Risk of cancer, tuberculosis and serious infections in patients with ankylosing spondylitis, psoriatic arthritis, and psoriasis treated with IL-17 and TNF-α inhibitors: a nationwide nested case-control analysis

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Abstract

Objective

Targeting interleukin (IL)-17 and tumour necrosis factor (TNF)-α is recommended for the management of severe/refractory ankylosing spondylitis (AS), psoriatic arthritis (PsA) and psoriasis (PsO); however, safety data comparing these agents, especially in a large Asian population are unavailable.

Methods

Patients with AS, PsA and PsO were searched using the Health Insurance Review and Assessment Service database, defined according to the International Classification of Diseases-10 and unique insurance codes for rare diseases. By including patients newly diagnosed with AS, PsA, and PsO between 2010-2020, the outcomes of cancer, tuberculosis (TB), and serious infections following IL-17 and TNF-α inhibitor usage were evaluated. To investigate the association between treatments and outcomes, nested case-control analyses matching patients to controls (maximum of 1:10 ratio) according to index age, sex, index year, and follow-up duration were performed.

Results

Among 40322, 4953 and 5347 patients with AS, PsA and PsO, respectively, three different datasets were generated to evaluate incidence of outcomes. Conditional logistic regression analysis revealed that cyclosporine use (odds ratio [OR] 2.286, p=0.0176) increased cancer, and a higher Charlson Comorbidity Index (CCI) score (OR 1.085, p=0.0406) and IL-17 inhibitor use only (OR 0.126, p=0.0457) showed a positive and negative association with TB, respectively. Serious infections increased in patients with high CCI scores (OR 1.117, p<0.0001), cyclosporine users (OR 1.445, p=0.0098), and medical-aided individuals (OR 1.667, p<0.0001).

Conclusion

In this nationwide cohort of IL-17 and TNF-α inhibitor users, both treatments conferred comparable risk of cancer and serious infections, while IL-17 inhibitors may be advantageous for TB.

Key words

IL-17 inhibitor, TNF-α inhibitor, safety, comparison

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Introduction

Ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis (PsO) are a group of immune-mediated inflammatory diseases (IMIDs) that affect the joints and skin and have a significant impact on a patient's quality of life (1, 2). Although a complex relationship between genetic and environmental factors has been proposed, the aetiology of AS, PsA, and PsO is still not clearly characterised (3). However, the overexpression of inflammatory cytokines, which largely accounts for the imbalance between inflammatory and anti-inflammatory responses, is a typical feature of these disorders that persists inflammation and results in progressive organ injury (4, 5). Conventional medications used to treat AS, PsA, and PsO include glucocorticoids, non-steroidal anti-inflammatory drugs, and disease-modifying anti-rheumatic drugs (DMARDs) (6-8). However, insufficient treatment responses following conventional medication administration and increased insight into disease pathogenesis have led to the development of therapeutic agents targeting pivotal cytokines that induce inflammation in these diseases.

The emergence of novel biological agents specifically targeting the cytokines tumour necrosis factor alpha (TNF-α) and interleukin (IL)-17 has revolutionised the treatment of patients with AS, PsA, and PsO, contributing to the management of severe or refractory diseases (9-11). Currently, TNF-α inhibitors, such as etanercept, adalimumab, golimumab, and infliximab, are prescribed for patients with AS, PsA, and PsO. However, secukinumab, a selective IL-17A inhibitor which first gained U.S. Food and Drug Administration approval for the treatment of PsO in 2015, obtained indications for its use in AS and PsA in 2016 and is now prescribed in more than 70 countries worldwide (12). In addition, a different IL-17A antagonist, ixekizumab, is now authorised for the treatment of AS, PsA, and PsO (13). The results of clinical trials demonstrated that secukinumab and ixekizumab are highly efficacious in treating these patients by alleviating joint and/or skin inflammation which may be explained by the crucial effect of this cytokine. Meanwhile, with regards to drug safety, compared to the long-term effects reported following TNF-α inhibition, there is limited data on IL-17 inhibitors.

Evidence has reported a favourable and acceptable safety profile among patients receiving IL-17 inhibitors. An integrated analysis of pooled clinical trials and post-marketing surveillance data of over 7000 patients with PsO, PsA, and AS reported that the risk of serious adverse events was very low in patients treated with secukinumab, advocating its long-term use in patients with chronic IMIDs (14). Similarly, safety findings were reproduced when the clinical trial data of ixekizumab were analysed (15). An Italian multicentre study conducted on secukinumab users reported a lower rate of drug discontinuation owing to adverse events (16). Nevertheless, although the efficacy and safety outcomes may differ in patients in real-world clinical settings, little information on the safety of IL-17 inhibitors exists compared to that of TNF-α inhibitors, which is mainly attributed to its recent approval, and the direct comparison of safety profiles following IL-17 and TNF-α suppression in a large population across treatment indications is poorly described in the literature. Finally, there is a lack of evidence demonstrating the safety of IL-17 inhibitors, particularly in Asian populations. Hence, the present study aimed to assess the safety of IL-17 and TNF-α inhibitors in patients with AS, PsA, and PsO using the South Korean Health Insurance Review and Assessment Service (HIRA) database.

