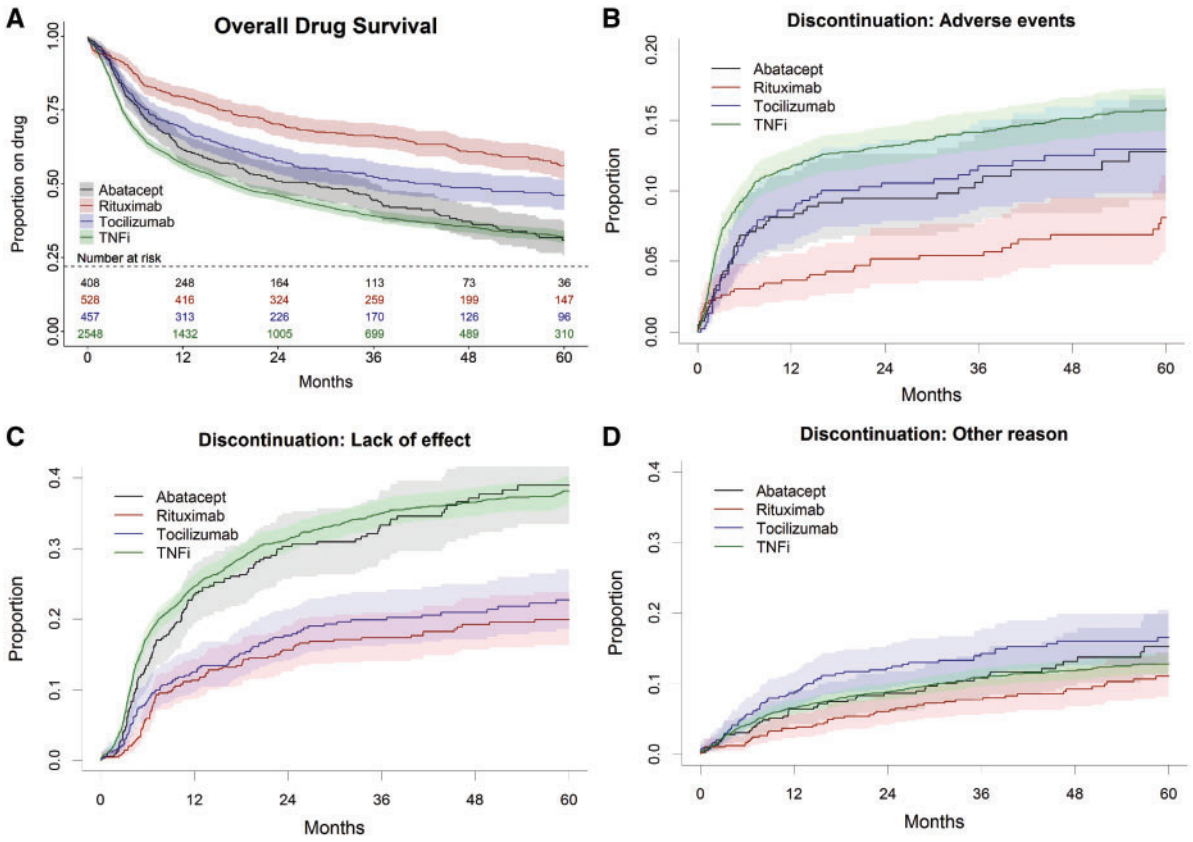
Covariate data was virtually complete for demographic and medical variables derived from national registers, and for treatment discontinuation dates, but a proportion of patients lacked data on clinical response. Missingness at the baseline visit ranged from 5% for joint counts to 16% for DAS28, while 13% of patients lacked a valid baseline visit, and 39% lacked a recorded visit in the 1-year evaluation time window. The latter missingness reflects clinical practice, where timing of return visits vary greatly.

Our main analyses were based on multiple imputation, to increase statistical power and reduce potential bias from restricting the study to patients with valid data. Complete-case analysis (i.e. analysis excluding subjects missing relevant covariate data) resulted in lower precision but very similar results (Supplementary Table S1, available at *Rheumatology* online). Extreme imputation, coding patients without valid return visits as ‘good’ or ‘poor’ response, expectedly led to unrealistically high, and low, respectively, proportions with response (Supplementary Table S2, available at *Rheumatology* online), but had limited influence on the comparison across groups. The only noteworthy change was when coding absence of visits as ‘good response’, which removed all significant differences between abatacept and TNFi as first bDMARD.

