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Risk of hematologic malignancies in psoriasis and rheumatoid arthritis patients using long term TNF-α inhibitors: a retrospective nationwide study

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This retrospective cohort study included all user of tumor necrosis factor-α inhibitors (TNFi), including etanercept, infliximab, adalimumab, and golimumab, among Korean patients with psoriasis and rheumatoid arthritis (N of user = 7,645) and the non-user who was diagnosed with same diseases, never used TNFi, and was served as the reference. Cumulative usage of TNFi was calculated between the newly diagnosed date and index date (2-year from the diagnosed date). Adjusted hazard ratio (aHR [95% confidence intervals (CIs)]) for colorectal, liver, lung, kidney, breast, and thyroid cancer were not significantly increased or decreased: 0.92 [0.61–1.38], 0.90 [0.53–1.53], 1.00 [0.73–1.37], 1.20 [0.62–2.34], 0.91 [0.62–1.34], and 0.91 [0.66–1.26], respectively. The increased risk of lymphoma in the infliximab user (2.49 [1.33–4.66]; $p < 0.01$) was statistically significant. Similarly, the risk of leukemia increased significantly in the etanercept (3.87 [1.71–8.76]; $p < 0.01$) and adalimumab (3.36 [1.65, 6.84]; $p < 0.001$) user. Accumulated prescriptions of TNFi for two years did not increase the incidence of cancer, except lymphoma and leukemia. Since the use of TNFi increases the risk of leukemia and lymphoma, a decision for frequent prescription of TNF-α inhibitors should be more careful.

Keywords Cohort study, TNF-alpha, Cancer, Leukemia, Lymphoma

The long-term use of immunosuppressive drugs (immunosuppressant) raises many concerns, as they might be potentially harmful and then cause unforeseen diseases such as the initiation and development of cancer[1,2]. Biologics, which consist of mono-clonal antibody immunosuppressants such as tumor necrosis factor-alpha (TNF-α) inhibitors, are not exempt from these concerns as they usually disrupt the immune system[3]. In fact, since several biologics, including the most commonly used TNF-α inhibitors, were approved and introduced to the market in the mid-2000s and early 2010s, reports of their adverse and side effects have been continuously emerging[4,5]. Acute complications such as thrombosis and cardiovascular disease[6,7] and long-term harmful events such as dementia and liver injury[8,9] are reported.

TNF-α, as a major mediator of inflammation, can easily disrupt the balance of immunity when its production and secretion are disrupted. Since TNF-α contributes to the destruction and recovery of tissue in chronic inflammatory conditions, inhibition and hypo-activation of TNF-α can cause serious diseases such as leukemia[10,11]. Recently, anti-TNF-α (etanercept, infliximab, adalimumab, and golimumab) has been progressively used due to their high efficacy for autoimmune diseases. However, there is a lack of information and evidence although it is necessary to secure safety. From this perspective, one of the unexpected adverse outcomes is the potential association between long-term exposure to TNF-α inhibitors and cancer risk, which remains questionable. Previous studies suggested that TNF-α inhibitors could act as the risk factor for the increased risk

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of cancer, mainly cutaneous malignancy[12]. However, there are also several contradictory studies showing no association[13–16]. Thus, whether TNF-α inhibitors could cause cancer is still a controversial issue.

Herein, this large and nationwide cohort study (N of user = 7,645) aimed to evaluate the risk of cancer according to a cumulative usage of anti-TNF-α in patients with psoriasis and rheumatoid arthritis (RA), who are known to have a similar risk of cancer compared to the general population, except to skin cancer[17,18]. All incidence cases of cancer (all and site-specific) were observed in those who received TNF-α inhibitors.