Methods

Data source and study population

HIRA is a national organisation run by the South Korean government that reviews and evaluates healthcare costs and quality of care. Health care providers in Korea are obligated to participate in this program. Herein we reviewed information from the HIRA database, including patient demographics, prescriptions, treatments, and diagnoses (17). Study approval was obtained from the institutional review board of Yonsei

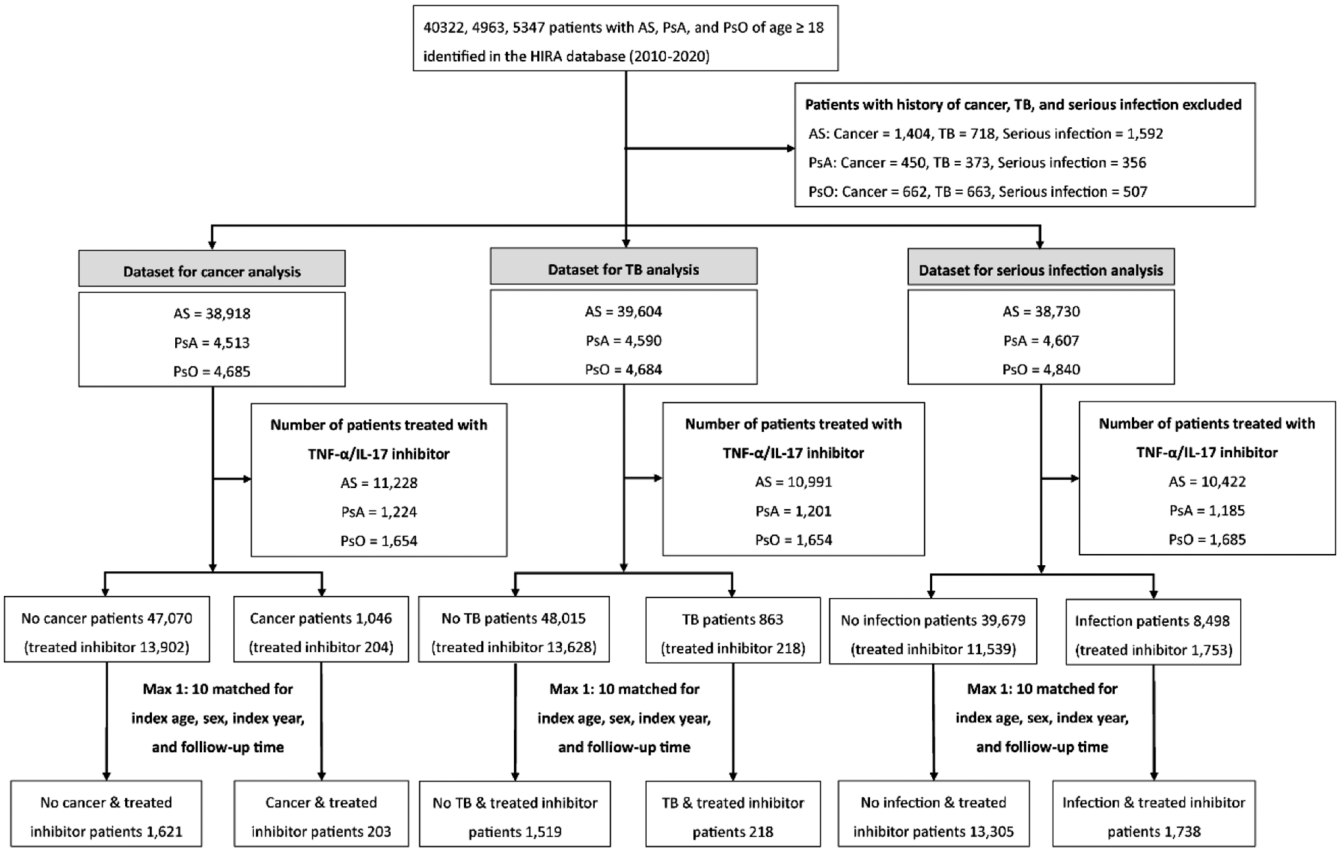

Fig. 1. Flowchart for patient selection and data analyses.
Patients that were selected from the HIRA database and the construction of three different datasets for the analyses of the outcomes of cancer, TB, and serious infection.
HIRA: Health Insurance Review and Assessment Service; TB: tuberculosis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; PsO: psoriasis; TNF: tumour necrosis factor; IL: interleukin.

University Health System (4-2021-0328). De-identification was performed and data usage was permitted by the National Health Information Data Request Review Committee of the HIRA.

Patients with AS, PsA, and PsO were identified by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes and the unique insurance codes for a rare disease diagnosis issued by the Korea National Health Insurance Service (NHIS), with a modification of previous definitions (Supplementary Table S1) (18, 19). Patients over the age of 18 years with AS, PsA, and PsO between 2008 and 2020 were screened. We applied a two-year washout period (excluding patients who were diagnosed with AS, PsA, and PsO that visited the hospital between 2008-2009) to identify patients newly diagnosed with AS, PsA, and PsO between 2010-2020. The first date of fulfilling the criteria for disease diagnosis was considered as the index date, and a total of 48,365 patients (AS, n=40,322; PsA, n=4,963; PsO, n=5,347) were enrolled in this study (Fig. 1).

