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Safety of biological and targeted synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis as used in clinical practice: results from the ARTIS programme

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ABSTRACT

Objective Longitudinal clinical registry-infrastructures such as Anti-Rheumatic Therapies in Sweden (ARTIS) allow simultaneous comparison of the safety of individual immunomodulatory drugs used in clinical practice, with consistent definitions of treatment cohorts, follow-up and outcomes. Our objective was to assess and compare incidence rates of key safety outcomes for individual targeted synthetic or biological disease-modifying antirheumatic drugs (b/ts DMARDs) in rheumatoid arthritis (RA), updating previous reports and including newer treatments including Janus Kinase inhibitors (JAKi).

Methods Nationwide register-based cohort study including all patients with RA in Sweden registered as starting any b/tsDMARD 1 January 2010 through 31 December 2020, followed until 30 June 2021 (N=20 117). The incidence rates of selected outcomes, identified through national healthcare registers, were compared between individual b/tsDMARDs, adjusted for confounding by demographics, RA disease characteristics and comorbidity.

Results There were marked differences in treatment discontinuations due to adverse events (rates per 1000 person-years ranged from 18 on rituximab to 57 on tofacitinib), but few significant differences were observed for the serious adverse events under study. Neither cardiovascular events nor general serious infections were more frequent on baricitinib or tofacitinib versus bDMARDs, but JAKi were associated with higher rates of hospital-treated herpes zoster (HR vs etanercept, 3.82 (95% CI 2.05 to 7.09) and 4.00 (1.59 to 10.06)). Low number of events limited some comparisons, in particular for sarilumab and tofacitinib.

Conclusion Data from ARTIS supports that the b/tsDMARDs currently used to treat RA have acceptable and largely similar safety profiles, but differences exist in particular concerning tolerability and specific infection risks.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ By enabling structured follow-up of large cohorts of patients representative of those treated in clinical practice, postapproval analyses of real-world data play a critical role in the evaluation of the safety, and of the relative safety, of antirheumatic drugs.

⇒ Anti-Rheumatic Therapies in Sweden (ARTIS) is a long-standing register-based drug evaluation framework, enabling the simultaneous comparison of the safety profiles of individual targeted synthetic or biological disease-modifying antirheumatic drug (b/tsDMARD) used in clinical practice against rheumatoid arthritis (RA), with consistent cohort definitions, follow-up and data capture across drugs.

WHAT THIS STUDY ADDS

⇒ We present incidence rates and relative risks of 10 key safety outcomes for individual b/tsDMARDs used to treat RA over the last decade, updating previous reports and extending analyses to newer treatments.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results support that the currently available b/tsDMARDs have acceptable and on the whole similar safety profiles in a real-world population, with some differences concerning tolerability, specific infection risks and certain serious but rare outcomes.

⇒ ARTIS and similar register-based safety monitoring programmes can provide comparative safety data across all treatment options used in clinical practice, which is instrumental for the postmarketing safety evaluation of recent as well as established immunomodulatory drugs in rheumatology.

INTRODUCTION

Over a dozen approved targeted synthetic or biological disease-modifying antirheumatic drugs (b/tsDMARDs) are available for the treatment of rheumatoid arthritis (RA).[1] The choice between these drugs should ideally be based on the risk-benefit balance of each drug versus the others for the individual patient.

In practice, the evidence that informs this choice is, even on a population level, limited.[1–3] While superior/non-inferior efficacy of one treatment over another can be demonstrated in relatively small studies with limited follow-up, many safety concerns require larger studies and longer follow-up times for differences to become clear, even when the induction time for a given safety event itself is not an issue. This is recognised by the regulatory framework where data from pivotal randomised controlled trials (RCTs) are usually considered sufficient for demonstrating the efficacy and non-toxicity of the drug, but postapproval safety studies (PASS) are required for several years to evaluate drug-associated risks.[4]

Much of what we currently know about risks associated with individual b/tsDMARDs thus come from observational studies comparing rates of adverse events among patients treated with different drugs in clinical practice.[2] Since—in clinical practice—the choice is neither between one drug versus all others nor between one class versus another class, but always between all individual available treatment options, it is unfortunate that many research studies, and certainly the vast majority of all PASS studies, are designed to compare a single drug to all other drugs grouped together or limited to just one or two specific alternative options.[5] Comparison of results across studies are then necessary to draw conclusions about the available options' relative safety vs each other. Such between-study comparisons and extrapolations are, however, inherently difficult since both target populations and outcome rates may differ substantially by cohort inclusion and exclusion criteria, variable definitions, method of data capture and also by analytical approach.[6] Therefore, whereas analytic methods may effectively accommodate confounding by indication *within* a study, it is far from evident that such methods guarantee comparability *across* studies.

Long-standing drug registers covering all individual treatment options for a disease, such as the Anti-Rheumatic Therapies in Sweden (ARTIS),[7] allowing the simultaneous comparison of each drug available for use in clinical practice, with consistent definitions of treatment cohorts, follow-up and outcome capture, have a critical role in the evaluation of the relative safety of b/tsDMARDs to inform individual risk-benefit assessment.

To enable the clinically much-needed direct comparisons across all available b/tsDMARDs approved for RA, we therefore investigated absolute and relative rates of key safety outcomes for all individual b/tsDMARDs available for the treatment of RA.

METHODS

This nationwide register-based cohort study included all patients with RA in Sweden who were recorded as starting any b/tsDMARD between 1 January 2010 and 31 December 2020, and followed them until 30 June 2021 to compare the incidence of selected outcomes between individual treatments while adjusting for a range of potential confounders.

Data sources

The ARTIS safety monitoring programme is described in online supplemental file 1 and is constructed by linking individual-level longitudinal data on treatments, disease activity and other clinical measurements from the Swedish Rheumatology Quality Register (SRQ),[7] covering around 90% of all b/tsDMARD initiations in Sweden,[8] to prospectively collected data in Swedish national healthcare registers.[9] This includes data on diagnoses recorded in inpatient and outpatient specialist care from the National Patient Register, all filled prescriptions in community pharmacies from the Prescribed Drug Register and demographics and migration dates from census/taxation registers.

Treatment exposure

All approved b/tsDMARDs used for RA in Sweden during the study period were included: antitumour necrosis factor (TNFi) bDMARDs: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab; other bDMARDS: abatacept, anakinra, rituximab, sarilumab, tocilizumab and the Janus Kinase inhibitors (JAKi) tsDMARDs: baricitinib, tofacitinib and upadacitinib. Drugs with fewer than 200 treatment episodes (here: anakinra (n=84) and upadacitinib (n=105)) were excluded from further analysis. Patients were considered exposed to a treatment from their first ever start of that specific b/tsDMARD, as recorded in the SRQ, until treatment switch or discontinuation. When a patient switched or discontinued treatment, we added a lag time of 90 days after the treatment was stopped (183 days for rituximab) to capture adverse events linked to treatment discontinuation but registered with some delay. Treatment stop date was defined as the first of: recorded stop in the SRQ, recorded start of another b/tsDMARD in the SRQ and filled prescription of another b/tsDMARD in the Prescribed Drug Register. If restarted within 90 days (183 days for rituximab), the two treatment episodes were merged. We did not differentiate between biosimilar versions of each drug, and switches between such were not considered treatment discontinuations. Patients could contribute with multiple treatment episodes on different drugs, but only the first ever start for each molecule.

Follow-up was censored at death or first emigration from Sweden after treatment start.

Comparator cohorts

A general population comparator group was drawn 1:5 age-sex-region matched to combined b/tsDMARD-treated cohort and free of chronic inflammatory joint disease at the index persons' date of treatment start. General population comparator subjects inherited the start date from their matched index individual with RA and were censored at death, emigration or any first recorded diagnosis of RA.

A cohort of b/tsDMARD-naïve patients with RA was defined as all patients with at least two separate dates of diagnosis with RA in the National Patient Register, with start date being the earliest of their second diagnosis date and 1 January 2010 and censored at the first ever recorded start of a b/tsDMARD. This cohort lacked data on disease activity.

Outcomes

Ten study outcomes were defined to capture important known or suspected risks associated with b/tsDMARD treatment: (1) treatment discontinuation due to adverse events, (2) major adverse cardiovascular events (MACE, including acute coronary syndrome (ACS), stroke and fatal cardiovascular events), (3) serious (requiring inpatient treatment) infection, (4) herpes zoster registered in specialty care, (5) tuberculosis, (6) non-steatosis liver disease, (7) diagnosed depression, (8) attempted or completed suicide, (9) any hospitalisation and (10) all-cause mortality. Reason for treatment discontinuation was recorded in the SRQ, laboratory-confirmed tuberculosis was retrieved from the Swedish Public Health Agency's register of communicable diseases; all other outcomes were defined by recorded diagnosis in the National Patient Register, covering inpatient and specialist outpatient care but not general practitioners, or as cause of death (definitions in online supplemental table 1). Malignancies and

thromboembolic events were omitted as they have been the subject of recent publications from ARTIS.[10 11]

Patients with a recent history of an outcome (prior 5 years, except for infection where only last year was considered) were excluded from analyses of the same outcome, except in analysis of discontinuation due to adverse events.

Covariates

Covariates were selected to broadly capture demographics, comorbidity and RA-related characteristics including disease activity. Census registries provided data on age, sex, immigration status and highest achieved education. SRQ provided data on smoking, RF/anti-citrullinated peptide antibodies (ACPA), RA duration, previous b/tsDMARD use, comedication with conventional synthetic DMARDs and glucocorticoids, the 28-joint disease activity score (DAS28-CRP) and the Health Assessment Questionnaire-Disability Index (HAQ). Comorbidity or medical history was assessed during the 5 years up until treatment start by registrations of ICD-10 diagnosis codes for malignancy, infections, joint surgery, chronic pulmonary disease, diabetes, cardiovascular disease, depression and the sum of prior days hospitalised. Different lookback period was sued for serious infections (1 year), joint surgery and malignancy (10 years). Detailed definitions are given in online supplemental table 2.

Statistical analyses

Crude and adjusted incidence rates were calculated for all outcomes and treatment groups. Only the first event in each treatment episode was counted. Cox regression by time since treatment start was used to estimate the HR using the largest treatment cohort (etanercept) as reference. HRs are only presented for contrasts with more than five observed events in both groups.

Incidence rates and Cox regressions were adjusted with stabilised inverse probability of treatment weights constructed as the inverse of the predicted probability to have received the treatment actually received, multiplied by the sample proportion with the same treatment.[12] Weights were truncated to the 99th percentile. Probabilities were predicted by multinomial logistic regression, regressing all covariates on treatment cohort. Balance was checked preweighting and postweighting (population standardised difference <0.1 was considered good balance). To allow comparison, standard multivariable Cox regression were run with the same variables and parameterisations.

Data were complete on treatments, outcomes and most covariates derived from national registers, but about 30% lacked data on baseline DAS28 and HAQ. Missing covariate data were accounted for by multiple imputation through chained equations, using fully conditional specifications with logistic models for categorical variables and predicted mean matching for continuous. We imputed 20 data sets, with 10 burn-in iterations. All covariates were parameterised as in the weight models, with second degree polynomials for continuous variables, and included the treatment assignment and all outcomes (event indicator and Nelson-Aalen estimate of the cumulative hazard). Robust SEs were used to calculate 95% CIs for all HRs, thus correcting for the weighting and the potential inclusion of the same patient in multiple treatment group, and combined across imputed dataset using Rubin's rule. Analyses were performed in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

Sensitivity analysis

The impact of the study period was tested by restriction to: (1) the time after JAKi market entry (excluding all b/tsDMARD starts before 1 January 2017) and (2) the time before the COVID-19 pandemic (follow-up terminated at 28 February 2020).

Patient and public involvement

Patient representatives were not involved in the design or interpretation of this study.

RESULTS

Over the 11-year study inclusion period, 2010–2020, we included 20 117 unique patients with RA who started at least one b/tsDMARD, contributing a total of 34 279 treatment episodes. The most commonly initiated b/tsDMARDs were the TNFi etanercept and adalimumab, while the recently introduced anti-IL-6R sarilumab was the least commonly started among the included treatments (table 1). Due to differences in market entry, the average follow-up per patient was about 3 years for most bDMARDs, below 2 years for JAKi and lowest for sarilumab, 1.3 years.

Evidence for channelling to therapy

In keeping with past and current treatment guidelines, TNFi were more often used as a first line b/tsDMARD (in particular infliximab), while sarilumab and the JAKi were predominately used later in the treatment course (table 1). TNFi initiators also had lower disease activity, less comorbidity and more concomitant conventional synthetic DMARD use compared with initiators of other modes of action. Rituximab was more common among older and RF/ACPA-positive patients. Rituximab initiators also had the highest comorbidity burden, followed by abatacept initiators who had similar rates of non-malignancy comorbidity.

Incidence rate by b/tsDMARD

As expected, channelling resulted in large differences in the crude incidence of several outcomes. For instance, the crude rates of several age-related outcomes (including all-cause mortality, serious infections, and MACE) were about twice as high on rituximab than on etanercept (figures 1 and 2, crude HRs in online supplemental table 5). These observed risk differences were largely explained by differences in patient characteristics, as evident from the much greater inter-drug similarity in weighted incidence rates.

After adjusting for baseline patient characteristics, substantial differences remained in the rate of treatment discontinuation due to adverse events (figure 1). The weighted incidence rate was 30 per 1000 person-years (PYs) on etanercept (ie, the predicted rate had the whole b/tsDMARD-treated RA population used etanercept), but the corresponding rate was 18%–53% higher on abatacept, infliximab, golimumab and certolizumab pegol and 28%–43% lower on tocilizumab, rituximab and baricitinib.

By contrast, the weighted rates of MACE was more similar across treatments, although a borderline significantly higher rate was seen on certolizumab pegol and rituximab versus etanercept. The pattern was similar for ACS and stroke (online supplemental figure S1). A lower rate of ACS was seen with baricitinib (vs etanercept), associated with broad confidence intervals (HR=0.42 (0.21–0.83)). Compared with the general population, patients with RA on b/tsDMARDs had a significant 60% higher rate of MACE (figure 3).

