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Cancer risk in patients with rheumatoid arthritis treated with janus kinase inhibitors: a nationwide Danish register-based cohort study

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ABSTRACT

Objectives

We aimed to investigate the risk of first primary cancer in patients with rheumatoid arthritis (RA) treated with janus kinase inhibitors (JAKi) compared with those who received biologic disease-modifying anti-rheumatic drugs (bDMARDs) in a real-world setting.

Methods

We performed an observational cohort study using the nationwide registers in Denmark. Patients with RA aged 18+ years, without a previous cancer diagnosis, and who initiated treatment with JAKi or bDMARDs from 1 January 2017 to 31 December 2020 were followed for any cancer (except non-melanoma skin cancer). We applied inverse probability of treatment weighting (IPTW) to account for covariate differences between treatment groups. IPTW-generated weights were used with cause-specific Cox (CSC) models to calculate hazard ratios (HRs) for cancer incidence in JAKi-treated compared with bDMARD-treated patients with RA.

Results

We identified 875 and 4247 RA patients treated with JAKi and bDMARDs, respectively. The JAKi group contributed 1315 person years (PYRS) and 19 cancers, the bDMARD group contributed 8597 PYRS and 111 cancers, with corresponding crude incidence rates per 1000 PYRS of 14.4 and 12.9. Comparing the two groups using weighted CSC models, a HR of 1.41 (95%CI 0.76 to 2.37, 95% confidence intervals) was seen for JAKi- versus bDMARD-treated patients with RA.

Conclusion

JAKi treatment in real-world patients with RA was not associated with a statistically significant increased risk of first primary cancer compared with those who received bDMARDs. However, several numerically increased risk estimates were detected, and a clinically important excess risk of cancer among JAKi recipients cannot be dismissed.

Keywords

Rheumatoid Arthritis, Cancer, Malignancy, Janus Kinase Inhibitors, Biologics, Real-World Evidence

Key messages

- Compared with bDMARDs, JAKi treatment in RA patients was not associated with increased cancer risk.
- Additional studies founded on real-world data investigating JAKI and cancer risk in RA are required.

INTRODUCTION

Cancer risk in patients with rheumatoid arthritis (RA) receiving various biologic disease-modifying anti-rheumatic drugs (bDMARDs) has been investigated and debated throughout the past decades.(1-3) Most recently, attention has turned to the janus kinase inhibitors (JAKi). The first approved JAKi for the treatment of RA, tofacitinib, has been available in the United States for 10 years, while both tofacitinib and baricitinib were not approved by the European Medicines Agency (EMA) until 2017.(4) JAKi are classified as targeted synthetic DMARDs and are small molecules able to inhibit cytokine signalling pathways, thereby also modulating dysfunctional innate and adaptive immune responses intrinsic to RA.(5, 6) While exerting their primary intended effects through a plethora of signalling pathways, JAKi also have several unwanted off-target effects of which only some are well-established. Concerns regarding the risk of cancer in JAKi-treated patients with RA escalated after the release of results from Pfizer's completed post-marketing randomized clinical trial, *ORAL Surveillance*, in January 2021.(7) The results were later published.(8) The trial, which included only patients with RA 50+ years of age with at least one additional cardiovascular risk factor, revealed increased risks of major adverse cardiovascular events and cancer — among several other reported adverse events — in tofacitinib recipients compared with those who received tumour necrosis factor inhibitors (TNFi). Precautionary considerations on JAKi use in high-risk subsets of patients with RA have since been issued by the US Food and Drug Administration (FDA) and by EMA.(9-11)

Considering the ongoing concerns about JAKi's safety profile, we sought to investigate JAKi's safety in terms of cancer risk among patients with RA utilising Danish nationwide high-quality registers.

METHODS

Study design

We performed an observational cohort study exploring the risk of first primary cancer in patients with RA treated with JAKi (tofacitinib and baricitinib) compared with RA patients treated with bDMARDs in the period 1 January 2017 to 31 December 2020.

Data sources

Patients diagnosed with RA were identified in the Danish Rheumatology Quality Register (DANBIO), which contains prospectively collected clinical information, start and stop dates for treatment with DMARDs, disease activity measures, smoking status, and more.(12, 13) Validity and completeness of RA diagnoses in DANBIO have been estimated to be high with a positive predictive value (PPV) of 96% and a completeness of 91% covering patients with RA.(13) All cancer diagnoses were collected from the Danish Cancer Registry (DCR).(14) Cancer diagnoses registered in DCR have been estimated to be highly valid and complete.(15-17) In Denmark, linkage between registers is possible on an individual-based level via the unique civil registration number (CPR number) from the Danish Civil Registration System (CRS). From CRS information on date of birth, sex, migration, and vital status was also collected.(18) Highest obtained education levels were

retrieved from the Danish Population Education Register.(19) Information on comorbidities and medication including hormone replacement therapy was collected by linkage to the Danish National Patient Register (DNPR) and the Danish National Prescription Registry (NPR).(20, 21) DNPR contains data comprising diagnosis codes registered at in- or outpatient hospital visits. NPR covers information on all redeemed drugs dispensed at Danish pharmacies, which are identifiable via coding in accordance with the global Anatomical Therapeutic Chemical classification system (ATC).

Study population and exposure

All patients with RA in DANBIO aged 18 or more and who initiated treatment with either JAKi or bDMARDs (index date) from 1 January 2017 to 31 December 2020 were included in the study. Patients with a registered cancer prior to the index date were excluded, except for those with prior non-melanoma skin cancer (NMSC).

The exposure group was composed of patients with RA who initiated any available JAKi in Denmark, i.e., tofacitinib or baricitinib, during the study period. Due to its Danish approval late 2020, no treatment series with upadacitinib were recorded for our study population.

The comparator group was composed of those who initiated a bDMARD treatment: Interleukin-6 inhibitors (tocilizumab/sarilumab); B-cell inhibitors via anti-CD20 (rituximab); T-cell co-stimulation inhibitors via CTLA-4 (abatacept); all types of TNFi (adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab) including both originators and biosimilars. For both groups, patients with previous bDMARD treatments were included.

Outcome

The study's primary outcome was defined as any primary cancer diagnosis (excluding NMSC) according to ICD-10 codes registered in DCR.