Outcomes

The outcomes were the first diagnosis of any cancer, tuberculosis (TB), and serious infection after biologic agent use. The cancer diagnoses were reviewed and categorised using ICD-10 codes and specific malignant disease insurance codes issued by the Korean NHIS (V193) for accurate diagnoses (20, 21). The diagnoses were defined by ICD-10 codes and the prescription of at least two of the first-line drugs for TB (22). Serious infection was defined as an infection requiring hospitalisation according to a predefined list of ICD-10 codes, with a slight modification to a previous study (Suppl. Table S1) (23). In this study, three different datasets were generated to evaluate the incidence of outcomes. The datasets that were used for cancer and TB analyses were created by excluding patients who were diagnosed with cancer and TB prior to the index date. Those who had codes corresponding to serious infections within one month before the index date were excluded (Fig. 1).

Exposures and covariates

The main exposure was the initiation of biologics, including TNF-α inhibitors (etanercept, adalimumab, golimumab, and infliximab) or IL-17 inhibitors (secukinumab and ixekizumab), after the diagnosis of AS, PsA, and PsO. Although both agents are used for the treatment of AS, PsA, and PsO, IL-17 inhibitors are only approved as a second-line therapy (in those with insufficient efficacy or drug side effects after TNF-α inhibitor treatment) for patients with AS and PsA in South Korea. Medication information was acquired using Anatomical Therapeutic Chemical Classification codes. DMARDs,

Table I. Characteristics of patients with ankylosing spondylitis, psoriatic arthritis, and psoriasis at disease diagnosis.

	Cancer			TB			Serious infection		
	Ankylosing spondylitis (n=38,918)	Psoriatic arthritis (n=4,513)	Psoriasis (n=4,685)	Ankylosing spondylitis (n=39,604)	Psoriatic arthritis (n=4,590)	Psoriasis (n=4,684)	Ankylosing spondylitis (n=38,730)	Psoriatic arthritis (n=4,607)	Psoriasis (n=4,840)
Mean age	41.36±15.94	49.59±15.06	45.25±14.04	41.68±16.02	49.81±15.02	45.53±14.21	41.67±16.00	49.97±15.05	45.71±14.19
Age distribution, n (%)									
<20	1,558 (4.00)	33 (0.73)	57 (1.22)	1,559 (3.94)	33 (0.72)	57 (1.22)	1,512 (3.90)	33 (0.72)	56 (1.16)
20-34	13,708 (35.22)	742 (16.44)	1,072 (22.88)	13,676 (34.53)	737 (16.06)	1,058 (22.59)	13,382 (34.55)	728 (15.80)	1,077 (22.25)
35-49	12,245 (31.46)	1,519 (33.66)	1,802 (38.46)	12,399 (31.31)	1,520 (33.12)	1,782 (38.04)	12,181 (31.45)	1,521 (33.01)	1,830 (37.81)
50-64	7,643 (19.64)	1,460 (32.35)	1,333 (28.45)	8,001 (20.20)	1,513 (32.96)	1,327 (28.33)	7,778 (20.08)	1,522 (33.04)	1,402 (28.97)
≥65	3,764 (9.67)	759 (16.82)	421 (8.99)	3,969 (10.02)	787 (17.15)]	460 (9.82)	3,877 (10.01)	803 (17.43)	475 (9.81)
Sex, n (%)									
Male	27,917 (71.73)	2,491 (55.20)	3,206 (68.43)	28,250 (71.33)	2,498 (54.42)	3,183 (67.95)	27,627 (71.33)	2,512 (54.53)	3,300 (68.18)
Female	11,001 (28.27)	2,022 (44.80)	1,479 (31.57)	11,354 (28.67)	2,092 (45.58)	1,501 (32.05)	11,103 (28.67)	2,095 (45.47)	1,540 (31.82)
Insurance type, n (%)									
National health insurance	35,792 (91.97)	3,900 (86.42)	4,489 (95.82)	36,401 (91.91)	3,951 (86.08)	4,485 (95.75)	35,542 (91.77)	3,972 (86.22)	4,631 (95.68)
Medical aid	3,126 (8.03)	613 (13.58)	196 (4.18)	3,203 (8.09)	639 (13.92)	199 (4.25)	3,188 (8.23)	635 (13.78)	209 (4.32)
Mean CCI†	1.77±1.81	2.11±1.99	1.19±1.57	1.85±1.91	2.19±2.08	1.27±1.69	1.84±1.89	2.19±2.08	1.27±1.69
CCI n (%)†									
0	12,731 (32.71)	1,199 (26.57)	2,056 (43.88)	12,680 (32.02)	1,185 (25.82)	2,005 (42.81)	12,482 (32.23)	1,188 (25.79)	2,069 (42.75)
1	7,296 (18.75)	824 (18.26)	1,266 (27.02)	7,220 (18.23)	812 (17.69)	1,230 (26.26)	7,083 (18.29)	818 (17.76)	1,274 (26.32)
2	7,116 (18.28)	865 (19.17)	644 (13.75)	7,188 (18.15)	874 (19.04)	653 (13.94)	7,048 (18.20)	882 (19.14)	671 (13.86)
≥3	11,775 (30.26)	1,625 (36.01)	719 (15.35)	12,516 (31.60)	1,719 (37.45)	796 (16.99)	12,117 (31.29)	1,719 (37.31)	826 (17.07)

†Calculated within one year of disease diagnosis.
TB: tuberculosis; CCI: Charlson Comorbidity Index.