The difference to the general population rate was also pronounced for infections, with more than doubled rate for

Table 1 Patient characteristics at start of b/tsDMARD therapy, among all Swedish patients with RA, 2010–2020

	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Abatacept	Rituximab	Tocilizumab	Sarilumab	Baricitinib	Tofacitinib
N patients	8748	5526	2971	2179	1889	3434	4220	2757	292	1837	426
Person-years of exposure	26508.3	13566.1	8217.7	6180.3	6051.1	8799.8	15821.5	8089.8	380.5	3401.8	648.9
Mean (SD)	3.0 (2.8)	2.5 (2.7)	2.8 (2.9)	2.8 (3.0)	3.2 (3.1)	2.6 (2.5)	3.7 (3.1)	2.9 (3.0)	1.3 (0.9)	1.9 (1.3)	1.5 (1.3)
Demographics											
Age, mean (SD)	58 (14)	58 (14)	58 (14)	56 (15)	57 (14)	61 (13)	64 (13)	59 (14)	59 (14)	61 (14)	59 (13)
Female, %	77	76	74	78	78	80	75	79	79	82	82
Highest education, %											
9 years or less	9	8	13	9	10	11	14	11	8	9	5
10 years to 12 years	58	58	60	57	58	59	59	59	64	58	65
>12 years	33	34	27	33	32	29	27	30	28	33	30
Swedish-born, %	86	86	82	88	86	86	84	86	84	85	87
Ever smoker, %	58	58	60	57	54	61	64	58	58	59	59
RA clinical characteristics											
Rheumatoid factor positive, %	72	71	73	73	73	76	86	76	74	74	71
Disease duration, years, mean (SD)	7.7 (10.6)	8.4 (11.5)	6.8 (10.8)	8.3 (12.1)	8.9 (10.9)	11.7 (11.7)	12.7 (11.7)	10.5 (11.0)	11.0 (10.2)	13.2 (11.7)	13.1 (11.1)
DAS28, mean (SD)	4.3 (1.2)	4.2 (1.2)	4.5 (1.2)	4.4 (1.2)	4.3 (1.3)	4.5 (1.2)	4.5 (1.2)	4.8 (1.2)	4.5 (1.2)	4.3 (1.1)	4.5 (1.3)
HAQ, mean (SD)	1.0 (0.6)	1.0 (0.6)	1.0 (0.7)	1.0 (0.6)	1.0 (0.7)	1.3 (0.6)	1.3 (0.7)	1.3 (0.6)	1.3 (0.6)	1.1 (0.7)	1.3 (0.7)
Conc. MTX, %	59	60	76	56	66	52	53	48	45	39	35
Conc. non-MTX csDMARD, %	16	14	18	15	15	13	17	11	9	10	7
Conc. oral steroids, %	43	40	44	47	41	52	54	53	38	45	52
Prior b/tsDMARDs, %											
0	62	50	75	53	48	18	31	16	6	15	9
1–2	32	42	20	33	39	51	46	53	50	38	29
3+	6	8	5	15	13	31	22	31	44	47	63
Medical history*											
Malignancy, %	3.6	3	3.1	3.5	2.3	5	11.1	4	2.4	4.4	4.5
Serious infection, %	9.2	8.7	8.5	9.3	9.1	18.2	17.3	12.2	11.3	15.1	14.8
Serious herpes zoster %	1	0.7	0.5	0.8	1	1	1.2	0.9	0.7	1	0.9
Joint surgery, %	8.6	8.4	8.3	9.5	9.1	13	13.6	12.7	13	12.8	14.8
COPD, %	2.8	2.2	2.6	2.2	1.7	5.4	5.6	3.4	3.1	4.2	4
Diabetes mellitus, %	7.2	7.1	6	6.7	5.7	10.4	9.4	7.7	9.6	8	8.9
ACS, %	1.7	1.8	1.6	1.3	1.7	3	2.8	2.2	2.7	2.6	1.6
Stroke, %	1	1	1	1.1	1	1.5	2.1	1.3	0.3	1.3	0.9
Days hospitalised, %											
0	75	76	74	72	73	61	57	66	75	67	64
1–9	16	15	17	18	17	21	22	19	15	19	23
10+	9	8	9	10	10	18	22	15	10	14	13

*Medical history in 5 years before treatment start, except serious infection (1 year before start) and malignancy or joint surgery (10 years before).
ACS, acute coronary syndrome; COPD, chronic obstructive lung disease; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire-Disability Index; RA, rheumatoid arthritis.

Outcome	Events	Crude IR	wIR	wHR (95% CI)
Stop for adverse events				
Etanercept	446	18.0	29.8	1.0 (Ref.)
Adalimumab	348	27.9	34.1	1.07 (0.92–1.25)
Infliximab	99	12.5	38.9	1.25 (0.99–1.58)
Certolizumab	203	33.9	43.6	1.53 (1.28–1.82)
Golimumab	191	32.7	40.8	1.44 (1.19–1.73)
Abatacept	459	55.2	36.8	1.18 (1.03–1.36)
Rituximab	328	21.8	18.3	0.67 (0.57–0.78)
Tocilizumab	241	31.1	20.5	0.72 (0.60–0.85)
Sarilumab	30	94.7	57.4	1.25 (0.79–1.98)
Baricitinib	114	39.0	23.0	0.57 (0.45–0.73)
Tofacitinib	56	97.6	50.1	1.25 (0.85–1.84)
Major adverse cardiovascular event				
Etanercept	240	10.1	12.3	1.0 (Ref.)
Adalimumab	145	12.2	13.6	1.12 (0.89–1.41)
Infliximab	86	11.3	12.2	1.00 (0.72–1.39)
Certolizumab	76	13.2	16.0	1.31 (0.99–1.73)
Golimumab	60	10.7	13.9	1.14 (0.82–1.58)
Abatacept	125	16.1	13.9	1.14 (0.87–1.48)
Rituximab	290	21.0	15.7	1.27 (1.04–1.55)
Tocilizumab	84	11.4	11.9	0.97 (0.70–1.33)
Sarilumab	4	13.1	15.8	
Baricitinib	30	10.7	9.9	0.83 (0.49–1.42)
Tofacitinib	7	12.9	9.2	0.78 (0.31–1.99)
Serious Infection				
Etanercept	571	24.8	30.8	1.0 (Ref.)
Adalimumab	343	29.6	35.3	1.12 (0.96–1.31)
Infliximab	265	36.0	41.1	1.32 (1.09–1.60)
Certolizumab	167	30.4	33.3	1.10 (0.91–1.33)
Golimumab	134	24.9	32.3	1.07 (0.86–1.32)
Abatacept	278	38.6	33.8	1.08 (0.91–1.29)
Rituximab	609	47.5	39.3	1.31 (1.15–1.50)
Tocilizumab	235	33.5	29.6	0.98 (0.80–1.19)
Sarilumab	7	23.3	21.8	0.61 (0.24–1.53)
Baricitinib	105	39.5	33.6	0.98 (0.75–1.29)
Tofacitinib	25	47.3	30.5	0.89 (0.47–1.69)
Diagnosed herpes zoster				
Etanercept	50	2.0	2.5	1.0 (Ref.)
Adalimumab	38	3.1	3.7	1.48 (0.90–2.43)
Infliximab	27	3.4	4.0	1.64 (0.90–2.99)
Certolizumab	18	3.0	3.2	1.32 (0.73–2.38)
Golimumab	15	2.6	3.0	1.20 (0.63–2.28)
Abatacept	23	2.8	2.2	0.89 (0.49–1.64)
Rituximab	55	3.7	3.0	1.21 (0.77–1.91)
Tocilizumab	14	1.8	2.6	1.06 (0.52–2.17)
Sarilumab	1	3.2	0.9	
Baricitinib	29	10.0	9.8	3.82 (2.05–7.09)
Tofacitinib	8	14.1	10.2	4.00 (1.59–10.06)

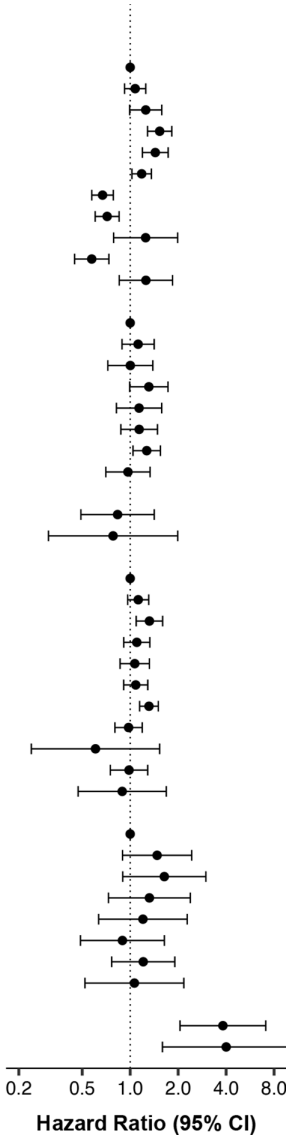

Figure 1 Crude and weighted incidence rate per 1000 person-years of selected safety outcomes by b/tsDMARD, and adjusted HRs versus etanercept, among all Swedish patients with RA who started treatment 2010–2020, followed until 30 June 2021. b/tsDMARDs, targeted synthetic or biological disease-modifying antirheumatic drugs; wHR, weighted HR from Cox regression; wIR, inverse probability of treatment weighted incidence rate per 1000 person-years, adjusted for demographics, RA clinical characteristics and comorbidity; RA, rheumatoid arthritis.

serious infections and more than tripled for herpes zoster among patients with RA on b/tsDMARDs. Infliximab and rituximab had about 30% higher rate of overall serious infections than etanercept, while the others had similar and non-significantly different rates. This differed from the pattern seen for herpes zoster as registered in specialty care, where the rate was almost four times higher on baricitinib and tofacitinib versus etanercept, but no other significant interdrug difference (vs etanercept) was observed. Though tuberculosis was rare, with only 16 events recorded across all treatment groups, this translated to a tripled rate compared with the general population (figure 3 and online supplemental table 5).

The weighted rate of non-steatosis liver disease was low (1–3 per 1000 PYs) across all b/tsDMARDs, about 40% higher than the rate seen in the general population (cf. figures 2 and 3). Similar patterns were seen for diagnosed depression (2–5 per 1000 PYs) and for (attempted) suicide (1–2 per 1000 PYs), about 10% and 40% higher than general population, respectively.

The weighted incidence rate of hospitalisation (for any cause) was 162 per 1000 PYs on b/tsDMARD, which was about 80% higher than the rate in the general population, with b/tsDMARDs. Significantly higher rates (vs etanercept) were observed on infliximab (18%), certolizumab pegol (15%) and rituximab (28%). The lowest rate was observed on tofacitinib (weighted HR=0.69 (0.49–0.96)).

All-cause mortality among patients with RA starting b/tsDMARD was about 30% higher than in the general population. Mortality rate was similar across TNFi, but about 30%–40% higher on the non-TNFi bDMARDs, with the numerically highest HR seen for baricitinib.

In age-sex standardised comparison to b/tsDMARD-naïve patients with RA (online supplemental figure S2), the b/tsDMARD-treated patients had significantly higher rates of serious infections, herpes zoster and tuberculosis, but slightly lower rate of MACE and diagnosed depression. Possibly indicative of substantial confounding, the b/tsDMARD-treated also

Outcome	Events	Crude IR	wIR	wHR (95% CI)
Liver disease				
Etanercept	29	1.2	1.5	1.0 (Ref.)
Adalimumab	14	1.1	1.1	0.73 (0.36–1.47)
Infliximab	18	2.3	2.8	1.87 (0.86–4.04)
Certolizumab	14	2.4	2.7	1.76 (0.87–3.54)
Golimumab	3	0.5	0.5	
Abatacept	14	1.7	2.4	1.60 (0.72–3.57)
Rituximab	33	2.2	2.3	1.58 (0.88–2.85)
Tocilizumab	11	1.4	1.6	1.06 (0.43–2.63)
Sarilumab	2	6.4	5.7	
Baricitinib	5	1.7	1.0	0.62 (0.18–2.16)
Tofacitinib	1	1.8	0.6	
Diagnosed depression				
Etanercept	91	3.8	4.0	1.0 (Ref.)
Adalimumab	42	3.5	3.9	0.97 (0.65–1.45)
Infliximab	31	4.0	4.5	1.12 (0.65–1.93)
Certolizumab	17	3.0	2.5	0.64 (0.37–1.11)
Golimumab	13	2.3	2.3	0.59 (0.32–1.10)
Abatacept	40	5.0	3.9	0.96 (0.60–1.53)
Rituximab	80	5.6	5.2	1.37 (0.95–1.97)
Tocilizumab	42	5.7	5.0	1.28 (0.82–1.99)
Sarilumab	1	3.3	1.3	
Baricitinib	18	6.5	5.3	1.15 (0.63–2.08)
Tofacitinib	5	9.0	4.6	0.98 (0.30–3.17)
Suicide (incl. attempted)				
Etanercept	35	1.4	1.7	1.0 (Ref.)
Adalimumab	21	1.7	1.8	1.03 (0.56–1.90)
Infliximab	13	1.7	2.3	1.32 (0.56–3.14)
Certolizumab	7	1.2	1.4	0.80 (0.33–1.97)
Golimumab	6	1.0	1.0	0.57 (0.22–1.48)
Abatacept	13	1.6	1.8	1.05 (0.45–2.46)
Rituximab	23	1.5	1.3	0.78 (0.41–1.47)
Tocilizumab	18	2.4	2.0	1.17 (0.58–2.34)
Sarilumab	2	6.5	2.8	
Baricitinib	6	2.1	1.5	0.94 (0.37–2.40)
Tofacitinib	1	1.8	0.3	
Any hospitalization				
Etanercept	2465	128.2	153.8	1.0 (Ref.)
Adalimumab	1329	139.3	167.3	1.04 (0.97–1.12)
Infliximab	961	164.6	186.6	1.18 (1.07–1.29)
Certolizumab	679	158.0	174.6	1.15 (1.05–1.26)
Golimumab	570	128.3	156.8	1.06 (0.96–1.17)
Abatacept	1183	202.7	171.1	1.08 (0.99–1.18)
Rituximab	2091	232.3	190.4	1.28 (1.19–1.37)
Tocilizumab	973	182.2	158.8	1.05 (0.96–1.16)
Sarilumab	53	194.1	274.5	1.40 (0.98–2.00)
Baricitinib	438	179.6	164.2	0.91 (0.80–1.04)
Tofacitinib	94	198.4	121.6	0.69 (0.49–0.96)
All-cause mortality				
Etanercept	219	8.8	12.1	1.0 (Ref.)
Adalimumab	100	8.0	10.3	0.88 (0.67–1.16)
Infliximab	92	11.6	12.5	1.05 (0.75–1.47)
Certolizumab	55	9.2	12.1	0.98 (0.71–1.35)
Golimumab	50	8.6	13.4	1.08 (0.75–1.55)
Abatacept	140	16.8	15.5	1.32 (1.01–1.73)
Rituximab	366	24.3	17.8	1.40 (1.15–1.71)
Tocilizumab	112	14.5	17.5	1.41 (1.06–1.88)
Sarilumab	3	9.5	9.8	
Baricitinib	55	18.8	22.0	2.27 (1.51–3.40)
Tofacitinib	5	8.7	10.5	1.09 (0.40–2.92)

