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Cancer risks with JAKi and biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis or psoriatic arthritis: a national real-world cohort study

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ABSTRACT

Objective Assess cancer risks with Janus kinase inhibitors (JAKi) versus biological disease-modifying antirheumatic drugs (bDMARDs) in clinical practice.

Methods Cohort study of patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) initiating treatment with JAKi, tumour necrosis factor inhibitors (TNFi) or other (non-TNFi) bDMARDs 2016–2020 using prospectively collected data from the Swedish Rheumatology Quality Register linked to other registers including the Cancer Register. We estimated incidence rates, and HRs via Cox regression, for all cancers excluding non-melanoma skin cancer (NMSC), and for individual cancer types including NMSC.

Results We identified 10 447 patients with RA and 4443 patients with PsA who initiated treatment with JAKi, a non-TNFi bDMARD or a TNFi. Median follow-up times in RA were 1.95, 2.83 and 2.49 years, respectively. In RA, based on 38 incident cancers other than NMSC with JAKi vs 213 with TNFi the overall HR was 0.94 (95% CI 0.65 to 1.38). Based on 59 vs 189 incident NMSC, the HR was 1.39 (95% CI 1.01 to 1.91). At 2 or more years since treatment start, the HR for NMSC was 2.12 (95% CI 1.15 to 3.89). In PsA, based on 5 vs 73 incident cancers other than NMSC, and 8 vs 73 incident NMSC, the corresponding HRs were 1.9 (95% CI 0.7 to 5.2) and 2.1 (95% CI 0.8 to 5.3).

Conclusion In clinical practice, the short-term risk of cancer other than NMSC in individuals initiating treatment with JAKi is not higher than for TNFi, but we found evidence of increased risk for NMSC.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some meta-analyses of trial data and data from the ORAL Surveillance safety phase 3b–4 trial have indicated an elevated risk for non-melanoma skin cancer, and of other types of cancer overall, in patients with rheumatoid arthritis (RA) treated with the Janus kinase inhibitor (JAKi) tofacitinib versus TNFi.

WHAT THIS STUDY ADDS

⇒ Our study, based on data on two JAKi (tofacitinib and baricitinib) as used in clinical practice, found no evidence of an increased short-term risk of cancer other than non-melanoma skin cancer in RA. By contrast, the risk of non-melanoma skin cancer may be increased already with short-term use. Furthermore, our study adds information on cancer risk by time since treatment initiation, on the distribution of non-melanoma skin cancer subtypes, in individuals with RA enriched for cardiovascular risk factors, and on the cancer risk in psoriatic arthritis (PsA) patients treated with JAKi. Finally, our study provides information on how these cancer risks with JAKi relate to those with non-TNFi biological disease-modifying antirheumatic drugs and in the general population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study adds evidence to suggest a possible increased risk for non-melanoma skin cancers with JAKi as used in clinical practice for RA and PsA.

INTRODUCTION

Patients with rheumatoid arthritis (RA) are at increased risk of cancer overall, mainly due to an increased occurrence of lung cancer and malignant lymphoma.[1–3] Increased risks of non-melanoma skin cancer (NMSC) have been reported in patients with RA[4] and also in patients with psoriatic arthritis (PsA).[5] Studies on cancer risks with biological disease-modifying antirheumatic drugs (bDMARDs) such as tumour necrosis factor inhibitors (TNFi) and other (non-TNFi) bDMARDs have overall been reassuring[6–11] but also pointed to signals of potential risk increases, with individual drugs and for individual cancer sites,[12] for example, NMSC.[8 9 13]

For the most recently introduced class of DMARDs, the targeted synthetic DMARDs (tsDMARD) janus kinase inhibitors (JAKi), concerns have been raised that the mechanism of JAK inhibition could increase risk of cancer.[14–16] These concerns were recently fueled by the results from the ORAL Surveillance safety trial of tofacitinib versus adalimumab/etanercept, including patients with RA above 50 years of age with at least one cardiovascular (CV) risk factor, in which a 50% relative increased risk of cancers excluding

NMSC, and at least an equally large risk increase for NMSC was reported among those treated with JAKi versus TNFi.[17] These findings have led regulatory agencies such as the Food and Drug Administration and the European Medicines Agency to issue warnings on cancer risks, extended to the entire class of JAKi drugs, even if it is still uncertain whether any increased cancer risk differ between individual JAKi considering their somewhat different pharmacological properties.

The ORAL surveillance clinical trial encompassed a population enriched with CV risk factors, whose underlying cancer risk may differ from that in clinical practice. It is unclear whether similar increased risks would apply to JAKi as used in younger (<50 years of age) patients with RA, in RA without CV risk factors and in patients treated with JAKi for other inflammatory conditions such as PsA. Further, due to the design of the ORAL Surveillance study, it remains unknown whether the observed higher occurrence of cancer with JAKi than with TNFi reflects an increased risk of cancer with tofacitinib, an unusually low risk of cancer in the TNFi arm or an increased risk of cancer with both drugs but higher for tofacitinib than for TNFi. So far, the cancer safety signals with JAKi have mainly emanated from clinical trials.[18–21] Data on cancer risks with JAKi as used in clinical practice are limited to two US studies, neither of which reported any increased cancer risk.[22 23]

Our primary aim was therefore to estimate incidence rates and HRs of cancer overall, and by type, in patients with RA or PsA treated with JAKi versus TNFi in clinical practice. Moreover, we aimed to compare these rates to those of patients with RA or PsA treated with other bDMARDs than TNFi, and to those in the general population. Finally, we aimed to assess whether the observed rates and HRs of cancer varied with time and when adding a similar CV risk factor enrichment as that in the ORAL surveillance trial.

SUBJECTS AND METHODS

Design and setting

We performed an observational cohort study using prospectively collected individual-level clinical data enriched through linkage to other national Swedish registers, 1 January 2016 to 31 December 2020. In Sweden, most patients with RA are treated by rheumatologists at public hospital-based outpatient clinics; the same applies to patients with PsA treated with DMARDs. Prescription medication is subsidised, and annual patient out-of-pocket costs are capped at €220.

Data sources

We used information from the following national Swedish data sources: The Swedish Rheumatology Quality register (SRQ), the National Patient Register, the Longitudinal Database for Insurance and Labor Market Studies (LISA), the Prescribed Drug Register, the Population and Cause of death register and the National Cancer register. Online supplemental table S1 describes the data sources and the information collected from each of these.

Study population, study period and exposures

We identified all individuals above 18 years of age registered with RA or PsA in SRQ. For each patient, five general population comparator subjects were identified, free from RA/PsA at their index case's first registration of RA/PsA and matched on age, sex and region of domicile, from the Population register. We used SRQ to identify all treatment initiations among patients with RA or PsA with: (1) TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), (2) non-TNFi bDMARD (rituximab, abatacept, tocilizumab, sarilumab) or (3) JAKi (baricitinib, tofacitinib, upadacitinib). All three JAKis were included as a class, baricitinib and tofactinib also as individual drugs (upadacitinib contributed to low number of treatments and zero events as a consequence of its introduction late during the study period). Filgotinib was not included as it was introduced after our study period. To increase statistical precision, we included treatment initiations (TNFi and non-TNFi) from 2016. For JAKi, we included treatment initiations from their market entry in 2017. Because of the new-user design, treatment episodes initiated before or ongoing at the start of the study period were not included (but contributed to the number of previously used b/tsDMARDs), but did not disqualify the same patient from contributing one or more new treatment episodes initiated during the study period. Patients who started one JAKi and later switched to a second (different) JAKi during the study period contributed twice to the JAKi cohort; the same applied for all other treatment episodes with different drugs within the same exposure category. For example, a patient who was on etanercept 2012–2015, abatacept 2017–2019 and baricitinib 2019–2020 contributed once to our non-TNFi group (then with a history of one previous b/tsDMARD) and once to our JAKi group (then with a history of two previous b/tsDMARDs). All study participants who had a history of any previous cancer other than NMSC were excluded from all analyses. No other inclusion/exclusion criteria were employed. Treatment initiations were followed until the first of the specific cancer type under study. Individuals who, during follow-up, developed cancer of another type than the one under study were not censored.

Follow-up

For the RA and PsA cohorts start of follow-up was defined as the date of treatment start with each b/tsDMARDs during the study period. For the general population cohort, start of follow-up was defined as the time point of the first recorded b/tsDMARD treatment start in its index case with RA/PsA during the study period. We used an ever-treated approach, in which each patient in each treatment cohort was followed from every treatment initiation until the occurrence of the outcome, death, emigration from Sweden or end of the study period on 31 December 2020. Treatment interruption of the same molecule shorter than 90 days (+183 days for rituximab) was considered the same treatment episode. No distinction was made between an originator product and its biosimilars.

Outcomes

To identify incident cancers overall and by subtype, we used International Classification of Disease version 10 codes and Systematised Nomenclature of Medicine codes as registered in the Cancer and Cause of death registers (online supplemental table S2). We defined the following cancer outcomes: (1) All cancers other than NMSC (main outcome), (2) NMSC including both basal cell carcinoma (BCC) and squamous cell carcinomas (SCC) (3) prostate, (4) testicular, (5) female breast, (6) all haematopoietic (leukaemias, immunoproliferative, myeloproliferative, lymphoproliferative disease and lymphomas) (7) malignant lymphomas, (8) renal, (9) lung, (10) colorectal, (11) ovarian, (12) cervical (13) urinary tract (bladder, urethra, ureter), (14) central nervous system, (15) uterus, (16) ear-nose-throat, (17) digestive tract (oesophagus, gastric, ileum and jejunum), (18) pancreas, (19) liver-gallbladder cancers and (20) malignant melanoma.