Table II. Clinical characteristics of IL-17 and TNF-α inhibitor initiators analysed for the incidence of cancer, tuberculosis, and serious infection.

	Cancer		TB		Serious infection	
	IL-17 inhibitor initiator (n=1,763)	TNF-alpha inhibitor initiator (n=12,343)	IL-17 inhibitor initiator (n=1,773)	TNF-alpha inhibitor initiator (n=12,073)	IL-17 inhibitor initiator (n=1,794)	TNF-alpha inhibitor initiator (n=11,498)
Mean age*	45.12 ± 13.32	39.75 ± 13.67	45.35 ± 13.38	39.80 ± 13.72	45.46 ± 13.39	39.83 ± 13.66
Age distribution, n (%)*						
<20	17 (0.96)	348 (2.82)	17 (0.96)	345 (2.86)	17 (0.95)	322 (2.80)
20-34	397 (22.52)	4,605 (37.31)	394 (22.22)	4,488 (37.17)	396 (22.07)	4,260 (37.05)
35-49	683 (38.74)	4,307 (34.89)	677 (38.18)	4,191 (34.71)	677 (37.74)	4,029 (35.04)
50-64	533 (30.23)	2,520 (20.42)	544 (30.68)	2,496 (20.67)	563 (31.38)	2,357 (20.50)
≥65	133 (7.54)	563 (4.56)	141 (7.95)	553 (4.58)	141 (7.86)	530 (4.61)
Sex, n (%)						
Male	1,222 (69.31)	9,096 (73.69)	1,221 (68.87)	8,815 (73.01)	1,236 (68.90)	8,456 (73.54)
Female	541 (30.69)	3,247 (26.31)	552 (31.13)	3,258 (26.99)	558 (31.10)	3,042 (26.46)
Insurance type, n (%)*						
National health insurance	1,701 (96.48)	11,750 (95.20)	1,708 (96.33)	11,517 (95.39)	1,727 (96.27)	10,974 (95.44)
Medical aid	62 (3.52)	593 (4.80)	65 (3.67)	556 (4.61)	67 (3.73)	524 (4.56)
Diagnosis, n (%)						
Ankylosing spondylitis	5 (0.28)	11,223 (90.93)	3 (0.17)	10,988 (91.01)	5 (0.28)	10,417 (90.60)
Psoriatic arthritis	389 (22.06)	835 (6.76)	397 (22.39)	804 (6.66)	391 (21.79)	794 (6.91)
Psoriasis	1,369 (77.65)	285 (2.31)	1,373 (77.44)	281 (2.33)	1,398 (77.93)	287 (2.50)
Mean CCI†	1.19 ± 1.46	2.12 ± 1.80	1.27 ± 1.55	2.15 ± 1.84	1.25 ± 1.54	2.11 ± 1.81
CCI, n (%)†						
0	746 (42.31)	2,985 (24.18)	728 (41.06)	2,917 (24.16)	745 (41.53)	2,834 (24.65)
1	469 (26.60)	1,959 (15.87)	460 (25.94)	1,900 (15.74)	464 (25.86)	1,809 (15.73)
2	274 (15.54)	2,478 (20.08)	279 (15.74)	2,406 (19.93)	283 (15.77)	2,321 (20.19)
≥3	274 (15.54)	4,921 (39.87)	306 (17.26)	4,850 (40.17)	302 (16.83)	4,534 (39.43)
DMARDs prescribed after biologics, n (%)¶						
Methotrexate	111 (6.30)	3,032 (24.56)	108 (6.09)	2,947 (24.41)	100 (5.57)	2,729 (23.73)
Sulfasalazine	25 (1.42)	4,159 (33.70)	24 (1.35)	4,031 (33.39)	25 (1.39)	3,669 (31.91)
Hydroxychloroquine	5 (0.28)	260 (2.11)	5 (0.28)	250 (2.07)	4 (0.22)	200 (1.74)
Cyclosporine	106 (6.01)	367 (2.97)	109 (6.15)	364 (3.01)	108 (6.02)	3.24 (2.82)
DMARDs within the previous 6 months, n (%)*						
Methotrexate	684 (38.80)	3,267 (26.47)	692 (39.03)	3,218 (26.65)	702 (39.13)	3,012 (26.20)
Sulfasalazine	47 (2.67)	8,675 (70.28)	44 (2.48)	8,449 (69.98)	45 (2.51)	7,997 (69.55)
Hydroxychloroquine	9 (0.51)	527 (4.27)	9 (0.51)	519 (4.30)	8 (0.45)	502 (4.37)
Cyclosporine	779 (44.19)	438 (3.55)	786 (44.33)	435 (3.60)	797 (44.43)	420 (3.65)

*Data on the period of biologics initiation are shown.
†CCI score was calculated within one year of the initial biological treatment.
¶Medications prescribed after biological use are presented.
TB: tuberculosis; IL: interleukin; TNF: tumour necrosis factor; CCI: Charlson Comorbidity Index; DMARD: disease-modifying anti-rheumatic drugs.

Table III. Frequency of site-specific infections in the total and matched population.