Follow-up

Follow-up started on the date upon first registered treatment with JAKi or bDMARDs after 1 January 2017. Follow-up was performed in a hierarchical ever-treated design, i.e., 'once exposed always exposed'. However, patients were able to switch from the bDMARD group to the JAKi group, mimicking the usual hierarchical treatment pattern for JAKi-treated patients according to Danish guidelines. Person years (PYRS) of follow-up and number of cancers were allocated to each JAKi and bDMARD group, respectively, by following patients from the index date and until date of: Cancer, death, emigration, initiation of JAKi (bDMARD group censoring only), or 31 December 2020, whichever occurred first. *See figure 1.*

Statistical methods

We used inverse probability of treatment weighting (IPTW) to account for covariate differences between treatment groups. In all analyses, average treatment effect *on the treated* (ATT), i.e., the JAKi-treated patients with RA in our study, was estimated.(22) In case of missing covariate values,

the IPTW model attempted to balance missingness in the constructed weights. The ATT weights were assessed by comparing the covariates' standardized mean difference (SMD) pre and post weighting. Differences below 10% were considered negligible. SMD is a useful tool for comparison of means across continuous, dichotomous, and multilevel covariates between treatment group, regardless of covariates measured in different units.(22) Covariates with SMD > 10% ($\pm$ 0.1) post weighting were added to the weighted cause-specific Cox (CSC) model for adjustment. Death was considered a competing risk due to its preclusion of cancer occurrence. We calculated 95% bootstrap confidence intervals (95%CI) with 500 iterations for all weighted models.(23)

Crude incidence rates (IR) of cancer per 1000 PYRS were calculated and presented for both JAKi and bDMARD groups. Based on the IPTW-generated ATT weights and with age as underlying timescale, we used CSC proportional hazard regression models to calculate hazard ratios (HRs) for cancer incidence in those who had received JAKi treatment compared with bDMARD-treated patients. Assessing the robustness of our IPTW-modelling, we constructed three comparative unweighted CSC proportional hazard regression models for all estimates.

Additionally, for select analyses we estimated and displayed the absolute risk of cancer as a function of follow-up time using Aalen-Johansen cumulative incidence functions (CIFs). These were performed while considering the competing risk of death and ATT-generated weights.

All statistical modelling and analyses were performed in R (version 4.0.3). IPTW-generated ATT weights and IPTW-balancing diagnostics were performed via the "TWANG" package.(24) CSC proportional hazard regression models were estimated using the "riskRegression" package.(25) Aalen-Johansen CIFs were modelled in the "prodlim" package.(26)

Covariates

The objective of IPTW modelling is to balance the measured covariates between treatment groups. That said, not all covariates are of equal importance to balance according to Austin.(22) We chose to include only covariates associated with cancer (outcome) or those associated with both treatment choice (exposure) and cancer (outcome) in the IPTW model. All covariates were selected by the authors' expert knowledge in the fields of both RA and risk factors for cancer.

We chose to include the following comorbidities as covariates: lung disease (prior diagnosis of chronic obstructive pulmonary disease, interstitial lung disease, or two redeemed prescriptions for inhalers in a two-year period prior to index date); cardiovascular disease (prior diagnosis of venous thromboembolism, stroke, ischemic heart disease, or heart failure); and diabetes (prior diagnosis of diabetes; or two redeemed prescriptions for antidiabetic drugs in a two-year period prior to index date).(27) All of the above comorbidities were identified using coding according to Danish well-validated register-based algorithms.(28-31) We also included hormone replacement therapy (two redeemed prescriptions in a five-year period prior to index date) and smoking status.(32) Both RA itself and the extent of uncontrolled inflammation of RA is related to an increased risk of cancer, with lymphoma risk being particularly associated with high RA disease activity.(33, 34) Hence, we included information on numerous covariates reflective of RA characteristics at index date: disease duration of RA; seropositivity for rheumatoid factors or anti-citrullinated protein

antibodies; health assessment questionnaire (HAQ); disease activity score-28 with CRP (DAS28-CRP); concomitant use of systemic glucocorticoids (one redeemed prescription for prednisolone or one intra-muscular administration of prednisolone in a three-month period prior to index date); and number of bDMARDs previously received. All these covariates as well as age, sex, and education level were considered a mix of important predictors or confounders (or proxies hereof, e.g. lung disease as a proxy for smoking).(35, 36) *For full information regarding covariates, see supplementary table S1.*

Subgroup analyses

The ORAL Surveillance study included only patients with RA aged 50+, and EMA's recommendations on JAKi caution specifically address patients over 65 years as a high-risk group. Hence, we stratified the main analysis by age groups 50+ and 65+. Also, analyses stratified by length of follow-up (< 1 year and 1+ years) were performed.

Sensitivity analyses

We performed two so-called 'on-drug' analyses. These analyses took both initiation and discontinuation dates of treatment into account. In doing so, we allowed for 'switching' back and forth between JAKi and bDMARD groups, thereby also enabling each patient to potentially contribute with multiple treatment initiations (and index dates) to both groups. The two separate on-drug analyses were performed by following patients from drug initiation date to the date of cancer, death, emigration, 31 December 2020, or drug discontinuation date (+3 months/+ 6 months), whichever occurred first. By lagging discontinuation dates with 3 months and 6 months, respectively, we attempted to consider different definitions of 'carry-over effects' with regards to cancer and, importantly, the potential for drug discontinuation due to early cancer symptoms. If reinitiating the same type of treatment within the 3/6-month windows, uninterrupted by the opposite treatment, it was considered the same series of treatment. Cancers registered within the 3/6-month discontinuation windows and after the start of a drug belonging to the opposite treatment group were attributed to both groups.

We also performed sensitivity analyses in which we tested the impact of various inclusion criteria. First, we enforced a requirement of minimum one prior bDMARD treatment before index date to establish more prior-bDMARD-comparable groups of JAKi- and bDMARD-treated patients. Secondly, based on EMA's warning regarding JAKi use in current or past smokers, we performed an analysis including only patients who were 'ever' smokers. Lastly, we performed two additional and separate analyses with the bDMARD group consisting only of patients initiating TNFi and non-TNFI bDMARDs, respectively, while follow-up was stopped upon switching to the opposite bDMARD class. By doing so, we established comparator groups less heterogenous in respect of potentially distinct carcinogenic effects of TNFi and non-TNFI bDMARDs, herein also mimicking the pure TNFi exposure comparison of ORAL Surveillance.

