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ORIGINAL RESEARCH

Association between malignancy risk and Janus kinase inhibitors versus tumour necrosis factor inhibitors in Korean patients with rheumatoid arthritis: a nationwide population-based study

Yeo-Jin Song ,[1,2] Soo-Kyung Cho ,[1,2] Seung-Hun You,[3] Jeong-Yeon Kim,[3] Hyoungyoung Kim,[1,2] Sun-Young Jung,[3] Yoon-Kyoung Sung [1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Yoon-Kyoung Sung;
sungyk@hanyang.ac.kr

ABSTRACT

Objective To determine the risk of malignancy in Korean patients with rheumatoid arthritis (RA) receiving Janus kinase inhibitors (JAKis) compared with tumour necrosis factor inhibitors (TNFis).

Methods A retrospective cohort of patients with RA initiating their first JAKi or TNFi was established using the Korean National Health Insurance database between 2015 and 2019. They were followed up from treatment initiation to the occurrence of malignancy, drug discontinuation, death or until December 2019. Baseline features of the patients were balanced through inverse probability of treatment weighting (IPTW) using a propensity score. A Cox proportional hazard model was established to estimate the HR for malignancy risk in JAKi users compared with TNFi users.

Results A total of 4929 patients (1064 JAKi-treated and 3865 TNFi-treated patients) were included, and the observation periods were 1288.6 person-years (PYs) for JAKi users and 6823.8 PYs for TNFi users. The incidence rates of overall malignancy were 0.54 per 100 PYs (95% CI 0.26 to 1.14) in JAKi users and 0.85 per 100 PYs (95% CI 0.66 to 1.10) in TNFi users. In IPTW analysis with a balanced sample (4101 JAKi-treated and 5131 TNFi-treated patients), HR was 0.83 (95% CI 0.55 to 1.27) for overall malignancy: 0.77 (95% CI 0.50 to 1.19) for solid malignancy and 2.86 (95% CI 0.41 to 20.00) for haematological malignancy.

Conclusion Malignancy risk in Korean patients with RA was not increased with JAKi use compared with TNFi use.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tofacitinib does not increase malignancy risk and has a comparable incidence rate of malignancy to biological disease-modifying antirheumatic drugs.

⇒ Recently, the Oral Rheumatoid Arthritis Trial Surveillance reported the increased risk of malignancy in patients using tofacitinib compared with tumour necrosis factor inhibitors (TNFis).

WHAT THIS STUDY ADDS

⇒ There was no increased risk of overall, solid and haematological malignancy in Korean patients with rheumatoid arthritis treated with Janus kinase inhibitors (JAKis) compared with TNFis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study is expected to contribute to determining the safety of JAKis in real-world practice.

⇒ Further study with longer observation periods and more patients receiving baricitinib and other JAKis is necessary.

INTRODUCTION

Compared with the general population, patients with rheumatoid arthritis (RA) have an increased risk of malignancies, especially lung cancer and lymphoma.[1 2] One of the explanations for the increased risk of malignancy in patients with RA is the shared risk factor.[3] For instance, smoking has been identified to play a causal role in both lung cancer and RA.[4 5] However, this speculation does not fully explain the increased risk of other types of malignancies in patients with RA. Several theories explain the relationship between lymphoma and RA, including genetic predisposition, the persistence of long-standing disease activity with continued immune stimulation and the role of medications used for RA treatment.[6] However, the exact cause and underlying mechanism increasing the risk of other types of malignancies in patients with RA are still unknown.

Clinicians mostly focus on whether the drugs used for RA treatment are associated with an increased risk of malignancy. Recently, the early use of biological disease-modifying antirheumatic drugs (bDMARDs) or Janus kinase inhibitors (JAKis) has been recommended to achieve low disease activity or remission in patients with RA.[6 7] The safety of tumour necrosis factor inhibitors (TNFis) or non-TNFis in patients with RA has been studied, but the results have been debatable. Several meta-analyses have reported the increased risk of malignancy such as skin cancer and lymphoma in patients receiving TNFis.[8–10] However, some studies have suggested no significant association between TNFi use and malignancy risk.[11–13] Similar conclusions are reported for non-TNFis.[14 15] Moreover, a decreased incidence of malignancy was observed in patients with early RA treated with bDMARDs.[16]

Long-term safety data for JAKis, recently developed for RA treatment, are insufficient. A long-term extension study was conducted to determine the safety of tofacitinib, the first JAKi developed for RA treatment, which lasted up to 9.5 years.[17] In this study, the incidence rate (IR) of malignancy was stable over time and comparable to that reported in the data pooled from previous clinical studies.[17 18] In addition, a meta-analysis about the risk of malignancies in patients with RA treated with bDMARDs or tofacitinib reported that tofacitinib did not increase the risk of malignancy, and the IR was comparable to that of patients with RA receiving bDMARDs.[19]

A recent Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study demonstrated that major adverse cardiovascular event and cancer did not meet the non-inferiority criteria for tofacitinib versus TNFi.[20] However, there is a lack of evidence about this safety issue in Asian patients, including those from Korea. According to the previous studies, overall and sex-specific age-standardised incidence, mortality and mortality-to-incidence ratios of cancers varied across six continents.[21] For instance, there were disparities in incidence and carcinogenic risk factors for stomach cancer worldwide that may have been influenced by environmental and lifestyle differences.[22] Different rates of incidence between Asian and Western population have also been reported for subtypes of lymphoma,[23] and similar differences in cancer incidence between races were seen in patients with RA.[24 25] In this study, we aimed to determine the relative risk of malignancy in Korean patients with RA treated with JAKis versus TNFis.