Site of infection	Total population				Matched (nested cased-control) population			
Disease subgroup	Total (n=8498)	Ankylosing spondylitis (n=7,171)	Psoriatic arthritis (n=952)	Psoriasis (n=375)	Total (n=1,738)	Ankylosing spondylitis (n=1,478)	Psoriatic arthritis (n=145)	Psoriasis (n=115)
Respiratory tract	3,477 (40.92)	2,959 (41.26)	393 (41.28)	125 (33.33)	669 (38.49)	575 (38.90)	56 (38.62)	38 (33.04)
Central nervous system	86 (1.01)	80 (1.12)	4 (0.42)	2 (0.53)	22 (1.27)	22 (1.49)	0 (0.00)	0 (0.00)
Genitourinary	773 (9.10)	633 (8.83)	100 (10.50)	40 (10.67)	160 (9.21)	131 (8.86)	15 (10.34)	14 (12.17)
Skin/soft tissue	991 (11.66)	814 (11.35)	116 (12.18)	61 (16.27)	264 (15.19)	216 (14.61)	25 (17.24)	23 (20.00)
Bone/joint	240 (2.82)	212 (2.96)	26 (2.73)	2 (0.53)	36 (2.07)	31 (2.10)	5 (3.45)	0 (0.00)
Sepsis	290 (3.41)	240 (3.35)	37 (3.89)	13 (3.47)	45 (2.59)	39 (2.64)	3 (2.07)	3 (2.61)
Gastrointestinal/intraabdominal	2,648 (31.16)	2,239 (31.22)	277 (29.10)	132 (35.20)	543 (31.24)	465 (31.46)	41 (28.28)	37 (32.17)

The numbers indicate n (%).

including methotrexate, sulfasalazine, hydroxychloroquine, and cyclosporine, within the previous six months at the time of starting the first biologic agent and during follow-up were also evaluated. Age, sex, and insurance type were collected as baseline demographic data. Comorbidities were assessed using the Charlson Comorbidity Index (CCI) based on the ICD-10 codes of the claim records (24), which was calculated within one year.

Case and control selection

For primary analysis, a nested case-control study was performed to investigate the association between biologic (categorised as IL-17 and TNF-α inhibitors) use and outcomes. Case and control patients who were prescribed any biological agent were matched with exact matches on sex, index year (the first date of disease diagnosis of AS, PsA, or PsO), follow-up time, and closest matches with index age (within one year, in either way) at a maximum of 1:10 ratio using incidence density sampling (Fig. 1 and Suppl. Fig. S1) (25). Incidence sampling was applied separately for each outcome including cancer, TB, and serious infections.

Statistical analyses

Continuous variables were presented as means with standard deviations, and categorical variables were expressed as numbers with percentages. Separate conditional logistic regression analyses were performed to evaluate the association between biological agent use and the risk of cancer, TB, and serious infection. In addition to the matching variables (index age, sex, index year, and follow-up time), for the nested case-control study design, insurance type, CCI score, and DMARDs (methotrexate, sulfasalazine, hydroxychloroquine, and cyclosporine) usage after the use of biologics were adjusted. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the risks of cancer, TB, and serious infection. All statistical analyses were performed using R (v. 3.5.1; http://www.r-project.org; The R Foundation for Statistical Computing, Vienna, Austria) and SAS Enterprise Guide (v. 7.1; SAS Institute). *p*-values <0.05 were considered significant.

Results

Baseline characteristics of patients at disease diagnosis and initiation of biologics

Among the 48,365 patients with AS, PsA, and PsO identified in the database, three different datasets for the analyses of outcomes of cancer, TB, and serious infections were utilised after excluding those with a corresponding medical history. Table I presents the characteristics of the patients included in the datasets for disease diagnosis. The mean age of patients with PsA was the highest in the datasets, and patients with AS were the youngest. Men were more frequently affected by AS, PsA, and PsO across the three datasets; over 70% of patients with AS were men. The mean CCI was highest in those with PsA, followed by AS and PsO.

During follow-up, 1046, 863, and 8498 cases of cancer, TB, and serious infections occurred, respectively. The incidence rates of cancer, TB, and serious infection in the total population were 465.39 (95% CI 437.61–494.47), 382.63 (357.53–409.04), and 4307.87 (4216.76–4400.46) per 100,000 PY, respectively. The mean follow-up durations of the patients included in the cancer, TB, and serious infection dataset were 4.67 years, 4.61 years, and 4.09 years, respectively. In patients who were diagnosed with cancer, TB, and serious infection, the average follow-up duration was 3.28 years, 1.67, and 2.56 years, respectively.

Patient characteristics at initial biologics selection

A total of 14106, 13846, and 13292 patients were treated with IL-17 and TNF-α inhibitors after diagnosis with cancer, TB, and serious infection, respectively. Table II shows the initial clinical characteristics of patients treated with IL-17 and TNF-α inhibitors. In patients who were treated with both IL-17 and TNF-α inhibitors during follow-up, the baseline characteristics at the period of first biologic commencement were investigated. Patients in the IL-17 inhibition group were older than those in the TNF-α inhibition group. The majority (>90%) of patients who were initially treated with TNF-α inhibitors had AS, whereas psoriasis accounted for approximately 77% of the first IL-17 inhibitors. Meanwhile, the mean CCI was higher in those treated with TNF-α inhibitors than in those treated with IL-17 inhibitors. The medications that were most frequently prescribed after the biologics were methotrexate and cyclosporine in the IL-17 inhibitor group and sulfasalazine in the TNF-α inhibitor group. The incidence rate of cancer, TB, and

Table IV. Incidence of site-specific cancers in the total and matched population.