Results

Characteristics of the study population

A total of 7,645 Users were composed of 1,213 (15.9%) and 6,933 (90.7%) patients with either psoriasis and RA, respectively (Table 1). There were 504 overlapping patients with comorbidities of both psoriasis and RA. As antiTNF-α was prescribed in the order of the Adalimumab (N = 3,453), Etanercept (N = 2,078), Infliximab (N = 1,687), and Golimumab (N = 1,113), the average cumulative usage of anti-TNF-α in the Users was 20.2 times during two years. Single users, who never use other agents at all, were 1,701 (81.9% of 2,078), 1,364 (80.9% of 1,687), 2,910 (84.3% of 3,453), and 906 (81.4% of 1,113) in users of etanercept, infliximab, adalimumab, and golimumab, respectively. The average age (± standard deviation; SD) of the User (45.47 ± 14.76) was approximately 10.8 years younger than that of the Non-user (56.25 ± 15.52). In addition, the sex ratio (men per women) was 1.39 in the User, which differed in Non-users with 0.61; the number of men in the None-user and User groups was 575,765 and 4,452, respectively, while that of women was 944,539 and 3,193. As the analysis

	Non-user	User of TNF-α
Study population, N	1,520,304	7,645
Patients with psoriasis, N (%)	346,133 (22.8)	1,213 (15.9)
Patients with RA, N (%)	1,194,277 (78.6)	6,933 (90.7)
Usage[a, b] [times], mean (range)		20.2 (1-208)
Type of anti-TNFα [Used], N (%)		
Etanercept	-	2,078 (27.2)
Infliximab	-	1,687 (22.1)
Adalimumab	-	3,453 (45.2)
Golimumab	-	1,113 (14.6)
Age [years], mean ± SD	56.25 (15.52)	45.47 (14.76)
Age [years], N (%)		
20–39	234,741 (15.4)	2,887 (37.8)
40–59	643,320 (42.3)	3,324 (43.5)
60–79	547,511 (36.0)	1,366 (17.9)
≥ 80	94,732 (6.2)	68 (0.9)
Sex, N (%)		
Men	575,765 (37.9)	4,452 (58.2)
Women	944,539 (62.1)	3,193 (41.8)
Income level, quartile, N (%)		
L1 (Lowest)	498,434 (32.8)	2,441 (31.9)
L2	357,905 (23.5)	1,920 (25.1)
L3	288,698 (19.0)	1,542 (20.2)
L4 (Highest)	375,267 (24.7)	1,742 (22.8)
Charlson comorbidity index, N (%)		
0–2	1,124,924 (74.0)	6,001 (78.5)
3–5	317,807 (20.9)	1,392 (18.2)
≥ 6	77,573 (5.1)	252 (3.3)
Other drug prescriptions [Used], N (%)		
Azathioprin	8,318 (0.6)	358 (4.7)
Cyclophosphamide	1,045 (0.1)	14 (0.2)
Cyclosporin	37,503 (2.5)	366 (4.8)
Methotrexate	87,607 (5.8)	4,489 (58.7)

Table 1. Characteristics of the study population. [a]History of antibody-based inhibitors of TNF-α within 2 years after the initial diagnosis of psoriasis or RA: etanercept, infliximab, adalimumab, and golimumab. [b]Single users, who never use other agents at all, were 1,701 (81.9% of total), 1,364 (80.9%), 2,910 (84.3%), and 906 (81.4%) in users of etanercept, infliximab, adalimumab, and golimumab, respectively. N, number of patients; SD, standard deviation; RA, rheumatoid arthritis; TNF-α, tumor necrosis factor-alpha.

of the prescribed frequency of other immunosuppressive drugs, the percentage of methotrexate (58.7%) and azathioprine (4.7%) was particularly different from that of Non-users.