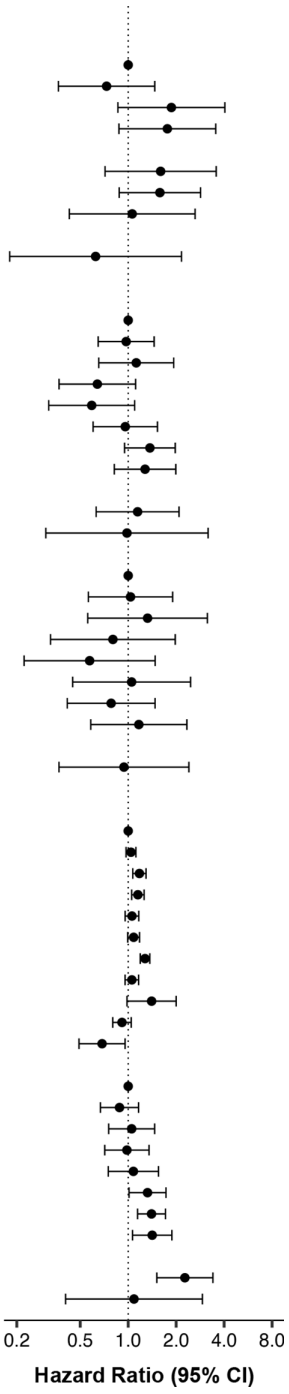

Figure 2 Crude and weighted incidence rate per 1000 person-years of selected safety outcomes by b/tsDMARD, and adjusted HRs vs etanercept, among all Swedish patients with RA who started treatment 2010–2020, followed until 30 June 2021. b/tsDMARDs, targeted synthetic or biological disease-modifying antirheumatic drugs; wHR, weighted HR from Cox regression; wIR, inverse probability of treatment weighted incidence rate per 1000 person-years, adjusted for demographics, RA clinical characteristics and comorbidity; RA, rheumatoid arthritis.

had significantly lower rate of all-cause mortality (HR=0.65 (0.61–0.69)), cautioning us from drawing firm conclusions from the other rates.

Analyses by adjustment method

While the weighting successfully balanced mean patient characteristics across the major treatment groups (online supplemental tables 3 and 4), it was not possible to reach acceptable balance for all variables in the two smallest groups (sarilumab, tofacitinib). Adjustment directly in multivariable Cox regressions gave very similar estimates throughout (online supplemental table 5). Due to differences in drug market entry, it was not possible to include an adjustment for year of treatment start in the weights. Similarly, availability of smoking data increased dramatically over time, which made it impossible to include in weight-models without losing balance in other covariates. Adjusting for year of treatment start and smoking in Cox models, however, left associations virtually unchanged (online supplemental table 5).

Sensitivity analyses

Restricting the study period to the time after JAKi market entry reduced sample sizes drastically, and several differences between

Outcome	Events	IR	HR (95% CI)
Major adverse cardiovascular event			
General pop., age/sex–matched	7331	8.4	1.0 (Ref.)
RA, b/tsDMARD treated	1147	13.1	1.61 (1.51–1.72)
Serious Infection			
General pop., age/sex–matched	10402	12.0	1.0 (Ref.)
RA, b/tsDMARD treated	2739	32.8	2.68 (2.56–2.81)
Diagnosed herpes zoster			
General pop., age/sex–matched	788	0.9	1.0 (Ref.)
RA, b/tsDMARD treated	278	3.1	3.65 (3.13–4.25)
Tuberculosis			
General pop., age/sex–matched	49	0.1	1.0 (Ref.)
RA, b/tsDMARD treated	16	0.2	3.14 (1.60–6.14)
Liver disease			
General pop., age/sex–matched	1054	1.2	1.0 (Ref.)
RA, b/tsDMARD treated	144	1.6	1.40 (1.16–1.68)
Diagnosed depression			
General pop., age/sex–matched	3136	3.6	1.0 (Ref.)
RA, b/tsDMARD treated	380	4.3	1.11 (0.99–1.24)
Suicide (incl. attempted)			
General pop., age/sex–matched	1008	1.1	1.0 (Ref.)
RA, b/tsDMARD treated	145	1.6	1.38 (1.14–1.66)
Any hospitalization			
General pop., age/sex–matched	55580	80.1	1.0 (Ref.)
RA, b/tsDMARD treated	10836	162.4	1.83 (1.79–1.87)
All–cause mortality			
General pop., age/sex–matched	9738	10.7	1.0 (Ref.)
RA, b/tsDMARD treated	1197	13.0	1.31 (1.23–1.40)

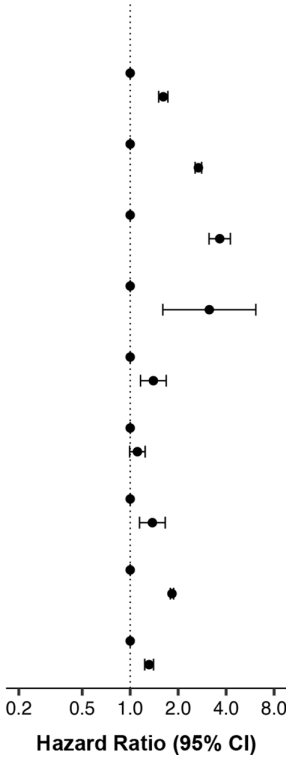

Figure 3 Incidence rate per 1000 person-years of selected safety outcomes, among all Swedish patients with RA who started b/tsDMARD 2010–2020, and a 5:1 age-sex matched general population sample, followed until 30 June 2021. HR, hazard ratio from Cox regression; RA, rheumatoid arthritis.

non-TNFi bDMARDs and etanercept were no longer significant, but it did not materially alter the comparison between the JAKi and etanercept (online supplemental figure S3). Ending follow-up at the onset of the COVID-19 pandemic had little impact on incidence rates or contrasts between bDMARDs, but the reduced sample size for sarilumab and JAKi excluded them from most comparative analyses for these groups (online supplemental figure S4).

DISCUSSION

This study followed close to 35 000 treatment initiations of b/tsDMARD among patients with RA in Sweden between 2010 and 2021 and estimated and compared the incidence of selected key safety outcomes between individual treatments while adjusting for a range of potential confounders. We found large differences in the rate of discontinuation of adverse events, several differences in rates of herpes zoster or overall serious infections and no clear difference in rate of MACE. Incident liver disease diagnoses and clinical depression were very rare in this cohort, independently of which b/tsDMARD was used.

These findings largely support previous reports and the currently established view of the relative safety of b/tsDMARDs. Largest differences were seen for the rate of discontinuation citing adverse events, where the ranked (highest to lowest) order we observed was similar to that by overall drug survival in a contemporary cohort of Danish patients with RA.[13] It may in reality be difficult to assign a single cause for the choice to discontinue therapy (missing data can be substantial[14]) and a lower rate of discontinuation citing safety should not be directly interpreted as a better drug safety profile. We saw the lowest rate on rituximab, consistent with previous reports that this drug has longer overall drug survival than other b/tsDMARDs,[14 15] despite a relatively higher rate of hospitalisation and serious infections. Also consistent with our data, previous reports found infliximab to have poorer drug survival and more discontinuation for adverse events compared with etanercept and adalimumab.[16 17]

With regard to cardiovascular risks, patients with RA starting etanercept b/tsDMARD were at increased risk of MACE compared with the matched general population comparators, a finding in line with previous studies.[18] We also replicate previous findings of similar rates of ACS on different bDMARDs.[18 19] In the ORAL surveillance trial of patients with RA with pre-existing cardiovascular risk factors, tofacitinib was associated with increased risk (vs TNFi) of MACE, at least beyond 18 months of follow-up.[20] The low number of events on tofacitinib in the present material makes the result inconclusive but note that we did not observe any increased rate of MACE on baricitinib, where in fact the rate of ACS was significantly lower than on etanercept (possibly due to residual confounding). Venous thrombotic events were not included in this study, but the previously reported risk signal for JAKi was recently replicated in ARTIS, reporting age-standardised and sex-standardised IR of 5.2 per 1000 PYs on TNFi and 11.3 on JAKi (adjusted HR was 1.73 (1.24 to 2.42)).[10] Another recent study from ARTIS compared overall cancer risks for patients with RA treat with b/tsDMARDs to the general population and found no increased risks for TNFi, rituximab or tocilizumab, a possible risk increase for abatacept (HR=1.3 (1.1–1.6)), and too limited follow-up for a comparison to the JAKi.[11]

It is well established that patients treated with b/tsDMARDs have an increased rate of serious infections and reactivation of latent varicella-zoster compared with the general population.[21–23] A particularly increased rate of herpes infections and herpes zoster has been reported in RCTs of JAKi in RA.[24] Compared with etanercept, we observed a more than tripled rate of herpes zoster on JAKi, which is similar to estimates from the

German RABBIT register,[25] and in line with a meta-analysis of randomised trials.[24] Also consistent with these studies, the rate of other serious infections was not higher on JAKi versus etanercept. A higher rate of serious infections on rituximab versus other bDMARDs has been suggested by some previous studies[21] and has been reported compared with other disease modifying drugs in multiple sclerosis.[26] In accordance with some previous reports,[27 28] we also observed a significantly increased rate of serious infections on infliximab versus etanercept.

Increased rates of hepatobiliary adverse events have been noted in some b/tsDMARD RCTs in RA, for example, of the etanercept biosimilar SB4.[29] Similar to previous studies,[30] the rate of liver disease was very low in our cohort, regardless of b/tsDMARD used, and we noticed no safety signal for this outcome. Similarly, there has been interest, including from regulatory agencies, in a possible effect of infliximab on the risk of depression and attempted suicide.[31 32] We did not observe any significant differences in the rate of diagnosed depression or attempted suicide by b/tsDMARD.

Finally, we observed several significant differences in the rate of all-cause hospitalisation and mortality. First, we found an overall modestly increased mortality in b/tsDMARD-treated RA compared with the general population (31% increase). Some evidence suggests an improving mortality in RA over recent decades,[33 34] and to ensure maximal relevance for contemporary clinical practice, we restricted our study to patients initiating b/tsDMARD therapies during the most recent ten (instead of maximally 24) years. We also observed several significant differences between b/tsDMARDs. These differences are difficult to interpret, reflecting a combination of possibly true and drug-related risk differences for a range of adverse events and the residual confounding by factors not adequately controlled for. It is possible that surveillance linked to the mode of administration also influence the likelihood to be hospitalised; drugs given through infusion had highest rates of hospitalisations (rituximab and infliximab), while lowest were seen for the oral JAKi. We note that rituximab was significantly associated with higher rates of both hospitalisation and mortality, in fact, associated with higher rates of all outcomes defined by hospitalisation. But it should also be noted that the confounder-adjustment markedly reduced these associations; the non-specificity of this increased risk may itself be a signal of residual confounding. This highlights the degree of channelling bias between these groups in the real-world clinical setting, where, as the crude incidence rates show, it would indeed be correct to say patients initiating some drugs are at a higher rate of serious adverse events without implying a risk increase conferred by the drug itself.[35]

Strengths of this study include the national coverage, giving a large cohort and avoiding selection bias and the collection of safety outcomes independently from drug assignment through national registers with an established high validity. We were able to simultaneously include all b/tsDMARDs used in clinical practice and could accommodate a broad range of possible confounding factors. We could further demonstrate that the method of adjustment (propensity weighting vs multivariable Cox regression) did not influence the findings of the study. For JAKi's in particular, our results add to a relatively limited evidence-base.

Our study also has several limitations. We used a common study design, including a shared model to adjust for confounding, across all outcomes. This allowed a streamlined analysis and simplifies the comparison across outcomes, but is more susceptible to residual confounding and other biases which a bespoke study design for each outcome might have avoided. That said, our set of covariates included a wealth of potential risk factors that are shared across outcomes and also markers of general frailty. Due to the multitude of statistical tests, several false positive findings may be expected. Despite the large, national cohort, the scarcity of TB, liver disease and suicide made these results inconclusive, with broad confidence intervals.

This study was only possible thanks to the well-established Swedish clinical register SRQ, and the ARTIS safety monitoring programme. The first decade of bDMARD therapy in Sweden was summarised by Simard *et al* in 2011,[36] emphasising the importance of patient characteristics when evaluating clinical outcomes. Together, studies from ARTIS have now provided relevant clinical data covering an observation period of over twenty years. This demonstrates that a register-initiative initiated and maintained by the clinical profession can persist over time and continue to provide important drug safety data, meeting the needs of healthcare and the pharmaceutical industry and regulatory agencies.[37] The experience from PASS studies of bDMARDs has been important for the development of efficient use of risk management plans in the European regulatory system.[38 39] Data from ARTIS and other similar registries, like the Danish DANBIO,[40] RABBIT in Germany[41] and BSRBR in the UK,[42] have been instrumental in the required postmarketing characterisation of long-term safety profiles for b/tsDMARDs.

In conclusion, this study provides a comprehensive assessment of safety outcomes of particular interest, for most b/tsDMARDs available for the treatment of RA. Our results corroborate and extend previous evidence that the currently available b/tsDMARDs have acceptable and on the whole similar safety profiles, but that differences exist in particular concerning tolerability, specific infection risks and for specific serious but rare outcomes. To inform risk-benefit trade-offs, these data on safety outcomes should be combined with corresponding data on effectiveness. We believe that studies which, like the current one, can include data on all used treatment options in one cohort are particularly valuable to avoid problems with generalisability across studies. While such effectiveness studies do exist,[10 15 18 25] both overall and in defined subsets of patients, they (similar to the situation for safety data) represent a minority of all publications on this topic. Finally, although data on safety and effectiveness of this kind are a necessary foundation for clinical decision-making, the value-based decision on what ratio of safety concerns and treatment benefits defines the 'best' treatment choice should reside with the individual patient and treating rheumatologist.