Disease subgroup	Total population				Matched (nested cased-control) population			
	Total	Ankylosing spondylitis	Psoriatic arthritis	Psoriasis	Total	Ankylosing spondylitis	Psoriatic arthritis	Psoriasis
Type of cancer	1046	848	156	42	203	165	27	11
Lip, oral cavity, and pharynx (C00-C14)	13 (1.24)	13 (1.53)	0 (0.00)	0 (0.00)	1 (0.49)	1 (0.61)	0 (0.00)	0 (0.00)
Oesophagus (C15)	9 (0.86)	8 (0.94)	0 (0.00)	1 (2.38)	3 (1.48)	2 (1.21)	0 (0.00)	1 (9.09)
Stomach (C16)	103 (9.85)	78 (9.20)	19 (12.18)	6 (14.29)	19 (9.36)	13 (7.88)	3 (11.11)	3 (27.27)
Colon and rectum (C18-C20)	102 (9.75)	82 (9.67)	17 (10.90)	3 (7.14)	18 (8.87)	15 (9.09)	3 (11.11)	0 (0.00)
Liver (C22)	58 (5.54)	46 (5.42)	12 (7.69)	0 (0.00)	8 (3.94)	6 (3.64)	2 (7.41)	0 (0.00)
Gallbladder etc. (C23-C24)	26 (2.49)	18 (2.12)	8 (5.13)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Pancreas (C25)	34 (3.25)	30 (3.54)	3 (1.92)	1 (2.38)	8 (3.94)	8 (4.85)	0 (0.00)	0 (0.00)
Larynx (C32)	5 (0.48)	4 (0.47)	1 (0.64)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Lung (C33-C34)	112 (10.71)	99 (11.67)	11 (7.05)	2 (4.76)	25 (12.32)	24 (14.55)	1 (3.70)	0 (0.00)
Breast (C50)	81 (7.74)	68 (8.02)	8 (5.13)	5 (11.90)	19 (9.36)	16 (9.70)	1 (3.70)	2 (18.18)
Cervix uteri (C53)	5 (0.48)	5 (0.59)	0 (0.00)	0 (0.00)	1 (0.49)	1 (0.61)	0 (0.00)	0 (0.00)
Corpus uteri (C54)	9 (0.86)	6 (0.71)	3 (1.92)	0 (0.00)	4 (1.97)	2 (1.21)	2 (7.41)	0 (0.00)
Ovary (C56)	8 (0.76)	7 (0.83)	1 (0.64)	0 (0.00)	4 (1.97)	3 (1.82)	1 (3.70)	0 (0.00)
Prostate (C61)	69 (6.60)	57 (6.72)	9 (5.77)	3 (7.14)	10 (4.93)	7 (4.24)	2 (7.41)	1 (9.09)
Testis (C62)	2 (0.19)	2 (0.24)	0 (0.00)	0 (0.00)	1 (0.49)	1 (0.61)	0 (0.00)	0 (0.00)
Kidney (C64)	34 (3.25)	31 (3.66)	2 (1.28)	1 (2.38)	5 (2.46)	5 (3.03)	0 (0.00)	0 (0.00)
Bladder (C67)	25 (2.39)	23 (2.71)	2 (1.28)	0 (0.00)	6 (2.96)	5 (3.03)	1 (3.70)	0 (0.00)
Brain and central nervous system (C70-C72)	13 (1.24)	12 (1.42)	1 (0.64)	0 (0.00)	1 (0.49)	1 (0.61)	0 (0.00)	0 (0.00)
Thyroid (C73)	165 (15.77)	133 (15.68)	25 (16.03)	7 (16.67)	40 (19.70)	32 (19.39)	7 (25.93)	1 (9.09)
Hodgkin Lymphoma (C81)	5 (0.48)	3 (0.35)	1 (0.64)	1 (2.38)	3 (1.48)	2 (1.21)	1 (3.70)	0 (0.00)
Non-Hodgkin Lymphoma (C82-C86, C96)	42 (4.02)	32 (3.77)	6 (3.85)	4 (9.52)	11 (5.42)	7 (4.24)	2 (7.41)	2 (18.18)
Multiple myeloma (C90)	19 (1.82)	16 (1.89)	2 (1.28)	1 (2.38)	2 (0.99)	2 (1.21)	0 (0.00)	0 (0.00)
Leukemia (C91-C95)	29 (2.77)	24 (2.83)	4 (2.56)	1 (2.38)	7 (3.45)	6 (3.64)	0 (0.00)	1 (9.09)
Other and ill-defined Sites (remainder of C00-C96)	154 (14.72)	114 (13.44)	31 (19.87)	9 (21.43)	22 (10.84)	18 (10.91)	4 (14.81)	0 (0.00)

The numbers indicate n (%).

serious infection in biologics users was 284.44 (95% CI 246.74–326.26), 317.40 (276.66–362.45), and 2871.60 (2738.73–3009.25) per 100,000 PY, respectively.

Site-specific infections and cancers

In the total population, infection in the respiratory tract was the most common in the AS and PsA groups (41.26% and 41.28%, respectively), while gastrointestinal/intra-abdominal infection was most frequently observed in the PsO group (35.20%). In the matched population, respiratory tract infection was identified as the most common infection in AS, PsA, and PsO (38.90, 38.62, and 33.04%, respectively) (Table III).