Sensitivity analyses

Kaplain–Meier curves of time to start of another bDMARD (instead of time to treatment discontinuation) gave the same pattern across drugs (Supplementary Fig. S5, available at *Rheumatology* online). In intention-to-treat like analysis, comparing clinical outcomes regardless of whether patients remained on original therapy after 1 year, all differences between treatment groups were,

FIG. 2 Five year drug survival on bDMARD after a first TNFi in RA



Overall proportion remaining on drug (**A**), and cumulative proportion discontinuing for specific reasons (**B**–**D**), among Swedish patients with RA initiating treatment during 2010 to 2016. Shaded regions are 95% confidence intervals. bDMARD: biologic DMARD; TNFi: TNF-inhibitors.

as expected, smaller (Supplementary Table S3, available at *Rheumatology* online). The only significant differences favoured tocilizumab over TNFi as first bDMARD for all measures, and regarding DAS28-based measures and CDAI remission after switch from TNFi, and favoured TNFi over abatacept after switch from TNFi.

Patients starting etanercept had better response than the combined TNFi-group, but comparing the non-TNFi treated to etanercept instead of TNFi yielded very similar differences (Supplementary Table S4, available at *Rheumatology* online).

Discussion

We compared all Swedish patients with RA who in clinical practice, 2010–2016, started different bDMARDs and found that the treatment response appeared better for patients starting a non-TNFi compared with TNFi as first bDMARD. This was observed despite a channelling of older and frailer patients to non-TNFi bDMARDs, which might be expected to give residual confounding biasing the results against the same drugs. After switch from a first TNFi, rituximab and tocilizumab, but not abatacept, were consistently associated with significantly better drug survival and response. Differences between treatments were in general smaller at 3 months than at 1 year. Although 3 months is a common clinical check point to evaluate initial response, it may be too early to evaluate the difference between these therapies where e.g. rituximab initiation may be delayed due to scheduling of infusions and the time until reaching full efficacy may differ between drugs.

Our findings are largely in line with previous research, although there are also several inconsistencies. Cochrane reviews of RCTs conclude no significant difference in efficacy or safety between (the groups) TNFi and non-TNFi bDMARDs [10, 11], but divergent results have been reported in meta-analyses focussing on individual drugs. One report (commissioned by Roche) found that tocilizumab was associated with better efficacy compared with abatacept, rituximab and TNFi [38], another reported no significant differences between bDMARDs in combination with methotrexate as first bDMARD, although in monotherapy, tocilizumab outperformed TNFi [39]. The power to detect differences may be low in network

meta-analyses, however, and they are susceptible to bias from heterogeneity in, e.g. inclusion criteria and outcome definition of the trials included [40]. One of few direct head-to-head RCTs did find greater effect on DAS28-based response measures for the group of non-TNFi *vs* a second TNFi after TNFi-failure, but was not designed to separately analyse the individual drugs [9]. The same report did not find a significant difference in HAQ, however, and tocilizumab, with a known effect on ESR/CRP values, made up 48% of their non-TNFi-group, which might raise some concerns about the implication of this finding, although the authors noted that the difference in DAS28 was not constrained only to acute phase reactants [9].

Considering the individual non-TNFi drugs, a recent open-label RCT found rituximab non-inferior to TNFi as first bDMARD, measured as DAS28-improvement among patients remaining on therapy after 1 year [8]. While not the primary end point, they also found fewer patients discontinuing rituximab than TNFi, with proportions remaining on drug after 12 months very similar to our real-world sample, 68% for TNFi and 81% for rituximab. A small RCT from the Netherlands reported similar efficacy, but superior cost-effectiveness, for rituximab compared with abatacept and TNFi, but with three treatment arms and only a total 139 patients entering the analysis, power was low to detect clinically relevant differences in effect [7]. Observational studies after initial TNFi-failure have supported better response on rituximab *vs* a second TNFi, with a range of measures including DAS28, HAQ and CDAI [12–17]. While replicating these previous findings in a large, independent sample, our data further suggest a better response to rituximab than TNFi when used as first bDMARD, which was not studied in previous observational studies. We also note that this difference was not only in drug survival. At least at switch from a first TNFi, the patients remaining on therapy at 1 year had better response measures in the rituximab *vs* the TNFi-group. We find this noteworthy as we might have expected a tendency to keep patients on rituximab despite a less than ideal response, but this data suggests that this would only be a partial explanation for the differences between TNFi and rituximab.