Statistics

For each treatment cohort and for the general population comparator cohort, we presented descriptive statistics, and for each outcome the number of events, and crude incidence rates. We calculated incidence rates standardising to the age and sex distribution in the TNFi cohort. We also fitted Cox proportional hazards models to estimate HRs comparing each treatment cohort (JAKi; overall and separately for tofacitinib and baricitinib, and the non-TNFi bDMARD cohort) to the TNFi cohort, using time since treatment initiation as the time scale. HRs were adjusted for age, sex, line of therapy, comorbidities (see online supplemental table S3), socioeconomic status and RA disease-related factors at treatment start (duration of disease, seropositive status, Disease Activity Score 28 C reactive protein (DAS28CRP), CRP, concomitant drug use (steroid, methotrexate, non-methotrexate csDMARD, prednisolone use, smoking status), with missing categories for those variables (RA disease-related factors, all other variables had negligible missing data) with missing information. Incrementally adjusted models are presented in online supplemental tables S6, S9 and S16, to display the impact of adjustment for specific factors. We only performed comparative analyses (ie, estimated HRs) where the number events in each cohort were ≥5. We used SAS and Stata V.16.1 to perform the analyses.

Additional analyses

We performed several additional analyses. First, we fitted models by time since treatment initiation (≤1, 1–2, ≥2 years) by inclusion of an interaction term and thereby relaxed the proportional hazards assumption. Second, we performed separate analyses by previous use of b/tsDMARDs (0, 1–2, ≥3). Third, we introduced a latency period of 90 days, so that only cancers diagnosed 90 days or later after treatment start would contribute to analyses. Fourth, we restricted the main analysis to a CV-enriched subset of the JAKi, non-TNFi and TNFi cohort (see online supplemental table S4 for definitions of this enrichment). Fifth, we performed a sensitivity analysis using an on-drug approach for all cancers other than NMSC and NMSC, respectively, for patients with RA. Sixth, the study period ended in December 2020 and the COVID pandemic could theoretically affect the results. We; therefore, introduced a sensitivity analysis restricting the follow-up to Feb 2020 (for patients with RA). Finally, in our main analysis, we performed a multiple imputation using chained equations with 30 repetitions for variables with missing information (DAS28CRP, CRP using multinomial logistic regression; disease duration, smoking, civil status and education using logistic regression). Imputation models were adjusted for all covariates included in the analysis model plus the event indicator and the Nelson-Aalen estimate of the cumulative hazard.

RESULTS

During the study period, a total of 10 447 unique individuals with RA without a previous cancer diagnosis started at least one b/tsDMARD. A total of 1967 patients with RA contributed to the JAKi initiator cohort, 3520 to the non-TNFi cohort and 7343 to the TNFi cohort. The total person time at risk in the JAKi, non-TNFi bDMARD and TNFi cohorts was 4022, 11 231 and 21 389 patient years, respectively. The median follow-up times were 1.95, 2.83 and 2.49 years (table 1).

We similarly included 4443 unique individuals with PsA without a previous cancer diagnosis; 379 contributed to the JAKi cohort, 185 to the non-TNFi cohort and 4186 to the TNFi cohort. The total person time at risk in the JAKi, non-TNFi bDMARD and TNFi cohorts was 585, 418 and 12 623 patient years, respectively. The median follow-up times were 1.52, 2.25 and 2.44 years (online supplemental table S5).

RA: occurrence and relative risk for cancer

Table 2 and figure 1 display number of events, incidence rates and fully adjusted HRs for patients with RA initiating treatment with JAKi, non-TNFi or a TNFi. Based on 38 incident cancers other than NMSC in the JAKi cohort, 141 in the non-TNFi cohort and 213 in the TNFi cohort, the fully adjusted HR for JAKi versus TNFi was 0.94 (95% CI 0.65 to 1.38). The corresponding HR for non-TNFi versus TNFi was 1.12 (95% CI 0.88 to 1.43). For tofacitinib, the fully adjusted HR (vs TNFi) was 1.08 (95% CI 0.52 to 2.24) and 0.92 (95% CI 0.61 to 1.38) for baricitinib (table 2). In the JAKi cohort, there were 7 breast cancers (HR=0.73, 95% CI 0.29 to 1.86, vs TNFi), 6 haematopoietic (HR=1.90, 95% CI 0.70 to 5.16) and 7 lung cancers (HR=1.15, 95% CI 0.57 to 2.32). For all other sites other than NMSC (table 2), there were less than five events observed among the JAKi treated and thus are not presented.

We identified 59 incident NMSC events in the JAKi cohort, 126 in the non-TNFi cohort and 189 in the TNFi cohort, which corresponded to fully adjusted HR of 1.39 (95%CI 1.01 to 1.91) for JAKi versus TNFi. The corresponding HR for non-TNFi versus TNFi was 1.00 (95%CI 0.78 to 1.28). The NMSC incidences in the JAKi, TNFi, non-TNFis groups were all higher than in the general population (table 2). The HR of NMSC for tofacitinib (vs TNFi) was 1.56 (95% CI 0.83 to 2.92) and 1.37 (95%CI 0.97 to 1.92) for baricitinib (table 2). These HRs did not vary appreciably between successively adjusted models (online supplemental table S6). The proportion of SCC among all NMSCs was largely similar in the JAKi, TNFi and non-TNFi groups (all of which were higher than in the general population) (online supplemental table S7). The proportion of patients with a history of NMSC (1.5%–1.9%) was largely equal across the treatment cohorts (table 1). Also, the proportion of incident NMSC events that occurred in individuals with a history of NMSC (12%–16%) was largely equal across these cohorts (online supplemental table S8).

Additional analyses

When allowing the effect of treatment to vary across time since treatment initiation, the HR for cancer other than NMSC for JAKi versus TNFi varied from 0.96 (95%CI 0.58 to 1.59) during 0–1 year since treatment start through 1.36 (95% CI 0.67 to 2.75) for 2 or more years since treatment start. For NMSC, the corresponding fully adjusted HRs varied from 1.12 (95% CI 0.70 to 1.78) during the first year since treatment start, to 2.12 (95% CI 1.15 to 3.89) at two or more years since treatment start (table 3), but these variations were not statistically significant (p values for interaction with time were 0.60 and 0.10, respectively). These HRs did not vary appreciably between successively adjusted models (online supplemental table S9).

Analyses by the previous number of b/tsDMARDs, and with a 90-day latency period, revealed HRs close to the main analysis (online supplemental tables S10 and S11). Furthermore, the HRs did not vary considerably when changing the main analysis from an ever-exposed model to a on drug model (online supplemental table S12). Also, multiple imputation for missing data and sensitivity analysis for COVID pandemic, respectively, did not appreciably alter the results of the main analysis (online supplemental tables S13 and S14).

Table 1 Baseline characteristics of the study cohorts of Swedish patients with RA initiating a b/tsDMARD treatment 2016–2020

	Initiators of tofacitinib	Initiators of baricitinib	Initiators of upadacitinib	Initiators of all JAKis	Initiators of a non-TNFi bDMARD	Initiators of a TNFi	General population Reference cohort
Observations (treatment initiations)	377	1676	90	2143	4128	8580	
Individuals	377	1676	90	1967	3520	7343	48 318
Age years, median (IQR)	58 (50–67)	59 (50–70)	56 (49–64)	59 (50–69)	60 (51–70)	56 (46–67)	57 (47–68)
Female, %	83	81	86	82	79	78	78
Median follow-up, years	2.15	1.98	0.14	1.95	2.83	2.49	2.73
Total person time at risk, years	799	3207	15	4022	11 231	21 389	130 026
Disease-related							
Disease duration years, median (IQR)	12.9 (7.2–23.9)	13.2 (6.7–21.9)	15.6 (7.8–22.1)	13.2 (6.8–22.3)	11.2 (4.9–20.0)	7.1 (2.6–14.7)	
Seropositive, %	76	80	73	79	84	76	
DAS28CRP, median (IQR)	4.6 (3.7–5.4)	4.4 (3.5–5.1)	4.2 (3.3–5.0)	4.4 (3.5–5.1)	4.5 (3.7–5.2)	4.1 (3.4–4.9)	
DAS28CRP missing, %	45	40	49	41	43	41	
CRP <5, %	46	47	54	47	40	48	
CRP5-9, %	13	18	18	17	18	18	
CRP 10–19, %	13	17	11	16	17	16	
CRP ≥20, %	27	19	18	20	25	18	
CRP missing, %	34	29	37	30	32	30	
Smoker, %	58	59	60	59	60	57	
Smoking missing, %	13	19	20	18	20	28	
0 previous b/tsDMARDs, %	9	13	6	12	20	63	
1–2 previous b/tsDMARDs, %	28	39	34	37	48	31	
3+previous b/tsDMARDs, %	63	48	60	51	31	6	
Treatment related, %							
Concomitant methotrexate use, %	36	43	39	42	46	63	1
Concomitant oral steroid use, %	68	64	61	64	68	61	2
Prednisolone use (average among users) mg prior 1 year, %	4.2 (2.7–6.8)	4.1 (2.1–6.2)	4.2 (2.1–5.7)	4.1 (2.1–6.3)	4.1 (2.7–6.8)	3.4 (1.4–5.5)	1.4 (0.7–4.8)
Comorbidities (previous 5 years), %							
History of diabetes types 1 and 2	10	10	6	10	11	10	8
History of ischaemic heart disease	5	5	1	5	6	3	2
History of hospitalised infections	13	13	6	12	13	6	3
History of chronic obstructive pulmonary disease	10	8	6	8	10	6	3
History of kidney failure	2	1	1	2	2	1	1
History of heart failure	2	2	2	2	3	1	1
History of stroke	5	5	3	5	6	2	3
History of VTE	4	3	3	3	3	2	1
History of joint surgery	7	8	3	8	7	5	2
History of hypertension	12	15	11	14	16	9	7
History of NMSC	1.6	1.9	3.3	1.9	1.9	1.5	1.0
Drug dispensations (previous 6 months), %							
Lipid lowering drugs	15	15	14	15	16	13	14
Other measures of comorbidities/health							
Hospital days in the previous year	5 (1–17)	5 (2–12)	5 (3–40)	5 (2–13)	7 (3–15)	4 (2–10)	5 (2–13)
Sick leave in the previous year, %	17	16	21	16	15	17	7
Disability pension in the previous year, %	2	1	0	1	1	1	0
Socioeconomics							
Education >12 years, %	29	33	36	33	31	35	38
Married/partner, %	54	51	62	52	51	50	49

b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; CRP, C reactive protein; DAS28, Disease Activity Score 28; JAKi, Janus kinase inhibitor; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

