Cancers and cardiovascular diseases in patients with seropositive rheumatoid arthritis treated with JAK inhibitors, biologics, and conventional synthetic DMARDs

S.S. Ahn[1], M. Han[2], I. Jung[3], H.W. Kim[4]

[1]Division of Rheumatology, Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea; [2]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Division of Biostatistics, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.

Abstract

Objective

Janus kinase inhibitors and biologics (JAKi/biologics) are cornerstone treatments for rheumatoid arthritis (RA). We evaluated the risks of cancers and cardiovascular diseases (CVDs) in patients with seropositive RA (SPRA) treated with JAKi/biologics.

Methods

Patients with new-onset SPRA during 2010–2020 in the national healthcare database were identified. Events of overall and site-specific cancers, as well as CVD outcomes, including deep vein thrombosis, pulmonary embolism, and composite cardiovascular events, were investigated. The relative risk of cancers and CVDs compared to conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) users was compared by evaluating the incidence rate ratios (IRRs). Time-dependent Cox analyses were performed to evaluate the relationship between JAKi/biologics usage and patient outcomes.

Results

A total of 101,816 and 96,220 patients with SPRA were analysed for cancers and CVD outcomes, respectively. Compared with patients treated only with csDMARDs, the IRRs of overall cancers and CVDs in patients administered JAKi/biologics were 0.88 (95% confidence interval [CI] 0.86–0.89) and 0.91 (95% CI 0.90–0.92), respectively. Site-specific lung, liver, prostate, and skin cancers were more frequent in JAKi/biologics users; JAKi did not confer a greater risk of overall CVDs and cancers compared with other biologics and csDMARDs. JAKi/biologics usage was not accounted for overall cancers and CVDs in adjusted Cox analyses.

Conclusion

The incidence of overall cancer and CVD were not increased in patients with SPRA treated with JAKi/biologics and was relatively lower than csDMARD only users, underscoring optimal disease control for risk mitigation. The higher incidence of several site-specific cancers requires further investigation.

Key words

Janus kinase inhibitor, biologics, cancer, cardiovascular disease, outcomes

*Sung Soo Ahn, MD, PhD**
*Minkyung Han, PhD**
Inkyung Jung, PhD
Hyung Woo Kim, MD

**Contributed equally as co-first authors.*

Please address correspondence to:
Hyung Woo Kim
Department of Internal Medicine,
College of Medicine,
Institute of Kidney Disease Research,
Yonsei University,
50-1 Yonsei-ro,
Seodaemun-gu,
Seoul 03722, Korea.
E-mail: drhwint@yuhs.ac

Received on November 18, 2022; accepted in revised form on February 13, 2023.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a representative autoimmune disorder characterised by inflammatory arthritis in the affected joints and is common among middle-aged women (1). RA typically involves the small-sized joints, such as those of the hands and feet, but can potentially occur in any joint. The primary goal of RA management is to attain optimal disease control and prevent joint injury using disease-modifying antirheumatic drugs (DMARDs) (2, 3). For the treatment of RA, conventional synthetic DMARDs (csDMARDs), including methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine, are initially recommended. Nonetheless, alternative treatment is required in those who fail to achieve low disease activity or remission with csDMARDs. In recent years, following the introduction of biologic DMARDs (bDMARDs, biologics), noticeable advances have been made regarding the treatment of RA (4, 5). On the other hand, the development of Janus kinase inhibitors (JAKi), which have been approved for the treatment of RA since 2012, has also remarkably influenced the medication prescription of rheumatologists in treating RA owing to its high efficacy and advantage in drug adherence (6).

While the joint is the primary inflamed site in patients with RA, other organs besides the joint, such as the lungs, eyes, skin, nervous system, and heart, are also affected in up to 40% of patients (7). In particular, extra-articular RA features described in the heart consists of pericardial effusion, pericarditis, myocarditis, heart failure, atherosclerosis, and ischaemic heart disease (8). Of note, patients with RA are reported to have a higher risk of cardiovascular events (CVE) and venous thromboembolic events (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), which is unexplained by the existence of traditional risk factors (9). The evolution of extra-articular manifestation negatively influences the quality of life of patients and has a significant impact on patient prognosis. Importantly, recent studies indicated that a higher rate of mortality is observed in patients with RA compared with the general population, and cardiovascular diseases (CVDs) account for the largest proportion of cause-specific death (10, 11). Altogether, these findings indicate that monitoring the incidence of CVDs in patients with RA should be emphasised. Conversely, it has been reported that patients with RA are at greater risk of being affected by cancers during the disease course, specifically lung cancer and lymphoma (12, 13). In particular, escalated disease activity is considered to have a substantial impact on the occurrence of lymphomas, independent of other factors (14). Older age is an important factor contributing to the risk of cancer and CVDs (15, 16), and the prevalence of RA shows an increment with increasing age. In addition, as patients with RA are prescribed various DMARDs for disease management, it is of particular interest whether RA promotes the occurrence of cancers and CVDs, especially regarding drugs used for RA.

In recent years, safety concerns regarding the occurrence of cardiac events, blood clots, and cancers in patients with RA being prescribed JAKi have been raised (17). Moreover, it is controversial whether JAKi and biologics (JAKi/biologics), which are increasingly prescribed in patients with RA, increase the risk of cancers and CVDs in RA. Thus, the safety of JAKi/biologics use for RA should be explored more extensively in a large population. Herein, we analysed the South Korean nationwide claims database to evaluate whether the use of JAKi/biologics is associated with increased risks of cancers and CVDs in patients with seropositive RA (SPRA).

Materials and methods

Data collection

The Health Insurance Review and Assessment Service (HIRA) is a national institution that evaluates the medical service fee and quality of health care implemented in Korea. In Korea, the utilisation of hospital care (either in the outpatient or inpatient setting) covered by national health insurance service is obligatorily recorded in the HIRA database, which enables identification of the usage of healthcare services of an individual upon permission from the

Table I. Baseline characteristics of patients with and without cancer during the follow-up.