We found similar response to abatacept and TNFi after an initial TNFi, but superior response when used as first bDMARD, driven by a higher drug survival. We are only aware of a few previous studies on the topic, but they also reported better drug survival for abatacept *vs* TNFi [24, 25], and the study from the CORRONA register found no significant difference in clinical response in abatacept *vs* TNFi after TNFi-failure [25]. The AMPLE RCT found no difference between abatacept and adalimumab among methotrexate non-responders [6]. Higher drug survival despite similar effectiveness would imply a difference in other reasons for switching. We saw a lower proportion stopping abatacept due to adverse events, which may deserve further investigation.

The bDMARD associated with highest overall response in our data was tocilizumab. The ADACTA RCT demonstrated superior efficacy of tocilizumab over the TNFi adalimumab, but only studied use as monotherapy (i.e. no concomitant conventional synthetic DMARD) [5]. Observational studies have reported superior effect of tocilizumab (*vs* TNFi) on DAS28-based response measures, also in combination therapy with conventional synthetic DMARDs [18, 23, 41]. Tocilizumab targets the IL-6 receptor, however, with a central role in regulating CRP/ESR levels, and in line with previous studies [20–22], we found a much weaker effect on non-DAS28-based response measures. Interestingly, our results did clearly favour tocilizumab over TNFi also with alternative response measures, which is in line with two previous studies assessing CDAI change at three and six months [18, 22]. In contrast, a study from the BSRBR found no significant 6-month difference in HAQ improvement [20], but their sample started at higher disability, and used intention-to-treat analysis, which may have attenuated any differences. A recent report found better drug survival for tocilizumab compared with TNFi, but equal CDAI low disease activity and remission on tocilizumab and TNFi at 1 year. The comparison between CDAI-based response proportions was not adjusted for any covariates or patient characteristics, however, despite substantial channelling where the patients starting tocilizumab also had higher CDAI at baseline [21], which seems likely to bias this comparison against tocilizumab. The same study did adjust for baseline differences while modelling the continuous change in CDAI over time, again finding no significant difference between treatment groups, but this analysis was constrained to patients remaining on therapy, and might thus miss patients stopping therapy due to lack of effect. These studies thus have limitations that might lead to underestimations of a true effect difference, but it is uncertain if this is to an extent necessary to explain the difference across studies. The potentially greater clinical response to tocilizumab remains contentious, but our well-powered analysis, able to measure and adjust for a substantial channelling to therapy, adds to the growing evidence that drug survival is higher on tocilizumab than on TNFi [20, 21, 24, 41].

Our study has several strengths and limitations linked to the data available through nationwide registers. Through these, we were able to obtain patients' medical history and other covariates using data prospectively collected independently of bDMARD treatment. The SRQ has a high coverage of bDMARD-treated RA in the Swedish population, avoiding the risk of selection bias [29]. Health care is publicly funded, and Swedish rheumatologists, in dialogue with the patient, are free to prescribe the treatment they expect will benefit the patient the most, lowering the risk for differential placebo/nocebo effects.

TNFi remains the most common choice for a first and second bDMARD in RA, however, and the relatively small proportion treated with non-TNFi bDMARDs underline the potential for confounding bias, where factors related to treatment assignment may also be associated with treatment outcome. Although we have previously reported that factors related to treatment choice were only weak predictors of EULAR response and drug survival in this population [35], we adjusted for all identified

moderate-to-strong predictors of treatment choice, and all identified predictors of EULAR response and drug survival. The risk of confounding from unmeasured factors, including lifestyle factors, BMI and smoking, remains a limitation.

A further limitation relates to rituximab, as this drug is administered through infusions with long time intervals. Our main source of information on treatment discontinuation was the physician's recorded decision to stop treatment, and it is possible that this was interpreted differently for rituximab *vs* the other drugs, or only updated at scheduled infusions. We note however, that the rituximab also had the longest time until start of a next bDMARD, which should not be subject to the same bias.

Finally, the SRQ captures data from visits according to clinical practice, not according to a pre-defined study/trial protocol. Therefore, there is substantial variation in the timing and intensity of return visits after a given treatment start. This led to high proportions without outcome data, as they simply had not been to a rheumatologist within the pre-specified time window, and we employed several sensitivity analyses to test different assumptions about this missingness. Although our main findings seemed robust to the missingness, it is not possible to fully evaluate this, and if for instance the lack of an evaluation visit implies poor response in one group, but good response in another, this would bias the comparison.