RESULTS

A total of 4601 unique individuals were included, with JAKi and bDMARD groups consisting of 875 and 4247 patients, respectively. During follow-up, the JAKi group contributed 1315 PYRS (median 1.48 years; interquartile range 0.98 to 1.93 years) and 19 cancers, while the bDMARD group contributed 8597 PYRS (1.98; 1.11 to 3.09) and 111 cancers. *For more information on the distribution of specific cancers, see supplementary table S2*.

All covariates and covariate levels had post-IPTW-weighting SMDs < 10%, and the majority were <5%. *See table 1.* Hence, no covariates were added to the weighted CSC regression model for adjustment in the main analysis for JAKi versus bDMARDs. In some subgroup and sensitivity analyses a few specific covariates showed post-IPTW-weighting SMDs above 10% (data not shown) and were therefore further adjusted for.

Crude IRs for JAKi and bDMARD groups were 14.4 and 12.9 per 1000 PYRS, respectively. Looking at cancer risk in the JAKi group compared with the bDMARD group, there was a numerically but statistically non-significant increased HR of 1.41 (95%CI 0.76 to 2.37) in the IPTW-weighted CSC model. Similar estimates were obtained in the three unweighted CSC models. Analyses stratified by age and by length of follow-up also displayed numerically increased yet statistically non-significant HRs, with the biggest difference observed between follow-up < 1 and follow-up 1+ years with HRs of 1.54 (95%CI 0.67 to 3.31) and 1.07 (95%CI 0.30 to 2.39). *See table 2.*

None of the sensitivity analyses showed any statistically significant HRs. *See table 3 and table 4.* Notably, the two on-drug analyses attenuated the numeric excess cancer risk among JAKi recipients: 0.82 (0.36 to 1.46) and 1.03 (0.49 to 1.74). Along with the main analysis, both on-drug analyses' cumulative incidence of cancer since treatment initiation were presented as Aalen-Johansen plots. The three CIFs demonstrated absolute risks of cancer that varied notably for both JAKi and bDMARD groups according to each distinct type of analysis. *For full information on Aalen-Johansen CIFs, see supplementary figure S1.*

DISCUSSION

In this population-based cohort study on Danish patients with RA, we found a numerically but statistically non-significant increase in first primary cancer risk among JAKi recipients compared with those who received bDMARDs with a HR of 1.41 (95%CI 0.76 to 2.37).

FDA's and EMA's precautionary recommendations regarding JAKi use in patients with RA were sparked by the ORAL Surveillance study. The RCT included more than 4000 participants, all aged 50+ and with ≥1 additional risk factor for CVD, and found a HR for cancer of 1.48 (95%CI 1.04 to 2.09) when comparing JAKi (tofacitinib) recipients with those who received TNFi.(8) The HR for cancer was particularly high in patients over 65 years (HR 1.70; 95%CI 1.00 to 2.90), while the tofacitinib dosage (5mg vs 10mg) did not seem to alter the estimate. Our study, albeit using patients treated with any type of bDMARD as comparators, found an overall HR of 1.41 (95%CI 0.76 to 2.37) and a HR of 1.37 (95%CI 0.75 to 2.30) in patients aged 50+. We did not find a signal of further increase in risk among those aged 65+ (HR 1.34; 95%CI 0.55 to 2.81). In addition to the ORAL Surveillance study, other studies based on clinical trials have investigated the risk of cancer

associated with various JAKi-treatment regimes.(37-40) None of these studies reported any excess cancer risk among patients with RA who received JAKi.

Few published register-based observational studies on JAKi and cancer in patients with RA currently exist.(41-43) To our knowledge, the present study is the first European study based on data from a real-world setting investigating cancer risk associated with JAKi use in patients with RA. While the Swedish study by Huss et al. investigated cancer risk associated with bDMARD and JAKi treatments, they were unable to evaluate JAKi separately.(41) Two American studies presented reassuring results regarding JAKi-treated patients with RA and their risk of cancer.(42, 43) A safety study on tofacitinib and bDMARDs by Kremer et al. compared cancer occurrence between JAKi and bDMARD initiators.(42) In their primary analysis, they found a HR of 1.04 (95%CI 0.68-1.61). A large study by Khosrow-Khavar et al. based on American insurance claims data investigated first primary cancer risk in tofacitinib compared with TNFi users.(43) They created a real-world RA population cohort and a cohort mimicking the eligibility criteria of the ORAL Surveillance trial, both of which demonstrated no statistically significant increased cancer risk in JAKi users: HR 1.01 (95%CI 0.83 to 1.22) and HR 1.17 (95%CI 0.85 to 1.62), respectively.

In our study, the risk of cancer among JAKi-treated patients was higher during the first year of follow-up compared with the risk beyond one year of JAKi/bDMARD exposure: HR 1.54 (95%CI 0.67 to 3.31) versus HR 1.07 (95%CI 0.30 to 2.39). An explanation for this could be protopathic bias, also known as reverse causation, where antecedent effects and wide-ranging inflammatory symptoms of an undiagnosed or developing cancer have — unknowingly — 'selected' these patients for JAKi treatment. In our analyses, potential protopathic may have been mitigated by lagging time at risk after treatment initiation as performed in the 1+ year of follow-up analysis. However, introducing this lag-time period may in the case of JAKi and cancer also falsely diminish an actual association. If treatment with JAKi diminishes the host's immunosurveillance for cancer in the later stages of carcinogenesis, JAKi may act as the final straw of immunocompromising factors that allow for the development a cancer. As a result, the possible relationship between treatment with JAKi and cancer would be detectable even during the early stages of JAKi exposure.(44) Either way, the small number of cancers registered in the JAKi group past the first year of follow-up makes comparisons between follow-up subgroups sensitive to imprecision.