In the CV risk-factor enriched subset outlined in online supplemental table S4, there were 17 incident cancers other than NMSC in JAKi cohort (n=543, 27% of the full cohort) and 79 in the TNFi cohort (n=1723, 23% of the full cohort), both corresponding to higher incidences than in the main analysis but a similar fully adjusted HR of 1.03 (95% CI 0.58 to 1.82) (online supplemental table S15). Comparing the 1551 and 6612 individuals in the JAKI and TNFi cohorts, respectively, who did

Table 2 Number of events, person years, crude and standardised incidence rates and HRs, for all cancers other than NMSC, and for cancer sites where at least five incident events were observed in the JAK cohort, in Swedish patients with RA treated with JAKi, non-TNFi bDMARDs or TNFi

Cohort	Events	Person years, no	Crude incidence rate per 1000 person-years	Standardised incidence rate per 1000 person-years	Fully adjusted HR*
All cancers other than NMSC					
All JAKi	38	3996	9.5	8.3	0.94 (0.65 to 1.38)
Tofacitinib	8	793	10.1	11.2	1.08 (0.52 to 2.24)
Baricitinib	30	3187	9.4	8.0	0.92 (0.61 to 1.38)
Non-TNFi bDMARD†	141	11 051	12.8	10.5	1.12 (0.88 to 1.43)
TNFi	213	21 122	10.1	10.1	1.0 (Reference)
General population	1245	128 224	9.7	9.2	n/a
NMSC					
All JAKi	59	3954	14.9	12.9	1.39 (1.01 to 1.91)
Tofacitinib	11	781	14.1	14.9	1.56 (0.83 to 2.92)
Baricitinib	48	3157	15.2	12.5	1.37 (0.97 to 1.92)
Non-TNFi bDMARD†	126	11 027	11.4	9.0	1.00 (0.78 to 1.28)
TNFi	189	21 083	9.0	9.0	1.0 (Reference)
General population	852	128 630	6.6	6.2	n/a
Breast cancer					
All JAKi	7	4014	1.7	1.6	0.73 (0.29 to 1.86)
Tofacitinib	1	797	1.3	–	–
Baricitinib	6	3201	1.9	1.7	0.77 (0.29 to 2.06)
Non-TNFi bDMARD†	23	11 197	2.1	1.9	0.88 (0.48 to 1.61)
TNFi	42	21 328	2.0	2.0	1.0 (Reference)
General population	262	129 601	2.0	2.0	n/a
All haematopoietic					
All JAKi	6	4018	1.5	1.5	1.90 (0.70 to 5.16)
Tofacitinib	1	798	1.3	–	–
Baricitinib	5	3203	1.6	1.6	1.96 (0.66 to 5.79)
Non-TNFi bDMARD†	12	11 217	1.1	0.9	1.04 (0.48 to 2.25)
TNFi	22	21 359	1.0	1.0	1.0 (Reference)
General population	99	129 854	0.8	0.7	n/a
Lung cancer					
All JAKi	7	4021	1.7	1.5	1.15 (0.57 to 2.32)
Tofacitinib	2	798	2.5	–	–
Baricitinib	5	3206	1.6	1.2	0.98 (0.44 to 2.23)
Non-TNFi bDMARD†	11	11 224	1.0	0.7	0.59 (0.31 to 1.15)
TNFi	30	21 368	1.4	1.4	1.0 (Reference)
General population	111	129 912	0.9	0.8	n/a

Estimated from Cox proportional hazards models. Standardised incidence rate standardised to the age and sex distribution in the TNFi cohort. – is displayed when too few events (<5) were observed.
*Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information.
†Non-TNFI bDMARD includes rituximab, abatacept, tocilizumab.
bDMARD, biological disease-modifying antirheumatic drug; JAKi, Janus kinas inhibitor; n/a, not available; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis; SES, socioeconomic status; TNFi, tumour necrosis factor inhibitor.

not fulfil the inclusion criteria to the CV-enriched cohort, the adjusted HR was 0.88 (95% CI 0.53 to 1.45).

PsA: Occurrence and relative risk for cancer

There were 5 events of cancer other than NMSC in the JAKi cohort and 73 events in the TNFi cohort resulting in an adjusted HR of 1.88 (95% CI 0.68 to 5.16) for JAKi versus TNFi (table 4). For NMSC, the corresponding HR was 2.05 (95% CI 0.79 to 5.31) based on 8 events in the JAKi cohort and 73 events in the TNFi cohort. These HRs did not vary appreciably between successively adjusted models (online supplemental table S16).

DISCUSSION

In this nationwide observational study of patients with RA or PsA initiating treatment with a JAKi (tofacitinib or baricitinib), non-TNFi bDMARD or a TNFi, we made several important observations: First, in patients with RA or PsA, the overall risk for cancer other than NMSC was not statistically significantly increased (JAKi vs TNFi) nor were there any clear trends towards increasing relative risks (RRs) by time since treatment start. Second, we found evidence of increased risk for NMSC (for RA) and a potential signal (for PsA) with JAKi, especially in the later follow-up strata although the trend over time was not formally statistically significant. For NMSC, the distributions of SCC and BCC were similar in the JAKi and in the bDMARD cohorts. Third, the risk-increase for NMSC (JAKi vs TNFi) was specific to JAKi and not mirrored by a similar increase for the class of non-TNFi bDMARDs. Fourth, in our RA population, we could not replicate the signal from the ORAL Surveillance trial of an increased risk of lung cancer with JAKi. Fifth, when restricting our analysis to CV risk-factor enriched patients, the incidence of cancer increased (as expected) but the HRs remained the same as in the main analysis (and qualitatively similar to the HR close to one among those without these risk factors).

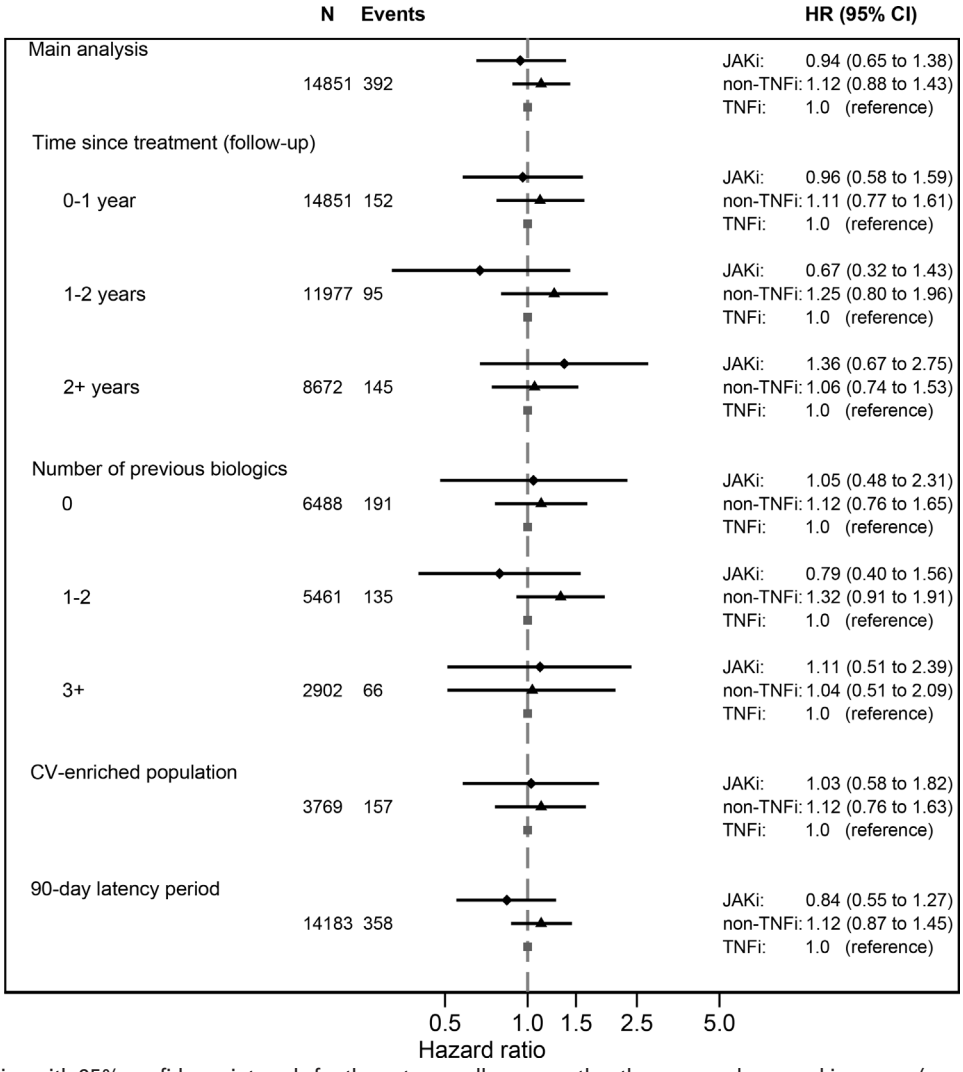

Figure 1 Hazard ratios with 95% confidence intervals for the outcome all cancers other than non-melanoma skin cancer (overall, and by time since treatment start, number of previous b/tsDMARDs, in a CV enriched population, and using a 90-day latency period) in Swedish patients with RA starting treatment with a JAKi, a TNFi or non-TNFi bDMARD.