For site-specific cancers, the incidence of thyroid cancer was the highest in the PsO group, followed by the PsA and AS groups (16.67%, 16.03%, and 15.68%, respectively), while the incidence of thyroid cancer was the highest in the AS and PsA groups (19.39% and 25.93% in the matched population), and stomach cancer was most frequent in patients with PsO (27.27%). Cancer occurring in the lung accounted for the second largest proportion of cancers, followed by that in the thyroid, both in the total and matched populations (Table IV).

Predictive factors of cancer, TB, and serious infection

Conditional logistic regression analysis showed that only the use of cyclosporine prescribed after the use of biologics was significantly associated with cancer (OR 2.286, 95% CI 1.155–4.525, p=0.0176) among the variables included. In contrast, an increase in the CCI score (OR 1.085, 95% CI 1.003–1.173, p=0.0406) and the use of IL-17 inhibitor-only (OR 0.126, 95% CI 0.016–0.961, p=0.0457) predicted the incidence of TB. Finally, for serious infections, higher CCI scores (OR 1.117, 95% CI 1.085–1.149, p<0.0001), insurance type of medical aid (OR 1.667, 95% CI 1.371–2.028, p<0.0001), and the prescription of cyclosporine after biologic initiation (OR 1.445, 95% CI 1.093–1.910, p=0.0098) were related to an increased risk of serious infection (Table V).

Discussion

In this study, we assessed the real-world safety of IL-17 and TNF-α inhibitors in patients with AS, PsA, and PsO following IL-17 and TNF-α inhibition. By searching the nationwide claims database between 2008-2020 and applying a wash-out period of 2008-2009, a total of 40332, 4963, and 5347 AS, PsA, and PsO patients were identified, respectively, and approximately 30% received IL-17 and/or TNF-α inhibitors. Considering the differences in the diagnoses, indications (IL-17 inhibition is still permitted as a second-line treatment in patients with AS and PsA in South Korea), and the timing of biologics initiation, a matching of up to 1:10 according to index age, sex, index year, and follow-up times was performed in cases that developed and those that did not develop cancer, TB, and serious infection among those receiving IL-17 and/or TNF-α inhibitor treatment. Our results demonstrated that the risk of cancer and serious infection was comparable in those who were treated with only TNF-α inhibitors, IL-17 inhibitors, and both TNF-α and IL-17 inhibitors.

Table V. Conditional logistic regression analysis for the outcomes of cancer, tuberculosis, and serious infection after biologics initiation.

	Cancer		TB		Serious infection	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
CCI score	1.054 (0.971-1.144)	0.2095	1.085 (1.003-1.173)	0.0406	1.117 (1.085-1.149)	<.0001
IL-17/TNF-α inhibitor usage						
TNF-α inhibitor use only	1 (ref)		1 (ref)		1 (ref)	
IL-17 inhibitor use only	1.191 (0.516-2.750)	0.6823	0.126 (0.016-0.961)	0.0457	1.165 (0.892-1.521)	0.2627
Both IL-17 and TNF-α inhibitor use	1.328 (0.480-3.676)	0.5844	0.471 (0.062-3.571)	0.4664	1.432 (0.967-2.121)	0.0733
Insurance type						
National health insurance	1 (ref)		1 (ref)		1 (ref)	
Medical aid	1.338 (0.791-2.263)	0.2780	0.752 (0.378-1.497)	0.4168	1.667 (1.371-2.028)	<.0001
DMARDs prescribed after biologics						
Methotrexate	1.026 (0.729-1.445)	0.8812	0.958 (0.683-1.344)	0.8035	1.012 (0.898-1.141)	0.8403
Sulfasalazine	0.938 (0.672-1.308)	0.7041	0.914 (0.660-1.265)	0.5879	1.053 (0.941-1.179)	0.3670
Hydroxychloroquine	0.565 (0.193-1.655)	0.2980	1.101 (0.373-3.250)	0.8614	1.142 (0.791-1.649)	0.4783
Cyclosporine	2.286 (1.155-4.525)	0.0176	0.501 (0.118-2.132)	0.3494	1.445 (1.093-1.910)	0.0098

TB: tuberculosis; OR: odds ratio; CI: confidence interval; CCI: Charlson comorbidity index; IL: interleukin; TNF: tumour necrosis factor; DMARDs: disease-modifying antirheumatic drugs.

Of interest, conditional logistic regression analysis in the matched population indicated that an increased CCI score is associated with the risk of TB, and patients treated with IL-17 inhibitors only had a significantly lower risk of developing TB compared to those who had undergone only TNF-α inhibition. Moreover, an increased risk of cancer was observed in those prescribed with cyclosporine, confirming that cyclosporine is associated with the incidence of cancer (26), whereas infection was more frequent in those with higher CCI scores, medical-aided, and cyclosporine treatment. Our study is unique that we present the largest, nationwide real-world evidence directly comparing the safety of IL-17 and TNF-α inhibitors, which has not been reported in the current literature.