Association of the use of anti-TNF-α with the risk of cancer

Any type of anti-TNF-α did not show statistically increased aHR. Moreover, aHRs (95% CIs) were 0.91 (0.65–1.27) or 0.92 (0.81–1.04) in patients with psoriasis or RA, respectively (Table 2). In **Supplementary information 1**, similarly, no statistical difference between the User and Non-user was identified in all-typed cancer among all patients with either psoriasis or RA. In Model 3, adjusted hazard ratios (aHR) and 95% confidence intervals (95% CIs), of the User was 0.92 (0.82–1.04). As the risk of site-specific cancer, among all patients with either psoriasis or RA, aHRs (95% CIs) for colorectal, liver, lung, kidney, breast, and thyroid cancer were not significantly increased or decreased: 0.92 (0.61–1.38), 0.90 (0.53–1.53), 1.00 (0.73–1.37), 1.20 (0.62–2.34), 0.91 (0.62–1.34), and 0.91 (0.66–1.26), respectively (Table 3). However, remarkable increased risks were identified in lymphoma and leukemia. The risks of lymphoma and leukemia in the overall user were 1.50 and 2.08 times higher than that in the Non-user. Especially, the risk of lymphoma in the User of Infliximab (aHR = 2.49; $p < 0.01$, adjusted-$p < 0.01$) was statistically significant, while that of leukemia in the User of Etanercept (aHR = 3.87; $p < 0.01$, adjusted-$p < 0.01$) and Adalimumab (aHR = 3.36; $p < 0.001$, adjusted-$p < 0.01$) increased significantly. The risk of lymphoma and leukemia among individual user with psoriasis or RA, separately, was higher than that in the None-user group; aHRs for leukemia in users with psoriasis or RA were 2.41 (0.57–10.2) and 2.02 (1.06–3.83), respectively (**Supplementary information 2**).

In the sensitive test after 1:5 Propensity score (PS) match, although the number of lymphoma and leukemia events in both matched Non-user and User was small (range ≤ 30), the risk of lymphoma significantly increased: aHR (95% CIs) was 2.72 (1.13–6.56) in the User of Infliximab (**Supplementary information 3**). After some potential outliers (< 10 or ≥ 90%) were excluded, the sensitive analysis showed consistently increased aHRs (95% CIs): 1.51 (0.98–2.35) for lymphoma and 1.43 (0.64–3.24) for leukemia in the overall User (**Supplementary information 4**). The risk was increased by 4.01-fold ($p < 0.01$) when aHR for leukemia was evaluated in the User of Etanercept. With the longer prescription period, 3 years of the accumulated usage, the increased risk for leukemia (aHR = 2.02 in the overall User; $p < 0.05$) was identified (**Supplementary information 5**). Furthermore, as some of the User, who received antiTNFα prior to the diagnosis date, were excluded, the results of the sensitive analysis were similar: the increased risk for leukemia in the User of Etanercept (aHR = 4.36) and Adalimumab (aHR = 2.95) (**Supplementary information 6**).

Discussion

In the nationwide retrospective cohort study of more than 1.5 million psoriasis and RA patients, including 7,645 users of TNF-α inhibitors, a cumulative prescription of TNF-α inhibitors was not associated with the incidence of cancer, except for hematologic malignancy. On the other hand, our observation identified that the long-term use of TNF-α inhibitors was associated with the increased risk for lymphoma in the User of Infliximab and leukemia in the User of Etanercept and Adalimumab.

Although the direct comparability between studies is limited due to different study designs, populations, and exposures, several studies on the use of anti-TNF-α drugs have been conducted[19,20]. Compared to the only synthetic antirheumatic drugs user, aHR with 95% CIs for the invasive solid or hematologic malignant neoplasm, excluding non-melanoma skin cancer, in the patients with RA and received antiTNF-α therapy was 0.89 (0.76–1.04). Additionally, the risk in the matched general population was approximately 1.00[15]. In another cohort of RA patients, however, the risk of lymphoma in the inhibitors of TNF-α User was similar to that in the non-user: (aHR = 1.00; 95% CIs 0.56–1.80), which contrasts with our findings[21]. To evaluate the unproven

	Non-user	User of anti-TNF-α				
		Overall	Etanercept	Infliximab	Adalimumab	Golimumab
	Patients with psoriasis					
Study population, N	346,133	1,213	264	279	608	172
Usage [times], mean (range)		20.3 (1-192)	35.9 (1-192)	9.1 (1–17)	19.3 (1-106)	12.1 (1–36)
All-type of cancer						
Events, N (%)	17,717 (5.1)	35 (2.9)	7 (2.6)	7 (2.5)	18 (3.0)	6 (3.5)
aHR (95% CIs)	1.00 (Reference)	0.91 (0.65, 1.27)	0.70 (0.33, 1.47)	0.83 (0.40, 1.75)	0.94 (0.59, 1.50)	1.19 (0.53, 2.64)
	Patients with rheumatoid arthritis					
Study population, N	1,194,277	6,933	1,931	1,487	3,097	1,047
Usage [times], mean (range)		20.1 (1-208)	33.0 (1-208)	8.0 (1–30)	17.0 (1-108)	10.3 (1–27)
All-type of cancer						
Events, N (%)	66,351 (5.6)	264 (3.8)	81 (4.2)	55 (3.7)	123 (4.0)	31 (3.0)
aHR (95% CIs)	1.00 (Reference)	0.92 (0.81, 1.04)	0.89 (0.72, 1.11)	0.97 (0.67, 1.13)	0.96 (0.80, 1.14)	0.93 (0.65, 1.32)