Signals of cancer risks with JAKi have been documented in (overlapping) meta-analyses of JAKi trials. Wang *et al* included 20 clinical trials of which seven had information on cancer covering 8982 JAKi treated patients with RA and reported RR of cancer in the JAKi versus comparator arms of 1.68, 95% CI 0.57 to 4.95.[24] Maneiro *et al* reported an OR for cancer other than NMSC in the tofacitinib versus placebo arms of 2.39 (95% CI 0.50 to 11.50).[25] Oliviera *et al* assessed the association between JAKi and NMSC in 23 trials (13 tofacitinib, 4 baricitinib, 1 filgotinib and 7 upadacitinib trials) across indications; RA, psoriasis, inflammatory bowel disease and ankylosing spondylitis, including 26,334 JAKi-treated patients. Across indications, the RR of NMSC with JAKi versus comparator was 1.05 (95% CI 0.47 to 2.35). Oliviera *et al* also assessed the risk of cancers other than NMSC, in 33 phase 2–3 trials (20 tofacitinib, 5 baricitinib, 1 filgotinib and 7 upadacitinib trials) across the same indications, including 32 131 JAKi exposed patients, an reported an RR with JAKi versus placebo/comparator of 1.39 (95% CI 0.68 to 2.85). When RA was assessed as a separate indication (13 trials), the HR was HR 1.59 (95% CI 0.71 to 3.56).[26] Solipuram *et al* focused on the cancer risk in patients with RA receiving combination therapy with methotrexate and JAKi in 13 randomised controlled trials (6911 patients) and reported that the addition of JAKi to MTX provided no statistically significant increased risk for malignancies excluding NMSC (RR 1.12, 95% CI 0.40 to 3.13) nor for NMSC (RR 1.44, 95% CI 0.36 to 5.76) compared with MTX monotherapy.[21]

The recent ORAL surveillance trial was a large, randomised, open-label, non-inferiority, postauthorisation and safety end-point trial with a median follow-up of 4.0 years, which included patients with active RA over 50 years of age with a least one CV risk factor. The results included a statistically significant 50% relative higher risk of cancer overall for tofacitinib compared with adalimumab/etanercept, including a signal for lung cancer (HR 2.17, 95% CI 0.95 to 4.93), and also a significantly increased risk of NMSC (HR 1.90, 95% CI 1.04 to 3.47).[17] Our results do not offer any immediate support for an increased risk of cancer overall other than NMSC with JAKi (our upper 95% CI bound=1.38), and do not support the signal for lung cancer although precision for the latter estimate was limited. We did not note any major differences in HRs for tofacitinib (vs TNFi) and baricitinib (vs TNFi) although the upper 95% CI bounds in the drug-specific analysis encompassed clinically significant risk increases.

So far, other data on cancer risks with JAKi as used in clinical practice are scare. A US multicentre, observational register study (US Corrona RA registry) included 1999 patients initiating tofacitinib, with mean follow-up of 2.25 years, noted 28

Table 3 Number of events, person years, crude and standardised incidence rates of all cancers other than NMSC and NMSC, in patients with RA treated with JAKis, non-TNFi bDMARDs or TNFi, by time since treatment initiation

	Events	Person years, no	Crude incidence rate per 1000 person-years	Standardised incidence rate per 1000 person-years	Fully adjusted HR*
All cancers other than NMSC					
0–1 year					
JAKi	20	1884	10.6	9.4	0.96 (0.58 to 1.59)
Non-TNFi	52	3815	13.6	11.4	1.11 (0.77 to 1.61)
TNFi	80	7759	10.3	10.3	1.0 (Reference)
1–2 years					
JAKi	8	1358	5.9	4.9	0.67 (0.32 to 1.43)
Non-TNFi	36	3049	11.8	9.2	1.25 (0.80 to 1.96)
TNFi	51	6000	8.5	8.5	1.0 (Reference)
2 or more years					
JAKi	10	754	13.2	12.2	1.36 (0.67 to 2.75)
Non-TNFi	53	4187	12.7	10.7	1.06 (0.74 to 1.53)
TNFi	82	7363	11.1	11.1	1.0 (Reference)
NMSC					
0–1 year					
JAKi	24	1880	12.8	11.2	1.12 (0.70 to 1.78)
Non-TNFi	40	3818	10.5	8.3	0.85 (0.57 to 1.26)
TNFi	75	7755	9.7	9.7	1.0 (Reference)
1–2 years					
JAKi	20	1338	14.9	12.8	1.48 (0.87 to 2.51)
Non-TNFi	47	3041	15.5	11.8	1.43 (0.95 to 2.15)
TNFi	51	5991	8.5	8.5	1.0 (Reference)
2 or more years					
JAKi	15	735	20.4	18.3	2.12 (1.15 to 3.89)
Non-TNFi	39	4168	9.4	7.3	0.86 (0.57 to 1.31)
TNFi	63	7338	8.6	8.6	1.0 (Reference)

Non-TNFI includes; rituximab; abatacept; tocilizumab. All HRs estimated from Cox models including an interaction between time since treatment initiation (0–1, 1–2, 2+ years) and treatment exposure cohort. Standardised incidence rate standardised to the age and sex distribution in the TNFi cohort.
*Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information.
bDMARDs, biological disease-modifying antirheumatic drugs; JAKi, Janus kinase inhibitor; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis; SES, socioeconomic status; TNFi, tumour necrosis factor inhibitor.

events of malignancies excluding NMSC. They found neither an overall increase in the risk of cancer other than NMSC (HR 1.04, 95% CI 0.68 to 1.61) nor any increased risk of NMSC (HR 1.02, 95% CI 0.69 to 1.50) for tofacitinib versus other bDMARDs.[23] Another US study, using claims data from three sources (Optum Clinformatics, IBM MarketScan Research Databases and Medicare) included a total of 83 296 patients with RA but found no increased risk of cancer with tofacitinib (HR 1.01 95% CI 0.83 to 1.22) compared with TNFi, nor any statistically significant increased risk of NMSC (HR 1.15, 95% CI 0.96 to 1.39) (though based on a mean follow-up time of less than 1 year).[22]

Table 4 Number of events, crude and standardised incidence rates and HR for all cancers other than NMSC and NMSC, in Swedish patients with PsA treated with JAKi

Cohort	Events	Crude incidence rate per 1000 person-years	Standardised incidence rate per 1000 person-years	Fully adjusted HR*
All cancers other than NMSC				
JAKi	5	8.6	7.3	1.88 (0.68 to 5.16)
Non-TNFi	2	4.8	–	–
TNFi	73	5.8	5.8	1.0 (Reference)
Gen population	317	5.9	6.0	n/a
NMSC				
JAKi	8	13.9	11.7	2.05 (0.79 to 5.31)
Non-TNFi	2	4.8	–	–
TNFi	73	5.8	5.8	1.0 (Reference)
Gen population	209	3.9	3.9	n/a

Non-TNFI includes rituximab, abatacept and tocilizumab. Estimated from proportional hazards Cox regression models. Standardised incidence rate standardised to the age- and sex distribution in the TNFi cohort. – is displayed when too few events (<5) were observed.
*Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information.
JAKi, Janus kinas inhibitor; n/a, not available; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; SES, socioeconomic status; TNFi, tumour necrosis factor inhibitor.

Limitations

Our study has some limitations. The median follow-up time for JAKi was somewhat short (1.95 years) due to their relatively recent introduction on the Swedish market. Also, while we could present results for the combined group of JAKi, drug-specific HRs were less precise, due to relatively few events for each specific JAKi. Furthermore, although we performed analyses restricted to subjects with CV risk factors, these restrictions were not identical to those in the ORAL surveillance study. Further restrictions (to RA disease activity, to concomitant csDMARDs, etc) would have removed the vast majority of all JAKi treated patients (indirectly demonstrating that the ORAL Surveillance trial is not directly comparable to patients in clinical practice). Also, the ORAL surveillance study consisted of patients treated with tofacitinib 5 mg or 10 mg two times per day. In Sweden, only the 5 mg two times per day dosage is used. Nevertheless, when restricting our RA cohort to a CV enriched subgroup the overall cancer risk other than NMSC with JAKi was not statistically significant increased, in this respect in line with the study by Khosrow-Khavar *et al*.[22] There were differences in the characteristics between patients initiating a JAKi and those initiating a TNFi. Although we adjusted for several such factors, we cannot formally rule out residual or unmeasured confounding by indication.

Strengths

Strengths of our study include the use of nationwide, population-based prospective registers with high coverage and validity in which exposure (JAKi/bDMARD treatment) could be assessed independently of outcome (cancer), with a new-user design. This ensured the inclusion of the vast majority of all Swedish RA and PsA patients (without previous cancers) treated with b/tsDMARDs, and a statistical precision to rule out substantially increased overall cancer risks other than NMSC (upper 95% CI=1.38). We were additionally able to assess cancer risks overall and by the most common cancer sites and could study NMSC by type (BCC/SCC) and history, and found limited potential for channelling to or away from JAKi related to a history of NMSC. The inclusion of cohorts treated with non-TNFi bDMARDs, and the general population cohort, allowed us to put the observed rates and HRs with JAKi versus TNFi into context. Our finding of an increased risk of NMSC with JAKi, in a population already at increased risk of skin malignancies, underscores the importance of dermatological vigilance among these patients. In addition, we were able to assess the overall cancer risk, and risks for NMSC, in PsA treated with JAKi, which has not previously been presented.