	Total (n=101816)	RA patients with cancer (n=4817)	RA patients without cancer (n=96999)	*p*-value
Age at diagnosis, mean ± SD	55.96 ±13.85	61.19 ±12.27	55.70 ±13.88	<0.001
Age group at diagnosis				
<20	354 (0.4)	1 (0.0)	353 (0.4)	<0.001
20-34	6510 (6.4)	103 (2.1)	6407 (6.6)	
35-49	24855 (24.4)	735 (15.3)	24120 (24.9)	
50-64	41643 (40.9)	1927 (40.0)	39716 (40.9)	
≥65	28454 (28.0)	2051 (42.6)	26403 (27.2)	
Sex, n (%)				
Female	78376 (77.0)	3101 (64.4)	75275 (77.6)	<0.001
Male	23440 (23.0)	1716 (35.6)	21724 (22.4)	
Type of insurance, n (%)				
National Health Insurance	95307 (93.6)	4519 (93.8)	90788 (93.6)	0.569
Medical aid	6509 (6.4)	298 (6.2)	6211 (6.4)	
Underlying disease, n (%)				
Hypertension	34790 (34.2)	2075 (43.1)	32715 (33.7)	<0.001
Diabetes mellitus	23412 (23.0)	1332 (27.7)	22080 (22.8)	<0.001
Dyslipidaemia	52805 (51.9)	2431 (50.5)	50374 (51.9)	0.049
RA diagnosis year, n (%)				
2010-2014	45131 (44.3)	3153 (65.5)	41978 (43.3)	<0.001
2015-2020	56685 (55.7)	1664 (34.5)	55021 (56.7)	
csDMARD usage				
Methotrexate	79717 (78.3)	3552 (73.7)	76165 (78.5)	<0.001
Hydroxychloroquine	67953 (66.7)	3261 (67.7)	64692 (66.7)	0.153
Sulfasalazine	38645 (38.0)	1800 (37.4)	36845 (38.0)	0.397
Tacrolimus	18069 (17.8)	702 (14.6)	17367 (17.9)	<0.001
Leflunomide	35872 (35.2)	1368 (28.4)	34504 (35.6)	<0.001
Biologics and JAKi usage, n (%)				
Non-TNFi				
Abatacept/Tocilizumab	2226 (2.2)	79 (1.6)	2147 (2.2)	0.009
TNFi	6753 (6.6)	280 (5.8)	6473 (6.7)	0.021
Infliximab	960 0.9)	39 (0.8)	921 (1.0)	0.366
Adalimumab	2601 (2.6)	122 (2.5)	2479 (2.6)	0.959
Etanercept	2037 (2.0)	86 (1.8)	1951 (2.0)	0.298
Golimumab	1155 (1.1)	33 (0.7)	1122 (1.2)	0.003
JAK inhibitor	1662 (1.6)	19 (0.4)	1643 (1.7)	<0.001
Tofactinib	892 (0.9)	14 (0.3)	878 (0.9)	<0.001
Baricitininb	765 (0.8)	5 (0.1)	760 (0.8)	<0.001
Upadacitinib	5 (0.0)	0 (0.0)	5 (0.0)	1.000

RA: rheumatoid arthritis, csDMARD: conventional synthetic disease-modifying anti-rheumatic drug, JAKi: Janus kinase inhibitor, TNFi: tumour necrosis factor-α inhibitor.

HIRA. A detailed description of the HIRA database has been reported previously (18). In the present study, we collected information regarding demographics, diagnoses, prescribed medications, and performed procedures for data analyses. The study was conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards, and the research protocol was approved by the Institutional Review Board of Severance Hospital (4-2021-0328). Owing to the retrospective design of this study and the use of de-identified patient data, the requirement to obtain patient informed consent was waivered.

Definition of patients with RA and eligibility criteria

SPRA was defined according to the 10th revision of the International Statistical Classification of Diseases (ICD-10) codes (M05) – seropositivity included either rheumatoid factor and/or anti-citrullinated protein/peptide antibody positivity – and a designated unique insurance code for patients with rare and intractable diseases (V223) accredited by the South Korean government (19). We adopted this definition as patients with seropositive RA having the unique insurance code are granted a financial subsidiary for healthcare utilisation related to RA treatment.

From the HIRA database, 169,587 patients with the diagnosis of RA from January 2008 to December 2020 were initially screened. Patients who received hospital care for RA during 2008–2009 were excluded to identify prevalent RA cases; patients aged <18 years were also excluded. Finally, a total of 111,334 cases of incident RA were included in this study. To evaluate the incidence of cancer and CVDs, patients with the diagnosis of cancer or CVDs prior to the diagnosis of RA were excluded and analysed separately thereafter (Supplementary Fig. S1-S2).

Treatment exposures and assessed variables

The main treatment exposure of the patients was the type of DMARDs used after the diagnosis of RA to the last follow-up, which included csDMARDs (methotrexate, hydroxychloroquine, sulfasalazine, tacrolimus, and leflunomide), non-tumour necrosis factor-α inhibitor (non-TNFi) of abatacept and tocilizumab, TNFi (infliximab, adalimumab, etanercept, and golimumab), and JAKi (tofacitinib, baricitinib, and upadacitinib). The prescription of medications was defined per the Anatomical Therapeutic Chemical Classification codes. Regarding baseline patient characteristics, demographic data including age, sex, insurance types at RA diagnosis, and the presence of comorbidities (hypertension [ICD-10 code: I10-15], diabetes mellitus [ICD-10 code: E10-14], and dyslipidaemia [ICD-10 code: E78] within 1 year of diagnosis were assessed.