The mean age of patients with AS, PsA, and PsO at disease diagnosis was similar to that reported previously (14). We observed an incidence of cancer and serious infection of 465.39/100,000 PY and 4307.87/100,000 PY, respectively, in the overall population, which does not appear to be higher than that in the existing literature (23, 27). Intriguingly, the incidence rates of cancer and serious infection were numerically lower in biologics users than in the entire population, illustrating that IL-17 and TNF-α inhibitors themselves did not significantly affect the occurrence of these events. Notably, among the types of infections, the incidence of respiratory tract infection was the most frequent in both the total and matched populations, in line with a previous report (23). However, among site-specific cancers, thyroid cancer was most common, followed by lung cancer, which was identical in the total and nested case-control population. Similarly, according to the cancer statistics of South Korea 2021, lung cancer was the most common cancer, and thyroid cancer was the second most frequently diagnosed cancer (28). Upon evaluating the predictive factors associated with cancer and serious infection in the nested case-control population, we found that the risk was not higher in those who were prescribed TNF-α inhibitors, IL-17 inhibitors, or both TNF-α and IL-17 inhibitors, demonstrating a comparable safety profile. Meanwhile, cyclosporine use was associated with a greater risk of developing cancer and infections. Furthermore, those who were medical-aided and had a higher CCI prior to the use of TNF-α and IL-17 inhibitors were determinants of serious infections, suggesting the importance of judicious monitoring in those who were socially deprived, had coexisting multiple comorbidities, and received potent immunosuppressive therapies.

TB is an infectious disease caused by *Mycobacterium tuberculosis* and has a substantial influence on the public community, accounted for by its markedly high transmissibility (29). While preventive and therapeutic strategies are being administered to decrease this potentially life-threatening disease, people newly diagnosed with TB still exceeds 5 million/year (30). Notably, the use of TNF-α inhibitors increases susceptibility to TB, and studies have reported approximately 1.6–25.1 times to the heightened TB incidence following TNF-α inhibition (31). This could be explained by the effect of its blockade in the T-helper 1 response, especially interferon-γ-mediated, which plays a critical role in host defence against TB and breakdown of TB granuloma which is thought to act as a source of dissemination of TB (32). Furthermore, TNF-α blockade impairs the apoptosis of macrophages infected with TB and hampers immune cell migration/accumulation at the site of infection, thereby decreasing the elimination of TB in the human body and increasing TB risk (31, 33). Additionally, as the presence of IMIDs is associated with a higher risk of TB, concerns regarding TB are raised in patients with IMIDs undergoing TNF-α inhibition (34). Likewise, our data also demonstrated that the IR of TB in the total population was 382.63/100,000 PY, which is significantly higher than the estimates for the general population of South Korea (35). However, we did not observe an increase of TB following the use of biologics, which may be attributed to the diminished TB risk

when treatment for latent TB infection was implemented (36, 37).

Similar to TNF-α, IL-17 is recognised as a pro-inflammatory cytokine that contributes to the development of an abnormal immune response, and targeting TNF-α and IL-17 has been found to be an attractive approach in the management of IMIDs, such as, PsA, PsO, rheumatoid arthritis, and inflammatory bowel disease (38). However, because both cytokines are also important players in maintaining normal host immunity (39, 40), safety issues related to cancer, TB, and serious infections have garnered special interest in patients undergoing these treatments. However, according to our data, there was no difference in the occurrence of cancer and serious infections, indicating that the safety of both biologics appears to be comparable. Notably, compared to patients treated with only TNF-α inhibitors, the risk of TB was significantly lower in those treated with only IL-17 inhibitors. The relatively lower incidence of TB in those receiving IL-17 inhibitor compared to TNF-α is unknown; however, it could be partly explained by the higher contribution of TNF-α than IL-17 in the host immunity against TB, as described above. Of note, a recent publication by Elewski *et al*. identified that there were no cases of new-onset TB in secukinumab users (41), supporting that the risk of TB may be lower in patients who are subject to IL-17 inhibition compared to TNF-α inhibition. Therefore, selection of IL-17 inhibitors may be a feasible treatment option for TB, particularly in patients at a higher risk of TB. More-over, those with a previous history of TB and individuals residing in a TB-endemic area might be prioritised for IL-17 inhibitor treatment, although additional studies are warranted to verify our findings.

While the strength of our study is to compare the safety of TNF-α and IL-17 inhibitors in a large Asian nationwide cohort, there are also several limitations. First, this study was conducted using the South Korean National Claims Database, and data used for analyses were retrospectively collected. Second, because IL-17 inhibitors are still not approved as a first-line treatment for AS and PsA, this could have affected the results of our study, although a matching was performed to adjust this limitation. Third, disease-specific factors, such as severity and extent of disease, presence of extra-articular manifestations, and additional information on lifestyle measures and laboratory data, could not be investigated according to the HIRA database. However, biological agents are only approved by the South Korean government for those with moderate to high disease activity, even after continuous treatment. Fourth, because of the small number of patients included in the nested case-control population, the influence of specific TNF-α inhibitors (either non-soluble monoclonal antibodies or soluble receptors) on the outcomes of interest could not be separately analysed and robust subgroup analyses according to patient diagnosis were not possible. Fifth, whether the two different posologies of secukinumab have a different influence in the safety profiles could not be addressed by the results of this study.

In conclusion, the analyses of this nationwide cohort of IL-17 and TNF-α inhibitor users revealed that both treatments conferred a comparable risk of cancer and serious infections, while IL-17 inhibitors may be advantageous for the incidence of TB. The lower risk of TB in IL-17 inhibitor-only users suggests that selection of IL-17 inhibitors may be a feasible treatment option for TB, which should be verified in future studies.

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