CONCLUSION

In conclusion, among individuals with RA or PsA, we found no evidence of an increased short-term risk of all cancers other than NMSC for patients initiating JAKi compared with TNFi, but the risk of NMSC may be increased, at least in patients with RA. Although our results add to the concerns regarding the safety of JAKi with regard to NMSC, a causative biological mechanism remains to be determined and the risks must be viewed in light of the elevated risks for several other comorbidities and adverse outcomes in patients with active RA for whom alternative treatment options may not exist.

Collaborators The ARTIS Study Group conducts scientific analyses using data from the Swedish Biologics Register ARTIS, run by the Swedish Society for Rheumatology. The following were members of the ARTIS Study Group during study completion: Gerd-Marie Alenius (Department of Public Health and Clinical Medicine/Rheumatology, Umeå University), Eva Baecklund (Department of Medical Sciences, Uppsala University), Katerina Chatzidionysiou (Department of Medicine Solna, Karolinska Institutet), Nils Feltelius (Swedish Medical Products Agency, Department of Public Health and Caring Sciences, Uppsala University), Helena Forsblad-d'Elia (Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg), Alf Kastbom (Department of Biomedical and Clinical Sciences, Linköping University), Lars Klareskog (Department of Medicine Solna, Karolinska Institutet), Ann Knight (Department of Medical Sciences, Uppsala University), Elisabet Lindqvist (Department of Clinical Sciences, Rheumatology, Lund University, Skåne University Hospital), Ulf Lindström (Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg), Lotta Ljung (Department of Medicine Solna, Karolinska Institutet), Carl Turesson (Rheumatology, Department of Clinical Sciences, Malmö, Lund University), Christopher Sjöwall (Department of Biomedical and Clinical Sciences, Linköping University), and Johan Askling (Department of Medicine Solna, Karolinska Institutet).We also would like to thank all Swedish RA patients and rheumatologists for entering data into the Swedish Rheumatology Quality Register.

Contributors VH is guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.VH, HB, KH, TF and JA had full access to all the data in the study and participated in the design of the study. HB and VH conducted the statistical analyses. All authors participated in designing the analyses and in the interpretation of the results. All authors contributed to the drafting of the manuscript.

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Competing interests VH and KH have no competing interests to declare. JA has had or have research agreements with Abbvie, Astra-Zeneca, BMS, Eli Lilly, MSD, Pfizer, Roche, Samsung Bioepis, Sanofi, and UCB, mainly in the context of safety monitoring of biologics via ARTIS/Swedish Biologics Register. TF and HB are partly employed by the ARTIS project.

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 The study was approved by the Swedish Ethics Review Authority 2015-1844-31.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data in this study is part of a linkage between registers performed by Karolinska Institutet. Further sharing of the data is limited due to legal restrictions.

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Supplementary table S1. Data sources

Swedish Rheumatology Quality Register (SRQ)	A nationwide longitudinal clinically integrated register operated by The Swedish Society for Rheumatology, started in 1996. Patients with RA and other rheumatologic diseases are registered in the SRQ and it covers 89 000 patients. SRQ contains information about disease activity and additional information such as treatment and smoking status. SRQ covers 90% of all patients with RA treated with b/tsDMARDs in Sweden.
Swedish Patient Register (NPR)	A national register maintained by The National Board of Health and Welfare. Hospital discharges from inpatient care and patients visits in non-primary outpatient care, have been registered, since 1964 and 2001 respectively. Diagnoses are coded according to the Swedish version of the International Classification of Disease (ICD).
Longitudinal database for insurance and labor market-studies (LISA)	A national register maintained by Statistics Sweden. It contains information about sick leave, parental leave and employment status in Sweden from 1990
Prescribed Drug Register (PDR)	A national register maintained by The National Board of Health and Welfare. It contains information about all drugs dispensed on prescription in Sweden and is linked to the personal identification number since 2005.
Swedish population register	A national register maintained by Swedish Tax agency. Contains information such as home district, civil status and migration data.
Cause of Death Register	The Cause of Death Register is a national register containing 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. 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
Cancer register	A national register started in 1958. The coverage of the cancer register is estimated to more than 95%; the register contains data on date of diagnosis and type of incident cancers.

Supplementary Table S2. Definitions of cancer outcomes

Outcome definition	ICD10 codes from Cancer Register and Cause of Death Register
Malignant melanomas	ICD10: C43
Skin cancer NMSC (basal cell carcinoma and squamous cell carcinoma)	SCC = ICD7: 191 and snomed10: 80703 (Cancer register only) and basal cell cancers identified using the basal cell cancer registry. For a history of cancer where NMSC was removed ICD7=191 was used to identify NMSC
Invasive prostate cancer	ICD10: C61
Invasive testicular cancer	ICD10: C62
Invasive female breast cancer	ICD10: C50
All invasive hematopoietic cancer (leukemias, immunoproliferative-, myeloproliferative-, lymphoproliferative disease and lymphomas)	ICD10: C81, C82, C83, C84, C85, C90, C91, C92, C93, C94, C95
Malignant lymphomas	Non-Hodgkin lymphoma: C82, C83, C84, C85, C86, C88, C914. Hodgkin lymphoma C81. Chronic lymphocytic leukemia (CLL) C911, C913, C916
Invasive renal cancer	ICD10: C64
Invasive lung and pleura cancer	ICD10: C34, C38
Invasive colorectal cancer	ICD10: C18, C19, C20, C21
Invasive ovarian cancer	ICD10: C56
Invasive cervixcancer	ICD10: C53
Invasive urinary tract cancer	ICD10: C66, C67, C68
Invasive CNS cancer	ICD10: C70, C71
Invasive uterine cancer	ICD10: C54
Invasive ear, nose and throat cancer	ICD10: C09. C30, C31, C32, C33
Invasive digestive tract cancer (esophagus, ileum, jejunum, ventricle)	ICD10: C15, C16, C17,
Invasive pancreas cancer	ICD10: C25
Invasive liver and gallbladder cancer	ICD10: C22, C23, C24

Supplementary Table S3. Variable definitions including ATC and ICD codes used for comorbidities and drugs

Variable	Description
Baseline characteristics	
Age	Age at cohort entry (categorized according to quartiles for analysis)
Female	Indicator for sex of individual
Comorbidities	
History of cancer	History of cancer recorded within 5 years prior to cohort entry. Non-benign cancers excluding non-melanoma skin cancer (ICD7=191). Data retrieved from the Cancer Register. Indicator variable (Y/N).
History of diabetes	History of diabetes recorded in the 5 years recorded prior to cohort entry. Defined as a record in the National Patient Register (inpatient and outpatient components, ICD10: E10-E14) or dispensation of treatment (ATC: A10) in the Prescribed Drug Register. Indicator variable (Y/N).
History of heart failure	History of heart failure recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient component, ICD10: I50). Indicator variable (Y/N).
History of ischemic heart disease	History of ischemic heart disease recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient component, ICD10: I20-I25). Indicator variable (Y/N).
History of hospitalized infections	History of infections recorded in the 5 years prior to cohort entry. Defined as recorded in National Patient Register (inpatient component, ICD10: A00-B99, D73.3, E06.0, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N10, N11, N12, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1). Indicator variable (Y/N).
History of lung disease	History of lung disease other than infectious pneumonia recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient and outpatient components, ICD10: J40-J94). Indicator variable (Y/N).
History of kidney failure	History of kidney failure recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient and outpatient components, ICD10:N17-N19). Indicator variable (Y/N).
History of joint surgery	History of joint surgery recorded in the 10 years prior to cohort entry. Defined as record in National Patient Register (inpatient and outpatient components, operational codes: NGB, NFB, NBB, NHB, NHC,

	NHE, NHF, NHG, 8423, 8424, 8426, 8419, 8437, 8436, 8420, 8421, 8422, 8400-8415). Indicator variable (Y/N).
History of VTE	I80-I82 and I26. Defined as record in National Patient Register (inpatient and outpatient components), in the 5 years prior to treatment initiation/cohort entry.
History of Stroke	I50-I69. Defined as record in National Patient Register (inpatient and outpatient components), in the 5 years prior to treatment initiation/cohort entry.
History of NMSC	ICD7 191. Defined as any previous diagnosis of NMSC in the Swedish Cancer Register (both benign and non-benign NMSC).
Socioeconomics	
Education	Highest education achieved as recorded in the year prior to cohort entry. Data obtained from the Longitudinal integrated database for health insurance and labor market studies (LISA). Categorized into <12 years or ≥12 years.
Civil status	Civil status recorded in the year prior to cohort entry. Categorized into married/partner, or single.
Disease-related	
Disease duration	Calculated as the difference between the disease debut date and cohort entry. Categorized as <5 years and ≥5 years in statistical analyses
Seropositivity	Indicator for seropositive disease (versus seronegative/unknown). Calculated using RF and ACPA values in the SRQ diagnoses.
DAS28CRP	Taken from the visit closest to cohort entry within -60 and +15 days. Categorized into quartiles.
Smoker	Taken from SRQ visit information using a window of -5 years to +30 days of cohort entry. Indicator variable: smoker or non-smoker.
CRP	Taken from the visit closest to cohort entry within -60 and +15 days. Categorized as: <5, 5-9, 10-19, ≥20.
Number of previous biologics	Calculated using all available b/tsDMARD (biological/targeted synthetic disease modifying anti rheumatic drugs) information from the SRQ, since its inception in 1999. Categorized into 0, 1-2 and ≥3 for inclusion in statistical analyses.
Treatment-related	
b/tsDMARDs	Etanercept: L04AB01, Adalimumab: L04AB04, Certolizumab pegol: L04AB05, Infliximab: L04AB02, Golimumab: L04AB06, Rituximab: L01XC02, Abatacept: L04AA24, Tocilizumab: L04AC07, Baracitinib: L04AA37, Tofacitinib: L04AA29, Upadacitinib L04AA44, Sarilumab L04AC14
csDMARD	Sulfasalazine: A07EC01, Leflunomide: L04AA13, Cyclosporine: L04AD01, Azathioprine: L04AX01, Methotrexate: L04AX03, L01BA01, Hydroxychloroquine and Chloroquine P01BA01, P01BA02