Patient outcomes

The outcomes of patients investigated were the occurrence of overall cancer and CVDs. Diagnosis of cancer was ascertained according to the corresponding ICD-10 codes (C00-C96) and the unique insurance codes for those with confirmed cancer (V193), organised in the order of the 10 most frequent cancers (20). Conversely, CVDs consisted of three different events of DVT, PE, and composite CVEs. VTE (DVT and PE) was defined as the ICD-10 codes I80.2, I80.3, I26, I126.0, and I26.9 with the prescription of anticoagulants

Table II. Number, incidence rate, and incidence rate ratios of 10 most common cancers according to treatment.

	Number of events		Age- and sex- adjusted incidence rate/100,000 person-year		Incidence rate ratio (95% CI)
	Patients treated with JAKi/biologics	Patients treated with only csDMARDs	Patients treated with JAKi/biologics	Patients treated with only csDMARDs	
Lung (C34)	54	634	218.87	202.93	1.08 (1.04-1.12)
Thyroid (C73)	49	504	43.47	77.58	0.56 (0.52-0.60)
Stomach (C16)	47	454	96.09	115.07	0.84 (0.79-0.88)
Breast (C50)	38	428	25.47	42.50	0.60 (0.55-0.66)
Colon (C18)	19	248	47.57	66.43	0.72 (0.67-0.77)
Liver (C22)	17	160	48.40	37.55	1.29 (1.19-1.39)
Prostate (C61)	9	167	114.61	85.50	1.34 (1.27-1.41)
Skin (C44)	16	142	53.92	32.98	1.63 (1.51-1.77)
Pancreas (C25)	16	103	26.27	28.31	0.93 (0.84-1.02)
Rectum (C20)	2	96	1.00	34.74	0.03 (0.02-0.04)
Others	111	1081	194.38	270.63	0.72 (0.69-0.74)
Total	378	4017	870.04	994.21	0.88 (0.86-0.89)

JAKi: Janus kinase inhibitor, csDMARD: conventional synthetic disease-modifying anti-rheumatic drug, CI: confidence interval.

for DVT and PE (21). The occurrence of composite CVEs was defined as the ICD-10 codes I21, I60, I61, I63, I64, and G45 with hospital admission or procedural code for coronary artery intervention or bypass surgery (M6551, M6552, M6561, M6562, M6563, M6564, M6571, M6572, O1641, O1642, O1647, OA641, OA642, OA647) and admission to a hospital (22, 23).

Statistical analyses

Baseline characteristics are presented as means and standard deviations for continuous variables, and numbers and percentages for categorical variables. The age- and sex- adjusted incidence rates per 100,000 person-years were calculated using Poisson regression analyses with an offset for person-years to compare the incidence rate ratio (IRR) and 95% confidence interval (CI) of the groups treated with JAKi/biologics and only csDMARDs. The Kaplan-Meier method and log-rank tests with multiple comparison adjustments were used to estimate the cumulative incidence rates of cancer and CVDs according to patient treatment. In the Cox-proportional hazards models, the following potential confounding variables were adjusted for: index age, sex, type of insurance, and pre-existing comorbidities of hypertension, diabetes mellitus, and dyslipidaemia as time-fixed covariates; usage of medications such as csDMARDs, non-TNFi, TNFi, and JAKi was considered as time-dependent covariates. All statistical analyses were performed using SAS Enterprise Guide (v. 7.1; SAS Institute). The level of significance was set at $p<0.05$ in all analyses.

Table III. Time-dependent Cox-proportional hazard analysis of variables associated with cancer incidence.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.04 (1.04-1.04)	<0.001	1.04 (1.03-1.04)	<0.001
Sex				
Female	1.00 (ref)		1.00 (ref)	
Male	2.04 (1.93-2.17)	<0.001	1.89 (1.78-2.00)	<0.001
Type of insurance				
National Health Insurance	1.00 (ref)		1.00 (ref)	
Medical Aid	1.12 (0.99-1.26)	0.064	0.95 (0.84-1.08)	0.421
Underlying disease				
Hypertension	1.61 (1.52-1.70)	<0.001	1.02 (0.96-1.09)	0.469
Diabetes mellitus	1.52 (1.43-1.62)	<0.001	1.09 (1.01-1.16)	0.021
Dyslipidaemia	1.19 (1.13-1.26)	<0.001	0.98 (0.93-1.05)	0.608
csDMARD usage	0.88 (0.80-0.98)	0.014	1.10 (0.99-1.22)	0.088
Non-TNFi usage	1.07 (0.89-1.29)	0.477	1.09 (0.90-1.32)	0.357
TNFi usage	0.98 (0.87-1.11)	0.780	1.08 (0.96-1.23)	0.210
JAKi usage	1.10 (0.82-1.48)	0.536	1.20 (0.89-1.62)	0.241

HR: hazard ratio, CI: confidence interval, csDMARD: conventional synthetic disease-modifying anti-rheumatic drug, TNFi: tumour necrosis factor-α inhibitor, JAKi: Janus kinase inhibitor.

Results

Characteristics of patients who developed and did not develop cancer

Of the 101,816 patients with SPRA included in the analysis, a total of 4817 and 96999 patients developed and did not develop cancer, respectively. The mean age and the proportion of men were significantly higher among patients with cancer compared with those without cancer, whereas there was no difference in the insurance type between the groups. Underlying diseases, including hypertension, diabetes mellitus, and dyslipidaemia, were more frequently found in those with cancer than in those without. For csDMARD usage during the follow-up, the proportion of methotrexate, tacrolimus, and leflunomide usage was higher in those who did not develop cancer. Regarding biologics and JAKi, non-TNFi, TNFi, and JAKi were more often administered in those without cancer (Table I). Comparison of patient characteristics

at the initial period of commencing JAKi/biologics, a significant difference of baseline characteristics was present in patients who developed cancer and without cancer, with an exception of type of insurance and hydroxychloroquine usage within six months of starting the first JAKi/biologics (Suppl. Table S1).

