의학석사 학위논문

항 TNF-α 제제와 비교한 베돌리주맙과 우스테키누맙의 중증 감염과 결핵 위험 비교: 염증성 장질환 환자를 대상으로 한 전국 인구 기반 연구

Comparative risk of serious infections and tuberculosis of vedolizumab and ustekinumab compared with anti-TNF-α agents: A nationwide population-based study of South Korean patients with inflammatory bowel disease

울산대학교 대학원

의 학 과

김 민 지

항 TNF-α 제제와 비교한 베돌리주맙과 우스테키누맙의 중증 감염과 결핵 위험 비교: 염증성 장질환 환자를 대상으로 한 전국 인구 기반 연구

지 도 교 수 조 경 욱

이 논문을 의학석사 학위 논문으로 제출함

2023 년 8 월

울산대학교 대학원

의 학 과

김 민 지

김민지의 의학석사 학위 논문을 인준함

심사위원 이 재 승 인

심사위원 조 경 욱 인

심사위원 김 호 철 인

울 산 대 학 교 대 학 원

2023 년 8 월

국문요약

연구배경: 베돌리주맙/우스테키누맙과 항 TNF-α 제제를 투여받은 염증성 장 질환(IBD) 환자에서 중증 감염과 활동성 결핵 발병 위험을 비교하고자 하였다.

연구방법: 국민 전체 인구의 97%를 차지하는 건강보험심사평가원 청구자료에서 2017 년부터 2020 년까지의 추적관찰 기간 동안 두 군 사이에 입원/응급실 방문을 요하는 중증 감염 또는 활동성 결핵 발생의 차이를 분석하였다.

연구결과: 각각 1.55 ± 1.05 년과 0.84 ± 0.69 년의 평균 추적기간동안, 항 TNF-α 제제 또는 베돌리주맙/우스테키누맙제제를 투여받은 환자들의 중증 감염 발생률은 각각 100 인년 당 9.43 건과 6.87 건이었다. 다변량분석결과, 베돌리주맙/우스테키누맙과 항 TNF-α 제제 사이의 중증 감염 발병에는 통계적으로 유의한 차이가 없었으며, 보정 후 상대위험도(RR)는 0.81(95% 신뢰구간 [CI], 0.46-1.44, P = 0.478)였다. 또한, 항 TNF-α 제제 또는 베돌리주맙/우스테키누맙을 투여 받은 환자들 중에서 활동성 결핵 발생률은 각각 100 인년 당 0.87 건과 0.37 건이었으며, 베돌리주맙/우스테키누맙과 항-TNF-α 제 사이의 RR 은 0.31(95% CI, 0.07-1.26, P = 0.101)였다.

연구결론: 베돌리주맙/우스테키누맙 치료는 국내 IBD 환자들에서 항 TNF-α 제제와 비교하여 중증 감염 또는 활동성 결핵 발생률이 유사하게 나타났다.

Contents

Abstract

Background We aimed to compare the risk of serious infection and active tuberculosis development in patients with biologics-naïve inflammatory bowel disease (IBD) received vedolizumab/ustekinumab and anti- tumor necrosis factor (TNF)-α agents.

Methods From the claim data of the Health Insurance Review and Assessment Service (which represents 97% of the total South Korean population), we selected the IBD patients who initiated vedolizumab/ustekinumab or anti-TNF α agents (n = 6123) from 2017 to 2020. We analyzed the difference of the serious infection requiring hospitalization/emergency department visit or active tuberculosis development between the two groups during the follow-up period.

Results During mean follow-up of 1.55 ± 1.05 years and 0.84 ± 0.69 years, the incidence of serious infection was 9.43/100 and 6.87/100 person-years (PY) in the patients treated with anti-TNF α agents or vedolizumab/ustekinumab, respectively. Multivariable analysis showed that no statistical difference of serious infection development was noted between vedolizumab/ustekinumab and the anti-TNF-α agents; the adjusted relative risk (RR) of vedolizumab/ustekinumab compared with anti-TNF-α agents was 0.81 (95% confidence interval [CI], 0.46–1.44, P = 0.478). Additionally, among the patients received anti-TNF α agents or vedolizumab/ustekinumab, the incidence rate of active tuberculosis was 0.87 per 1,00 PYs and 0.37 per 1,00 PYs, respectively; the RR of vedolizumab/ustekinumab compared with anti-TNF-α agents was 0.31 (95% CI, 0.07–1.26, P = 0.101).

Conclusion The treatment of vedolizumab/ustekinumab resulted in the similar rate of serious infection or active tuberculosis development compared with anti-TNF-α agents in the patients with biologics-naïve IBD.

Introduction

Inflammatory bowel disease, which includes ulcerative colitis (UC), and Crohn's disease (CD), are a group of disorders characterized by chronic, relapsing, and progressive intestinal inflammation(1). IBD is accompanied by massive infiltration of circulating leukocytes into the intestinal mucosa, leading to intestinal inflammation and tissue damage(2). The dysregulation of immune response and impairment of intestinal barrier function are key features of IBD, contributing to the persistence of symptoms and the progression of the disease. Thus, therapeutic approaches in IBD often focus on reducing inflammation, inducing and maintaining clinical remission which can be achieved by modulating the immune response, using immunosuppressants, and biologics that target specific cytokines or immune cell populations while minimizing the adverse effects of medications.