Concomitant steroid use	Dispensation of steroids (ATC: H02AB06) recorded in the Prescribed Drug Register in the 183 days prior to cohort entry.
Concomitant methotrexate use	Concomitant methotrexate use defined as dispensation of recorded in the Prescribed Drug Register within the 183 days prior to cohort entry where the dispensation occurs after the order date of the treatment defining the exposure cohort (ATC code: L04AX03)
Concomitant csDMARD use	Concomitant csDMARD use defined as dispensation of csDMARD recorded in the Prescribed Drug Register within the 90 days prior to cohort entry (ATC codes: L04AX01, A07EC01, L04AD01, P01BA01, M01CB01, L04AA06, L01AA01, P01BA02, L04AA13, M01CB03) Note methotrexate is not included here.
Prednisolone treatment prior 1 year	Total milligrams of prednisolone dispensed during a 1 year look back. Dispensations recorded in the prescribed drug register (ATC H02AB06)
Prednisolone treatment prior 1 year categorized	Daily prednisolone (defined as above divided by 365.25) categorized into 0, 1-5,6-10, ≥10
Lipid lowering drug use	Dispensation of ATC C10A, C10B recorded in 183 days prior to cohort entry.

Supplementary table S4. Inclusion criteria for the cardiovascular risk factor enriched subset of the RA treatment cohorts

Patients aged 50 or older at treatment initiation

At least one cardiovascular disease risk (CVD) factor:

1. Hypertension diagnosis in the past 5 years (National Patient Register)
2. Dispensation of a lipid-lowering drug in the past 183 days (Prescribed Drug Register ATC=C10A, C10B)
3. History of diabetes in the past 5 years (both National Patient Register and Prescribed Drug Register)
4. History of CVD in the past 5 years (ICD10 I20-I25)
   Family history of CVD ever. For female first-degree relatives: events that occur at age 65 or younger. For male first-degree relatives: events that occur at age 55 or younger (Total Population Register for selecting relatives, CVD from inpatient records with ICD10 I20-I25, plus main cause of death I00-I99)

No hospitalised infection recorded in the previous 6 months (inpatient component of the National Patient Register)

No previous cancer diagnosis ever (Swedish Cancer Register)

Supplementary table S5. Baseline characteristics of the study cohorts of Swedish patients with psoriatic arthritis by treatment status

	JAKis				Non-TNFi	TNFi	General population
	Tofacitinib	**Baricitinib**	**Upadacitinib**	**All JAKis**			
Individuals	305	83	7	379	185	4186	21 285
Age years, median (IQR)	52 (45–61)	54 (47–63)	48 (41–54)	52 (45–61)	54 (45–62)	50 (41–59)	49 (41–59)
Female, %	71%	70%	71%	71%	71%	55%	54%
Median follow-up, years	1.49	1.98	0.40	1.52	2.25	2.44	2.56
Total person time at risk, years	426	156	3	585	418	12623	54005
Disease-related							
Disease duration years, median (IQR)	12.2 (6.5–19.1)	13.9 (7.8–18.4)	16.8 (11.3–19.8)	12.7 (6.8–19.0)	12.4 (6.5–19.4)	8.2 (3.6–15.5)	
Seropositivity, %	0%	0%	0%	0%	0%	0%	
DAS28CRP, median (IQR)	4.2 (3.75.0)	4.0 (3.0–4.5)	4.3 (4.3–4.7)	4.1 (3.5–4.9)	4.2 (3.4–5.1)	3.8 (3.0–4.5)	
DAS28CRP missing, %	48%	52%	29%	49%	54%	51%	
CRP <5, %	50%	55%	80%	52%	47%	58%	
CRP5-9, %	15%	14%	0%	15%	17%	18%	
CRP 10-19, %	17%	14%	0%	16%	17%	14%	
CRP ≥20, %	18%	18%	20%	18%	19%	10%	
CRP missing, %	33%	39%	29%	34%	42%	38%	
Smoker, %	57%	62%	80%	58%	59%	55%	
Smoking missing, %	14%	18%	29%	15%	20%	38%	
0 previous b/tsDMARDs	7%	8%	(n/a)	7%	11%	65%	
1-2 previous b/tsDMARDs	41%	35%	29%	40%	41%	30%	
3+ previous b/tsDMARDs	52%	57%	71%	53%	48%	5%	
Treatment-related							

Concomitant steroid use, %	43%	49%	43%	45%	53%	34%	2%
Concomitant methotrexate use, %	36%	40%	43%	37%	39%	50%	0%
Prednisolone use mg prior 1 year, %	2.7 (1.4–5.5)	3.5 (1.4–5.6)	4.2 (2.8–5.6)	2.7 (1.4–5.5)	4.1 (1.4–7.0)	2.7 (1.4–4.2)	1.4 (0.7–4.1)
Comorbidities (previous 5 years), %							
History of diabetes type 1 and 2	14%	11%	0%	13%	12%	8%	6%
History of ischemic heart disease	5%	4%	14%	5%	7%	2%	1%
History of hospitalized infections	13%	15%	0%	13%	13%	6%	2%
History of Chronic obstructive pulmonary disease	8%	7%	0%	8%	9%	5%	2%
History of kidney failure	2%	1%	0%	2%	7%	1%	1%
History of heart failure	1%	4%	0%	1%	1%	1%	1%
History of stroke	4%	8%	29%	5%	4%	2%	2%
History of VTE	2%	2%	0%	2%	4%	2%	1%
History of joint surgery	5%	8%	14%	6%	9%	3%	1%
History of hypertension	13%	7%	29%	12%	13%	7%	4%
History of NMSC	1%	2.4%	0%	1.3%	0.5%	0.5%	0.4%
Drug dispensations (previous 6 months), %							
Lipid lowering	13%	12%	0%	13%	17%	11%	9%

Other measures of comorbidities/health							
Hospital days in the previous year	6 (4–11)	15 (6–18)	. (.-.)	7 (4–15)	8 (3–18)	5 (3–11)	4 (2–12)
Sick leave in the previous year, %	23%	23%	0%	23%	19%	20%	8%
Disability pension in the previous year, %	2%	1%	0%	2%	0%	1%	0%
Socioeconomics							
Education >12 years, %	35%	28%	43%	33%	33%	34%	40%
Married/partner, %	50%	55%	71%	51%	46%	49%	46%

Abbreviations: RA, rheumatoid arthritis; CRP, C-reactive protein, VTE, venous thromboembolism; NMSC, non-melanoma skin cancer; b/tsDMARD, biologic/targeted synthetic disease modifying anti-rheumatic drug; TNFi, Tumor necrosis factor inhibitor; JAKi, Janus kinase inhibitor, DAS28CRP, disease activity score 28 C-reactive protein; IQR, interquartile range (25^{th} percentile – 75^{th} percentile).

Supplementary table S6. Hazard Ratios (HR1-4), events, crude and standardized incidence rates, for all cancers other than NMSC and for cancer sites where at least five incident events were observed in the JAK cohort, in Swedish patients with RA treated with JAKi, non-TNFi bDMARDs, or TNFi

Cohort	Events	Crude incidence rate	Standardized incidence rate	HR1*	HR2*	HR3*	HR4*
All cancers other than NMSC							
JAKi	38	9.5	8.3	0.93 (0.64 to 1.35)	0.84 (0.57 to 1.25)	0.65 (0.34 to 1.23)	0.94 (0.65 to 1.38)
Tofacitinib	8	10.1	11.2	1.13 (0.55 to 2.33)	0.95 (0.44 to 2.08)	1.04 (0.35 to 3.10)	1.08 (0.52 to 2.24)
Baricitinib	30	9.4	8.0	0.90 (0.60 to 1.35)	0.82 (0.54 to 1.26)	0.56 (0.27 to 1.16)	0.92 (0.61 to 1.38)
Non-TNFi bDMARD*	141	12.8	10.5	1.17 (0.93 to 1.47)	1.09 (0.86 to 1.38)	1.29 (0.89 to 1.85)	1.12 (0.88 to 1.43)
TNFi	213	10.1	10.1	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
General population	1245	9.7	9.2	0.86 (0.73 to 1.01)	0.90 (0.76 to 1.07)	n/a	n/a
NMSC							
All JAKi	59	14.9	12.9	1.41 (1.03 to 1.92)	1.39 (1.02 to 1.90)	1.56 (0.96 to 2.56)	1.39 (1.01 to 1.91)
- Tofacitinib	11	14.1	14.9	-	-	-	-
- Baricitinib	48	15.2	12.5	-	-	-	-
Non-TNFi bDMARD*	126	11.4	9.0	1.03 (0.81 to 1.31)	1.03 (0.81 to 1.32)	1.22 (0.83 to 1.79)	1.00 (0.78 to 1.28)
TNFi	189	9.0	9.0	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
General population	852	6.6	6.2	0.71 (0.59 to 0.85)	0.71 (0.59 to 0.86)	n/a	n/a
Breast cancer							
All JAKi	7	1.7	1.6	0.68 (0.28 to 1.65)	0.67 (0.27 to 1.66)	0.85 (0.22 to 3.27)	0.73 (0.29 to 1.86)
- Tofacitinib	1	1.3	-	-	-	-	-
- Baricitinib	6	1.9	1.7	-	-	-	-
Non-TNFi bDMARD*	23	2.1	1.9	0.87 (0.50 to 1.52)	0.79 (0.44 to 1.43)	1.09 (0.45 to 2.65)	0.88 (0.48 to 1.61)