METHODS

Data source

The National Health Insurance (NHI) system covers almost the entire population in Korea. Therefore, the medical data of more than 50 million patients, or approximately 97% of the Korean population, are available in the NHI database.[26] This database includes information about healthcare usage, health examination, socio-demographic variables and mortality. We used the NHI claims database to extract the data of patients with RA who claimed insurance between 2009 and 2019.

Study population

Patients with prevalent RA were defined using diagnostic codes of RA and prescription of any DMARDs. This operational definition of RA was validated by a previous study.[27] Patients with RA who received their first JAKi or TNFi between 2015 and 2019 were included in this study because, in Korea, JAKi was first approved in 2015. The day of the first prescription of JAKi or TNFi was defined as the index date. We excluded all patients with prescriptions of JAKi or TNFi before the index date, to clarify the effect of JAKi or TNFi on the incidence of malignancy; so all JAKi users were considered to be naïve to TNFi.

Patients under 18 years of age or diagnosed with ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease or juvenile idiopathic arthritis were excluded. Since patients with malignancy are considered to be in remission if there is no recurrence for 5 years, patients with prior malignancy in the past 5 years from the index date were excluded. Patients with observation periods of less than 6 months were also excluded.

Outcome definitions

The outcome was the incidence of overall malignancy during the observation periods, defined as an appearance of a new malignancy according to a defined diagnostic code. A special code is issued for patients diagnosed with a malignancy in addition to the International Classification of Diseases, 10th Revision (ICD-10) code in Korea, and the government supports 95% of the medical cost for those with special codes. Hence, the diagnosis of malignancy was defined as having both an ICD-10 code and a special code for malignancy, which has been proven to improve the accuracy of cancer diagnosis.[28] The identified cases of overall malignancies were classified as solid or haematological, and subsequently, according to the primary site.

Study design

A retrospective cohort of patients with RA who started their first JAKi or TNFi was established. According to the type of targeted therapy received by these patients, they were divided into JAKi and TNFi groups. They were followed up from the index date to the occurrence of malignancy, drug discontinuation, death or the end of the study in December 2019. A permissible gap was applied to drug discontinuation because JAKis or TNFis could be stopped for a while for other reasons such as surgery and infection. A permissible gap is a threshold of a period without treatment, and there is no established definition of the appropriate length of a permissible gap.[29] In this study, a gap of less than 12 weeks in addition to the usual drug interval was not considered drug discontinuation. Patients who were lost to follow-up were not considered separately because they were censored

due to drug discontinuation. We assumed there was no latent period (the period between drug initiation and a specific reaction, which is malignancy in this study). This was to reflect real clinical practice that physicians usually stop targeted therapy if a patient is diagnosed with cancer even after only a short period of use.

We compared the demographics and clinical characteristics of the two groups. Demographics including age, sex, type of insurance and type of institution on the index date were noted. For comorbidities, the presence of a diagnostic code for a given comorbidity during the baseline period, defined as the period of a year before the index date, was identified. Then, the Charlson Comorbidity Index score was calculated. Prescriptions for DMARDs, oral corticosteroids and non-steroidal anti-inflammatory drugs during the baseline period, apart from the index date, were investigated to identify previous medications. Concomitant medication was defined as prescription of a drug on the index date.

The IR of malignancy in each group was calculated including overall malignancy, solid, haematological and specific malignancies. In addition, subgroup analyses were performed according to sex, age and concomitant use of methotrexate (MTX).

Statistical analysis

To control potential confounding factors, we applied inverse probability of treatment weighting (IPTW) to balance characteristics between the JAKi and TNFi groups. To calculate the probability of being prescribed JAKi, we used a multivariable logistic regression model taking into account numerous demographic and clinical characteristics for the propensity score: age, sex, geographical region, level of household income, type of insurance, type of institution, year of initiating JAKi or TNFi, seropositivity of RA, comorbidities, medication use and healthcare usage. Trimming of the cases was not implemented when performing IPTW in this study. The variables with an absolute standardised difference (ASD) of less than 0.1 between the two groups were considered to be accurately balanced. The crude IR of malignancy was calculated per 100 person-years (PYs) with a 95% CI. As-treated analysis was performed to compare the risk of malignancy between the two groups. A Cox proportional hazard model considering death as a competing risk was used to estimate the HR for the risk of malignancy in JAKi users compared with TNFi users. The crude HR before IPTW and weighted HR after IPTW were calculated.