Table 2. Association of anti-TNF-α use with the risk of cancer. Hazard ratios were calculated by Cox proportional hazards regression analysis adjusted for the following covariates: age, sex, income level, Charlson comorbidity index, and other drug prescriptions. N, number of patients; TNF-α, tumor necrosis factor-alpha; aHR, adjusted hazard ratio; CIs, confidence intervals.

	Patients with psoriasis or rheumatoid arthritis					
		User of anti-TNF-α				
	Non-user	Overall	Etanercept	Infliximab	Adalimumab	Golimumab
Type of cancer, N (%)						
Total cancer						
Events, N	82,948	282	87	60	129	35
Colorectal cancer						
Events, N (%)	9,463 (11.4)	24 (8.5)	7 (8.0)	4 (6.7)	12 (9.3)	3 (8.6)
aHR (95% CIs)	1.00 (Reference)	0.92 (0.61, 1.38)	0.85 (0.41, 1.80)	0.69 (0.26, 1.84)	1.03 (0.58, 1.81)	1.02 (0.33, 3.17)
Pancreatic cancer						
Events, N (%)	3,108 (3.7)	12 (4.3)	4 (4.6)	3 (5.0)	4 (3.1)	2 (5.7)
aHR (95% CIs)	1.00 (Reference)	1.64 (0.92, 2.92)	1.61 (0.60, 4.32)	1.96 (0.63, 6.13)	1.24 (0.46, 3.32)	NA
Liver cancer						
Events, N (%)	5,266 (6.3)	14 (5.0)	10 (11.5)	1 (1.7)	4 (3.1)	0
aHR (95% CIs)	1.00 (Reference)	0.90 (0.53, 1.53)	2.04 (1.09, 3.82)*,†	NA	0.57 (0.21, 1.53)	NA
Lung cancer						
Events, N (%)	10,722 (12.9)	40 (14.2)	12 (13.8)	6 (10.0)	22 (17.1)	4 (11.4)
aHR (95% CIs)	1.00 (Reference)	1.00 (0.73, 1.37)	0.92 (0.52, 1.63)	0.69 (0.31, 1.54)	1.22 (0.80, 1.86)	0.92 (0.34, 2.45)
Kidney cancer						
Events, N (%)	1,881 (2.3)	9 (3.2)	3 (3.4)	1 (1.7)	3 (2.3)	2 (5.7)
aHR (95% CIs)	1.00 (Reference)	1.20 (0.62, 2.34)	1.31 (0.42, 4.10)	NA	0.88 (0.28, 2.75)	NA
Breast cancer[a]						
Events, N (%)	8,762 (10.6)	27 (9.6)	12 (13.8)	6 (10.0)	12 (9.3)	3 (8.6)
aHR (95% CIs)	1.00 (Reference)	0.91 (0.62, 1.34)	1.30 (0.74, 2.30)	0.89 (0.40, 1.98)	0.89 (0.50, 1.58)	0.82 (0.26, 2.55)
Thyroid cancer						
Events, N (%)	8,868 (10.7)	37 (13.1)	9 (10.3)	12 (20.0)	13 (10.1)	5 (14.3)
aHR (95% CIs)	1.00 (Reference)	0.91 (0.66, 1.26)	0.76 (0.39, 1.46)	1.29 (0.73, 2.28)	0.70 (0.40, 1.20)	1.00 (0.42, 2.41)
Lymphoma						
Events, N (%)	3,196 (3.9)	26 (9.2)	6 (6.9)	10 (16.7)	9 (7.0)	3 (8.6)
aHR (95% CIs)	1.00 (Reference)	1.50 (1.01, 2.22)*	1.12 (0.5, 2.50)	2.49 (1.33, 4.66)**,†	1.14 (0.60, 2.20)	1.55 (0.50, 4.83)
Leukemia						
Events, N (%)	1,226 (1.5)	11 (3.9)	6 (6.9)	2 (3.3)	8 (6.2)	1 (2.9)
aHR (95% CIs)	1.00 (Reference)	2.08 (1.13, 3.82)*,†	3.87 (1.71, 8.76)**,†	NA	3.36 (1.65, 6.84)#,†	NA