TNFi	42	2.0	2.0	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
General population	262	2.0	2.0	1.07 (0.72 to 1.59)	1.12 (0.75 to 1.68)	n/a	n/a
All Hematopoetic							
All JAKi	6	1.5	1.5	1.76 (0.67 to 4.60)	1.74 (0.66 to 4.61)	1.29 (0.28 to 6.04)	1.90 (0.70 to 5.16)
- Tofacitinib	1	1.3	-	-	-	-	-
- Baricitinib	5	1.6	1.6	-	-	-	-
Non-TNFi bDMARD*	12	1.1	0.9	1.03 (0.51 to 2.10)	1.03 (0.51 to 2.08)	1.13 (0.38 to 3.37)	1.04 (0.48 to 2.25)
TNFi	22	1.0	1.0	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
General population	99	0.8	0.7	0.66 (0.39 to 1.11)	0.69 (0.40 to 1.17)	n/a	n/a
Lung cancer							
All JAKi	7	1.7	1.5	1.58 (0.70 to 3.53)	0.84 (0.31-2.27)	0.46 (0.05 to 4.36)	1.15 (0.57 to 2.32)
- Tofacitinib	2	2.5	-	-	-	-	-
- Baricitinib	5	1.6	1.2	-	-	-	-
Non-TNFi bDMARD*	11	1.0	0.7	0.68 (0.34 to 1.36)	0.54 (0.27-1.10)	0.80 (0.32 to 1.97)	0.59 (0.31 to 1.15)
TNFi	30	1.4	1.4	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
General population	111	0.9	0.8	0.53 (0.34 to 0.83)	0.57 (0.35-0.93)	n/a	n/a

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinas inhibitor, *Non-TNFI bDMARD includes rituximab, abatacept, tocilizumab.
Incidence rates presented per 1,000 person-years.

***** HR1: adjusted for age, sex, line of therapy (for these variables, there was no missingness)
*****HR2: as HR1 but adjusted for comorbidities and SES (for these variables, there was no missingness)
*****HR3: as HR2 but additionally adjusted for disease-related factors, complete case approach
*****HR4: as HR3 but with missing categories included for those variables with missing information
n/a presented where analyses not performed (due to disease-related factors not being available for the general population comparator)

Supplementary table S7. Number of incident BCC and SCC events contributing to the NMSC outcome, by cohort

Cohort	NMSC events	BCC events	SCC events
JAKi	59	51	8
Tofacitinib	11	11	0
Baricitinib	48	40	8
Non-TNFi bDMARD*	126	108	19
TNFi	189	158	31
General population	852	776	76

Abbreviations: NMSC; non-melanoma skin cancer, BCC; basal cell carcinoma (BCC), SCC; squamous cell carcinomas, TNFi; tumor necrosis factor inhibitor, JAKi; janus kinas inhibitor, *Non-TNFI bDMARD includes rituximab, abatacept, tocilizumab

Supplementary table S8. Distribution of events across cohort and history of NMSC

Cohort	Events overall	Events, history of NMSC (% of overall)
All cancers other than NMSC		
All JAKi	38	2 (5)
-Tofacitnib	8	0 (0)
- Baricitinib	30	2 (7)
Non-TNFi bDMARD †	141	6 (4)
TNFi	213	7 (3)
General population	1245	30 (2)
NMSC		
All JAKi	59	7 (12)
-Tofacitnib	11	0 (0)
- Baricitinib	48	7 (15)
Non-TNFi bDMARD †	126	20 (16)
TNFi	189	24 (13)
General population	852	74 (9)

Abbreviations: NMSC; non-melanoma skin cancer, BCC; basal cell carcinoma (BCC), SCC; squamous cell carcinomas, TNFi; tumor necrosis factor inhibitor, JAKi; janus kinas inhibitor, *Non-TNFI bDMARD includes rituximab, abatacept, tocilizumab

Supplementary table S9. Hazard Ratios (HR1-4) for all cancers other than NMSC, and NMSC, in patients with RA treated with; JAKis, non-TNFis and TNFis by time since treatment initiation

	HR1*	HR2*	HR3*	HR4*
All cancers other than NMSC				
0-1 year				
JAKi	1.01 (0.60 to 1.67)	0.85 (0.48 to 1.48)	0.62 (0.26 to 1.50)	0.96 (0.58 to 1.59)
Non-TNFi	1.19 (0.83 to 1.72)	1.09 (0.74 to 1.59)	1.34 (0.78 to 2.30)	1.11 (0.77 to 1.61)
TNFi	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-2 years				
JAKi	0.67 (0.32 to 1.42)	0.66 (0.31 to 1.40)	0.32 (0.07 to 1.40)	0.67 (0.32 to 1.43)
Non-TNFi	1.26 (0.82 to 1.95)	1.16 (0.74 to 1.81)	1.21 (0.62 to 2.38)	1.25 (0.80 to 1.96)
TNFi	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2 or more years				
JAKi	1.35 (0.67 to 2.71)	1.30 (0.64 to 2.62)	1.20 (0.44 to 3.30)	1.36 (0.67 to 2.75)
Non-TNFi	1.05 (0.73 to 1.50)	1.00 (0.70 to 1.43)	1.30 (0.78 to 2.15)	1.06 (0.74 to 1.53)
TNFi	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
NMSC				
0-1 year				
JAKi	1.09 (0.69 to 1.73)	1.11 (0.70 to 1.77)	1.24 (0.64 to 2.41)	1.12 (0.70 to 1.78)
Non-TNFi	0.85 (0.57 to 1.25)	0.85 (0.57 to 1.27)	1.06 (0.60 to 1.86)	0.85 (0.57 to 1.26)
TNFi	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-2 years				
JAKi	1.44 (0.84 to 2.45)	1.39 (0.81 to 2.39)	2.55 (1.13 to 5.78)	1.48 (0.87 to 2.51)
Non-TNFi	1.42 (0.95 to 2.14)	1.47 (0.98 to 2.22)	1.89 (0.95 to 3.75)	1.43 (0.95 to 2.15)
TNFi	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2 or more years				

JAKi	2.11 (1.15 to 3.87)	2.08 (1.14 to 3.82)	1.29 (0.42 to 3.91)	2.12 (1.15 to 3.89)
Non-TNFi	0.86 (0.57 to 1.30)	0.87 (0.58 to 1.32)	1.03 (0.56 to 1.91)	0.86 (0.57 to 1.31)
TNFi	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinase inhibitor, Non-TNFI includes rituximab, abatacept, tocilizumab.

* HR1: adjusted for age, sex, line of therapy (for these variables, there was no missingness)
*HR2: as HR1 but adjusted for comorbidities and SES (for these variables, there was no missingness)
*HR3: as HR2 but additionally adjusted for disease-related factors, complete case approach
*HR4: as HR3 but with missing categories included for those variables with missing information

Supplementary table S10. Events, crude and standardized rates and fully adjusted hazard ratio (HR) estimated from Cox proportional hazards models for all cancers other than NMSC and for NMSC, in patients with RA initiating treatment with a JAKi, a non-TNFi or TNFi by previous number of b/tsDMARDs

	Events	Crude incidence rate per 1,000 person-years	Standardized incidence rate per 1,000 person-years	Fully adjusted HR*
All cancers other than NMSC				
0 previous b/tsDMARDs				
JAKi	7	14.8	13.0	1.05 (0.48 to 2.31)
Non-TNFi	41	18.0	11.8	1.12 (0.76 to 1.65)
TNFi	143	10.7	10.7	1.0 (Reference)
1-2 previous b/tsDMARDs				
JAKi	10	7.06	6.1	0.79 (0.40 to 1.56)
Non-TNFi	67	12.3	10.1	1.32 (0.91 to 1.91)
TNFi	58	8.6	8.6	1.0 (Reference)
3 or more previous b/tsDMARDs				
JAKi	21	10.0	9.0	1.11 (0.51 to 2.39)
Non-TNFi	33	9.9	8.3	1.04 (0.51 to 2.09)
TNFi	12	9.6	89.6	1.0 (Reference)
NMSC				

0 previous b/tsDMARDs				
JAKi	6	12.7	6.0	0.99 (0.44 to 2.23)
Non-TNFi	34	15.0	10.0	1.23 (0.82 to 1.85)
TNFi	117	8.8	8.8	1.0 (Reference)
1-2 previous b/tsDMARDs				
JAKi	17	12.1	11.4	1.10 (0.63 to 1.91)
Non-TNFi	62	11.4	9.2	0.91 (0.63 to 1.30)
TNFi	63	9.7	9.7	1.0 (Reference)
3 or more previous b/tsDMARDs				
JAKi	36	17.3	16.0	2.49 (1.15 to 5.43)
Non-TNFi	30	9.0	8.7	1.24 (0.58 to 2.64)
TNFi	9	7.2	7.2	1.0 (Reference)

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinase inhibitor, Non-TNFI includes rituximab, abatacept, and tocilizumab. Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information. Estimated from a proportional hazards Cox regression model. Standardized incidence rate standardized to the age- and sex- distribution in the TNFi cohort.