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Contributors TF and HB had full access to all data and take responsibility for the integrity of the data and the accuracy of the data analysis. TF performed analyses, drafted the first version of the manuscript, and acts as guarantor for the study. 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.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Regional Ethics Committee of Stockholm, DNR 2015/1844-31, as revised by the Swedish Ethical Review Authority, DNR 2021-00096. Under Swedish jurisdiction, this is not required for register-based studies with pseudonymised data and research ethics approval.

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Data availability statement Data may be obtained from a third party and are not publicly available. The data was retrieved from national Swedish registers, which can only be accessed with specific permissions from the Swedish register-holding authorities.

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Online Supplement for

Safety of b/tsDMARDs for RA as used in clinical practice - results from the ARTIS program

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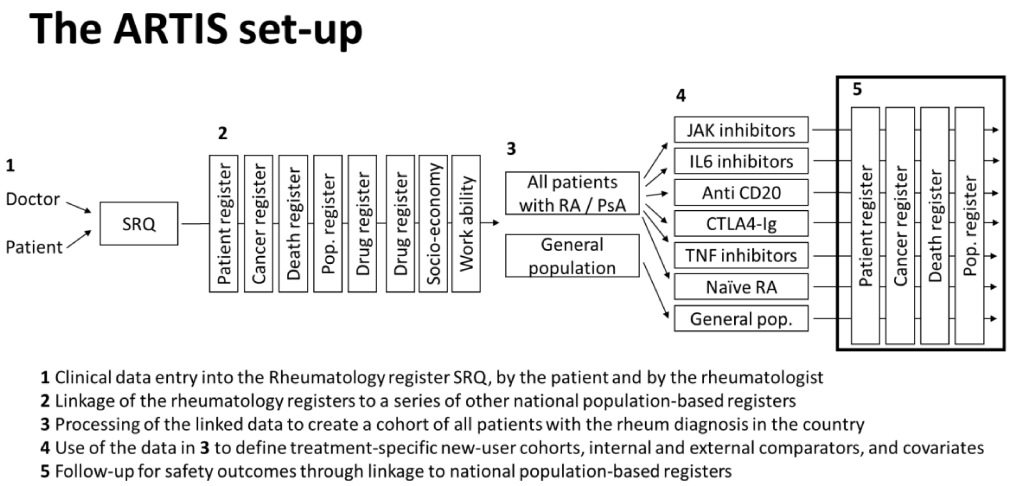
The ARTIS surveillance program for immunomodulatory drugs against chronic inflammatory arthritis

In Sweden, the first biologic disease modifying anti-rheumatic drugs (bDMARDs) were made available for the treatment of RA in 1999. At that time, the ARTIS (Anti-Rheumatic Treatment in Sweden) monitoring system was started in collaboration with the Swedish Medical Products Agency, and serves as a national surveillance program for investigation of safety and effectiveness of new anti-rheumatic drugs. The ARTIS database is constructed by regular (often annual) extractions of data from the Swedish Rheumatology Quality Register (SRQ), linked to data from other national Swedish registers, as depicted in the figure below and further described under Data sources.

Figure. Schematic illustration of the ARTIS study database



The ARTIS study database is built by identifying an index population of patients with chronic inflammatory joint diseases in Sweden and a matched general population comparator cohort, with information on patient characteristics, safety and treatment effectiveness outcomes retrieved through national registers.

Data sources

Setting

Swedish health-care is tax-funded and offers universal access. Hospital referral is based on geography rather than insurance-status. Patients with inflammatory arthritides are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics. Health and demographic information is recorded in a series of registers with a very high degree of completeness resulting from the mandatory and semi-automated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born thereafter, linkage of data from different registers is possible.[1] The registers are maintained by governmental bodies (the main registers used in this project are

held by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden), who may perform data linkages and provide de-identified data for research purposes.

The Swedish Rheumatology Quality Register (SRQ) and ARTIS

The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Rheumatology Society to improve the healthcare and treatment for patients with RA. SRQ followed on regional register initiatives, to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonized national register. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases including ankylosing spondylitis and psoriatic arthritis, Currently, some 29,000 patients with RA initiating over 70,000 biological treatments have been registered in SRQ. The register also contains early RA patients, and increasingly, RA patients can be followed from their first RA diagnosis and onwards. In conjunction with each patient visit, the treating rheumatologist enters data on disease activity and anti-rheumatic treatment, and the patient enters data on symptoms and health-status. The coverage of the SRQ is high, and was in 2015 estimated to be about 90% for new initiations of bDMARDs among patient with RA in Sweden.[2]

The National Patient Register

The Swedish National Patient Register collects information on all hospitalized (inpatient treated) patients, and all visits to physicians in non-primary outpatient care (such as a visit to a rheumatologist).[3] Diagnoses are assigned by the discharging physician, and coded according to the ICD, with version 8 used until 1986, version 9 from 1987 to 1996, and version 10 since 1997. The register also collects information of the treating hospital, medical specialty, medical procedures or interventions, and dates of hospitalization and discharge. The inpatient component was originally initiated by several counties in 1964, had 85% country-wide coverage in 1983, and is considered complete since 1987. The outpatient component of the Patient register was initiated with nationwide coverage in 2001, but the coverage was poor for several medical areas in the first years, with substantial missingness in e.g. diagnosis. This improved quickly in the first five years of the outpatient component, and since 2010, the missingness in diagnosis is stable about 1% for inpatient care and 3% for outpatient care.

Reporting data to the register is mandatory for all health care providers in Sweden, and was done on an annual basis until 2015, when the frequency increased to monthly. Data is mostly reported by Sweden's 21 Regions (the intermediate governmental level, responsible for providing public health care), who have established different local processes for extracting the mandatory information from their regional electronic medical records system, and uploading it through the National Board of Health and Welfare's secure file transfer protocol. About 1% of inpatient healthcare visits and 5% of outpatient healthcare visits are reported directly from private healthcare providers (this can be privately funded healthcare, or because the private provider for some other reason does not share electronic medical records with the healthcare Region). The local files are combined and subjected to automated and semi-automated checks of logical consistency and content deviations from e.g. expected frequency of healthcare visits.

Due to the automated processes for extracting and reporting data, the register is today expected to correspond well to the information recorded in the local medical records. Historically, validation against medical files have found an overall error rate in the main diagnoses of 4% at the ICD chapter level, and 12% at the three digit level.[4] Diagnoses recorded in the medical record can of course also be incorrect, and chart reviews and validation of the RA diagnosis based on different algorithms applied to the register data indicate a positive predictive value for a register-based diagnosis of RA around 90%.[5-7]

The Prescribed Drug Register

Started in July 2005, the National Prescribed Drug Register contains data on all dispensations of prescription medication at Swedish pharmacies. The data reporting is mandatory, and linked to the softwares used in all pharmacies that dispenses regulated (i.e., prescription) medication. Data is uploaded daily to the Swedish eHealth Agency, who sends monthly summaries to the National Board of Health and Welfare where the register is finalized. The register contains information on the prescription (who wrote it, when, who is filling it, and was there a note on dosage made) and on the dispensed item (the package ID, the number of packages). The package ID is according to a national list and can be translated to the brand name, ATC code, mode of delivery, amount of drug, and cost of drug. Due to the automated set-up, the register is considered completely accurate. The register does not capture the indication for treatment, and will not cover medications used in a hospital setting (as they are not dispensed from pharmacies) or which are bought at pharmacies without prescriptions (i.e., over the counter drugs).

The National Cancer Register.

The Swedish National Cancer Register was established in 1958 and contains information on date of cancer (and some selected pre-cancers) onset, and type of cancer according to the ICD classification and morphology/histology. About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as selected types of cancer in situ) is mandatory and semi-automated, resulting in an estimated coverage greater than 95%.[8,9] In practice, reporting to the Cancer register often required two complementary reports: a pathologists report of morphological characteristics and a clinican's report of clinical stage and ICDO-coded diagnosis. As soon as one of these reports is sent to the Cancer register's regional center, it will start a process of investigation with reminders sent out until the report can be completed, and only then is it formally recorded in the register. The pathology reports are sent directly from the medical records system used at clinical laboratories, and have little lag time and high degree of completeness, while the clinical report can have substantial lag. For cancers which are never biopsied, this means that the coverage is much less complete. This is known to lead to underestimates of internal cancers with poor prognosis, in particular in older patients, and as much as 30% of pancreatic cancer has been estimated to be missing from the Cancer register.[10,11] For such types of cancer, it is recommended to also use data from the Cause of Death register.

The Cause of Death Register

The National Cause of Death Register contains information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. The register was started in 1952, and the data is considered complete since 1961.[12] From that year and onward, cause of death is missing for less than 0.5% of deceased individuals, and in 2002, a validation study estimated that only 3.3% had any errors at the three-digit level of the ICD-coded underlying cause of death. The register depends on a semi-manual process of data collection, where the medical doctor who signs the death certificate is responsible for uploading the causal chain leading to the death directly to the National Board of Health and Welfare, where coding consistency is checked and follow-up questions can be sent out to confirm or complete records. The high completeness of the register is possible since the Board have access to the quickly updated census information, and send out reminders and follow-up questions for each recorded death lacking a valid cause of death certificate.

The Tuberculosis Register

The Public Health Agency maintains a register of certain communicable diseases, including a sub register on tuberculosis. This *Tuberculosis (TB) Register* started in 1969 on a national level and contains data on active TB diagnoses. Reporting incident TB cases to this register is done in parallel by both the microbiological laboratories and clinicians when a patient is culture-positive. In addition, any individual

clinically diagnosed with TB is reported to the TB register's web-based reporting system by the clinician. Completeness and quality of the data retrieved is monitored weekly, resulting in 100% coverage of all cases verified by culture.[13,14]

The Total Population Register

The Total Population Register is maintained by Statistics Sweden as the backbone of the Swedish system of national register.[15] Derived from the continuously updated census data at the Swedish Taxation Office, the register lists data on residency at a given point in time since it was founded in 1961, and dates of emigration/immigration for all subjects ever resident in Sweden since 1961. This register is used to identify the general population comparison cohorts, and to censor subjects who die or emigrate during follow-up.

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Supplemental table 1: Outcome definitions

Outcome	Data source	Codes
Treatment stop due to adverse event	SRQ	The recorded reason for discontinuation. Discontinuation listing adverse event or safety as reason. All other reasons, or missing, were considered censoring events.
Acute coronary syndrome	Patient register: in- and outpatient, main or secondary diagnosis Causes of death register: main or contributing cause of death	I20.0, I21, I22
Stroke	Patient register: in- and outpatient, main or secondary diagnosis Causes of death register, main or contributing cause of death	I60-I64
Serious infection	Patient register: Main diagnosis in inpatient care	A00 - B99 D733 E060 E321 G00 G01 G02 G042 G050 G051 G052 G06 G07 H000 H010 H030 H031 H061 H10 H130 H131 H160 H162 H190 H191 H192 H220 H30 H440 H600 H601 H603 H620 H621 H622 H623 H66 H670 H671 H68 H70 H730 H750 H940 I301 I330 I39 I400 I410 I411 I412 I430 I520 I521 I681 I980 I981 J00 J01 J02 J03 J04 J05 J06 J09 J10 J11 J12 J13 J14 J15 J16 J170 J171 J172 J173 J178 J18 J20 J21 J22 J32 J340 J36 J37 J383F J383R J390 J391 J440 J85 J86 K044 K045 K046 K047 K050 K052 K102 K113 K122 K140 K230 K35 K570 K572 K574 K578 K61 K630 K650 K67 L00 L01 L02 L03 L04 L05 L08 L303 M00 M01 M03 M462 M463 M465 M490 M491 M492 M493 M600 M630 M631 M632 M650 M651 M710 M711 M726 M86 M900 M901 M902 N080 N088 N10 N11 N136 N151 N159 N160 N290 N291 N300 N308 N33 N340 N341 N342 N390 N412 N431 N450 N481 N482 N49 N51 N61 N700 N710 N72 N730 N733 N74 N751 N760 N762 N770 N771 O070 O075 O080 O23 O353 O411 O753 O85 O86 O91 O98
Tuberculosis	The Public Health Agency's register of communicable diseases.	N/A

	Mandatory registration of laboratory confirmed cases.	
Herpes Zoster	Patient register: in- and outpatient, main or secondary diagnosis	B01, B02
Diagnosed depression	Patient register: in- and outpatient, main or secondary diagnosis	F32-F33
Suicide (including attempted suicide)	Patient register: External cause codes in inpatient care Causes of death register, main or contributing cause of death	X60-X84, Y10-Y34
Non-steatosis diseases of liver	Patient register: in- and outpatient, main or secondary diagnosis Causes of death register, main or contributing cause of death	K70-K77, except K76.0
Any hospitalization	Patient register	Any overnight hospital stay
All-cause mortality	Register of the total population.	Any listed date of death

Supplemental table 2: Covariate definitions

Demographics			
Variable	**Data source**	**Type/Parameterization**	**Defined at time**
Age	From national ID	Second degree polynomial	Treatment start
Sex	From national ID	Binary: Male/female	Last recorded
Country of birth	Register of total population	Binary: Swedish/non-Swedish	Time fixed
Education level	LISA	Categorical: <9 yrs, 9-12 yrs, 12+ yrs	Year before treatment start
Smoking	SRQ (patient-reported)	Binary: Ever (current or former) vs Never	Closest to treatment start, up to two years after
Clinical characteristics of RA			
Variable	**Data source**	**Type/Parameterization**	**Defined at time**
Seropositive RA	SRQ	Binary: by diagnosis in SRQ, if RF+ or ACPA+ then Yes, else No	Treatment start
RA duration	SRQ	Second degree polynomial	Treatment start
Number of previous b/tsDMARDs	SRQ	Categorical: 0, 1-2, 3+	Counting all before treatment start
DAS28CRP	SRQ	Second degree polynomial	Treatment start
HAQ	SRQ	Second degree polynomial	Treatment start
Co-medication with methotrexate	SRQ	Binary: yes vs no	Treatment start
Co-medication with other csDMARD	SRQ	Binary: yes vs no	Treatment start
Co-medication with corticosteroids	SRQ	Binary: yes vs no	Treatment start
Days hospitalized	The Patient register	Categorical: 0, 1-9, 10+	5 yrs before treatment start
Definitions of baseline diseases considered as potential confounders (all binary: yes vs no)			
Disease	**Data source**	**ICD10 or NOMESCO**	**Look-back time**
Malignancy	The Cancer register	All except benign tumors	10 yrs
Infection	As the outcome	As the outcome	5 yr
Herpes zoster	As the outcome	As the outcome	5 yr
Knee or hip prosthesis	Procedure codes from the Patient register	NGB, NFB	10 yrs
Chronic pulmonary disease	The Patient Register	J41-J44	5 yrs
Diabetes	The Patient Register	E10-E14, O24	5 yrs
CVD	ACS or stroke, per outcome definitions	ACS or stroke, per outcome definitions	5 yrs
Depression	As the outcome	As the outcome	5 yrs