Frequency, incidence rate, and predictors of cancer

The 10 most common site-specific cancers observed in our cohort during the mean follow-up period of 5.21 years are described in Table II. Lung cancer was the most common type of cancer, followed by thyroid, stomach, and breast cancer, and this tendency was not different between patients treated with JAKi/biologics and those treated with only csDMARDs. The highest incidence rate of lung cancer was observed in both JAKi/biologics treated and only csDMARD treated groups. Prostate and stomach cancers had the second highest incidence rates among those treated with JAKi/biologics and csDMARDs only, respectively. A comparison of site-specific cancer incidence revealed that the incidence of lung, liver, prostate, and skin was higher in those being treated with JAKi/biologics, while the risks for remaining cancers and overall cancers were lower (Table II).

Kaplan-Meier analysis revealed that there was no difference in cancer development between the groups treated with JAKi/biologics and only csDMARDs. In addition, the incidence of cancer was comparable in those who selected JAKi, non-TNFi, and TNFi as the first-line treatment, even when the analysis was confined to those only treated with JAKi, non-TNFi, and TNFi (but not other biologics) during the follow-up (Suppl. Fig. S3a-c). Finally, it was found that there was no difference in the incidence of overall cancers according to the type of biologics, JAKi, and csDMARDs usage (Suppl. Fig. S3d). An identical result was obtained when a separate analysis was performed in patients who were aged ≥65 years on starting JAKi, non-non-TNFi, and TNFi and were not prescribed other biologics (Suppl. Fig. S4a).

Table IV. Baseline patient characteristics that were and were not subject to CVDs during follow-up.

	Total (n=96220)	RA patients with CVD (n=5297)	RA patients without CVD (n=90923)	*p*-value
Age at diagnosis, mean ± SD	54.89 ±13.48	64.70 ±11.16	54.32 ±13.38	<0.001
Age group at diagnosis				
<20	353 (0.4)	1 (0.0)	352 (0.4)	<0.001
20-34	6512 (6.8)	50 (0.9)	6462 (7.1)	
35-49	25184 (26.2)	421 (8.0)	24763 (27.2)	
50-64	40636 (42.2)	1974 (37.3)	38662 (42.5)	
≥65	23535 (24.5)	2851 (53.8)	20684 (22.8)	
Sex, n (%)				
Female	74362 (77.3)	3531 (66.7)	70831 (77.9)	<0.001
Male	21858 (22.7)	1766 (33.3)	20092 (22.1)	
Type of insurance, n (%)				
National Health Insurance	90740 (94.3)	4855 (91.7)	85885 (94.5)	<0.001
Medical aid	5480 (5.7)	442 (8.3)	5038 (5.5)	
Underlying disease, n (%)				
Hypertension	28896 (30.0)	2881 (54.4)	26015 (28.6)	<0.001
Diabetes mellitus	20085 (20.9)	1751 (33.1)	18334 (20.2)	<0.001
Dyslipidaemia	47895 (49.8)	2810 (53.1)	45085 (49.6)	<0.001
RA diagnosis year, n (%)				
2010-2014	43027 (44.7)	3563 (67.3)	39464 (43.4)	<0.001
2015-2020	53193 (55.3)	1734 (32.7)	51459 (56.6)	
csDMARD usage				
Methotrexate	76329 (79.3)	3796 (71.7)	72533 (79.8)	<0.001
Hydroxychloroquine	64939 (67.5)	3407 (64.3)	61532 (67.7)	<0.001
Sulfasalazine	36951 (38.4)	1939 (36.6)	35012 (38.5)	0.006
Tacrolimus	17479 (18.2)	757 (14.3)	16722 (18.4)	<0.001
Leflunomide	34320 (35.7)	1887 (35.6)	32433 (35.7)	0.957
Biologics and JAKi usage, n (%)				
Non-TNFi				
Abatacept/Tocilizumab	2097 (2.2)	83 (1.6)	2014 (2.2)	0.002
TNFi	6456 (6.7)	309 (5.8)	6147 (6.8)	0.010
Infliximab	909 (0.9)	42 (0.8)	867 (1.0)	0.271
Adalimumab	2508 (2.6)	117 (2.2)	2391 (2.6)	0.068
Etanercept	1957 (2.0)	107 (2.0)	1850 (2.0)	0.981
Golimumab	1082 (1.1)	43 (0.8)	1039 (1.1)	0.031
JAK inhibitor	1620 (1.7)	18 (0.3)	1602 (1.8)	<0.001
Tofactinib	881 (0.9)	13 (0.3)	868 (1.0)	<0.001
Baricitininb	735 (0.8)	5 (0.1)	730 (0.8)	<0.001
Upadacitinib	4 (0.0)	0 (0.0)	4 (0.0)	1.000

CVD: cardiovascular disease, RA: rheumatoid arthritis, csDMARD: conventional synthetic disease-modifying anti-rheumatic drug, JAKi: Janus kinase inhibitor, TNFi: tumour necrosis factor-α inhibitor.

Time-dependent Cox-proportional hazard analysis showed that an increase in age (hazard ratio [HR] 1.04, 95% CI 1.04–1.04, $p<0.001$), male sex (HR 2.04, 95% CI 1.93–2.17, $p<0.001$), underlying diseases, such as hypertension, diabetes mellitus, and dyslipidaemia (HRs 1.61, 1.52, and 1.19 respectively, all $p<0.001$), were associated with greater risk of cancers, whereas csDMARDs usage demonstrated a lesser risk (HR 0.88, 95% CI 0.80–0.98, $p=0.014$) of cancers. The adjusted analysis revealed that age (HR 1.04, 95% CI 1.03–1.04, $p<0.001$), male sex (HR 1.89, 95% CI 1.78–2.00, $p<0.001$), and diabetes mellitus (1.09, 95% CI 1.01–1.16, $p=0.021$) increased the risk of cancers, while the usage of medications was not associated with cancers (Table III).