Another important finding from our study is how the choice of follow-up design impacted our study's estimates. The hierarchical 'once exposed, always exposed' type of study design has been a typical approach in observational studies investigating bDMARDs impact on cancer in patients with RA, usually comparing 'bionaïve', i.e., never-bDMARD-exposed, with bDMARD-treated groups.(2, 45) Our main analysis' corresponding approach comparing JAKi-naïve-bDMARD-treated with JAKi-treated patients showed a numerically increased HR for cancer among the JAKi recipients. Interestingly, the excess risk disappeared in the on-drug analyses. However, while the on-drug design in many settings is the typical epidemiological choice, the temporal relationship between JAKi/bDMARD exposure and cancer in patients with RA is unknown. It is also possible that early cancer symptoms in some patients led to discontinuation of treatment and, by extension, registrations of cancer diagnoses were not attributed to each respective treatment

group in our on-drug analyses. That said, we tried to accommodate for this phenomenon by incorporating 3/6-month time-lagged discontinuation dates.

When using real-world data on JAKi and bDMARD treatments in patients with RA, one is limited to available data and applicable treatment guidelines. Such hierarchical treatment guidelines lead to a very high proportion of patients in the JAKi group (82.3%) previously treated with a bDMARD, i.e., the comparator, and makes it difficult to separate potential carcinogenic effects of JAKi from those of prior bDMARDs. The research question answered in this real-world setting is therefore chiefly the cancer risk associated with JAKi *after* previous bDMARD use compared with bDMARD use only. In this context, by incorporating the number of previously received bDMARDs at the index date in the IPTW model, we attempted to achieve weighting-induced balance between JAKi and bDMARD groups in terms of potential carcinogenic effects from previous bDMARDs. Furthermore, the sensitivity analysis with a criterion of minimum one prior bDMARD treatment — comparing solely JAKi and bDMARD initiators previously exposed to bDMARDs — showed a risk estimate similar to the main analysis'. Another limitation was the relatively short follow-up time and low number of incident primary cancers in the JAKi group. Circumscribed by EMA's approval of tofacitinib and baricitinib in 2017, real-world data from DANBIO simply does not currently allow for long-term follow-up of patients with RA who received JAKi. The pooling of two different JAKi warrants mentioning as well. Each type of JAKi might impact the risk of cancer differently.(5, 6) This is further complicated by the arrival of newer JAKi for RA like upadacitinib and filgotinib, which might need to be accounted for in future studies. However, for now, FDA's and EMA's precautionary considerations encompass all types of JAKi due to their similar mechanisms of action.

Our study also has several strengths. DANBIO serves as an excellent real-world data source with high validity and completeness of RA diagnosis and DMARD treatments(12, 13) Additionally, we were able to collect well-validated cancer diagnoses as well as numerous covariates on an individual-based level. A strength was also the use of IPTW-modelling, where we managed to build well-balanced ATT weights that sought to minimize confounding, although unmeasured confounding cannot be ruled out. Furthermore, inspired by ORAL Surveillance's results and considering EMA's special warnings regarding tofacitinib, we assessed the cancer risk in both all and certain potential high-risk Danish patients with RA treated with JAKi in routine care.(8, 9) In doing so, we tried to mimic the real-world treatment availability by including all bDMARDs (vs only TNFi) as the comparator in our main analysis. This may make our results easier to integrate into clinical decision making, where it's typically a treatment choice between JAKi and multiple types of bDMARDs. Lastly, despite not allowing for long-term follow-up, the study period ending 31 December 2020 makes our results less susceptible to both surveillance and selection bias compared with data from 2021 onwards. The results from ORAL Surveillance regarding increases in cancer risk with JAKi treatment were reported in January 2021, which will likely impact the clinicians' propensity to prescribe JAKi as well as increase their cancer vigilance in those who do eventually receive JAKi. Observational studies on JAKi and cancer based on real-world data from 2021 onwards will have to take this into consideration.

In conclusion, our study demonstrated no statistically significant increased risk of first primary cancer in JAKi-treated compared with bDMARD-treated patients with RA. However, the risk estimates in many analyses were elevated, and therefore we cannot rule out an excess risk of cancer among those who received JAKi. Considering the sparse evidence and the importance of the topic, we strongly encourage additional studies founded on real-world data to investigate the safety of JAKI in terms of cancer risk in patients with RA.

ETHICS STATEMENTS

Patient consent for publication

Not applicable.

Ethics approval

The study complies with the Declaration of Helsinki. Registry-based research does not require approval from the Danish National Research Ethics Committee. The study was approved by the regional Danish Data Protection Agency
(ID-nr. 2021-084).

CONTRIBUTORS

R Westermann, R Cordtz, and K Duch had direct access to the underlying data and take full responsibility for the integrity of the data as well as corresponding statistical analyses. All authors were involved in critical appraisal and interpretation of data. R Westermann, R Cordtz, K Duch, and L Dreyer conceptualised the study with respect to devising appropriate study design and statistical methods as well as acquiring essential data approvals from Danish institutions and authorities. All authors engaged in drafting, critically reviewing, and editing of the manuscript. Also, all authors approved the final version of the manuscript and take responsibility for the decision to submit it for publication.

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DATA AVAILABILITY STATEMENT

Some data can be shared upon reasonable request to the corresponding author. Enquiry about data sharing will be handled in accordance with the data-handling laws from the European

General Data Protection Regulation (GDPR). The Danish Data Protection Agency and Statistics Denmark prohibit extraction and sharing of any data making individuals identifiable.

CONFLICTS OF INTEREST

Rasmus Westermann and Kirsten Duch have no conflicts of interests to declare.
René Cordtz is employed by IQVIA outside the present study.
Lene Mellemkjær has an immediate family member employed at Novo Nordisk and has an immediate family member who owns stocks in Novo Nordisk.
Merete Lund Hetland has received research grants (paid to her institution) from AbbVie, Biogen, BMS, Celtrion, Eli Lilly Denmark A/S, Janssen Biologics B.V, Lundbeck Fonden, MSD, Novartis, Pfizer, Roche, Samsung Biopis, Sandoz; honoraria (paid to her institution) from Pfizer, Medac and Sandoz; participated in a advisory board (AbbVie) (paid to her institution). She has chaired the steering committee of the Danish Rheumatology Quality Registry (DANBIO, DRQ), which receives public funding from the hospital owners and funding from pharmaceutical companies. MLH co-chairs EuroSpA, which generates real-world evidence of treatment of psoriatic arthritis and axial spondylorthritis based on secondary data and is partly funded by Novartis.
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Lene Dreyer has received research grant (paid to her institution) from BMS outside the current manuscript. She is member of the steering committee of the Danish Rheumatology Quality Registry (DANBIO, DRQ), which receives public funding from the hospital owners and funding from pharmaceutical companies