Sensitivity analyses were performed to explore the robustness of our findings. As cancer would not appear in such a short period, a latent period of 6 months or 1 year was applied, whereby any patient with overall malignancy occurring during each period after the initiation of exposure was defined as censoring.[30 31] Additionally, a permissible gap of 24 weeks or without a permissible gap was included in the sensitivity analyses. Moreover, the intention-to-treat analyses were performed during the total observation period or 1 year. All analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA), and p values<0.05 were considered statistically significant.

RESULTS

Baseline characteristics of study participants

Among 4929 patients included in this study, 1064 were JAKi users and 3865 were TNFi users (figure 1). The observation period was 8112.4 PYs in total: 1288.6 PYs for JAKi users and 6823.8 PYs for TNFi users. The mean age of the study population was 54.5 (±13.1) years, and female patients accounted for 79.9% of the total number of patients. There was no significant difference in most comorbidities between JAKi and TNFi users (table 1).

There were differences in several previous medications between the two groups. MTX, hydroxychloroquine and sulfasalazine were used more in the TNFi group, whereas tacrolimus, abatacept and tocilizumab were used more in the JAKi group. Those who were naïve to all targeted therapy including non-TNFis and rituximab accounted for 87.8% of the JAKi user group and 95.8% of the TNFi user group. Regarding concomitant medication, MTX was used more in the TNFi group, and there was no difference in the concomitant use of oral corticosteroids. Among JAKi users, 92.5% of the patients used tofacitinib, and the most commonly used TNFi was adalimumab (36.0%).

After performing IPTW, 4101 JAKi users and 5131 TNFi users were included. The different characteristics between the two groups, including age and the previous use of non-TNFis, were balanced after IPTW with ASD of less than 0.1. Additional information about the variables included for calculating the propensity score is presented in online supplemental table 1. There were still unbalanced covariates including the year of initiating JAKi or TNFi treatment, seropositivity, cerebrovascular disease, previous conventional synthetic DMARD (csDMARD) use, and concomitant MTX and oral corticosteroid use.

IR and HR of overall malignancies in JAKi users versus TNFi users

The mean observation period was 1.2±0.7 years for JAKi users and 1.8±1.3 years for TNFi users. There were 65 patients who developed cancer, and all of them were newly-developed cases. After IPTW, the gap of the observation period between the two groups was narrowed to 1.2±1.7 years for JAKi users and 1.6±1.4 years for TNFi users. With a balanced sample by IPTW, the IR of overall malignancy was 0.67 per 100 PYs (95% CI 0.48 to 0.94) in JAKi users and 0.85 per 100 PYs (95% CI 0.67 to 1.07) in TNFi users (table 2). The IR of solid malignancy was 0.61 per 100 PYs (95% CI 0.43 to 0.87) in JAKi users and 0.82 per 100 PYs (95% CI 0.65 to 1.04) in TNFi users. In terms of haematological malignancy, the IR was 0.06 per 100 PYs (95% CI 0.02 to 0.19) in JAKi users and 0.02 per 100 PYs (95% CI 0.01 to 0.10) in TNFi users. The HR after IPTW was 0.83 (95% CI 0.55 to 1.27) for all malignancies:

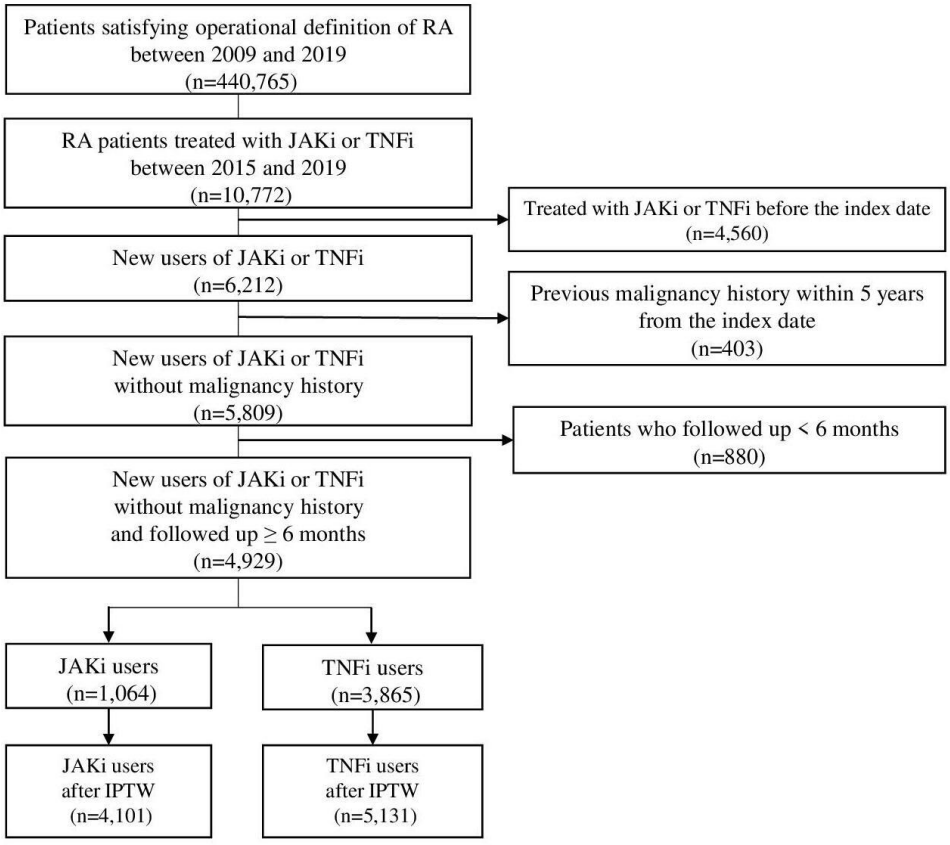

Figure 1 Flowchart of patient selection. DMARD, disease-modifying antirheumatic drug; IPTW, inverse probability of treatment weighting; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

0.77 (95% CI 0.50 to 1.19) for solid malignancy and 2.86 (95% CI 0.41 to 20.00) for haematological malignancy, respectively.

We performed an additional analysis by adjusting for all variables that were still unbalanced after IPTW. Adjusted HRs were 0.76 (95% CI 0.49 to 1.20) for all malignancies, 0.71 (95% CI 0.44 to 1.13) for solid malignancy and 3.51 (95% CI 0.81 to 15.20) for haematological malignancy (online supplemental table 2).

In the subgroup analyses, the risk of malignancy was not significantly increased in JAKi users after IPTW (figure 2). We also compared the risk of tofacitinib users versus TNFi users, and the results were similar to those of the main analysis (online supplemental table 3). In the sensitivity analyses, there was also no significant difference in the risk of malignancy between the JAKi and TNFi groups (figure 3). When the analyses were performed without the permissible gap, HR could not be calculated because there was no event of malignancy in the JAKi group.

IR and HR of specific malignancies in JAKi users versus TNFi users

Table 3 summarises the IR of specific malignancies in the JAKi and TNFi groups and the HR calculated before and after IPTW. In the JAKi group, thyroid cancer was most common in two cases, and there was a case each of lung, breast and skin cancers and non-Hodgkin's lymphoma. In the TNFi group, breast cancer was the most commonly developed cancer, followed by thyroid, lung and colorectal cancers. The HRs were calculated for specific malignancies of which there were cases in both groups: lung, breast, thyroid, skin and other specified cancers, and non-Hodgkin's lymphoma. There were no significant differences in all the specific malignancies between JAKi users and TNFi users, although the point estimate of weighted HR was increased in several cancers: breast cancer (HR 1.92, 95% CI 0.94 to 3.90), non-melanoma skin cancer (NMSC, HR 3.46, 95% CI 0.59 to 20.26), non-Hodgkin's lymphoma (HR 2.86, 95% CI 0.41 to 20.01) and other unspecified cancers (HR 2.02, 95% CI 0.69 to 5.94).

DISCUSSION

In this study, we aimed to determine the risk of malignancy in Korean patients with RA receiving JAKis compared with TNFis. Our results showed no significant difference in the risk of overall, solid and haematological malignancies between JAKi and TNFi users. The incidences of specific malignancies were also similar between the two groups.

Our results also showed increased prescription of targeted therapy for RA treatment in Korea. Targeted therapy was initiated in 1827 patients between 2015 and 2016, while 3102 patients started targeted therapy