Supplemental Results

Supplemental table 3. Post-weighting patient characteristics at start of b/tsDMARD therapy, among all Swedish RA patients, 2010-2020

	ETA	ADA	INF	CTZ	GOL	ABA	RTX	TCZ	SAR	BAR	TOF
Demographics											
Age, mean	58	58	57	58	58	58	58	58	60	59	57
Female	77%	78%	76%	78%	78%	77%	78%	78%	79%	79%	74%
Highest education, 9y or less	11%	11%	11%	11%	11%	11%	11%	11%	11%	12%	9%
Highest education, 10y to 12y	58%	59%	59%	59%	58%	58%	58%	59%	58%	56%	57%
Highest education, >12y	31%	31%	30%	31%	31%	31%	30%	30%	32%	32%	34%
Swedish-born	85%	86%	85%	85%	85%	85%	85%	86%	88%	84%	85%
RA clinical characteristics											
Rheumatoid factor positive	75%	75%	73%	75%	74%	75%	75%	75%	75%	74%	69%
Disease duration, yrs, mean	12.9	12.7	12.3	12.7	12.8	12.5	13.2	12.3	12.7	13.4	11.8
DAS28	4.4	4.4	4.3	4.4	4.4	4.4	4.3	4.4	4.4	4.3	4.3
HAQ	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.2	1.1	1.1
Conc. MTX	56%	56%	57%	56%	56%	56%	55%	55%	51%	53%	49%
Conc. non-MTX csDMARD	14%	15%	16%	15%	15%	15%	15%	13%	10%	13%	12%
Conc. oral steroids	46%	46%	46%	46%	47%	45%	48%	44%	46%	43%	42%
Prior b/tsDMARDs											
0	44%	44%	44%	44%	43%	43%	40%	42%	28%	39%	34%
1-2	39%	39%	41%	39%	38%	40%	41%	40%	49%	43%	46%
3+	18%	18%	15%	18%	19%	18%	20%	18%	22%	19%	21%
Medical history*											
Malignancy	5%	5%	5%	5%	5%	5%	5%	5%	3%	5%	5%
Serious infection	12%	12%	12%	12%	12%	12%	13%	11%	16%	12%	11%
Serious herpes zoster	1%	1%	1%	1%	1%	1%	1%	1%	0%	1%	1%
Joint surgery	11%	10%	9%	11%	11%	11%	11%	10%	11%	11%	10%
COPD	4%	3%	3%	4%	4%	4%	4%	4%	4%	3%	4%
Diabetes mellitus	8%	8%	7%	8%	8%	8%	8%	7%	8%	8%	8%
ACS	2%	2%	2%	2%	2%	2%	2%	3%	2%	2%	2%
Stroke	1%	1%	1%	1%	1%	1%	1%	1%	0%	1%	0%
Days hospitalized											
0	68%	70%	68%	69%	69%	68%	68%	70%	71%	70%	74%
1-9	18%	18%	20%	18%	18%	19%	19%	17%	15%	17%	17%
10+	14%	13%	12%	13%	13%	13%	13%	13%	14%	13%	10%

Notes: *) Medical history in five years before treatment start, except Serious infection (one year before start) and malignancy or joint surgery (ten years before)

Supplemental table 4. Post-weighting population standardized bias

	ETA	ADA	INF	CTZ	GOL	ABA	RTX	TCZ	SAR	BAR	TOF
Demographics											
Age, mean	0.01	-0.02	-0.06	-0.01	0.00	0.00	0.03	0.00	0.12	0.07	-0.08
Female	0.00	0.01	-0.04	0.00	0.00	-0.01	0.01	0.02	0.03	0.04	-0.09
Highest education, 9y or less	0.00	-0.01	-0.01	-0.01	0.02	0.00	0.02	0.00	-0.01	0.02	-0.07
Highest education, 10y to 12y	0.00	0.01	0.02	0.00	0.00	0.00	0.00	0.01	-0.01	-0.04	-0.03
Highest education, >12y	0.00	0.00	-0.01	0.00	-0.01	0.00	-0.01	-0.01	0.02	0.03	0.07
Swedish-born	0.00	0.02	-0.01	0.01	-0.02	0.00	-0.02	0.02	0.09	-0.05	-0.01
RA clinical characteristics											
Rheumatoid factor positive	0.01	0.01	-0.05	0.01	0.00	0.00	0.01	0.00	0.01	-0.02	-0.13
Disease duration, yrs, mean	0.01	0.00	-0.04	-0.01	0.00	-0.03	0.04	-0.04	0.00	0.06	-0.09
DAS28	0.00	0.00	-0.01	0.00	0.01	0.01	-0.01	0.02	0.05	-0.03	-0.08
HAQ	0.00	-0.01	-0.02	-0.01	0.01	0.00	0.02	0.03	0.07	0.02	-0.07
Conc. MTX	0.01	0.01	0.03	0.01	0.00	0.01	-0.01	-0.03	-0.10	-0.07	-0.14
Conc. non-MTX csDMARD	0.00	0.00	0.04	0.01	0.01	0.01	0.01	-0.04	-0.13	-0.04	-0.07
Conc. oral steroids	0.00	0.01	0.01	0.00	0.01	-0.02	0.05	-0.05	0.01	-0.06	-0.08
Prior b/tsDMARDs											
0	0.02	0.03	0.02	0.02	0.02	0.01	-0.06	-0.01	-0.29	-0.08	-0.18
1-2	-0.02	-0.02	0.03	-0.01	-0.04	0.00	0.02	0.00	0.20	0.06	0.13
3+	-0.01	-0.01	-0.07	-0.01	0.03	-0.01	0.04	0.01	0.11	0.02	0.07
Medical history[a]											
Malignancy	0.01	0.00	0.00	-0.01	-0.01	0.01	0.01	-0.02	-0.10	0.01	0.02
Serious infection	0.01	0.00	0.00	-0.01	-0.02	0.00	0.01	-0.02	0.12	0.00	-0.04
Serious herpes zoster	-0.01	0.01	0.01	0.00	0.00	-0.01	0.01	0.00	-0.05	-0.01	0.05
Joint surgery	0.01	-0.01	-0.04	0.00	0.02	0.01	0.01	0.00	0.01	0.02	-0.02
COPD	0.01	-0.02	-0.01	-0.01	0.00	0.02	0.00	0.00	0.04	-0.02	0.03
Diabetes mellitus	0.00	-0.01	-0.03	0.01	0.01	0.01	0.02	-0.02	0.01	0.00	0.00
ACS	0.01	-0.02	0.00	0.01	0.00	-0.01	-0.01	0.03	-0.02	0.01	-0.03
Stroke	0.01	-0.01	0.01	0.00	0.01	0.01	0.01	0.00	-0.08	-0.01	-0.08
Days hospitalized											
0	-0.02	0.02	-0.01	0.02	0.00	-0.01	-0.02	0.02	0.05	0.02	0.11
1-9	0.00	-0.01	0.04	0.00	-0.01	0.01	0.01	-0.03	-0.08	-0.02	-0.04
10+	0.02	-0.02	-0.04	-0.02	0.00	0.01	0.01	0.00	0.02	0.00	-0.10

Notes: a) Medical history in five years before treatment start, except serious infection (one year before start) and malignancy or joint surgery (ten years before). Standardized bias larger than 0.1 was considered indicative of poor balance, marked in red.

Supplemental table 5. Comparison of hazard ratios from crude, multivariable, and weighted Cox regression

Outcome	Events	IR/1000 PYR	Crude HR	Multivariable[a] Cox HR	Multivariable[a] + start year and smoking Cox HR	IPTW[a] Cox HR
Stop due to Adverse event						
Etanercept	446	18.0	1.0 (Ref.)			
Adalimumab	348	27.9	1.46 (1.27-1.68)	1.15 (1.00-1.32)	1.17 (1.02-1.35)	1.07 (0.92-1.25)
Infliximab	99	12.5	0.69 (0.55-0.85)	1.23 (0.99-1.54)	1.22 (0.98-1.53)	1.25 (0.99-1.58)
Certolizumab pegol	203	33.9	1.96 (1.66-2.32)	1.73 (1.46-2.04)	1.70 (1.44-2.00)	1.53 (1.28-1.82)
Golimumab	191	32.7	1.93 (1.63-2.29)	1.51 (1.28-1.79)	1.45 (1.22-1.71)	1.44 (1.19-1.73)
Abatacept	459	55.2	2.90 (2.56-3.29)	1.19 (1.04-1.36)	1.19 (1.04-1.36)	1.18 (1.03-1.36)
Rituximab	328	21.8	1.30 (1.14-1.50)	0.66 (0.58-0.77)	0.65 (0.56-0.75)	0.67 (0.57-0.78)
Tocilizumab	241	31.1	1.77 (1.52-2.07)	0.71 (0.61-0.83)	0.70 (0.60-0.82)	0.72 (0.60-0.85)
Sarilumab	30	94.7	3.45 (2.38-5.01)	1.18 (0.82-1.71)	1.32 (0.90-1.91)	1.25 (0.79-1.98)
Baricitinib	114	39.0	1.62 (1.32-1.98)	0.57 (0.46-0.70)	0.63 (0.50-0.78)	0.57 (0.45-0.73)
Tofacitinib	56	97.6	4.03 (3.06-5.31)	1.30 (0.98-1.72)	1.40 (1.05-1.86)	1.25 (0.85-1.84)
Major adverse cardiovascular event						
Etanercept	240	10.1	1.0 (Ref.)			
Adalimumab	145	12.2	1.22 (0.99-1.50)	1.24 (1.01-1.53)	1.25 (1.01-1.54)	1.12 (0.89-1.41)
Infliximab	86	11.3	1.13 (0.88-1.44)	1.04 (0.81-1.33)	1.05 (0.82-1.36)	1.00 (0.72-1.39)
Certolizumab pegol	76	13.2	1.31 (1.02-1.70)	1.42 (1.10-1.82)	1.41 (1.09-1.83)	1.31 (0.99-1.73)
Golimumab	60	10.7	1.06 (0.80-1.40)	1.26 (0.96-1.67)	1.28 (0.97-1.70)	1.14 (0.82-1.58)
Abatacept	125	16.1	1.61 (1.30-2.00)	1.08 (0.86-1.36)	1.08 (0.86-1.36)	1.14 (0.87-1.48)
Rituximab	290	21.0	2.07 (1.75-2.46)	1.23 (1.03-1.48)	1.24 (1.04-1.49)	1.27 (1.04-1.55)
Tocilizumab	84	11.4	1.13 (0.88-1.45)	0.92 (0.71-1.20)	0.93 (0.72-1.21)	0.97 (0.70-1.33)
Sarilumab	4	13.1				
Baricitinib	30	10.7	1.10 (0.75-1.61)	0.81 (0.55-1.20)	0.82 (0.54-1.22)	0.83 (0.49-1.42)
Tofacitinib	7	12.9	1.32 (0.62-2.81)	1.02 (0.49-2.16)	1.05 (0.50-2.21)	0.78 (0.31-1.99)
Acute Coronary Syndrome						
Etanercept	127	5.2	1.0 (Ref.)			
Adalimumab	74	6.1	1.16 (0.87-1.54)	1.17 (0.87-1.56)	1.15 (0.86-1.55)	1.00 (0.73-1.38)
Infliximab	44	5.7	1.08 (0.77-1.52)	0.99 (0.70-1.41)	1.00 (0.70-1.41)	0.96 (0.61-1.52)
Certolizumab pegol	37	6.3	1.20 (0.83-1.73)	1.29 (0.89-1.87)	1.29 (0.88-1.88)	1.20 (0.81-1.80)
Golimumab	31	5.4	1.04 (0.70-1.53)	1.21 (0.82-1.79)	1.23 (0.83-1.83)	1.01 (0.64-1.59)
Abatacept	65	8.2	1.55 (1.15-2.10)	1.11 (0.80-1.52)	1.11 (0.81-1.53)	1.10 (0.76-1.59)
Rituximab	160	11.2	2.14 (1.70-2.71)	1.40 (1.09-1.80)	1.41 (1.10-1.81)	1.31 (1.00-1.71)
Tocilizumab	39	5.2	0.99 (0.69-1.42)	0.82 (0.56-1.20)	0.83 (0.57-1.22)	0.89 (0.56-1.41)
Sarilumab	1	3.3				
Baricitinib	12	4.2	0.79 (0.44-1.43)	0.62 (0.34-1.13)	0.62 (0.33-1.14)	0.42 (0.21-0.83)
Tofacitinib	4	7.3				
Stroke						
Etanercept	98	4.0	1.0 (Ref.)			
Adalimumab	61	5.0	1.25 (0.91-1.72)	1.25 (0.91-1.73)	1.24 (0.90-1.72)	1.21 (0.84-1.74)
Infliximab	41	5.3	1.32 (0.91-1.90)	1.22 (0.84-1.77)	1.24 (0.85-1.80)	1.25 (0.77-2.02)
Certolizumab pegol	33	5.6	1.41 (0.95-2.08)	1.48 (1.01-2.18)	1.49 (1.01-2.20)	1.38 (0.90-2.10)
Golimumab	29	5.0	1.25 (0.83-1.90)	1.46 (0.96-2.20)	1.49 (0.98-2.27)	1.59 (0.97-2.61)
Abatacept	52	6.4	1.62 (1.16-2.26)	1.07 (0.75-1.52)	1.07 (0.75-1.53)	1.15 (0.76-1.74)
Rituximab	118	8.1	2.00 (1.53-2.62)	1.18 (0.89-1.56)	1.19 (0.89-1.58)	1.28 (0.95-1.74)
Tocilizumab	40	5.3	1.31 (0.91-1.89)	1.07 (0.73-1.57)	1.09 (0.74-1.60)	1.08 (0.67-1.75)
Sarilumab	3	9.5				
Baricitinib	13	4.5	1.20 (0.67-2.14)	0.83 (0.46-1.52)	0.81 (0.44-1.51)	0.91 (0.42-1.96)
Tofacitinib	1	1.8				