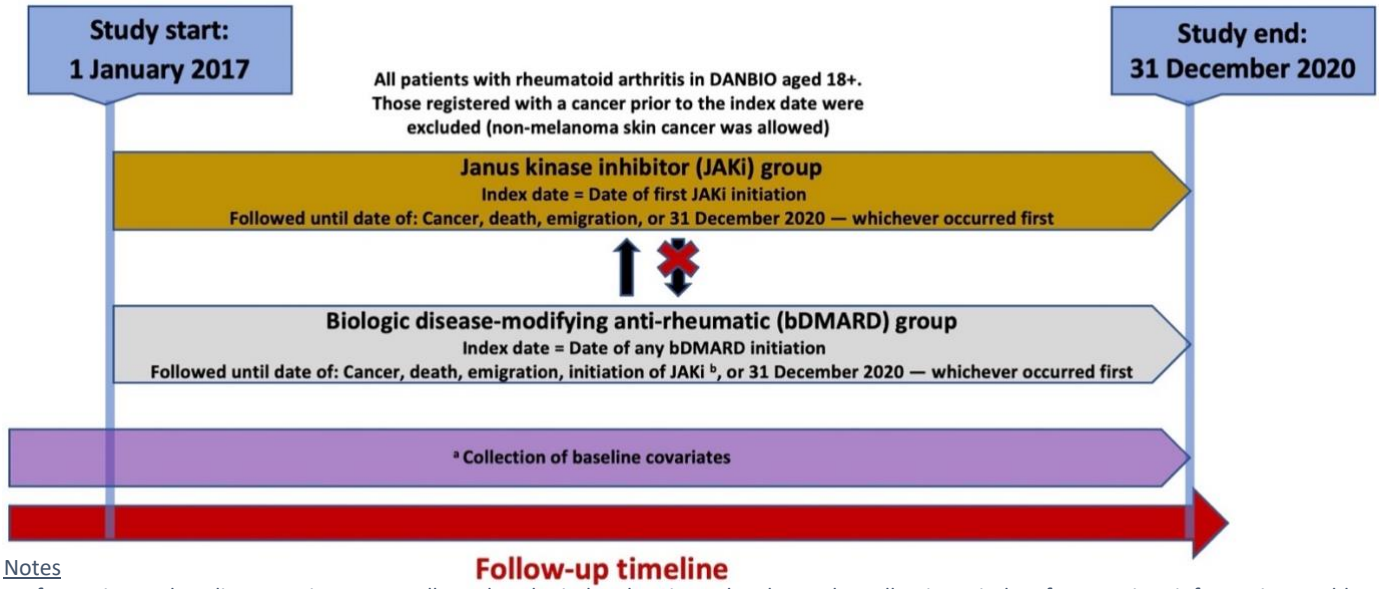
REFERENCES

1. Wadstrom H, Frisell T, Askling J, Anti-Rheumatic Therapy in Sweden Study G. Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice: A Nationwide Cohort Study From Sweden. JAMA Intern Med. 2017;177(11):1605-12.
2. Dreyer L, Mellemkjaer L, Andersen AR, Bennett P, Poulsen UE, Juulsgaard Ellingsen T, et al. Incidences of overall and site specific cancers in TNFalpha inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. Ann Rheum Dis. 2013;72(1):79-82.
3. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-85.
4. Winthrop KL, Cohen SB. Oral surveillance and JAK inhibitor safety: the theory of relativity. Nat Rev Rheumatol. 2022;18(5):301-4.
5. McLornan DP, Pope JE, Gotlib J, Harrison CN. Current and future status of JAK inhibitors. Lancet. 2021;398(10302):803-16.
6. Hosseini A, Gharibi T, Marofi F, Javadian M, Babaloo Z, Baradaran B. Janus kinase inhibitors: A therapeutic strategy for cancer and autoimmune diseases. J Cell Physiol. 2020;235(9):5903-24.
7. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing.
8. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med. 2022;386(4):316-26.
9. https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-7-10-june-2021-prac-meeting_en.pdf.
10. https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death.
11. https://www.ema.europa.eu/en/documents/referral/janus-kinase-inhibitors-jaki-article-20-referral-ema-confirms-measures-minimise-risk-serious-side_en-0.pdf.
12. Ibfelt EH, Jensen DV, Hetland ML. The Danish nationwide clinical register for patients with rheumatoid arthritis: DANBIO. Clin Epidemiol. 2016;8:737-42.
13. Ibfelt EH, Sorensen J, Jensen DV, Dreyer L, Schiottz-Christensen B, Thygesen PH, et al. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish National Patient Registry. Clin Epidemiol. 2017;9:627-32.
14. Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health. 2011;39(7 Suppl):42-5.
15. Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. Eur J Cancer Prev. 2002;11(4):359-64.
16. Pedersen SA, Schmidt SAJ, Klausen S, Pottegard A, Friis S, Holmich LR, et al. Melanoma of the Skin in the Danish Cancer Registry and the Danish Melanoma Database: A Validation Study. Epidemiology. 2018;29(3):442-7.

17. https://sundhedsdatastyrelsen.dk/-/media/sds/filer/registre-og-services/nationale-sundhedsregistre/sygdomme-laegemidler-og-behandlinger/cancerregisteret/valideringsrapport-cancerregisteret.pdf?la=da. Validering af Cancerregisteret og udvalgte kliniske cancerdatabaser (Danish). 2012.
18. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-9.
19. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health. 2011;39(7 Suppl):91-4.
20. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
21. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-f.
22. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-79.
23. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 2016;35(30):5642-55.
24. Ridgeway G, McCaffrey D, Morral A, Burgette L, Griffin BA. Toolkit for Weighting and Analysis of Nonequivalent Groups: A tutorial for the twang package. RAND Corporation 2020.
25. Gerds TA, Ohlendorff JS, Blanche P, Mortensen RW, M., Tollenaar N, Muschelli J, et al. Risk Regression Models and Prediction Scores for Survival Analysis with Competing Risks (version 2022.03.22). 2022
26. Gerds TA. https://cran.r-project.org/web/packages/prodlim/prodlim.pdf. 2022.
27. Lau ES, Paniagua SM, Liu E, Jovani M, Li SX, Takvorian K, et al. Cardiovascular Risk Factors are Associated with Future Cancer. JACC CardioOncol. 2021;3(1):48-58.
28. Thomsen RW, Lange P, Hellquist B, Frausing E, Bartels PD, Krog BR, et al. Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. Respir Med. 2011;105(7):1063-8.
29. Sundboll J, Adelborg K, Munch T, Froslev T, Sorensen HT, Botker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open. 2016;6(11):e012832.
30. Luhdorf P, Overvad K, Schmidt EB, Johnsen SP, Bach FW. Predictive value of stroke discharge diagnoses in the Danish National Patient Register. Scand J Public Health. 2017;45(6):630-6.
31. Green A, Sortso C, Jensen PB, Emneus M. Validation of the danish national diabetes register. Clin Epidemiol. 2015;7:5-15.
32. Collaborative Group on Hormonal Factors in Breast C. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019;394(10204):1159-68.
33. Wilton KM, Matteson EL. Malignancy Incidence, Management, and Prevention in Patients with Rheumatoid Arthritis. Rheumatol Ther. 2017;4(2):333-47.
34. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54(3):692-701.