In conclusion, the treatment outcomes observed among RA patients treated in Swedish clinical practice suggest an equal, or even superior, effectiveness of non-TNFi bDMARDs compared with TNFi. This should be weighed against other existing evidence on their relative effectiveness and, not analysed in this study, evidence on the safety and cost-effectiveness of individual bDMARDs.

Acknowledgements

The ARTIS Study Group is a scientific advisory group nominated by the Swedish Society of Rheumatology that oversees studies on bDMARDs in rheumatology. The following were members of the ARTIS Study Group during the completion of this study: J.A., Sofia Ernestam, Lars Klareskog, Ralph Nisell (Karolinska Institutet, Stockholm, Sweden), N.F. (Medical Products Agency, Uppsala, Sweden), Eva Baecklund (Uppsala University, Uppsala, Sweden), Alf Kastbom (Linköping University, Linköping, Sweden), Lennart Jacobsson (Sahlgrenska Academy, Göteborg, Sweden), C.T. and Elisabet Lindqvist (Lund University, Malmö/Lund, Sweden), Helena Forsblad d'Elia and Solbritt Rantapää-Dahlqvist (Umeå University, Umeå, Sweden). T.F. had full access to all data and takes responsibility for the integrity of the data and the accuracy of the data analysis. T.F. performed all analyses and drafted the first version of the manuscript. All authors were involved in drafting the study protocol before analyses, reviewed the manuscript for important intellectual content, and approved the final version to be published. The views in this paper are those of the authors and not representative of the Medical Products Agency at which one of the authors (N.F.) is employed.

Funding: This work was supported by the Swedish Foundation for Strategic Research, Swedish Research Council (DNR 2016–01355), Swedish Cancer Society, Swedish Heart-Lung Foundation, ALF funding collaboration between Karolinska Institute and Stockholm County, and the IMI-funded EU project BeTheCure.

Disclosure statement: The work was supported by agreements between Karolinska Institutet and Abbvie, BMS, MSD, Eli Lilly, Pfizer, Roche, Samsung Bioepis and UCB, mainly regarding the safety monitoring of bDMARDs in rheumatology. Companies with products mentioned in this manuscript were given a courtesy review of the manuscript before publication, but were not involved in planning the study, performing the analysis, or interpreting the results. C.T. has received research grants or consulting fees from Bristol Myers-Squibb and Roche, and speaker fees from Abbvie, Bristol-Myers Squibb, Janssen, MSD, Pfizer, Roche and UCB. Karolinska Institutet has received remuneration for J.A. participating in ad boards arranged by Lilly, Novartis and Pfizer.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Singh JA, Furst DE, Bharat A *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625–39.

2 Singh JA, Saag KG, Bridges SL Jr *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1–26.

3 Smolen JS, Landewe R, Bijlsma J *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

4 Smolen JS, Landewe R, Breedveld FC *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964–75.

5 Gabay C, Emery P, van Vollenhoven R *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541–50.

6 Schiff M, Weinblatt ME, Valente R *et al*. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis 2014;73:86–94.

7 Manders SH, Kievit W, Adang E *et al*. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. Arthritis Res Ther 2015;17:134.

8 Porter D, van Melckebeke J, Dale J *et al*. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet 2016;388:239–47.

9 Gottenberg JE, Brocq O, Perdriger A *et al*. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug. A randomized clinical trial. JAMA 2016;316:1172–80.

10 Singh JA, Hossain A, Tanjong Ghogomu E *et al*. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. Cochrane Database Syst Rev 2016;5:CD012183.

11 Singh JA, Hossain A, Tanjong Ghogomu E *et al*. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. Cochrane Database Syst Rev 2017;3:CD012591.

12 Finckh A, Ciurea A, Brulhart L *et al*. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56:1417–23.

13 Kekow J, Mueller-Ladner U, Schulze-Koops H. Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNFalpha blocker failure. Biologics 2012;6:191–9.

14 Soliman MM, Hyrich KL, Lunt M *et al*. Rituximab or a second anti-tumor necrosis factor therapy for rheumatoid arthritis patients who have failed their first anti-tumor necrosis factor therapy? Comparative analysis from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken) 2012;64:1108–15.

15 Emery P, Gottenberg JE, Rubbert-Roth A *et al*. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: sWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis 2015;74:979–84.

16 Harrold LR, Reed GW, Magner R *et al*. Comparative effectiveness and safety of rituximab versus subsequent anti-tumor necrosis factor therapy in patients with rheumatoid arthritis with prior exposure to anti-tumor necrosis factor therapies in the United States Corrona registry. Arthritis Res Ther 2015;17:256.