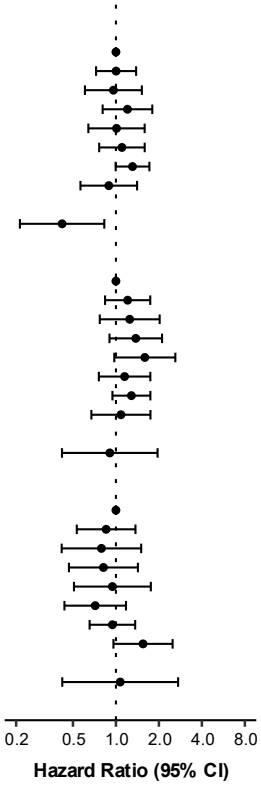
Fatal cardiovascular event						
Etanercept	68	2.7	1.0 (Ref.)			
Adalimumab	36	2.9	1.08 (0.72-1.63)	1.18 (0.79-1.77)	1.13 (0.75-1.70)	0.85 (0.53-1.37)
Infliximab	25	3.1	1.15 (0.73-1.82)	1.02 (0.65-1.61)	0.97 (0.61-1.55)	0.79 (0.42-1.50)
Certolizumab pegol	18	3.0	1.08 (0.65-1.82)	1.17 (0.70-1.96)	1.12 (0.66-1.90)	0.82 (0.47-1.43)
Golimumab	17	2.9	1.04 (0.61-1.77)	1.36 (0.79-2.32)	1.32 (0.77-2.28)	0.94 (0.51-1.76)
Abatacept	33	4.0	1.48 (0.98-2.24)	0.80 (0.52-1.25)	0.81 (0.52-1.28)	0.72 (0.44-1.18)
Rituximab	96	6.4	2.26 (1.65-3.09)	1.05 (0.75-1.47)	1.02 (0.73-1.44)	0.94 (0.65-1.36)
Tocilizumab	41	5.3	1.91 (1.30-2.82)	1.53 (1.00-2.35)	1.51 (0.98-2.32)	1.55 (0.96-2.50)
Sarilumab	0	0.0				
Baricitinib	11	3.8	1.58 (0.83-3.01)	1.02 (0.52-1.99)	1.15 (0.57-2.33)	1.07 (0.42-2.73)
Tofacitinib	2	3.5				
Liver disease						
Etanercept	29	1.2	1.0 (Ref.)			
Adalimumab	14	1.1	0.95 (0.50-1.80)	0.94 (0.49-1.79)	0.91 (0.47-1.77)	0.73 (0.36-1.47)
Infliximab	18	2.3	1.92 (1.07-3.46)	1.98 (1.08-3.64)	2.05 (1.11-3.79)	1.87 (0.86-4.04)
Certolizumab pegol	14	2.4	1.97 (1.04-3.73)	2.18 (1.15-4.15)	2.36 (1.23-4.52)	1.76 (0.87-3.54)
Golimumab	3	0.5				
Abatacept	14	1.7	1.43 (0.75-2.72)	1.22 (0.61-2.44)	1.23 (0.62-2.47)	1.60 (0.72-3.57)
Rituximab	33	2.2	1.90 (1.16-3.12)	1.55 (0.89-2.68)	1.57 (0.91-2.72)	1.58 (0.88-2.85)
Tocilizumab	11	1.4	1.21 (0.60-2.42)	1.12 (0.53-2.37)	1.15 (0.54-2.42)	1.06 (0.43-2.63)
Sarilumab	2	6.4				
Baricitinib	5	1.7	1.41 (0.54-3.69)	1.20 (0.45-3.20)	0.99 (0.35-2.82)	0.62 (0.18-2.16)
Tofacitinib	1	1.8				
All-cause mortality						
Etanercept	219	8.8	1.0 (Ref.)			
Adalimumab	100	8.0	0.93 (0.73-1.18)	1.03 (0.81-1.30)	1.02 (0.81-1.29)	0.88 (0.67-1.16)
Infliximab	92	11.6	1.31 (1.03-1.67)	1.14 (0.89-1.46)	1.16 (0.91-1.49)	1.05 (0.75-1.47)
Certolizumab pegol	55	9.2	1.03 (0.77-1.38)	1.12 (0.84-1.49)	1.12 (0.84-1.50)	0.98 (0.71-1.35)
Golimumab	50	8.6	0.95 (0.70-1.29)	1.19 (0.87-1.61)	1.23 (0.90-1.67)	1.08 (0.75-1.55)
Abatacept	140	16.8	1.99 (1.61-2.45)	1.27 (1.01-1.59)	1.27 (1.01-1.60)	1.32 (1.01-1.73)
Rituximab	366	24.3	2.65 (2.24-3.14)	1.36 (1.14-1.63)	1.38 (1.15-1.64)	1.40 (1.15-1.71)
Tocilizumab	112	14.5	1.62 (1.29-2.04)	1.44 (1.13-1.84)	1.47 (1.15-1.88)	1.41 (1.06-1.88)
Sarilumab	3	9.5				
Baricitinib	55	18.8	2.60 (1.93-3.51)	1.90 (1.38-2.61)	1.86 (1.33-2.60)	2.27 (1.51-3.40)
Tofacitinib	5	8.7	1.23 (0.51-2.98)	1.02 (0.43-2.41)	1.04 (0.44-2.45)	1.09 (0.40-2.92)
Any hospitalization						
Etanercept	2465	128.2	1.0 (Ref.)			
Adalimumab	1329	139.3	1.04 (0.97-1.11)	1.07 (1.00-1.15)	1.07 (1.00-1.14)	1.04 (0.97-1.12)
Infliximab	961	164.6	1.27 (1.18-1.36)	1.26 (1.17-1.36)	1.21 (1.12-1.31)	1.18 (1.07-1.29)
Certolizumab pegol	679	158.0	1.24 (1.14-1.35)	1.26 (1.16-1.38)	1.20 (1.10-1.31)	1.15 (1.05-1.26)
Golimumab	570	128.3	1.04 (0.95-1.14)	1.10 (1.01-1.21)	1.06 (0.96-1.16)	1.06 (0.96-1.17)
Abatacept	1183	202.7	1.50 (1.40-1.61)	1.08 (1.01-1.16)	1.08 (1.01-1.16)	1.08 (0.99-1.18)
Rituximab	2091	232.3	1.82 (1.72-1.93)	1.25 (1.18-1.34)	1.23 (1.15-1.31)	1.28 (1.19-1.37)
Tocilizumab	973	182.2	1.41 (1.31-1.52)	1.12 (1.04-1.22)	1.11 (1.02-1.20)	1.05 (0.96-1.16)
Sarilumab	53	194.1	1.19 (0.91-1.55)	0.92 (0.69-1.23)	1.05 (0.78-1.41)	1.40 (0.98-2.00)
Baricitinib	438	179.6	1.19 (1.07-1.31)	0.90 (0.80-1.00)	1.00 (0.90-1.12)	0.91 (0.80-1.04)
Tofacitinib	94	198.4	1.29 (1.05-1.59)	0.96 (0.77-1.19)	1.07 (0.86-1.33)	0.69 (0.49-0.96)
Serious infection						
Etanercept	571	24.8	1.0 (Ref.)			
Adalimumab	343	29.6	1.17 (1.02-1.33)	1.20 (1.05-1.37)	1.21 (1.06-1.39)	1.12 (0.96-1.31)
Infliximab	265	36.0	1.45 (1.26-1.68)	1.41 (1.21-1.63)	1.37 (1.18-1.59)	1.32 (1.09-1.60)
Certolizumab pegol	167	30.4	1.25 (1.05-1.48)	1.28 (1.07-1.53)	1.22 (1.02-1.46)	1.10 (0.91-1.33)
Golimumab	134	24.9	1.03 (0.85-1.24)	1.13 (0.93-1.37)	1.09 (0.90-1.32)	1.07 (0.86-1.32)
Abatacept	278	38.6	1.53 (1.32-1.76)	1.12 (0.97-1.30)	1.11 (0.96-1.29)	1.08 (0.91-1.29)
Rituximab	609	47.5	1.96 (1.75-2.19)	1.29 (1.14-1.46)	1.28 (1.13-1.44)	1.31 (1.15-1.50)
Tocilizumab	235	33.5	1.36 (1.17-1.58)	1.09 (0.93-1.27)	1.07 (0.91-1.26)	0.98 (0.80-1.19)
Sarilumab	7	23.3	0.80 (0.38-1.67)	0.60 (0.28-1.27)	0.72 (0.34-1.53)	0.61 (0.24-1.53)
Baricitinib	105	39.5	1.43 (1.16-1.77)	1.11 (0.89-1.38)	1.26 (1.00-1.58)	0.98 (0.75-1.29)
Tofacitinib	25	47.3	1.69 (1.14-2.52)	1.30 (0.88-1.94)	1.46 (0.98-2.18)	0.89 (0.47-1.69)
Tuberculosis						

Etanercept	1	0.0				
Adalimumab	3	0.2				
Infliximab	4	0.5				
Certolizumab pegol	4	0.7				
Golimumab	2	0.3				
Abatacept	0	0.0				
Rituximab	2	0.1				
Tocilizumab	0	0.0				
Sarilumab	0	0.0				
Baricitinib	0	0.0				
Tofacitinib	0	0.0				
Herpes zoster						
Etanercept	50	2.0	1.0 (Ref.)			
Adalimumab	38	3.1	1.50 (0.99-2.30)	1.53 (1.01-2.34)	1.48 (0.97-2.27)	1.48 (0.90-2.43)
Infliximab	27	3.4	1.68 (1.06-2.69)	1.67 (1.03-2.69)	1.62 (1.00-2.64)	1.64 (0.90-2.99)
Certolizumab pegol	18	3.0	1.50 (0.87-2.57)	1.55 (0.90-2.66)	1.49 (0.86-2.58)	1.32 (0.73-2.38)
Golimumab	15	2.6	1.28 (0.72-2.28)	1.36 (0.76-2.45)	1.34 (0.74-2.41)	1.20 (0.63-2.28)
Abatacept	23	2.8	1.39 (0.85-2.28)	0.98 (0.59-1.63)	0.99 (0.59-1.64)	0.89 (0.49-1.64)
Rituximab	55	3.7	1.82 (1.24-2.68)	1.21 (0.80-1.82)	1.21 (0.80-1.82)	1.21 (0.77-1.91)
Tocilizumab	14	1.8	0.90 (0.49-1.62)	0.71 (0.38-1.33)	0.70 (0.37-1.31)	1.06 (0.52-2.17)
Sarilumab	1	3.2				
Baricitinib	29	10.0	5.01 (3.15-7.96)	3.73 (2.27-6.13)	4.13 (2.37-7.19)	3.82 (2.05-7.09)
Tofacitinib	8	14.1	7.04 (3.33-14.90)	5.28 (2.39-11.67)	5.92 (2.64-13.30)	4.00 (1.59-10.06)
Depression						
Etanercept	91	3.8	1.0 (Ref.)			
Adalimumab	42	3.5	0.92 (0.64-1.32)	0.95 (0.66-1.37)	0.94 (0.65-1.37)	0.97 (0.65-1.45)
Infliximab	31	4.0	1.08 (0.72-1.62)	1.07 (0.71-1.62)	1.04 (0.69-1.58)	1.12 (0.65-1.93)
Certolizumab pegol	17	3.0	0.81 (0.48-1.35)	0.75 (0.45-1.26)	0.73 (0.43-1.23)	0.64 (0.37-1.11)
Golimumab	13	2.3	0.63 (0.35-1.13)	0.63 (0.35-1.13)	0.63 (0.35-1.13)	0.59 (0.32-1.10)
Abatacept	40	5.0	1.29 (0.89-1.87)	1.13 (0.77-1.65)	1.13 (0.77-1.65)	0.96 (0.60-1.53)
Rituximab	80	5.6	1.52 (1.13-2.06)	1.32 (0.96-1.83)	1.31 (0.95-1.82)	1.37 (0.95-1.97)
Tocilizumab	42	5.7	1.53 (1.06-2.20)	1.35 (0.92-1.99)	1.35 (0.92-1.99)	1.28 (0.82-1.99)
Sarilumab	1	3.3				
Baricitinib	18	6.5	1.44 (0.87-2.40)	1.34 (0.79-2.28)	1.51 (0.85-2.67)	1.15 (0.63-2.08)
Tofacitinib	5	9.0	2.00 (0.81-4.93)	1.60 (0.64-3.96)	1.76 (0.70-4.41)	0.98 (0.30-3.17)
Suicidality						
Etanercept	35	1.4	1.0 (Ref.)			
Adalimumab	21	1.7	1.18 (0.69-2.01)	1.19 (0.69-2.04)	1.29 (0.74-2.22)	1.03 (0.56-1.90)
Infliximab	13	1.7	1.15 (0.61-2.17)	1.07 (0.56-2.06)	1.11 (0.57-2.14)	1.32 (0.56-3.14)
Certolizumab pegol	7	1.2	0.82 (0.37-1.83)	0.77 (0.34-1.72)	0.71 (0.31-1.63)	0.80 (0.33-1.97)
Golimumab	6	1.0	0.72 (0.30-1.71)	0.71 (0.30-1.69)	0.68 (0.28-1.62)	0.57 (0.22-1.48)
Abatacept	13	1.6	1.10 (0.59-2.09)	0.94 (0.48-1.84)	0.91 (0.47-1.76)	1.05 (0.45-2.46)
Rituximab	23	1.5	1.09 (0.64-1.84)	0.92 (0.53-1.60)	0.93 (0.53-1.63)	0.78 (0.41-1.47)
Tocilizumab	18	2.4	1.64 (0.93-2.91)	1.44 (0.79-2.64)	1.45 (0.80-2.64)	1.17 (0.58-2.34)
Sarilumab	2	6.5				
Baricitinib	6	2.1	1.42 (0.60-3.38)	1.38 (0.55-3.44)	1.71 (0.65-4.47)	0.94 (0.37-2.40)
Tofacitinib	1	1.8				

Notes: [a)] model included (i.e., adjusted for) age, sex, immigrant status, highest achieved education, RF/ACPA, RA duration, previous b/tsDMARD use, co-medication with conventional synthetic DMARDs and glucocorticosteroids, the 28-joint disease activity score (DAS28-CRP),the Health Assessment Questionnaire-Disability Index (HAQ), history of malignancy, infections, joint surgery, chronic pulmonary disease, diabetes, cardiovascular disease, depression, and the sum of days hospitalized in last five years.