35. Hvidberg L, Pedersen AF, Wulff CN, Vedsted P. Cancer awareness and socio-economic position: results from a population-based study in Denmark. BMC Cancer. 2014;14:581.
36. Larsen IK, Myklebust TA, Babigumira R, Vinberg E, Moller B, Ursin G. Education, income and risk of cancer: results from a Norwegian registry-based study. Acta Oncol. 2020;59(11):1300-7.
37. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open. 2020;6(3).
38. Taylor PC, Takeuchi T, Burmester GR, Durez P, Smolen JS, Deberdt W, et al. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. Ann Rheum Dis. 2022;81(3):335-43.
39. Cohen SB, van Vollenhoven RF, Winthrop KL, Zerbini CAF, Tanaka Y, Bessette L, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis. 2021;80(3):304-11.
40. Wang F, Sun L, Wang S, Davis JM, 3rd, Matteson EL, Murad MH, et al. Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Mayo Clin Proc. 2020;95(7):1404-19.
41. Huss V, Bower H, Wadstrom H, Frisell T, Askling J, group A. Short- and longer-term cancer risks with biologic and targeted synthetic disease-modifying antirheumatic drugs as used against rheumatoid arthritis in clinical practice. Rheumatology (Oxford). 2022;61(5):1810-8.
42. Kremer JM, Bingham CO, 3rd, Cappelli LC, Greenberg JD, Madsen AM, Geier J, et al. Postapproval Comparative Safety Study of Tofacitinib and Biological Disease-Modifying Antirheumatic Drugs: 5-Year Results from a United States-Based Rheumatoid Arthritis Registry. ACR Open Rheumatol. 2021;3(3):173-84.
43. Khosrow-Khavar F, Desai RJ, Lee H, Lee SB, Kim SC. Tofacitinib and risk of malignancy: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) Study. Arthritis Rheumatol. 2022.
44. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.
45. Mercer LK, Regierer AC, Mariette X, Dixon WG, Baecklund E, Hellgren K, et al. Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: a European registries collaborative project. Ann Rheum Dis. 2017;76(12):2025-30.

Figure 1. *Study population, treatment groups, and follow-up of patients with rheumatoid arthritis*



Notes

[a] Information on baseline covariates was collected at the index date in each cohort. The collection window for covariate information could span before the time of study start 1 January 2017. See supplementary table S1 for full list of covariates including specified details on collection.

[b] Patients were allowed to switch from the bDMARD group to the JAKi group upon the date of JAKi treatment (censoring time), but once exposed to JAKi treatment that patient would remain in the JAKi group until end of follow-up.

Table 1. *Pre-weighting baseline characteristics for JAKi- and bDMARD-treated patients with rheumatoid arthritis, including standardized mean differences pre and post inverse probability of treatment weighting*

	JAKi group (N=875)	bDMARD group (N=4247)	Pre-IPTW SMD	Post-IPTW SMD
Tofacitinib, N	694			
Baricitinib, N	181			
TNFi, N		3691		
Tocilizumab/sarilumab, N		246		
Rituximab, N		207		
Abatacept, N		103		
Female, N (%)	698 (79.8)	3191 (75.1)	0.115	0.033
Age in years, mean (SD)	57.8 (± 13.05)	57.6 (± 13.83)	0.015	0.025
Disease duration in years, mean (SD)	10.5 (± 9.09)	10.6 (± 9.66)	-0.012	0.007
Disease duration missing, N (%)	37 (4.2)	195 (4.6)	-0.019	0.006
Seropositive, N (%)	679 (77.6)	3279 (77.2)	0.009	-0.011
Smoking ever, N (%)	444 (50.7)	2045(48.2)	0.052	0.012
Education level, N (%)				
Low	245 (28.0)	1133 (26.7)	0.029	-0.023
Medium	575 (65.7)	2792 (65.7)	-0.001	0.02
High	38 (4.3)	269 (6.3)	-0.098	-0.012
Missing	17 (1.9)	53 (1.2)	0.050	0.026
HAQ, mean (SD)	1.4 (± 0.72)	1.1 (± 0.72)	0.410	0.047
HAQ missing, N (%)	119 (13.6)	718 (16.9)	-0.096	-0.002
DAS28-CRP, mean (SD)	4.4 (± 1.19)	3.9 (± 1.40)	0.416	0.054
DAS28-CRP missing, N (%)	173 (19.8)	951 (22.4)	-0.066	0.002
Concomitant use of prednisolone, N (%)	277 (31.7)	1211 (28.5)	0.068	0.014
Hormone replacement therapy, N (%)	132 (15.1)	610 (14.4)	0.020	-0.024
Lung disease, N (%)	175 (20.0)	654 (15.4)	0.115	0.013
Cardiovascular disease, N (%)	134 (15.3)	495 (11.7)	0.102	0.032
Diabetes, N (%)	88 (10.1)	360 (8.5)	0.053	0.028
Prior bDMARDs, N (%)				
0	155 (17.7)	2230 (52.5)	-0.911	-0.074
1	199 (22.7)	1185 (27.9)	-0.123	0.009
2	198 (22.6)	479 (11.3)	0.271	0.010
3 or more	323 (36.9)	353 (8.3)	0.593	0.042

Abbreviations / Notes

bDMARDs: biological disease-modifying anti-rheumatic drugs, bDMARD group: comprises Interleukin-6 inhibitors (tocilizumab/sarilumab) + anti-CD20 (rituximab) + T-cell co-stimulation inhibitors via CTLA-4 (abatacept) + tumour necrosis factor inhibitors (TNFi), N: number of, RA: Rheumatoid arthritis, SD: Standard deviation, Education level according to the International Standard Classification of Education but condensed to 3 levels, IPTW: inverse probability of treatment with average treatment effect on the treated (ATT) weights, SMD: standardized mean difference, Pre-IPTW SMD: standardized mean difference before weighting, Post-IPTW SMD: standardized mean difference after weighting, Missing: no value recorded, Seropositive: seropositivity for rheumatoid factors or anti-citrullinated protein antibodies, DAS28-CRP (Disease activity score), HAQ: health assessment questionnaire (0–3).