Comparison of characteristics between patients experiencing CVDs and without

On the other hand, among the 96220 patients who were analysed for CVDs, 5297 patients experienced CVD events. The baseline characteristics of patients revealed significantly higher age at diagnosis, proportion of male sex, and the type of medical insurance

Table V. Frequency of CVD outcomes and incidence rates according to patient treatment.

	Number of events		Age- and sex- adjusted incidence rate/100,000 person-year		Incidence rate ratio (95% CI)
	Patients treated with JAKi/biologics	Patients treated with only csDMARDs	Patients treated with JAKi/biologics	Patients treated with only csDMARDs	
DVT	65	510	133.41	149.75	0.89 (0.85-0.93)
PE	35	377	58.30	124.33	0.47 (0.44-0.50)
Composite cardiovascular event	321	3539	1021.75	1054.63	0.97 (0.95-0.98)
Total CVDs‡	410	4330	1178.06	1294.29	0.91 (0.90-0.92)

‡In those having DVT, PE, and composite cardiovascular event simultaneously, the events were counted separately.
CVD: cardiovascular diseases, JAKi: Janus kinase inhibitor, csDMARD: conventional synthetic disease-modifying anti-rheumatic drug, CI: confidence interval, DVT: deep vein thrombosis, PE: pulmonary embolism.

aid in those who developed CVDs than in those without CVDs. Furthermore, the incidence of hypertension, diabetes mellitus, and dyslipidaemia was also higher among those who developed CVDs. Meanwhile, the use of csDMARDs except leflunomide, and biologics and JAKi, was higher in those who did not develop CVDs during the follow-up (Table IV). In the meantime, all of the included baseline characteristics at the time of starting JAKi/biologics differed in those analysed for CVDs (Suppl. Table S2).

CVD events in patients with SPRA according to treatment and factors associated with CVDs

Regarding the incidence of CVD outcomes during the mean follow-up time of 5.23 years, the number of patients with composite CVE was the highest, followed by DVT and PE, both in the JAKi/biologics and only csDMARD treated group. In particular, a statistically lower incidence rate of CVDs, regardless of the outcomes, was observed in patients who were treated with JAKi/biologics compared with those treated only with csDMARDs (Table V).

The Kaplan-Meier curve demonstrated that the events of CVDs were similar in the JAKi/biologics and the only csDMARD treated groups. Consistently, comparable incidence of CVDs was shown for those who were treated with first-line JAKi, non-TNFi, and TNFi, as well as for those who only received JAKi, non-TNFi, and TNFi during the observation period. Furthermore, significant differences were not noted in overall CVD outcomes based on the biologic types, JAKi, and csDMARD usage (Suppl. Fig. S5a-d). Consistently, patients aged ≥65 years who were prescribed only JAKi, non-TNFi, and TNFi demonstrated comparable risk of CVDs (Suppl. Fig. S4b).

Table VI. Cox-proportional hazard analysis associated with CVDs.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.07 (1.07-1.08)	<0.001	1.06 (1.06-1.07)	<0.001
Sex				
Female	1.00 (ref)		1.00 (ref)	
Male	1.90 (1.79-2.01)	<0.001	1.62 (1.53-1.71)	<0.001
Type of insurance				
National Health Insurance	1.00 (ref)		1.00 (ref)	
Medical Aid	1.79 (1.62-1.97)	<0.001	1.22 (1.10-1.35)	<0.001
Underlying disease				
Hypertension	3.10 (2.94-3.28)	<0.001	1.54 (1.45-1.63)	<0.001
Diabetes mellitus	2.27 (2.14-2.41)	<0.001	1.24 (1.16-1.32)	<0.001
Dyslipidaemia	1.46 (1.39-1.54)	<0.001	0.99 (0.94-1.06)	0.969
csDMARD usage	0.65 (0.59-0.71)	<0.001	0.99 (0.91-1.09)	0.935
Non-TNFi usage	1.02 (0.86-1.22)	0.809	1.11 (0.93-1.34)	0.254
TNFi usage	0.96 (0.85-1.07)	0.434	1.09 (0.99-1.30)	0.071
JAKi usage	0.87 (0.64-1.19)	0.392	1.06 (0.78-1.46)	0.704

CVD: cardiovascular diseases, HR: hazard ratio, CI: confidence interval, csDMARD: conventional synthetic disease-modifying anti-rheumatic drug, TNFi: tumour necrosis factor-α inhibitor, JAKi: Janus kinase inhibitor.

Cox-proportional hazard analysis using medications as a time-dependent covariate revealed a significant association of age, male sex, the insurance type of medical aid, underlying diseases, including hypertension, diabetes mellitus, and dyslipidaemia, and csDMARDs with CVDs in univariable analysis. Multivariable analysis demonstrated an increased risk of CVDs in older patients (HR 1.06, 95% CI 1.06–1.07, $p<0.001$), men (HR 1.62, 95% CI 1.53–1.71, $p<0.001$), those who were medical-aided (HR 1.22, 95% CI 1.10–1.35, $p<0.001$), and those who had hypertension (HR 1.54, 95% CI 1.45–1.63, $p<0.001$) and diabetes mellitus (HR 1.24, 95% CI 1.16–1.32, $p<0.001$). There was no significant influence of csDMARDs, biologics, and JAKi treatment on the occurrence of CVDs after adjustment (Table VI).