17 Gomez-Reino JJ, Maneiro JR, Ruiz J *et al*. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. Ann Rheum Dis 2012;71:1861–4.

18 Backhaus M, Kaufmann J, Richter C *et al*. Comparison of tocilizumab and tumour necrosis factor inhibitors in rheumatoid arthritis: a retrospective analysis of 1603 patients managed in routine clinical practice. Clin Rheumatol 2015;34:673–81.

19 Iannone F, Ferraccioli G, Sinigaglia L *et al*. Real-world experience of tocilizumab in rheumatoid arthritis: subanalysis of data from the Italian biologics' register GISEA. Clin Rheumatol 2018;37:315–21.

20 Kihara M, Davies R, Kearsley-Fleet L *et al*. Use and effectiveness of tocilizumab among patients with rheumatoid arthritis: an observational study from the British Society for Rheumatology Biologics Register for rheumatoid arthritis. Clin Rheumatol 2017;36:241–50.

21 Lauper K, Nordstrom DC, Pavelka K *et al*. Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheumatic drug: analyses from the pan-European TOCERRA register collaboration. Ann Rheum Dis 2018;77:1276–82.

22 Romao VC, Santos MJ, Polido-Pereira J *et al*. Comparative effectiveness of tocilizumab and TNF inhibitors in rheumatoid arthritis patients: data from the rheumatic diseases portuguese register, Reuma.pt. Biomed Res Int 2015;2015:279890.

23 Yoshida K, Tokuda Y, Oshikawa H *et al*. An observational study of tocilizumab and TNF-alpha inhibitor use in a Japanese community hospital: different remission rates, similar drug survival and safety. Rheumatology 2011;50:2093–9.

24 Jones G, Hall S, Bird P *et al*. A retrospective review of the persistence on bDMARDs prescribed for the treatment of rheumatoid arthritis in the Australian population. Int J Rheum Dis 2018;21:1581–90.

25 Harrold LR, Reed GW, Kremer JM *et al*. The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor. Ann Rheum Dis 2015;74:430–6.

26 Askling J, Fored CM, Geborek P *et al*. Swedish registers to examine drug safety and clinical issues in RA. Ann Rheum Dis 2006;65:707–12.

27 Frisell T, Holmqvist M, Kallberg H *et al*. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. Arthritis Rheum 2013;65:2773–82.

28 Eriksson JK, Askling J, Arkema EV. The Swedish Rheumatology Quality Register: optimisation of rheumatic disease assessments using register-enriched data. Clin Exp Rheumatol 2014;32(5 Suppl 85):S-147–9.

29 Wadstrom H, Eriksson J, Neovius M, Askling J, on behalf of The Artis Study Group. How good is the coverage and how accurate are exposure data in the Swedish Biologics Register (ARTIS)? Scand J Rheumatol 2015;44:22–8.

30 Wettermark B, Hammar N, Fored CM *et al*. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726–35.

31 Socialstyrelsen. Inpatient diseases in Sweden 1987–2008. Stockholm, 2008 (in Swedish). https://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/17782/2009-10-114.pdf.

32 Ludvigsson JF, Andersson E, Ekbom A *et al*. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.

33 Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;48:27–33.

34 Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum 2006;54:600–6.

35 Frisell T, Baecklund E, Bengtsson K *et al*. Patient characteristics influence the choice of biological drug in RA, and will make non-TNFi biologics appear more harmful than TNFi biologics. Ann Rheum Dis 2018;77:650–7.

36 Cheung YB. A modified least-squares regression approach to the estimation of risk difference. Am J Epidemiol 2007;166:1337–44.

37 Neovius M, Arkema EV, Olsson H *et al*. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2015;74:354–60.

38 Bergman GJD, Hochberg MC, Boers M *et al*. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum 2010;39:425–41.

39 Buckley F, Finckh A, Huizinga TW, Dejonckheere F, Jansen JP. Comparative efficacy of novel DMARDs as monotherapy and in combination with methotrexate in rheumatoid arthritis patients with inadequate response to conventional DMARDs: a network meta-analysis. J Manag Care Spec Pharm 2015;21:409–23.

40 Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med 2011;9:79.

41 Iannone F, Ferraccioli G, Sinigaglia L *et al*. Real-world experience of tocilizumab in rheumatoid arthritis: subanalysis of data from the Italian biologics' register GISEA. Clin Rheumatol 2018;37:315–21.