Figure S1. MACE component outcomes among all Swedish RA patients who started b/tsDMARD 2010-2020.

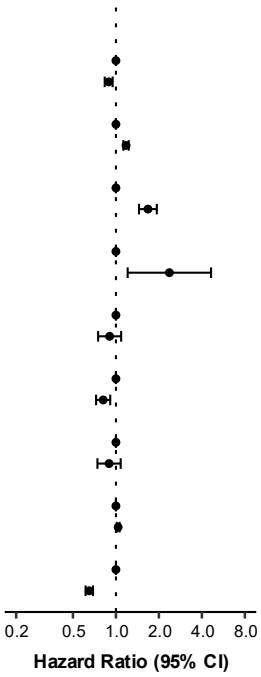
Outcome	Events	Crude IR	wIR	wHR (95% CI)
Acute coronary syndrome				
Etanercept	127	5.2	6.6	1.0 (Ref.)
Adalimumab	74	6.1	6.7	1.00 (0.73-1.38)
Infliximab	44	5.7	6.4	0.96 (0.61-1.52)
Certolizumab	37	6.3	8.0	1.20 (0.81-1.80)
Golimumab	31	5.4	6.7	1.01 (0.64-1.59)
Abatacept	65	8.2	7.3	1.10 (0.76-1.59)
Rituximab	160	11.2	8.7	1.31 (1.00-1.71)
Tocilizumab	39	5.2	5.9	0.89 (0.56-1.41)
Sarilumab	1	3.3	4.3	
Baricitinib	12	4.2	2.8	0.42 (0.21-0.83)
Tofacitinib	4	7.3	4.6	
Stroke				
Etanercept	98	4.0	4.8	1.0 (Ref.)
Adalimumab	61	5.0	5.7	1.21 (0.84-1.74)
Infliximab	41	5.3	5.9	1.25 (0.77-2.02)
Certolizumab	33	5.6	6.5	1.38 (0.90-2.10)
Golimumab	29	5.0	7.6	1.59 (0.97-2.61)
Abatacept	52	6.4	5.4	1.15 (0.76-1.74)
Rituximab	118	8.1	6.2	1.28 (0.95-1.74)
Tocilizumab	40	5.3	5.2	1.08 (0.67-1.75)
Sarilumab	3	9.5	11.2	
Baricitinib	13	4.5	4.1	0.91 (0.42-1.96)
Tofacitinib	1	1.8	0.6	
Fatal cardiovascular event				
Etanercept	68	2.7	4.4	1.0 (Ref.)
Adalimumab	36	2.9	3.7	0.85 (0.53-1.37)
Infliximab	25	3.1	3.5	0.79 (0.42-1.50)
Certolizumab	18	3.0	3.7	0.82 (0.47-1.43)
Golimumab	17	2.9	4.3	0.94 (0.51-1.76)
Abatacept	33	4.0	3.1	0.72 (0.44-1.18)
Rituximab	96	6.4	4.4	0.94 (0.65-1.36)
Tocilizumab	41	5.3	7.0	1.55 (0.96-2.50)
Sarilumab	0	0.0	0.0	
Baricitinib	11	3.8	4.0	1.07 (0.42-2.73)
Tofacitinib	2	3.5	3.9	



Crude and weighted incidence rate per 1000 person-years of cardiovascular outcomes by b/tsDMARD, and adjusted hazard ratios versus etanercept. wIR, inverse probability of treatment weighted incidence rate per 1000 person-years, adjusted for demographics, RA clinical characteristics, and comorbidity; wHR, weighted hazard ratio from Cox regression.

Figure S2. Incidence rate of safety outcomes comparing Swedish RA patients who started b/tsDMARD 2010-2020 to b/tsDMARD-naive patients with RA.

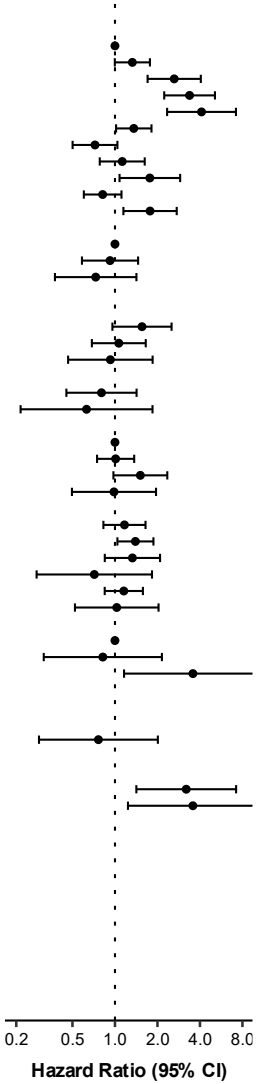
Outcome	Events	IR	HR (95% CI)
Major adverse cardiovascular event			
RA, bionaïve	8989	24.8	1.0 (Ref.)
RA, b/tsDMARD treated	1147	13.1	0.89 (0.83-0.95)
Serious Infection			
RA, bionaïve	12859	36.9	1.0 (Ref.)
RA, b/tsDMARD treated	2739	32.8	1.18 (1.13-1.23)
Diagnosed herpes zoster			
RA, bionaïve	903	2.3	1.0 (Ref.)
RA, b/tsDMARD treated	278	3.1	1.68 (1.45-1.93)
Tuberculosis			
RA, bionaïve	21	0.1	1.0 (Ref.)
RA, b/tsDMARD treated	16	0.2	2.37 (1.21-4.64)
Liver disease			
RA, bionaïve	774	1.9	1.0 (Ref.)
RA, b/tsDMARD treated	144	1.6	0.90 (0.75-1.09)
Diagnosed depression			
RA, bionaïve	1793	4.6	1.0 (Ref.)
RA, b/tsDMARD treated	380	4.3	0.81 (0.73-0.91)
Suicide (incl. attempted)			
RA, bionaïve	673	1.7	1.0 (Ref.)
RA, b/tsDMARD treated	145	1.6	0.90 (0.74-1.08)
Any hospitalization			
RA, bionaïve	38575	167.7	1.0 (Ref.)
RA, b/tsDMARD treated	10836	162.4	1.04 (1.01-1.06)
All-cause mortality			
RA, bionaïve	16036	39.7	1.0 (Ref.)
RA, b/tsDMARD treated	1197	13.0	0.65 (0.61-0.69)



IR: age and sex-standardized incidence rate per 1000 person-years, and age-sex adjusted hazard ratios from Cox regression.

Figure S3. Crude and weighted incidence rate per 1000 person-years of selected safety outcomes by b/tsDMARD, and adjusted hazard ratios versus etanercept, among all Swedish RA patients who started treatment *2017-2020*, from JAKi market entry, followed until 30 June 2021.

Outcome	Events	Crude IR	wIR	wHR (95% CI)
Stop for adverse events				
Etanercept	109	14.7	26.1	
Adalimumab	129	35.6	41.5	1.33 (1.00-1.77)
Infliximab	29	28.5	75.1	2.63 (1.70-4.06)
Certolizumab	33	69.4	97.9	3.38 (2.23-5.11)
Golimumab	18	89.3	115.0	4.10 (2.34-7.19)
Abatacept	114	57.1	37.2	1.36 (1.02-1.81)
Rituximab	57	23.0	18.9	0.72 (0.50-1.04)
Tocilizumab	55	46.9	29.9	1.13 (0.78-1.63)
Sarilumab	30	94.7	57.4	1.77 (1.08-2.90)
Baricitinib	114	39.0	23.0	0.82 (0.60-1.11)
Tofacitinib	52	95.9	50.2	1.77 (1.15-2.74)
Major adverse cardiovascular event				
Etanercept	68	9.5	12.5	1.0 (Ref.)
Adalimumab	36	10.3	11.0	0.92 (0.58-1.46)
Infliximab	12	12.1	8.9	0.73 (0.38-1.42)
Certolizumab	4	8.5	10.5	
Golimumab	2	10.5	11.4	
Abatacept	40	21.4	19.2	1.55 (0.96-2.52)
Rituximab	42	18.0	13.4	1.06 (0.69-1.65)
Tocilizumab	14	12.5	11.7	0.93 (0.47-1.85)
Sarilumab	4	13.1	15.8	
Baricitinib	30	10.7	9.9	0.80 (0.45-1.42)
Tofacitinib	6	11.7	7.7	0.63 (0.21-1.84)
Serious Infection				
Etanercept	159	22.7	28.1	1.0 (Ref.)
Adalimumab	93	26.6	30.4	1.01 (0.75-1.37)
Infliximab	42	44.1	43.9	1.51 (0.98-2.35)
Certolizumab	10	21.5	28.8	0.98 (0.50-1.95)
Golimumab	4	21.4	32.6	
Abatacept	65	37.4	33.5	1.17 (0.83-1.65)
Rituximab	102	46.0	39.3	1.40 (1.04-1.87)
Tocilizumab	44	40.2	37.7	1.33 (0.85-2.09)
Sarilumab	7	23.3	21.8	0.71 (0.28-1.83)
Baricitinib	105	39.5	33.6	1.16 (0.85-1.58)
Tofacitinib	24	48.0	29.9	1.03 (0.52-2.04)
Diagnosed herpes zoster				
Etanercept	15	2.0	2.9	1.0 (Ref.)
Adalimumab	8	2.2	2.4	0.82 (0.31-2.15)
Infliximab	8	8.0	10.3	3.56 (1.16-10.96)
Certolizumab	0	0.0	0.0	
Golimumab	0	0.0	0.0	
Abatacept	4	2.0	2.1	
Rituximab	8	3.3	2.2	0.76 (0.29-2.01)
Tocilizumab	2	1.7	3.8	
Sarilumab	1	3.2	0.9	
Baricitinib	29	10.0	9.8	3.20 (1.42-7.21)
Tofacitinib	8	14.9	10.7	3.56 (1.24-10.28)



Outcome	Events	Crude IR	wIR	wHR (95% CI)
Liver disease				
Etanercept	13	1.8	2.8	1.0 (Ref.)
Adalimumab	4	1.1	1.0	
Infliximab	2	2.0	3.0	
Certolizumab	2	4.2	6.2	
Golimumab	0	0.0	0.0	
Abatacept	6	3.1	3.7	1.31 (0.39-4.40)
Rituximab	5	2.1	1.6	0.58 (0.19-1.81)
Tocilizumab	2	1.7	3.9	
Sarilumab	2	6.4	5.7	
Baricitinib	5	1.7	1.0	0.34 (0.09-1.29)
Tofacitinib	1	1.9	0.7	
Diagnosed depression				
Etanercept	27	3.8	4.5	1.0 (Ref.)
Adalimumab	11	3.2	3.3	0.63 (0.29-1.36)
Infliximab	2	2.0	2.1	
Certolizumab	3	6.7	5.4	
Golimumab	0	0.0	0.0	
Abatacept	4	2.1	2.4	
Rituximab	11	4.7	4.9	1.07 (0.41-2.77)
Tocilizumab	9	8.1	7.9	1.73 (0.69-4.35)
Sarilumab	1	3.3	1.3	
Baricitinib	18	6.5	5.3	1.08 (0.52-2.25)
Tofacitinib	5	9.5	4.8	0.98 (0.28-3.41)
Suicide (incl. attempted)				
Etanercept	10	1.4	1.5	1.0 (Ref.)
Adalimumab	5	1.4	1.4	0.94 (0.26-3.32)
Infliximab	1	1.0	3.2	
Certolizumab	1	2.1	2.1	
Golimumab	0	0.0	0.0	
Abatacept	3	1.5	4.1	
Rituximab	3	1.2	0.9	
Tocilizumab	0	0.0	0.0	
Sarilumab	2	6.5	2.8	
Baricitinib	6	2.1	1.5	1.06 (0.31-3.69)
Tofacitinib	1	1.9	0.3	
Any hospitalization				
Etanercept	788	122.9	146.1	1.0 (Ref.)
Adalimumab	449	138.7	168.1	1.07 (0.94-1.21)
Infliximab	134	156.7	156.4	1.03 (0.81-1.31)
Certolizumab	85	216.1	213.2	1.39 (1.09-1.77)
Golimumab	26	152.9	224.8	1.49 (0.98-2.25)
Abatacept	316	196.9	164.4	1.10 (0.94-1.30)
Rituximab	416	221.4	183.5	1.25 (1.08-1.44)
Tocilizumab	179	186.5	180.5	1.22 (0.98-1.52)
Sarilumab	53	194.1	274.5	1.71 (1.19-2.46)
Baricitinib	438	179.6	164.2	1.09 (0.93-1.26)
Tofacitinib	87	192.8	119.2	0.79 (0.56-1.13)
All-cause mortality				
Etanercept	52	7.0	9.9	1.0 (Ref.)
Adalimumab	19	5.2	7.1	0.90 (0.48-1.70)
Infliximab	14	13.8	12.4	1.36 (0.61-3.01)
Certolizumab	5	10.5	15.0	1.72 (0.65-4.52)
Golimumab	0	0.0	0.0	
Abatacept	41	20.5	20.3	2.15 (1.30-3.56)
Rituximab	50	20.2	16.5	1.67 (1.05-2.63)
Tocilizumab	17	14.5	16.7	1.70 (0.87-3.32)
Sarilumab	3	9.5	9.8	
Baricitinib	55	18.8	22.0	2.43 (1.48-4.00)
Tofacitinib	4	7.4	9.1	