Discussion

In the present study, the risks of cancers and CVDs in patients with SPRA were assessed by utilising a national claims database. Herein, we restricted our patients into a subgroup of patients with SPRA, as patients with seronegative RA (SNRA) are only partially reimbursed for JAKi/biologics usage which makes it difficult for them to be treated with such agents. In addition, the proportion of patients with SPRA is generally regarded to be larger than those with SNRA (24). Finally, the presence

of antibodies, such as rheumatoid factor and anti-citrullinated peptide antibodies, is thought to be related to the risk of CVDs in patients with RA (25). Analyses of patients with SPRA who were prescribed JAKi/biologics demonstrated that the risk of cancers and CVDs were lower compared with those who were treated with only csDMARDs, implying that the treatment with JAKi/biologics may decrease the onset of cancers and CVDs in patients with RA. Notably, it was observed that JAKi did not confer a greater risk of cancers and CVDs, relative to non-TNFi and TNFi, as well as csDMARDs. Finally, the time-dependent Cox-proportional hazard analyses indicated that older age, male sex, and underlying diabetes mellitus were associated with cancer incidence, whereas age, male sex, the insurance type of medical aid, and underlying hypertension and diabetes mellitus independently predicted CVDs.

Regarding the incidence of cancers, we found that cancers in the lungs, thyroid, and stomach were the most common, which had a different incidence pattern than that of the cancer statistics in South Korea (26). However, our data revealed that there was no significant difference in the incidence of cancers, according to JAKi/biologics use. Furthermore, the overall risk of cancers and CVDs showed a decline in patients treated with JAKi/biologics. The diminished risk of these events in JAKi/biologics users could be interpreted as a consequence of the robust disease-modifying effect of these treatments. Generally, the decrease in disease activity is thought to be a modifiable factor that can mitigate the risk of developing CVDs (27). Several studies demonstrated that the use of biologics may mitigate the occurrence of CVDs, supporting the results of our study (28, 29). In addition, given that higher disease activity affects the risk of cancers in patients with RA, optimal disease treatment is beneficial in reducing the incidence of cancers. Recent meta-analyses revealed that treatment with JAKi/biologics did not influence the incidence of cancers, even in those who previously had cancers (30, 31). However, it was observed that several site-specific cancers of the lungs, liver, prostate, and skin were more frequent in patients treated with JAKi/biologics, which is also described in previous literature (32). Herein, it was not possible to provide a separate analysis regarding the incidence of site-specific cancers, owing to the small number of patients experiencing the respective outcomes. Thus, even though the decreased risk of cancers in patients with RA receiving JAKi/biologics in our study is reassuring, further studies are necessary to better understand the effect of JAKi/biologics on the incidence of site-specific cancers.

Findings from the ORAL Surveillance study that included patients with RA aged ≥50 years and having at least one additional cardiovascular risk factor, indicated that the incidence rates of cancer were higher among patients of age ≥65 years than those with the age of <65 years and major adverse cardiovascular events were more frequently observed in patients treated with tofacitinib compared with TNFi (17). Reflecting these results, the U.S. Food and Drug Administration recently announced a safety concern regarding the occurrence of cardiac events and blood clots in RA patients prescribed with JAKi (33). In addition, the European Medicines Agency recommended that patients who are at risk of blood clots should be prescribed JAKi with caution (34). As elevated inflammation influences the development of CVDs and cancers in patients with RA, the paradoxical effects of JAKi on the cardiovascular system and malignancies are not clearly understood; however, the selectivity of JAKi in the JAK/signal transducers and activators of transcription pathway affecting the balance of pro- and anti-thrombotic cytokines (35) and the effect of immunosuppression in host defence against cancers could be a possible explanation (36). In this context, there are studies indicating that the use of JAKi in clinical practice more frequently experience VTE compared to biologics (37, 38).

In our study, we found that age and male sex were shared risk factors for CVDs and cancers, which is similar to the general population (39). Moreover, in line with the current evidence, the association of hypertension and diabetes mellitus with CVDs, and diabetes mellitus with cancer was also demonstrated (40, 41). However, a subgroup analysis comparing patients treated with JAKi, non-TNFi, and TNFi showed that the risks of CVDs and cancers were not significantly different. Notably, these results were identified to be consistent even when a comparison was made between those who were prescribed JAKi, non-TNFi, and TNFi as a first-line treatment, as well as those who were only treated with JAKi, non-TNFi, and TNFi in the follow-up. This trend remained unchanged in those aged ≥65 years, suggesting that the risk of CVDs and cancers is not elevated even in the elderly. Importantly, our data seem to replicate results derived from observational studies that investigated cancer and CVDs incidence and indicated a non-significant increase in these events following JAKi treatment (42-45). Of note, the Kaplan-Meier plot indicated that the cumulative incidence of CVDs and cancers had a similar pattern, and steadily increased during the observation period. This indicates that the treatment does not lead to an abrupt *de novo* occurrence of CVDs and cancers. However, compared to non-TNFi and TNFi, JAKi has been authorised for the treatment of RA and has been subsidised by the national health insurance relatively recently. Indeed, as shown in the Kaplan-Meier analyses, different duration of follow-up with the JAKi/biologics could have also influenced in the patient outcomes and data interpretation. Thus, it is apparent that additional large-scale data are required to extrapolate the long-term effects of JAKi compared to that of other biologics.

An important strength of this study is that we demonstrated that JAKi/biologics was not associated with increased risks of cancers and CVDs in a nationwide, population-based, real-life setting. However, there are also important limitations of this study. First, owing to the limitations of the data available in the national claims database, detailed information such as objective disease activity, responses after treatment, smoking habits, and specific laboratory results of traditional cardiovascular

risk factors could not be included as a covariate for assessment. Second, the effect of treatment in the outcomes of cancers and CVDs could not be directly estimated, as data were collected retrospectively from the HIRA database. Third, the selection of JAKi/biologics was done according to the decision of the attending physician, which may result in a possibility of bias. Fourth, it was capable of identifying only those with SPRA according to the disease definition adopted in this study. Therefore, data from large, prospective studies are further required in the future to verify the findings from our study, especially in a subset of SNRA.