Table 1 Baseline characteristics of the study population

Variables	Before IPTW			After IPTW		
	JAKi (n=1064)	TNFi (n=3865)	ASD	JAKi (n=4101)	TNFi (n=5131)	ASD
Age, years	55.7±12.5	54.2±13.3	0.12	54.4±25.5	54.5±15.0	<0.01
Sex, female	881 (82.8)	3058 (79.1)	0.09	3159 (77.0)	4108 (80.1)	0.07
Initiation of JAKi or TNFi, year			1.03			0.25
2015~2016	61 (5.7)	1766 (45.7)		993 (24.2)	1825 (35.6)	
2017~2019	1003 (94.3)	2099 (54.3)		3108 (75.8)	3307 (64.4)	
Type of insurance			0.03			
Health insurance	1010 (94.9)	3640 (94.2)		3890 (94.9)	4837 (94.3)	0.03
Medicaid	54 (5.1)	225 (5.8)		211 (5.1)	294 (5.7)	
Type of institution			0.18			0.10
Tertiary referral hospital	646 (60.7)	2226 (57.6)		2576 (62.8)	2986 (58.2)	
General hospital	253 (23.8)	1185 (30.7)		1026 (25.0)	1455 (28.4)	
Community hospital/clinic	165 (15.5)	454 (11.8)		499 (12.2)	691 (13.5)	
Seropositivity			0.14			0.17
Seropositive	1012 (95.1)	3545 (91.7)		3574 (87.2)	4741 (92.4)	
Seronegative	52 (4.9)	320 (8.3)		526 (12.8)	391 (7.6)	
Comorbidities						
Myocardial infarction	6 (0.6)	40 (1.0)	0.05	14 (0.4)	52 (1.0)	0.08
Congestive heart failure	41 (3.9)	140 (3.6)	0.01	163 (4.0)	170 (3.3)	0.04
Peripheral vascular disorders	112 (10.5)	413 (10.7)	0.01	410 (10.0)	533 (10.4)	0.01
Cerebrovascular disease	68 (6.4)	217 (5.6)	0.03	359 (8.7)	295 (5.8)	0.12
Chronic pulmonary disease	342 (32.1)	1305 (33.8)	0.03	1483 (36.2)	1727 (33.7)	0.05
Diabetes without complication	208 (19.6)	764 (19.8)	0.01	923 (22.5)	977 (19.1)	0.09
Diabetes with complication	56 (5.3)	218 (5.6)	0.02	191 (4.7)	274 (5.4)	0.03
Renal disease	14 (1.3)	66 (1.7)	0.32	98 (2.4)	92 (1.8)	0.04
Number of comorbidities			0.04			0.09
0–2	628 (59.0)	2202 (57.0)		2200 (53.7)	2940 (57.3)	
3–5	385 (36.2)	1450 (37.5)		1714 (41.8)	1933 (37.7)	
≥6	51 (4.8)	213 (5.5)		187 (4.6)	259 (5.0)	
CCI score	2.5±1.5	2.6±1.6	0.07	2.6±2.9	2.6±1.8	0.02
Previous medications						
Methotrexate	916 (86.1)	3568 (92.3)	0.20	3264 (79.6)	4474 (87.2)	0.20
Hydroxychloroquine	464 (43.6)	2103 (54.4)	0.21	1841 (44.9)	2571 (50.1)	0.10
Leflunomide	484 (45.5)	1756 (45.4)	<0.01	1643 (40.1)	2237 (43.6)	0.07
Sulfasalazine	311 (29.2)	1567 (40.5)	0.24	1345 (32.8)	1883 (36.7)	0.08
Tacrolimus	367 (34.5)	978 (25.3)	0.20	973 (23.7)	1340 (26.1)	0.06
Oral corticosteroids	983 (92.4)	3657 (94.6)	0.09	3642 (88.8)	4723 (92.0)	0.11
NSAIDs	1021 (96.0)	3764 (97.4)	0.08	3926 (95.7)	4888 (95.3)	0.02
Non-TNFi						
Abatacept	59 (5.6)	73 (1.9)	0.19	192 (4.7)	145 (2.8)	0.10
Tocilizumab	66 (6.2)	82 (2.1)	0.21	242 (5.9)	280 (5.5)	0.02
Rituximab	2 (0.2)	1 (0.0)	0.05	4 (0.1)	8 (0.2)	0.01
Number of previous csDMARDs			0.17			0.29
0	37 (3.5)	28 (0.7)		121 (3.0)	265 (5.2)	
1	66 (6.2)	183 (4.7)		497 (12.1)	258 (5.0)	
2	464 (43.6)	1607 (41.6)		1758 (42.9)	2067 (40.3)	

Continued

Table 1 Continued

Variables	Before IPTW			After IPTW		
	JAKi (n=1064)	TNFi (n=3865)	ASD	JAKi (n=4101)	TNFi (n=5131)	ASD
≥3	497 (46.7)	2047 (53.0)		1725 (42.1)	2541 (49.5)	
Concomitant medications						
Methotrexate	777 (73.0)	3035 (78.5)	0.13	2854 (69.6)	3909 (76.2)	0.15
Dose, mg/week	12.7±3.5	12.4±5.5	0.05	12.7±8.6	12.4±4.7	0.04
Oral corticosteroids	835 (78.5)	2905 (75.2)	0.08	2894 (70.6)	3875 (75.5)	0.11
Prednisolone-equivalent dose, mg/day	5.3±2.9	5.6±3.8	0.07	5.5±5.5	5.5±4.2	0.02
Type of targeted therapy			NC			NC
JAKi						
Tofacitinib	984 (92.5)			3872 (94.4)		
Baricitinib	80 (7.5)			229 (5.6)		
TNFi						
Adalimumab		1391 (36.0)			1917 (37.4)	
Etanercept		975 (25.2)			1284 (25.0)	
Infliximab		556 (14.4)			676 (13.2)	
Golimumab		943 (24.4)			1255 (24.5)	

Values are presented as means±SD or numbers (%).
ASD, absolute standardised difference; CCI, Charlson Comorbidity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IPTW, inverse probability of treatment weighting; JAKi, Janus kinase inhibitor; NC, not calculated; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor.