Table 2. *Number of patients, person years, cancers, crude incidence rates, and hazard ratios for cancer by type of analysis, by choice of statistical model, and by groups of JAKi- and bDMARD-treated patients with rheumatoid arthritis*

	N patients	N PYRS	N Cancers (except NMSC)	Crude IR (per 1000 years)	HR (95%CI)
JAKi vs bDMARD (all patients)					
JAKi group	875	1315	19	14.4	
bDMARD group	4247	8597	111	12.9	
IPTW + CSC [a]					**1.41 (0.76 to 2.37)**
CSC model 1 [b]					**1.17 (0.72 to 1.91)**
CSC model 2 [c]					**1.37 (0.81 to 2.32)**
CSC model 3 [d] (CC: JAKi vs bDMARD)	645 vs 3072	976 vs 6351	16 vs 81	16.4 vs 12.8	**1.50 (0.83 to 2.72)**
Age 50+					
JAKi group [e]	653	-	≥15	18.3	
bDMARD group	3099	6274	103	16.4	
IPTW + CSC					1.37 (0.75 to 2.30)
CSC model 1					1.19 (0.72 to 1.97)
CSC model 2					1.40 (0.81 to 2.42)
CSC model 3 (CC: JAKi vs bDMARD)	483 vs 2230	740 vs 4603	15 vs 78	20.3 vs 16.9	1.47 (0.79 to 2.74)
Age 65+					
JAKi group	268	401	11	27.4	
bDMARD group	1364	2711	65	24.0	
IPTW + CSC					1.34 (0.55 to 2.81)
CSC model 1					1.20 (0.62 to 2.29)
CSC model 2					1.25 (0.61 to 2.56)
CSC model 3 (CC: JAKi vs bDMARD)	189 vs 952	300 vs 1940	9 vs 46	30.0 vs 23.7	1.35 (0.61 to 2.97)
Follow-up < 1 year					
JAKi group	875	792	13	16.4	
bDMARD group	4247	3752	48	12.8	
IPTW + CSC					1.54 (0.67 to 3.31)
CSC model 1					1.30 (0.69 to 2.43)
CSC model 2					1.74 (0.90 to 3.36)
CSC model 3 (CC: JAKi vs bDMARD)	645 vs 3072	591 vs 2724	11 vs 32	18.6 vs 11.7	1.95 (0.90 to 4.21)
Follow-up 1+ year					
JAKi group	649	523	6	11.5	
bDMARD group	3284	4845	63	13.0	

IPTW + CSC					1.07 (0.30 to 2.39)
CSC model 1					0.93 (0.40 to 2.13)
CSC model 2					0.83 (0.35 to 1.94)
CSC model 3 (CC: JAKi vs bDMARD)	532 vs 2745	432 vs 4139	5 vs 53	11.6 vs 12.8	0.79 (0.30 to 2.09)

Abbreviations / Notes

JAKi: janus kinase inhibitors (tofacitinib + baricitinib), bDMARDs: biological disease-modifying anti-rheumatic drugs, bDMARD group: comprises Interleukin-6 inhibitors (tocilizumab/sarilumab) + anti-CD20 (rituximab) + T-cell co-stimulation inhibitors via CTLA-4 (abatacept) + tumour necrosis factor inhibitors, N.: number of, PYRS: person years, IR: incidence rate, HR: hazard ratio, 95%CI: 95% confidence intervals, NMSC: non-melanoma skin cancer, IPTW: inverse probability of treatment with average treatment effect on the treated (ATT) weights, CSC: cause-specific Cox proportional hazard regression with death as the competing risk, CC: complete case, vs: versus.

a: IPTW-generated ATT weights combined with CSCcox.

b: CSC model 1 unweighted with age as underlying timescale and adjustment for sex.

c: CSC model 2 unweighted with age as underlying timescale and adjustment for covariates with no missing information: sex, seropositivity, smoking status, concomitant use of prednisolone, hormone replacement therapy, lung disease, cardiovascular disease, diabetes, and number of prior bDMARDs.

d: CSC model 3 unweighted with age as underlying timescale and adjustment for all covariates, i.e., as a complete case analysis, with information and estimates on patients included in this specific model explicitly shown.

e: PYRS and N cancers not shown according to Danish data legislation on indirect anonymisation.

Table 3. *On-drug analyses: Number of treatment initiations, person years, cancers, crude incidence rates, and hazard ratios for cancer by choice of lagged discontinuation date definition (3 months and 6 months) by choice of statistical model, and by groups of JAKi- and bDMARD-treated patients with rheumatoid arthritis*

	N Initiations	N PYRS	N Cancers (except NMSC)	Crude IR (per 1000 years)	HR (95%CI)
JAKi vs bDMARD: 3 months					
JAKi group	899*	993	11	11.1	
bDMARD group	4745	8221	111	13.5	
IPTW + CSC [a]					0.82 (0.36 to 1.46)
CSC model 1 [b]					0.87 (0.47 to 1.61)
CSC model 2 [c]					0.89 (0.46 to 1.74)
CSC model 3 [d] (CC: JAKi vs bDMARD)	661 vs 3440	727 vs 6032	9 vs 82	12.4 vs 13.6	0.93 (0.44 to 1.95)
JAKi vs bDMARD: 6 months					
JAKi group	889	1073	15	14.0	
bDMARD group	4628	8481	115	13.6	
IPTW + CSC					1.03 (0.49 to 1.74)
CSC model 1					1.08 (0.65 to 1.80)
CSC model 2					1.07 (0.63 to 1.82)
CSC model 3 (CC: JAKi vs bDMARD)	656 vs 3359	789 vs 6243	12 vs 84	15.2 vs 13.5	1.34 (0.69 to 2.62)