In conclusion, the overall risks of cancers and CVD were shown to decrease in patients with RA receiving JAKi/biologics compared with those receiving only csDMARDs. In addition, the use of JAKi/biologics did not lead to a greater risk of cancer and CVDs, irrespective of the timing of treatment and age of treatment initiation. However, because several site-specific cancers were shown to increase in JAKi/biologics users compared to this who were only treated with csDMARDs, greater clinical attention for certain cancers is indicated, which also requires further confirmation.

References

1. ALETAHA D, SMOLEN JS: Diagnosis and management of rheumatoid arthritis: a review. *JAMA* 2018; 320: 1360-72. https://doi.org/10.1001/jama.2018.13103
2. FRAENKEL L, BATHON JM, ENGLAND BR *et al*.: 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2021; 73: 1108-23. https://doi.org/10.1002/art.41752
3. SMOLEN JS, LANDEWë RBM, BERGSTRA SA *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023; 82: 3-18. https://doi.org/10.1136/ard-2022-223356
4. SMOLEN JS, ALETAHA D, BARTON A *et al*.: Rheumatoid arthritis. *Nat Rev Dis Primers* 2018; 4: 18001. https://doi.org/10.1038/nrdp.2018.1
5. PETRELLI F, MARIANI FM, ALUNNO A, PUXEDDU I: Pathogenesis of rheumatoid arthritis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40: 475-82. https://doi.org/10.55563/clinexprheumatol/l9lyen
6. TANAKA Y: Recent progress in treatments of rheumatoid arthritis: an overview of developments in biologics and small molecules, and remaining unmet needs. *Rheumatology* (Oxford) 2021; 60: vi12-vi20. https://doi.org/10.1093/rheumatology/keab609
7. FIGUS FA, PIGA M, AZZOLIN I, MCCONNELL R, IAGNOCCO A: Rheumatoid arthritis: Extra-articular manifestations and comorbidities. *Autoimmun Rev* 2021; 20: 102776. https://doi.org/10.1016/j.autrev.2021.102776
8. VOSKUYL AE: The heart and cardiovascular manifestations in rheumatoid arthritis. *Rheumatology* (Oxford) 2006; 45 Suppl 4: iv4-7. https://doi.org/10.1093/rheumatology/kel313
9. OZEN G, PEDRO S, SCHUMACHER R, SIMON T, MICHAUD K: Risk factors for venous thromboembolism and atherosclerotic cardiovascular disease: do they differ in patients with rheumatoid arthritis? *RMD Open* 2021; 7. https://doi.org/10.1136/rmdopen-2021-001618
10. WIDDIFIELD J, PATERSON JM, HUANG A, BERNATSKY S: Causes of death in rheumatoid arthritis: how do they compare to the general population? *Arthritis Care Res* (Hoboken) 2018; 70: 1748-55. https://doi.org/10.1002/acr.23548
11. ENGLAND BR, SAYLES H, MICHAUD K *et al*.: Cause-specific mortality in male US veterans with rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2016; 68: 36-45. https://doi.org/10.1002/acr.22642
12. WILTON KM, MATTESON EL: Malignancy incidence, management, and prevention in patients with rheumatoid arthritis. *Rheumatol Ther* 2017; 4: 333-47. https://doi.org/10.1007/s40744-017-0064-4
13. SIMON TA, THOMPSON A, GANDHI KK, HOCHBERG MC, SUISSA S: Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther* 2015; 17: 212. https://doi.org/10.1186/s13075-015-0728-9
14. BAECKLUND E, ILIADOU A, ASKLING J *et al*.: Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 692-701. https://doi.org/10.1002/art.21675
15. WHITE MC, HOLMAN DM, BOEHM JE, PEIPINS LA, GROSSMAN M, HENLEY SJ: Age and cancer risk: a potentially modifiable relationship. *Am J Prev Med* 2014; 46: S7-15. https://doi.org/10.1016/j.amepre.2013.10.029
16. RODGERS JL, JONES J, BOLLEDDU SI *et al*.: Cardiovascular risks associated with gender and aging. *J Cardiovasc Dev Dis* 2019; 6. https://doi.org/10.3390/jcdd6020019
17. YTTERBERG SR, BHATT DL, MIKULS TR *et al*.: Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022; 386: 316-26. https://doi.org/10.1056/nejmoa2109927
18. KIM JA, YOON S, KIM LY, KIM DS: Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci* 2017; 32: 718-28. https://doi.org/10.3346/jkms.2017.32.5.718
19. EUN Y, JEON KH, HAN K *et al*.: Menopausal factors and risk of seropositive rheumatoid arthritis in postmenopausal women: a nationwide cohort study of 1.36 million women. *Sci Rep* 2020; 10: 20793. https://doi.org/10.1038/s41598-020-77841-1
20. MYUNG J, CHOI JH, YI JH, KIM I: Cancer incidence according to the National Health Information Database in Korean patients with end-stage renal disease receiving hemodialysis. *Korean J Intern Med* 2020; 35: 1210-9. https://doi.org/10.3904/kjim.2018.400
21. HONG J, LEE JH, YHIM HY *et al*.: Incidence of venous thromboembolism in Korea from 2009 to 2013. *PLoS One* 2018; 13: e0191897. https://doi.org/10.1371/journal.pone.0191897
22. KANG EH, PARK EH, SHIN A, SONG JS, KIM SC: Cardiovascular risk associated with allopurinol vs. benzbromarone in patients with gout. *Eur Heart J* 2021; 42: 4578-88. https://doi.org/10.1093/eurheartj/ehab619
23. KIM KS, HONG S, HAN K, PARK CY: Assessing the validity of the criteria for the extreme risk category of atherosclerotic cardiovascular disease: a nationwide population-based study. *J Lipid Atheroscler* 2022; 11: 73-83. https://doi.org/10.12997/jla.2022.11.1.73
24. GRØNWALL C, LILJEFORS L, BANG H *et al*.: A comprehensive evaluation of the relationship between different IgG and IgA anti-modified protein autoantibodies in rheumatoid arthritis. *Front Immunol* 2021; 12: 627986. https://doi.org/10.3389/fimmu.2021.627986
25. FAZELI MS, KHAYCHUK V, WITTSTOCK K *et al*.: Cardiovascular disease in rheumatoid arthritis: risk factors, autoantibodies, and the effect of antirheumatic therapies. *Clin Med Insights Arthritis Musculoskelet Disord* 2021; 14: 11795441211028751. https://doi.org/10.1177/11795441211028751
26. JUNG KW, WON YJ, HONG S, KONG HJ, IM JS, SEO HG: Prediction of cancer incidence and mortality in Korea, 2021. *Cancer Res Treat* 2021; 53: 316-22. https://doi.org/10.4143/crt.2021.290
27. SOLOMON DH, REED GW, KREMER JM *et al*.: Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol* 2015; 67: 1449-55. https://doi.org/10.1002/art.39098
28. KARPOUZAS GA, ORMSETH SR, HERNANDEZ E, BUDOFF MJ: Biologics may prevent cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque formation and stabilizing high-risk lesions. *Arthritis Rheumatol* 2020; 72: 1467-75. https://doi.org/10.1002/art.41293
29. FRAGOULIS GE, SOULAIDOPOULOS S, SFIKAKIS PP, DIMITROULAS T, G DK: Effect of biologics on cardiovascular inflammation: mechanistic insights and risk reduction. *J Inflamm Res* 2021; 14: 1915-31. https://doi.org/10.2147/jir.S282691
30. WETZMAN A, LUKAS C, GAUJOUX-VIALA C *et al*.: Risk of cancer after initiation of targeted therapies in patients with rheumatoid arthritis and a prior cancer: systematic review with meta-analysis. *Arthritis Care Res* (Hoboken) 2023; 75(2); 260-71. https://doi.org/10.1002/acr.24784
31. SINGH N, LI CI: Impact of rheumatoid arthritis and biologic and targeted synthetic disease modifying antirheumatic agents on cancer risk and recurrence. *Curr Opin Rheumatol* 2021; 33: 292-9. https://