between 2017 and 2019. This trend was observed dominantly in the JAKi group since 2017 when tofacitinib, the first JAKi, was approved in Korea as the second-line therapy for patients with an inadequate response to csDMARDs. The prices of JAKi and TNFi were generally similar, but biosimilars of TNFi tended to be less expensive. In terms of accessibility, JAKi was more used than TNFi in the capital (27.0% vs 20.4%) and tertiary referral hospitals (60.7% vs 57.6%) due to its recent approval. However, we included the year of initiation of JAKi or TNFi, region, type of institution and income when calculating the propensity score, and tried to

Table 2 The risk of malignancy in patients with RA treated with JAKi versus TNFi

	Type of targeted therapy	Number of patients	Number of events	Total observation periods (person-year)	IR (95% CI)	HR (95% CI)
Before IPTW						
Overall malignancy	JAKi	1064	7	1288.6	0.54 (0.26 to 1.14)	0.69 (0.30 to 1.56)
	TNFi	3865	58	6823.8	0.85 (0.66 to 1.10)	
Solid malignancy	JAKi	1064	6	1288.6	0.47 (0.21 to 1.04)	0.61 (0.26 to 1.47)
	TNFi	3865	56	6823.8	0.82 (0.63 to 1.07)	
Haematological malignancy	JAKi	1064	1	1288.6	0.08 (0.01 to 0.55)	2.41 (0.15 to 37.99)
	TNFi	3865	2	6823.8	0.03 (0.01 to 0.12)	
After IPTW						
Overall malignancy	JAKi	4101	34	4985.3	0.67 (0.48 to 0.94)	0.83 (0.55 to 1.27)
	TNFi	5131	72	8457.1	0.85 (0.67 to 1.07)	
Solid malignancy	JAKi	4101	30	4985.3	0.61 (0.43 to 0.87)	0.77 (0.50 to 1.19)
	TNFi	5131	70	8457.1	0.82 (0.65 to 1.04)	
Haematological malignancy	JAKi	4101	3	4985.3	0.06 (0.02 to 0.19)	2.86 (0.41 to 20.00)
	TNFi	5131	2	8457.1	0.02 (0.01 to 0.10)	

Incidence rate per 100 person-years was calculated.
IPTW, inverse probability of treatment weighting; IR, incidence rate; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

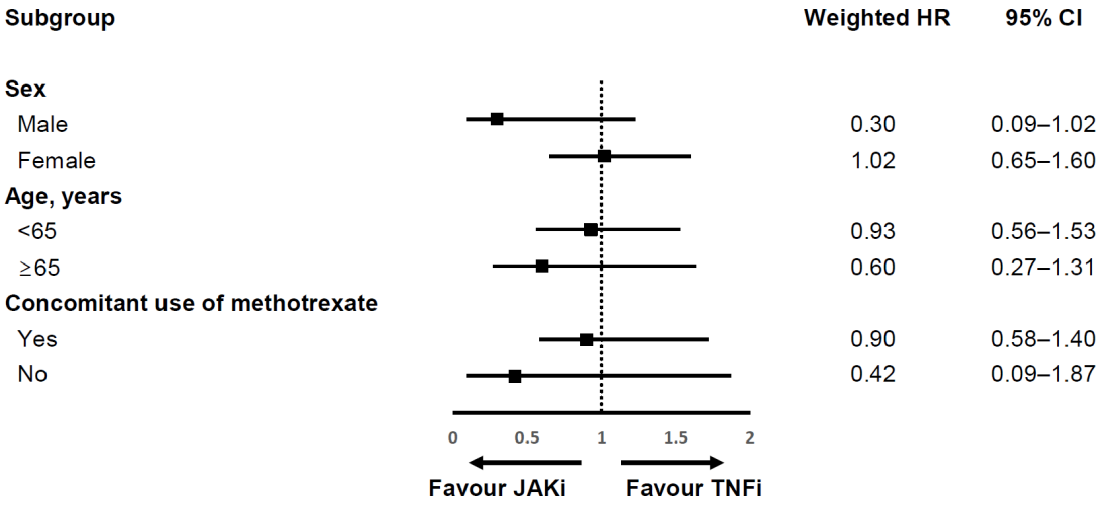

Figure 2 Subgroup analysis for risk of malignancy in patients with RA treated with JAKi versus TNFi. JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

balance other confounding factors that might influence the selection of JAKi or TNFi.