Supplementary table S11. Fully adjusted hazard ratios estimated from Cox proportional hazards models comparing the rate of site-specific cancer for JAKi and non-TNFi, versus TNFi in patients with RA for both the main analysis, and when applying a 90-day latency period

Cohort	**Main analysis:** start of follow-up immediately after initiating treatment	**Latency period:** Start of follow up 90 days after initiating treatment
	Fully adjusted HR*	**Fully adjusted HR***
All cancers		
JAKi	0.94 (0.65 to 1.38)	0.84 (0.55 to 1.27)
Non-TNFi	1.12 (0.88 to 1.43)	1.12 (0.87 to 1.45)
TNFi	1.0 (Reference)	1.0 (Reference)
NMSC		
JAKi	1.39 (1.01 to 1.91)	1.38 (0.98 to 1.94)
Non-TNFi	1.00 (0.78 to 1.28)	1.01 (0.78 to 1.31)
TNFi	1.0 (Reference)	1.0 (Reference)
Breast cancer		
JAKi	0.73 (0.29 to 1.86)	0.55 (0.18 to 1.67)
Non-TNFi	0.88 (0.48 to 1.61)	0.86 (0.46 to 1.60)
TNFi	1.0 (Reference)	1.0 (Reference)
All Hematopoetic		
JAKi	1.90 (0.70 to 5.16)	1.65 (0.52 to 5.26)
Non-TNFi	1.04 (0.48 to 2.25)	0.99 (0.45 to 2.15)
TNFi	1.0 (Reference)	1.0 (Reference)
Lung cancer		
JAKi	1.15 (0.57 to 2.32)	0.99 (0.41 to 2.35)
Non-TNFi	0.59 (0.31 to 1.15)	0.55 (0.27 to 1.09)
TNFi	1.0 (Reference)	1.0 (Reference)

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinase inhibitor, Non-TNFI includes rituximab, abatacept, and tocilizumab.

Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information. Estimated from proportional hazards Cox regression models.

Supplementary Table S12. Alternative definition of follow-up from the main analysis "ever-exposed" to a "on-drug". Number of events, crude and standardized incidence rates and hazard ratios (HR), for all cancers other than NMSC and NMSC in Swedish patients with RA treated with JAKi, non-TNFi bDMARDs, or TNFi. Also, fully adjusted HR for ever-exposed analysis (fully presented in Table 2)

Cohort	Events	Crude incidence rate per 1,000 person-years	Standardized incidence rate per 1,000 person-years	On-drug analysis Fully adjusted HR*	Ever-exposed analysis Fully adjusted HR* presented in Table 2.
All cancers other than NMSC					
All JAKi	27	9.9	8.5	1.01 (0.64 to 1.58)	0.94 (0.65 to 1.38)
- Tofacitinib	4	8.7	10.4	0.99 (0.36 to 2.73)	1.08 (0.52 to 2.24)
- Baricitinib	23	10.1	8.7	1.01 (0.64 to 1.62)	0.92 (0.61 to 1.38)
Non-TNFi bDMARD †	95	14.0	11.0	1.20 (0.89 to 1.62)	1.12 (0.88 to 1.43)
TNFi	139	10.0	10.0	1.0 (Reference)	1.0 (Reference)
General population	1245	9.7	9.4	n/a	n/a
NMSC					
All JAKi	41	15.1	13.2	1.35 (0.91 to 1.99)	1.39 (1.01 to 1.91)
- Tofacitinib	6	13.3	13.0	1.32 (0.56 to 3.12)	1.56 (0.83 to 2.92)
- Baricitinib	35	15.6	13.0	1.36 (0.90 to 2.04)	1.37 (0.97 to 1.92)
Non-TNFi bDMARD †	74	10.9	8.0	0.83 (0.61 to 1.14)	1.00 (0.78 to 1.28)
TNFi	129	9.4	9.4	1.0 (Reference)	1.0 (Reference)
General population	852	6.6	6.4	n/a	n/a

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinas inhibitor, † Non-TNFI bDMARD includes rituximab, abatacept, tocilizumab. n/a: analyses not performed

*****Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information. Estimated from Cox proportional hazards models. Standardized incidence rate standardized to the age- and sex- distribution in the TNFi cohort. - is displayed when too few events (<5) were observed

Supplementary Table 13. Fully adjusted HR (presented in Table 2) and fully adjusted HR after multiple imputation for all cancers other than NMSC in Swedish patients with RA treated with JAKi, non-TNFi bDMARDs, or TNFi.

Cohort	Fully adjusted HR* presented in Table 2	Fully adjusted HR after multiple imputation**
All cancers other than NMSC		
All JAKi	0.94 (0.65 to 1.38)	0.93 (0.64 to 1.36)
- Tofacitinib	1.08 (0.52 to 2.24)	1.09 (0.52 to 2.29)
- Baricitinib	0.92 (0.61 to 1.38)	0.91 (0.60 to 1.36)
Non-TNFi bDMARD †	1.12 (0.88 to 1.43)	1.11 (0.87 to 1.42)
TNFi	1.0 (Reference)	1.0 (Reference)
General population	n/a	n/a

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinas inhibitor, † Non-TNFI bDMARD includes rituximab, abatacept, tocilizumab. n/a: analyses not performed

*****Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information. Estimated from Cox proportional hazards models. Standardized incidence rate standardized to the age- and sex- distribution in the TNFi cohort. - is displayed when too few events (<5) were observed

**multiple imputation using chained equations performed with 30 repetitions for variables with missing information (DAS28CRP, CRP using multinomial logistic regression; disease duration, smoking, civil status and education using logistic regression). Imputation models were adjusted for all covariates included in the analysis model plus the event indicator and the Nelson-Aalen estimate of the cumulative hazard.

Supplementary Table 14. Fully adjusted HR (presented in Table 2) and fully adjusted HR after sensitivity analysis restricting the follow-up to Feb 2020 (COVID Pandemic), for all cancers other than NMSC in Swedish patients with RA treated with JAKi, non-TNFi bDMARDs, or TNFi.

Cohort	Fully adjusted HR* presented in Table 2	Fully adjusted HR * after sensitivity analysis
All cancers other than NMSC		
All JAKi	0.94 (0.65 to 1.38)	0.78 (0.48 to 1.26)
- Tofacitinib	1.08 (0.52 to 2.24)	0.92 (0.37 to 2.33)
- Baricitinib	0.92 (0.61 to 1.38)	0.74 (0.44 to 1.26)
Non-TNFi bDMARD †	1.12 (0.88 to 1.43)	1.14 (0.86 to 1.51)
TNFi	1.0 (Reference)	1.0 (Reference)
General population	n/a	n/a

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinas inhibitor, † Non-TNFI bDMARD includes rituximab, abatacept, tocilizumab. n/a: analyses not performed

*****Fully adjusted HR: adjusted for age, sex, line of therapy, for comorbidities, SES, disease-related factors and with missing categories included for those variables with missing information. Estimated from Cox proportional hazards models. Standardized incidence rate standardized to the age- and sex- distribution in the TNFi cohort. - is displayed when too few events (<5) were observed

Supplementary Table S15. Events, crude and standardized rates and fully adjusted hazard ratio (HR) estimated from Cox proportional hazards models for cancers other than NMSC in a cardiovascular risk-factor enriched subset (defined in supplementary Table S4)

Cohort	Events	Crude incidence rate	Standardized incidence rate	HR1*	HR2*	HR3*	HR4*
All JAKi	17	15.5	14.7	1.04 (0.59 to 1.84)	1.01 (0.56 to 1.82)	0.60 (0.20 to 1.82)	1.03 (0.58 to 1.82)
- Tofacitinib	3	14.2	-	-	-	-	-
- Baricitinib	14	15.8	13.9	1.01 (0.55 to 1.86)	0.98 (0.52 to 1.84)	0.37 (0.09 to 1.56)	1.01 (0.55 to 1.85)
Non-TNFi	61	19.7	18.2	1.16 (0.81 to 1.66)	1.05 (0.73 to 1.52)	1.33 (0.74 to 2.41)	1.12 (0.76 to 1.63)
TNFi	79	17.5	17.5	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinase inhibitor, Non-TNFI includes rituximab, abatacept, or tocilizumab.
Incidence rates presented per 1,000 person-years.
*HR1: adjusted for age, sex, line of therapy (for these variables, there was no missingness)
*HR2: as HR1 but adjusted for comorbidities and SES (for these variables, there was no missingness)
*HR3: as HR2 but additionally adjusted for disease-related factors, complete case approach
*HR4: as HR3 but with missing categories included for those variables with missing information

- Is displayed when too few events (<5) were observed

Supplementary table S16. Hazard Ratios (HR1-4), events, crude and standardized incidence rates and hazard ratios (HR) for all cancers other than NMSC and NMSC in Swedish patients with PsA treated with JAKi

Cohort	Events	Crude incidence rate	Standardized incidence rate	HR1*	HR2*	HR3*	HR4*
All cancers other than NMSC							
JAKi	5	8.6	7.3	1.64 (0.61 to 4.37)	1.69 (0.63 to 4.49)	1.11 (0.14 to 8.64)	1.88 (0.68 to 5.16)
Non-TNFi	2	4.8	-	-	-	-	-
TNFi	73	5.8	5.8	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Gen population	317	5.9	6.0	0.87 (0.66 to 1.16)	0.93 (0.70 to 1.23)	n/a	n/a
NMSC							
JAKi	8	13.9	11.7	2.27 (0.98 to 5.25)	2.40 (1.02 to 5.63)	1.82 (0.52 to 6.40)	2.05 (0.79 to 5.31)
Non-TNFi	2	4.8	-	-	-	-	-
TNFi	73	5.8	5.8	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Gen population	209	3.9	3.9	0.70 (0.51 to 0.96)	0.70 (0.51 to 0.97)	n/a	n/a

Abbreviations: TNFi; tumor necrosis factor inhibitor, JAKi; janus kinas inhibitor, Non-TNFI includes rituximab, abatacept, and tocilizumab.
Incidence rates presented per 1,000 person-years.
*HR1: adjusted for age, sex, line of therapy (for these variables, there was no missingness)
*HR2: as HR1 but adjusted for comorbidities and SES (for these variables, there was no missingness)
*HR3: as HR2 but additionally adjusted for disease-related factors, complete case approach
*HR4: as HR3 but with missing categories included for those variables with missing information
n/a presented where analyses not performed (due to disease-related factors not being available for the general population comparator)

- Is displayed when too few events (<5) were observed