Abbreviations / Notes

JAKi: janus kinase inhibitors (tofacitinib + baricitinib), bDMARDs: biological disease-modifying anti-rheumatic drugs, bDMARD group: comprises Interleukin-6 inhibitors (tocilizumab/sarilumab) + anti-CD20 (rituximab) + T-cell co-stimulation inhibitors via CTLA-4 (abatacept) + tumour necrosis factor inhibitors, N.: number of, PYRS: person years, IR: incidence rate, HR: hazard ratio, 95%CI: 95% confidence intervals, NMSC: non-melanoma skin cancer, IPTW: inverse probability of treatment with average treatment effect on the treated (ATT) weights, CSC: cause-specific Cox proportional hazard regression with death as the competing risk, CC: complete case, vs: versus.

a: IPTW-generated ATT weights combined with CSCcox.

b: CSC model 1 unweighted with age as underlying timescale and adjustment for sex.

c: CSC model 2 unweighted with age as underlying timescale and adjustment for covariates with no missing information: sex, seropositivity, smoking status, concomitant use of prednisolone, hormone replacement therapy, lung disease, cardiovascular disease, diabetes, and number of prior JAKi/bDMARDs.

d: CSC model 3 unweighted with age as underlying timescale and adjustment for all covariates, i.e., as a complete case analysis, with information and estimates on patients included in this specific model explicitly shown.

*Each patient could contribute with multiple treatment initiations to both groups. Reinitiating the same treatment within the 3-/6-month windows, uninterrupted by the opposite treatment, it was considered the same series of treatment.

Table 4. *Other sensitivity analyses: Number of patients, person years, cancers, crude incidence rates, and hazard ratios for cancer by type of sensitivity analysis, by choice of statistical model, and by groups of JAKi- and bDMARD-treated patients with rheumatoid arthritis*

	N patients	N PYRS	N Cancers (except NMSC)	Crude IR (per 1000 years)	HR (95%CI)
JAKi vs bDMARD: N prior bDMARDs ≥ 1					
JAKi group	720	1134	16	14.1	
bDMARD group	2017	4683	55	11.7	
IPTW + CSC [a]					1.53 (0.75 to 2.95)
CSC model 1 [b]					1.33 (0.76 to 2.32)
CSC model 2 [c]					1.38 (0.77 to 2.49)
CSC model 3 [d] (CC: JAKi vs bDMARD)	539 vs 1360	844 vs 3243	14 vs 39	16.6 vs 12.0	1.60 (0.83 to 3.09)
JAKi vs bDMARD: Ever smokers					
JAKi group	444	668	7	10.5	
bDMARD group	2045	4172	66	15.8	
IPTW + CSC					1.15 (0.38 to 2.41)
CSC model 1					0.74 (0.34 to 1.61)
CSC model 2					0.93 (0.43 to 2.03)
CSC model 3 (CC: JAKi vs bDMARD)	323 vs 1491	491 vs 3105	6 vs 52	12.2 vs 16.7	0.87 (0.37 to 2.04)
JAKi vs TNFi [e]					
JAKi group	875	1315	19	14.4	
TNFi group	3758	7040	92	13.1	
IPTW + CSC					1.19 (0.64 to 2.11)
CSC model 1					1.12 (0.68 to 1.85)
CSC model 2					1.25 (0.70 to 2.24)
CSC model 3 (CC: JAKi vs *TNFi*)	645 vs 2715	976 vs 5120	16 vs 66	16.4 vs 12.9	1.52 (0.80 to 2.86)
JAKi vs non-TNFi **bDMARDs** [e]					
JAKi group	875	1315	19	14.4	
non-TNFi bDMARD group [f]	864	1557	19	12.2	
IPTW + CSC					1.55 (0.76 to 3.49)
CSC model 1					1.43 (0.75 to 2.73)
CSC model 2					1.56 (0.81 to 2.99)
CSC model 3 (CC: JAKi vs non-TNFi)	645 vs 654	976 vs 1221	16 vs 13	16.4 vs 10.6	1.92 (0.92 to 4.00)

Abbreviations / Notes

JAKi: janus kinase inhibitors (tofacitinib + baricitinib), bDMARDs: biological disease-modifying anti-rheumatic drugs, TNFi: tumour necrosis factor inhibitors, bDMARD group: comprises Interleukin-6 inhibitors (tocilizumab/sarilumab) + anti-CD20 (rituximab) T-cell co-stimulation inhibitors via CTLA-4 (abatacept) + TNFi, non-TNFi bDMARD group: comprises Interleukin-6 inhibitors (tocilizumab/sarilumab) + anti-CD20 (rituximab) + T-cell co-stimulation inhibitors via CTLA-4 (abatacept) N.: number of, PYRS: person

years, IR: incidence rate, HR: hazard ratio, 95%CI: 95% confidence intervals, NMSC: non-melanoma skin cancer, IPTW: inverse probability of treatment with average treatment effect on the treated (ATT) weights, CSC: Cause-Specific Cox proportional hazard regression with death as the competing risk, CC: complete case, vs: versus.
a: IPTW-generated ATT weights combined with CSC.
b: CSC model 1 unweighted with age as underlying timescale and adjustment for sex.
c: CSC model 2 unweighted with age as underlying timescale and adjustment for covariates with no missing information: sex, seropositivity, smoking status, concomitant use of prednisolone, hormone replacement therapy, lung disease, cardiovascular disease, diabetes, and number of prior bDMARDs.
d: CSC model 3 unweighted with age as underlying timescale and adjustment for all covariates, i.e., as a complete case analysis, with information and estimates on patients included in this specific model explicitly shown.
e: The displayed number of TNFi and non-TNFI patients in each group differ from that of the main analysis. The main analysis' bDMARD group comprised only the first bDMARD initiation within our study period, whereas these two sensitivity analyses comprised the first TNFi and non-TNFi initiation, respectively, within our study period, hereby allowing for contributions to both analyses in case of patients switching bDMARD class.
f: Counts for each specific type of non-TNFI bDMARD: tocilizumab/sarilumab = 446, rituximab = 255, and abatacept = 163.