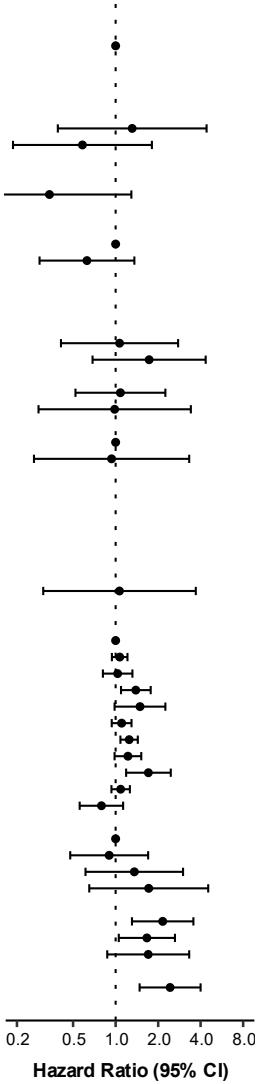
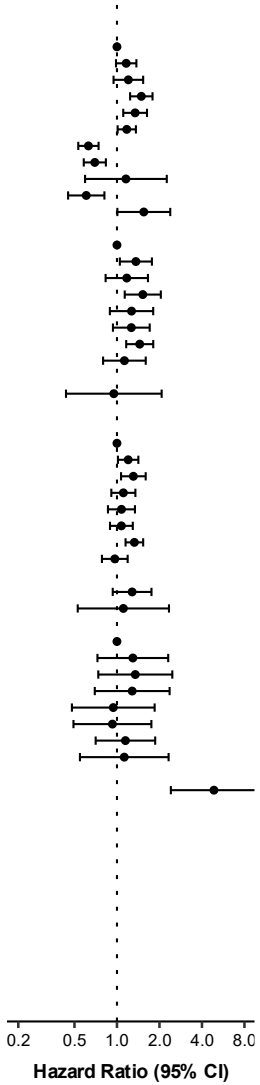
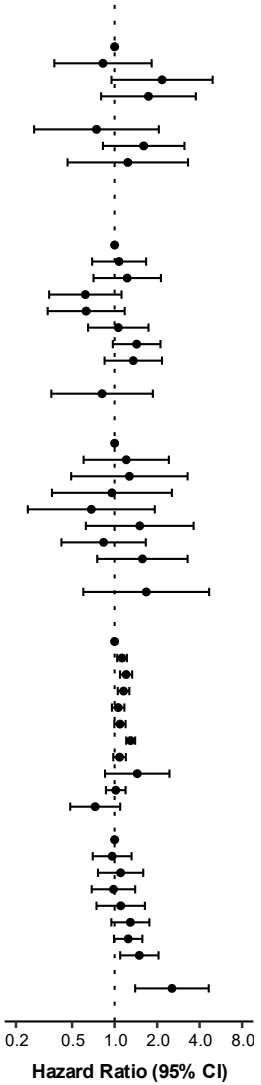


Figure S4. Crude and weighted incidence rate per 1000 person-years of selected safety outcomes by b/tsDMARD, and adjusted hazard ratios versus etanercept, among all Swedish RA patients who started treatment 2010-2020, followed *until the COVID-19 pandemic, 28 Feb 2020.*

Outcome	Events	Crude IR	wIR	wHR (95% CI)
Stop for adverse events				
Etanercept	397	19.9	32.9	
Adalimumab	291	30.9	38.0	1.16 (0.98-1.37)
Infliximab	92	12.9	40.6	1.20 (0.95-1.53)
Certolizumab	191	35.8	46.2	1.49 (1.24-1.79)
Golimumab	177	34.0	41.9	1.34 (1.11-1.63)
Abatacept	411	59.8	40.0	1.17 (1.01-1.36)
Rituximab	287	22.5	18.8	0.63 (0.53-0.74)
Tocilizumab	223	33.4	22.0	0.70 (0.58-0.83)
Sarilumab	13	104.6	64.1	1.16 (0.59-2.25)
Baricitinib	78	50.4	29.7	0.61 (0.45-0.81)
Tofacitinib	44	128.8	72.5	1.55 (1.01-2.38)
Major adverse cardiovascular event				
Etanercept	182	9.5	11.2	1.0 (Ref.)
Adalimumab	121	13.4	15.1	1.36 (1.05-1.77)
Infliximab	80	11.7	13.0	1.17 (0.83-1.66)
Certolizumab	71	13.8	16.9	1.52 (1.14-2.05)
Golimumab	53	10.5	14.1	1.27 (0.89-1.81)
Abatacept	100	15.5	14.0	1.26 (0.94-1.71)
Rituximab	256	21.8	16.3	1.45 (1.16-1.81)
Tocilizumab	72	11.3	12.6	1.13 (0.80-1.60)
Sarilumab	1	8.2	12.6	
Baricitinib	13	8.7	10.0	0.95 (0.44-2.07)
Tofacitinib	3	9.2	2.7	
Serious Infection				
Etanercept	488	26.3	32.4	1.0 (Ref.)
Adalimumab	280	32.0	38.9	1.20 (1.02-1.42)
Infliximab	247	37.3	42.6	1.31 (1.07-1.60)
Certolizumab	158	32.2	35.3	1.11 (0.91-1.35)
Golimumab	126	26.1	34.3	1.08 (0.86-1.34)
Abatacept	243	40.6	35.3	1.08 (0.89-1.29)
Rituximab	553	50.6	41.8	1.33 (1.15-1.53)
Tocilizumab	213	35.1	30.8	0.97 (0.78-1.19)
Sarilumab	4	33.3	43.1	
Baricitinib	76	54.2	48.4	1.28 (0.93-1.76)
Tofacitinib	19	59.5	41.3	1.11 (0.53-2.34)
Diagnosed herpes zoster				
Etanercept	45	2.3	2.7	1.0 (Ref.)
Adalimumab	26	2.8	3.5	1.30 (0.73-2.31)
Infliximab	24	3.4	3.7	1.35 (0.74-2.47)
Certolizumab	17	3.2	3.5	1.28 (0.70-2.36)
Golimumab	13	2.5	2.6	0.94 (0.48-1.85)
Abatacept	21	3.1	2.5	0.93 (0.49-1.75)
Rituximab	49	3.9	3.1	1.15 (0.71-1.87)
Tocilizumab	14	2.1	3.1	1.13 (0.55-2.32)
Sarilumab	1	8.1	2.2	
Baricitinib	20	13.0	12.9	4.87 (2.41-9.83)
Tofacitinib	4	11.8	10.2	



Outcome	Events	Crude IR	wIR	wHR (95% CI)
Liver disease				
Etanercept	22	1.1	1.4	1.0 (Ref.)
Adalimumab	11	1.2	1.2	0.83 (0.37-1.83)
Infliximab	17	2.4	3.1	2.17 (0.95-4.95)
Certolizumab	12	2.3	2.4	1.74 (0.80-3.76)
Golimumab	3	0.6	0.6	
Abatacept	7	1.0	1.1	0.74 (0.27-2.06)
Rituximab	27	2.2	2.2	1.61 (0.83-3.12)
Tocilizumab	10	1.5	1.7	1.24 (0.46-3.31)
Sarilumab	1	8.2	10.8	
Baricitinib	3	2.0	1.4	
Tofacitinib	0	0.0	0.0	
Diagnosed depression				
Etanercept	78	4.1	4.1	1.0 (Ref.)
Adalimumab	35	3.9	4.4	1.07 (0.69-1.67)
Infliximab	31	4.5	5.1	1.23 (0.71-2.13)
Certolizumab	15	2.9	2.5	0.62 (0.34-1.12)
Golimumab	13	2.6	2.6	0.63 (0.34-1.18)
Abatacept	36	5.5	4.4	1.06 (0.65-1.74)
Rituximab	74	6.1	5.7	1.43 (0.97-2.11)
Tocilizumab	39	6.1	5.5	1.35 (0.85-2.16)
Sarilumab	0	0.0	0.0	
Baricitinib	8	5.4	3.9	0.81 (0.36-1.86)
Tofacitinib	4	12.0	4.5	
Suicide (incl. attempted)				
Etanercept	26	1.3	1.4	1.0 (Ref.)
Adalimumab	16	1.7	1.8	1.21 (0.60-2.42)
Infliximab	11	1.6	1.9	1.27 (0.49-3.28)
Certolizumab	6	1.1	1.4	0.96 (0.36-2.54)
Golimumab	5	1.0	1.0	0.68 (0.24-1.93)
Abatacept	13	1.9	2.2	1.51 (0.63-3.63)
Rituximab	20	1.6	1.2	0.84 (0.42-1.66)
Tocilizumab	17	2.6	2.2	1.57 (0.75-3.29)
Sarilumab	0	0.0	0.0	
Baricitinib	5	3.3	2.7	1.68 (0.60-4.68)
Tofacitinib	0	0.0	0.0	
Any hospitalization				
Etanercept	2082	132.6	159.7	1.0 (Ref.)
Adalimumab	1075	150.2	181.1	1.13 (1.04-1.22)
Infliximab	910	170.7	196.6	1.21 (1.09-1.33)
Certolizumab	638	162.8	180.3	1.16 (1.05-1.27)
Golimumab	542	133.6	162.7	1.06 (0.96-1.17)
Abatacept	1049	213.0	178.5	1.09 (1.00-1.20)
Rituximab	1906	244.1	199.3	1.30 (1.21-1.40)
Tocilizumab	912	195.1	169.2	1.08 (0.98-1.20)
Sarilumab	26	227.1	313.8	1.45 (0.86-2.44)
Baricitinib	300	222.3	203.9	1.02 (0.87-1.20)
Tofacitinib	66	225.5	142.1	0.73 (0.48-1.09)
All-cause mortality				
Etanercept	165	8.3	11.3	1.0 (Ref.)
Adalimumab	76	8.1	10.9	0.96 (0.70-1.32)
Infliximab	76	10.7	12.3	1.10 (0.76-1.59)
Certolizumab	46	8.6	11.4	0.98 (0.69-1.40)
Golimumab	43	8.2	12.9	1.10 (0.74-1.64)
Abatacept	101	14.7	14.3	1.29 (0.95-1.76)
Rituximab	275	21.6	14.9	1.25 (0.99-1.57)
Tocilizumab	94	14.1	17.3	1.50 (1.10-2.04)
Sarilumab	1	8.0	12.3	
Baricitinib	22	14.2	20.6	2.55 (1.40-4.64)
Tofacitinib	2	5.9	6.0	



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Real-world safety of b/tsDMARDS in the ARTIS registry

Currently available b/tsDMARDs have acceptable and on the whole similar safety profiles in a real-world population

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease that mainly affects a person's joints, causing pain and disability. Rheumatoid arthritis can affect people of all ages, but it most often starts between the ages of 40 and 60. It is more common in women than men.

There are many treatments available for rheumatoid arthritis, including disease-modifying antirheumatic drugs (often shortened to DMARDs). The term DMARD includes traditional drugs such as methotrexate, as well as newer biologic and targeted synthetic therapies (b/tsDMARDs). These work by targeting specific molecules that cause inflammation. By doing so, they reduce inflammation in the joints and decrease pain and disease worsening.

All drugs go through clinical trials as part of their development, but they are also closely monitored once, they are approved and available to all patients in normal everyday care. Structured follow-up in registry projects allows researchers to collect real-world data that can play an important role in evaluating safety. Anti-Rheumatic Therapies in Sweden (ARTIS) is a long-standing registry in Sweden that is collecting information on b/tsDMARDs used in clinical practice for people with rheumatoid arthritis.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to assess and compare rates of key safety outcomes for individual b/tsDMARDs in people with rheumatoid arthritis, and to update previous reports to include newer treatments such as the Janus kinase inhibitors (JAKi).

WHO WAS STUDIED?

The study looked at over 20,000 patients with rheumatoid arthritis. Everyone was living in Sweden, and had been recorded as having started a b/tsDMARD between 2010 and 2020.

HOW WAS THE STUDY CONDUCTED?

This was a nationwide register-based cohort study in Sweden. Everyone taking part was followed through the ARTIS clinical register, which was linked to Sweden's system of national healthcare databases. People in a registry are not randomised to receive any particular drug, but instead are simply observed as they are looked after in normal clinical practice, and their data recorded.

The authors compared the rates of ten selected outcomes between individual b/tsDMARDs. The results were adjusted to take into account demographics, disease characteristics, and any other diseases that people had alongside their rheumatoid arthritis (often called a comorbidity).

The ten outcomes were (1) treatment discontinuation due to side effects, (2) major adverse cardiovascular events such as stroke or heart attacks, (3) serious infections requiring hospitalisation, (4) herpes zoster infection, (5) tuberculosis, (6) liver disease, (7) depression, (8) attempted or completed suicide, (9) any hospitalisation, and (10) all-cause mortality.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The main finding was that – with a few exceptions – similarities in safety profile outweighed differences. The safety of b/tsDMARDs has been monitored with regards to many pre-defined outcomes thus making these among the most extensively studied drugs on the market.

There were marked differences in the number of people who stopped taking a drug because of its side effects. The least frequent discontinuations were for rituximab, and the most frequent for tofacitinib, but few significant differences were observed for the serious adverse events under study.

Neither cardiovascular events nor general serious infections were more frequent on baricitinib or tofacitinib versus bDMARDs, but JAKi were associated with higher rates of hospital-treated herpes zoster.

The authors noted that low numbers of events limited some comparisons, in particular for sarilumab and tofacitinib. The scarcity of tuberculosis, liver disease, and suicide also made these results inconclusive.

ARE THESE FINDINGS NEW?

Yes. These findings provide new long-term data for side effects of older drugs, and new short-term data for side effects of newer drugs for the treatment of rheumatoid arthritis.

WHAT ARE THE LIMITATIONS OF THE STUDY?

One key limitation is that due to the study design the results might have certain inaccuracies. Also, despite this study looking at a large number of patients from across Sweden, the small number of people with tuberculosis, liver disease, and suicide made these results inconclusive. It would be good to add to these findings with some more specific studies that can be tailored to special circumstances, time scales, and potentially important factors for individual safety concerns.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

The authors think these findings will be important for updating treatment guidelines for rheumatoid arthritis. They will also be interesting to people involved in making policy decisions, and prescribers in everyday practice who need to make treatment choices for their patients. The authors will continue to monitor the relative safety of current and future treatments in rheumatology.

WHAT DOES THIS MEAN FOR ME?

This study found no new or previously unknown safety concerns. If you have rheumatoid arthritis, these are reassuring findings. There are a lot of different treatments available to you which can help to modify and limit your disease and its impact on your health and wellbeing.

If you have any concerns about your disease or its treatment, you should talk to your doctor or a healthcare professional involved in your care.

Date prepared: March 2023

Summary based on research article published on: 14 February 2023

From: Frisell T, *et al*. Safety of biological and targeted synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis as used in clinical practice: results from the ARTIS programme. Ann Rheum Dis 2023;82(5):601–10. doi:10.1136/ard-2022-223762