As the use of is JAKi increasing, determining its safety in the real world is becoming increasingly important. In a recent study on the safety of tofacitinib versus bDMARDs based on information available in the US Corrona RA registry, the risk of malignancies including NMSC was comparable in patients with RA receiving tofacitinib versus those receiving bDMARDs.[32] The IR of malignancy excluding NMSC was 0.88 per 100 PYs (95% CI 0.58 to 1.27) in tofacitinib users in this published study, which was similar to the result of our research (IR 0.54, 95% CI 0.26 to 1.14). However, we included baricitinib users as the study population and NMSC as an outcome. It was also comparable with the results from the long-term safety profile of tofacitinib from integrated data of the RA clinical development programme, which reported the IR of malignancy excluding NMSC as 0.8 per 100 PYs (95% CI 0.7 to 1.0).[17] There is insufficient data about the malignancy risk of baricitinib, which is more recently released than tofacitinib. In the integrated analysis of patients with active RA receiving baricitinib, the IR of overall malignancies excluding NMSC was 0.8 per 100 PYs (95% CI 0.6 to 1.0), and that of NMSC was 0.4 per 100 PYs (95% CI 0.2 to 0.5).[33]

An interesting finding of our study was that the HR of haematological malignancy increased when JAKi users were compared with TNFi users. The HR after IPTW was 2.86 (95% CI 0.41 to 20.00) with a wide CI, and the small number of lymphoma events should be taken into account. There was only one patient with haematological malignancy in the JAKi group, and two in the TNFi group. All three cases were non-Hodgkin's lymphoma. Though there were lymphoma events during the clinical trials of JAKis, the IR of lymphoma was similar to that in other clinical studies of patients with RA treated with bDMARDs.[17 33 34]

In terms of specific malignancies according to the primary sites, JAKi users developed thyroid, lung and breast cancers; NMSC; and non-Hodgkin's lymphoma. The clinical data of tofacitinib users reported the case of malignancies including lymphoma, melanoma, breast and lung cancers and NMSC.[17] The specific malignancies in JAKi users reported in our study were within the scope of the previous clinical data.

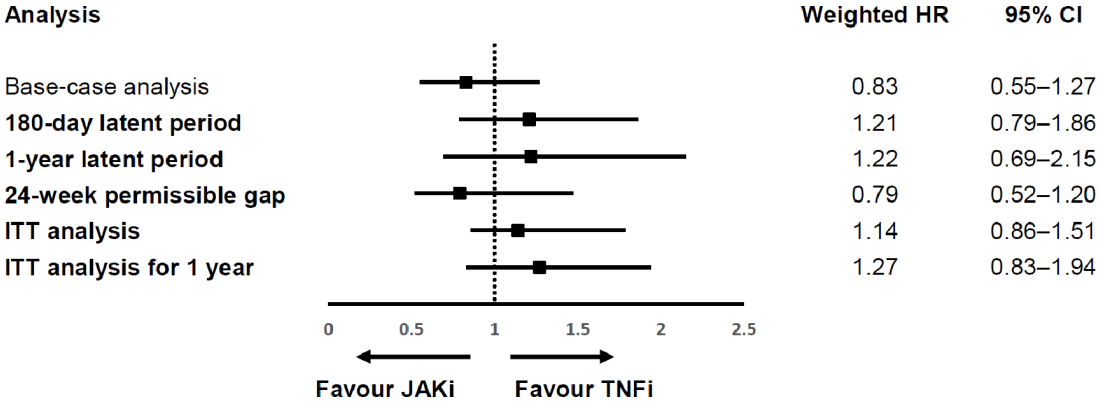

Figure 3 Sensitivity analyses for risk of malignancy in patients with RA treated with JAKi versus TNFi. ITT, intention-to-treat; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

Table 3 The risk of specific malignancies in patients with RA treated with JAKi versus TNFi

Type of malignancy	JAKi			TNFi				
	Events (N)	Crude IR (95% CI)	Weighted IR (95% CI)	Events (N)	Crude IR (95% CI)	Weighted IR (95% CI)	Crude HR (95% CI)	Weighted HR (95% CI)
Solid malignancies								
Stomach	–	–	–	4	0.05 (0.02 to 0.11)	0.05 (0.02 to 0.14)	–	
Colorectal	–	–	–	6	0.09 (0.04 to 0.20)	0.09 (0.04 to 0.18)	–	
Liver	–	–	–	1	0.01 (0.00 to 0.10)	0.02 (0.00 to 0.09)	–	
Biliary	–	–	–	5	0.07 (0.03 to 0.18)	0.08 (0.04 to 0.17)	–	
Pancreas	–	–	–	1	0.01 (0.00 to 0.10)	0.02 (0.00 to 0.09)	–	
Lung	1	0.08 (0.01 to 0.55)	0.11 (0.05 to 0.25)	7	0.10 (0.05 to 0.22)	0.12 (0.07 to 0.23)	0.82 (0.08 to 8.14)	0.96 (0.31 to 2.96)
Breast	1	0.08 (0.01 to 0.55)	0.27 (0.16 to 0.46)	12	0.18 (0.10 to 0.31)	0.15 (0.09 to 0.26)	0.64 (0.09 to 4.84)	1.92 (0.94 to 3.90)
Cervix (female)	–	–	–	2	0.03 (0.01 to 0.12)	0.03 (0.01 to 0.10)	–	
Uterine (female)	–	–	–	1	0.01 (0.00 to 0.10)	0.02 (0.00 to 0.09)	–	
Prostate (male)	–	–	–	1	0.01 (0.00 to 0.10)	0.01 (0.00 to 0.08)	–	
Kidney	–	–	–	2	0.03 (0.01 to 0.12)	0.02 (0.01 to 0.10)	–	
Thyroid	2	0.16 (0.04 to 0.62)	0.09 (0.04 to 0.23)	9	0.13 (0.07 to 0.25)	0.13 (0.07 to 0.23)	1.54 (0.29 to 8.34)	0.86 (0.28 to 2.62)
Skin*	1	0.08 (0.01 to 0.55)	0.07 (0.02 to 0.20)	2	0.03 (0.01 to 0.12)	0.02 (0.01 to 0.10)	3.39 (0.26 to 45.17)	3.46 (0.59 to 20.26)
Haematological malignancies								
Non-Hodgkin's lymphoma	1	0.08 (0.01 to 0.55)	0.06 (0.02 to 0.19)	2	0.03 (0.01 to 0.12)	0.02 (0.01 to 0.10)	2.41 (0.15 to 37.99)	2.86 (0.41 to 20.01)
Other unspecified	2	0.16 (0.04 to 0.62)	0.18 (0.09 to 0.34)	5	0.07 (0.03 to 0.18)	0.09 (0.04 to 0.18)	1.70 (0.29 to 10.05)	2.02 (0.69 to 5.94)