Table 3. The risk of site-specific cancer in the user of anti-TNF-α. Hazard ratios were calculated by Cox proportional hazards regression analysis adjusted for the following covariates: age, sex, income level, Charlson comorbidity index, other drug prescriptions, and history of psoriasis/rheumatoid arthritis. [a]only women. N, number of patients; TNFα, tumor necrosis factor-alpha; aHR, adjusted hazard ratio; CIs, confidence intervals; NA, not available. *p-value < 0.05; **p-value < 0.01; #p-value < 0.001. †Also, p-value < 0.05, when Benjamini-Hochberg adjustment was applied.

carcinogenic effect of these biologics, the multiple and ambivalent roles of TNF-α on the development of cancer need to be fully considered. Suppression of TNF-α can drive the following action: (1) blockade of the signal transduction triggered by TNF-α, (2) inactivation of cancerkilling immune cells, and (3) systemic interference in the cancer-targeted immunity, which may be essential to the survival and development of cancer initiative cell (CIC). The well-known signal transduction activated by TNF-α is a nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway[22]. As the fully activated NF-κB pathway creates an inflammatory environment, CIC can be easily killed by the boosted immunity, including anti-tumor macrophages (M1 type)[23]. Additionally, TNF-α is a crucial and essential effector for CD8 + cytotoxic T cell and Natural Killer cellmediated apoptosis of CIC[24]. For therapeutic purposes, the administration of high doses of TNF-α improved the efficacy of chemotherapy, by destroying tumor vasculature (vascular-toxic agent for tumor) and triggering apoptosis/necrosis of cancer cells. Despite TNF-α's anti-cancer actions, our study suggests that inhibition of TNF-α by biologics may not be associated with initiating cancer or increasing cancer risk. On the other hand, unlike the role of killing cancer as its name suggests (tumor necrosis), TNF-α holds a significant proportion to creating a cancerfriendly environment. Physiologically low concentration of TNF-α promotes genesis and growth of tumor[22,25]. Other secreted cytokines and cellular mechanisms stimulated by TNF-α contribute to DNA damage and then trigger the initiation of cancer[26]. Since TNF-α induces angiogenesis/metastasis-related factors, including matrix metalloproteinases, TNF-α contributes to the formation of tissue architecture for the growth of cancer (tumorassociated microenvironment). Additionally, TNF-α is known as the tumor-derived cytokines for recruitment and activation of pro-tumor macrophages (M2 type) in the early stage of the tumor[27]. Thus, as the

frequent and long-term usage of inhibitors keeps a relatively low level of TNF-α, the high survival rate of CIC might be guaranteed by the induced cancer-friendly environment.

Among the anti-TNF-α users, it is challenging to predict whether the accumulated usage of inhibition would cause cancer due to the contradictory roles of TNF-α: anti-cancerous at the high level and carcinogenic role at the low level. Therefore, the risk of cancer would be different, depending on the physiological level of TNF-α in the individual's body with the patient's history of prescription (dose, bio-half lifetime, and frequency of administration). High TNF-α levels with irregularly low doses of anti-TNF-α administration may contribute to CIC elimination, while relatively low levels with frequent anti-TNF-α prescriptions may promote cancer initiation and development[28]. In the case of lymphoma and leukemia, the previous study identified the possible risk of anti-TNF-α therapy for leukemia and lymphoma[29,30]. Although TNF-α related apoptosis inducing ligand causes apoptosis of human leukemia cells, TNF-α is conversely required for the evolution of myeloid malignancies[31–33]. Furthermore, signal control by TNF-α-induced NF-κB may regulate pathological conditions for various types of cancer, which suggests that TNF-α levels for cancer occurrence may vary by cancer type[34,35]. Thus, this increased risk of lymphoma and leukemia in our study can be supported by the hypothesis that they might be possibly more sensitive to dose and physiological level of TNF-α compared to other cancers; a lower threshold to develop the lymphoma and leukemia at even the slightly suppressed level of TNF-α.