doi.org/10.1097/bor.0000000000000796
32. ASKLING J, FORED CM, BRANDT L *et al*.: Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Ann Rheum Dis* 2005; 64: 1421-6. https://doi.org/10.1136/ard.2004.033993
33. FOOD US, DRUG A: FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions: Approved uses also being limited to certain patients. U.S. Food & Drug Administration; 2021. [updated December 7, 2021; cited January 30, 2023]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death
34. EUROPEAN MEDICINES A: Janus kinase inhibitors (JAKi). European Medicines Agency; 2023. [updated January 23, 2023; cited January 30, 2023]. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki
35. KOTYLA PJ, ENGELMANN M, GIEMZA-STOKŁOSA J, WNUK B, ISLAM MA: Thromboembolic adverse drug reactions in janus kinase (JAK) inhibitors: does the inhibitor specificity play a role? *Int J Mol Sci* 2021; 22. https://doi.org/10.3390/ijms22052449
36. SONG YK, SONG J, KIM K, KWON JW: Potential adverse events reported with the janus kinase inhibitors approved for the treatment of rheumatoid arthritis using spontaneous reports and online patient reviews. *Front Pharmacol* 2021; 12: 792877. https://doi.org/10.3389/fphar.2021.792877
37. MOLANDER V, BOWER H, FRISELL T, DELCOIGNE B, DI GIUSEPPE D, ASKLING J: Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis. *Ann Rheum Dis* 2023; 82: 189-97. https://doi.org/10.1136/ard-2022-223050
38. SALINAS CA, LOUDER A, POLINSKI J *et al*.: Evaluation of VTE, MACE, and serious infections among patients with RA treated with baricitinib compared to TNFi: a multi-database study of patients in routine care using disease registries and claims databases. *Rheumatol Ther* 2022: 1-23. https://doi.org/10.1007/s40744-022-00505-1
39. LAU ES, PANIAGUA SM, LIU E *et al*.: Cardiovascular risk factors are associated with future cancer. *JACC CardioOncol* 2021; 3: 48-58. https://doi.org/10.1016/j.jaccao.2020.12.003
40. GIOVANNUCCI E, HARLAN DM, ARCHER MC *et al*.: Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33: 1674-85. https://doi.org/10.2337/dc10-0666
41. FLORA GD, NAYAK MK: A brief review of cardiovascular diseases, associated risk factors and current treatment regimes. *Curr Pharm Des* 2019; 25: 4063-84. https://doi.org/10.2174/1381612825666190925163827
42. FANG YF, LIU JR, CHANG SH, KUO CF, SEE LC: Comparative safety of Janus kinase inhibitors and tumor necrosis factor inhibitors in patients undergoing treatment for rheumatoid arthritis. *Int J Rheum Dis* 2022. https://doi.org/10.1111/1756-185x.14414
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; 74: 1648-59. https://doi.org/10.1002/art.42250
44. KHOSROW-KHAVAR F, KIM SC, LEE H, LEE SB, DESAI RJ: Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study. *Ann Rheum Dis* 2022; 81: 798-804. https://doi.org/10.1136/annrheumdis-2021-221915
45. HOISNARD L, PINA VEGAS L, DRAY-SPIRA R, WEILL A, ZUREIK M, SBIDIAN E: Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study. *Ann Rheum Dis* 2023; 82: 182-8. https://doi.org/10.1136/ard-2022-222824