Incidence rate per 100 person-years was calculated.
*There were only cases of non-melanoma skin cancer.
IR, incidence rate; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

The results from the ORAL Surveillance report recently caused the US Food and Drug Administration to warn about the increased risk of major adverse cardiovascular events and cancer in patients treated with tofacitinib.[20] This study included 2911 tofacitinib users (1455 receiving 5 mg two times per day and 1456 receiving 10 mg two times per day) and 1451 TNFi users. The IRs of cancers excluding NMSC were 1.13 per 100 PYs (95% CI 0.94 to 1.35) in tofacitinib users and 0.77 per 100 PYs (95% CI 0.55 to 1.04) in TNFi users, resulting in an HR of 1.48 (95% CI 1.04 to 2.09). The risk of NMSC was also increased in tofacitinib users regardless of the quantity of administered dose compared with that in TNFi users. The IRs of these cancers were quite higher than the results from our study when considering point estimates. The reason might be that the ORAL Surveillance included patients 50 years of age or older with at least one additional risk factor for cardiovascular diseases. In addition, the proportion of Asian patients in the ORAL Surveillance study was as low as 4%. These different characteristics of the study population could explain the differences in their observations from those reported in our study.

Our study has several strengths. First, we used the national database for claims pertaining to the entire Korean population. Thus, a large population was included in this study. Second, we minimised the loss of sample size by study design performing IPTW analyses. Third, patients who received JAKis were included, although there is relatively insufficient data about the long-term safety of these drugs in a real-world setting. In addition, there have been issues about the safety of tofacitinib, extending the concerns to all JAKi users. Therefore, we believe that our study could be useful in providing information about the safety of JAKi, especially for Asian patients.

Our study also has limitations. First, patients who had used non-TNFis or rituximab were included. However, these patients accounted for only about 6% of the total study population, and we considered previous use of non-TNFis or rituximab as a covariate, which was balanced by IPTW. Second, the number of JAKi users was smaller than that of TNFi users, accounting for about a quarter of their number. Nevertheless, we tried to balance the difference in number of patients between the two groups by IPTW. In particular, far fewer patients received baricitinib than tofacitinib because baricitinib was approved more than a year later than tofacitinib in Korea. Third, since the observation period was less than 2 years for both groups, it may have been insufficient for malignancies to develop. In addition, long-term data were unavailable because of the relatively late approval of JAKi use for RA in Korea. The small number of specific malignancies, especially among JAKi users, may have been due to the short observation period. Fourth, information such as disease duration and erosive disease could not be included as variables in the study. We included patients with prevalent RA, not only incident cases, so we could not identify when patients were diagnosed with RA: since they could have been diagnosed with RA before 2009, disease duration could not be calculated. In addition, erosive disease can be identified by X-ray or from medical records, but that data was not available in the NHI database.

In conclusion, there was no increased risk of overall, solid and haematological malignancy in patients with RA who were treated with JAKis compared with those treated with TNFis in Korea. We believe that our large population-based, nationwide study could help determine the safety of JAKis.

Author affiliations
[1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea (the Republic of)
[2]Hanyang University Institute for Rheumatology Research, Seoul, Korea (the Republic of)
[3]College of Pharmacy, Chung-Ang University, Seoul, Korea (the Republic of)

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ORCID iDs
Yeo-Jin Song http://orcid.org/0000-0001-9420-2129
Soo-Kyung Cho http://orcid.org/0000-0003-4493-8837
Yoon-Kyoung Sung http://orcid.org/0000-0001-6691-8939

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