To interpret the result and discussion, major limitations of this study must be considered. Ideally, this study should have addressed dose-response relationships and therapy windows (information on concentration and half-life in the body) for each episode of biologic usage, which could not be identified from insurance claim data. The incidence of cancer among multi-class users and single-agent users, who either switched between agents or used only one agent, respectively, was not considered due to the small number of participants. Although the types of cancer across their sites were classified, data were collected for only a few patients who developed cancer subtypes. The types of cancer with fewer than 20 cases among all users included pancreas, liver, kidney cancers, and leukemia. If sufficient events of subtyped cancers are observed using a larger cohort, an evaluation of the association between cancer incidence and individual anti-TNF-α agents, including infliximab, could be conducted. Given that the mechanisms of action (e.g., direct binding to TNF-α or mimicking natural TNF receptors) and the half-life of each TNF-α inhibitor vary, a thorough verification of their effects is required[36]. In addition, the study population for long-term users might have selection bias and heterogeneity, compared to the general population, as they are few and health-vulnerable subjects. The user who was prescribed TNF-α for other purposes (not for psoriasis and RA) such as ankylosing spondylitis were excluded from the study population. Finally, although the operational definitions for psoriasis and RA in our study have been verified, the possibility of incorrect subject classification (including misclassification of inclusion as false negatives and exclusion as false positives) remains. Furthermore, due to the challenges in measuring the severity of psoriasis and RA, and the potential for drug users to present with more critical conditions, the consideration of severity remains incomplete.

In conclusion, both our results and those from previous studies suggest that the prescription of anti-TNF-α does not appear to increase the incidence of cancer. However, it is difficult to definitively dismiss an association of TNF-α inhibitors with cancer due to dual role of TNF-α in carcinogenesis. Moreover, since TNF-α inhibition can potentially lead to leukemia and lymphoma, careful consideration is warranted when prescribing anti-TNF-α agents, particularly with respect to long-term use.

Methods

Study population: the patient with psoriasis and user of antibodybased immunosuppressant

All prescription of antiTNF-α was claimed for national insurance in Korea with the nationsupported medical service from 2002. As the insurance claim data for almost all medical services were managed by the National Health Insurance Service (NHIS)[37,38], Users of antiTNF-α were derived from the NHIS database.

With permission from the NHIS and guidelines, all patients (age ≥ 20 years) who were newly diagnosed with psoriasis or RA from January 01, 2010 to December 31, 2018 were recruited. They were collected from the NHIS database with the International Classification of Diseases, Tenth Revision (ICD-10 codes for psoriasis: L40.0, L40.8, L40.9, and L40.5, accuracy = 96.5%[39]; for RA: M07.0, M07.1-M07.3, and M09.0, accuracy = 83.7%[40])[41] and operational definition (at least 3 times of outpatient visits or 2 days of hospitalization). The index date of patients with psoriasis and RA was designed as the date after 2 years of the first diagnosis date. Among 1,649,341 patients with psoriasis and RA, a total of 7,924 participants received antiTNF-α between the diagnosis date and index date (2-years), while 1,627,921 patients were classified as the Non-user who never have been received the prescription of any biologics (TNF-α or IL-4/6/12/17/23) from the diagnosis date to the end of follow-up (December 31, 2022). 8,245 participants, who were dead prior to the index date, were excluded. Additionally, to eliminate the previous events of cancer or incidence of skin cancer, 7,479 and 92,172 participants were also excluded from the User and Non-user, respectively. Thus, in this cohort study, 1,527,949 participants were used to evaluate the risk of cancer among the User and Non-user of antiTNF-α (**Supplementary information 7**). For the sensitive test, the User and Non-user were matched (1:5 PS match; logit PS for age-sex-income-Charlson comorbidity index-year of diagnosis; caliper = 0.1).

Exposure: antibodybased immunosuppressant: inhibitors of cytokine

In this study, the biologics include the following mono-antibody based inhibitors of cytokine: antiTNF-α (etanercept, infliximab, adalimumab, and golimumab), anti-IL-4 (dupilumab), anti-IL-6 (tocilizumab), anti-IL-12/23 (ustekinumab, guselkumab, and risankizumab), and anti-IL-17 (secukinumab and ixekizumab). The cumulative number [unit = times] of prescriptions of antiTNF-α in the user within 2 years was calculated. Overall antiTNF-α user was additionally classified based on their prescription history, with multiple uses: (1) etanercept, (2) infliximab, (3) adalimumab, and (4) golimumab. For the sensitive test, when < 10% or ≥ 90% of

them were excluded among the User, the cumulative usage for a certain range (10–90%) was then calculated. Also, the accumulated usage was re-calculated by changing the period longer (3 years).

Outcome: occurrence of cancer

The incidence case for cancer (malignant tumor) was collected based on ICD-10 code (C00C99): colorectal cancer (C18-C20), pancreatic cancer (C25), breast cancer (C50), thyroid cancer (C73), lymphoma (including Hodgkin/non-Hogkin's lymphoma: C81-C85, C88, C90, and C96), and leukemia (both acute/chronic lymphatic and myeloid leukemia: C91-C95)[42]. To financially support patients with cancer, all records of medical services for identified cancer patients are accompanied with V-code (V193 and V194). Thus, the cancer incidence was defined based on ICD-10 and V codes. A case of skin cancer (including non-melanoma skin cancer: C43C44) was fully excluded. In this retrospective cohort study, all participants were followed up from the index date to the date of event, death date, or December 31, 2022.

Statistical analysis

According to accumulated usage of biologics, the Cox proportional hazards model was used to evaluate the risk of cancer by calculating aHR for cancer and 95% CIs, after the goodness of fit test. The covariates were used as follows: age (continuous; years), sex (categorical), income level (categorical; quartile), Charlson comorbidity index (continuous), and other immunosuppressive drug prescriptions (categorical; Used or Not used, including azathioprin, cyclophosphamide, cyclosporine, and methotrexate). Income level was derived from the insurance premium which was dependent on the property and salary. Charlson comorbidity index was calculated according to the manual and used as a representative morbidity score. With the history of all prescribed drugs in the NHIS database, usage of other immunosuppressive drugs prior to the index date was also collected.

The resulting values are expressed as the number of subjects with percentage and a mean value with SD. Chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables were used to compare the differences in the distribution of variates (two-tailed). Statistical significance was defined as p-value < 0.05. To avoid errors of multiple comparisons, an adjusted p-value was derived from Benjamini-Hochberg adjustments. All data collection and statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Data availability

The data that support the findings of this study are available from the NHIS in Korea but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the NHIS.

Code availability

Unless it deviates from the national and organizational regulations, access to the code used in this study is available, only for noncommercial and academic purposes.

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J. Song and S.M. Park had full access to all of the data. Study concept and design: J Song, S.R. Kim, Y.J. Kim, and S.M. Park.Analysis of data: J Song, S.J. Park, and S. Jeong.Interpretation of data: All authors.Writing the manuscript: J Song, S.R. Kim, Y.J. Kim, and S.M. Park.Revision of the manuscript: All authors.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and Guideline

The Institutional Review Board (IRB) of Seoul National University Hospital (Seoul National University College of Medicine/Hospital Ethics Committee of Medical Research (SNUCM) and Center for Human Research Protection) approved this study (IRB No.: E-2307-131-1452), which complies with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study and the anonymized database from the National Health Insurance Service (NHIS), the requirement for informed consent was waived by the IRB. Additionally, this study (retrospective cohort and observation) was conducted by following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and checklist.

Additional information

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