One crucial inflammatory cytokine associated with IBD is tumor necrosis factor (TNF) alpha. TNF-α plays a role in stimulating cell proliferation, differentiation, and upregulation of adhesion molecules on the endothelium, promoting the migration of cells to the site of inflammation(3, 4). Among biologics, monoclonal antibodies against TNF-α (anti-TNF-α agents), have been the cornerstone of IBD as their efficacy have been demonstrated(5). However, upto 40% of patients with people with IBD may become unresponsive to anti-TNF-α agents(6), and effective established treatments have been lacking for such patients, highlighting the need for further drug development. Recently, novel biologic agents have been developed in response to this situation. Currently, two adhesion molecule antagonists (natalizumab and vedolizumab), interleukin (IL)-12/23 antagonist (ustekinumab), and an oral Janus kinas inhibitor, tofacitinib, have been recently approved by the U.S. Food and Drug Administration (USFDA) for IBD treatment(7). Among them, vedolizumab was proved effective in both induction and maintenance in a double-blinded, randomized clinical trial

involving patients with active UC who had failed conventional treatment(8). In addition, in a phase-3, randomized clinical trial involving patients with moderate-to-severe UC despite conventional or biologic therapy, ustekinumab was more effective than placebo for inducing and maintaining remission(9). Vedolizumab and ustekinumab were also demonstrated to increase the likelihood of clinical remission in patients with moderately to severely active CD in the previous clinical trials(10, 11).

Vedolizumab is a recombinant humanized IgG1 monoclonal antibody to the homing receptor α4β7 integrin complex. The α4β7 integrin is a heterodimeric cell surface receptor composed of α4 and β7 subunits. The α4 subunit binds to vascular cell adhesion molecule (VCAM-1) found on the endothelial cells of blood vessels of gut. Meanwhile, the β7 subunit binds to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is selectively expressed on the endothelial cells of blood vessels in the gastrointestinal tract(12). This interaction between α4β7 integrin and its ligands facilitates the adhesion and subsequent migration of immune cells from the bloodstream to the intestinal mucosa, contributing to the inflammatory response(13). Vedolizumab works by targeting α4β7 integrin, disrupting this migration process and reducing the infiltration of immune cells into the gut, thus alleviating inflammation associated with IBD(14).

Ustekinumab is a humanized IgG1 monoclonal antibody targeting the p40 subunit of IL-12/23. IL-12 is known to contribute to the differentiation of naïve T cells into T helper 1 effector cells (Th 1 cells). Th1 cells play a role in activating immune cells and promoting inflammation by producing pro-inflammatory cytokines such as interferon-gamma (IFN-ɣ) and TNF- α(15). The excessive production of IL-12 can lead to an imbalance in the Th1 immune response, resulting in sustained inflammation and tissue damage in the intestines(16). IL-23, on the other hand, promotes expansion and maintenance, but not differentiation of T helper 17

cells (Th17 cells). Th17 cells generate pro-inflammatory cytokines including IL-17A, IL-17F, and IL-11, which promote inflammation and recruitment immune cells to the site of inflammation(17). Dysregulated production of IL-23 leads to an amplified Th17 response, thereby mediating the chronic inflammation in the intestines. Ustekinumab, by inhibiting the binding of IL-12/23 to the T cells and NK-cells, modulates the dysregulated immune response and reduces intestinal inflammation(18).

The biggest threat related to the use of anti-TNF-α agents is the increased risk of serious infection, reported in clincial trials and real-word studies(19-23), especially within the first 90 days of treatment initiation(24). Moreover, as TNF has essential role of host defenses against *Mycobacterium tuberculosis* infection(25), the treatment with anti-TNF-α agents inadvertently result in the increased risk of tuberculosis disease development(26), which is considered as the most serious infectious complication associated with anti-TNF-α agents in tuberculosis-endemic country. Prevoius studies found that the use of vedolizumab or ustekinumab is relatively safe in terms of the development of serious infection(27, 28) or active tuberculosis(29). However, the number of studies comparing the risk of infectious complication between anti-TNF-α agents and the vedolizumab or ustekinumab is limited(30, 31). Particularly, there has been no study to concomitantly evaluate the risk of serious infection and active tuberculosis in the patients with IBD according to the use of anti-TNF-α agents *versus* vedolizumab/ustekinumab in Asian population. Therefore, this issue was investigated in the present study. We aimed to compare the risk of serious infection and active tuberculosis development in patients with biologics-naïve IBD received vedolizumab/ustekinumab and anti-TNF-α agents.

METHODS

Data sourse

We conducted population-based retrospective cohort study which used the Health Insurance Review and Assessment Service (HIRA) database of South Korea. A total of 97% of the entire South Korean population of approximately 50.0 million is obliged to enroll in the National Health Insurance program. The accuracy of claims for the National Health Insurance was assessed by HIRA, which is a government-affiliated agency. After reviewing incurred medical costs and reports from healthcare providers concerning medical services, HIRA provides reports called health insurance claims data. This claim data includes various information such as the diagnoses as determined by the International Classification of Diseases, 10th revision (ICD10) and status of inpatients and outpatients, demographics, procedures, drug, prescription date and periods, and performed tests(32). The database also provides registration of rare incurable diseases (RIDs) of a number of diseases including Crohn's disease (CD) and ulcerative colitis (UC). The RID system has high reliability as it requires the attending physician's additional certification through specified diagnostic criteria such as histologic examinations before registration(33). The data given by HIRA had anonymized identifiers, according to the Act on the Protection of Personal Information that is maintained by public agencies.

Study subjects and ethics

We obtained HIRA claim data of adults patients (≥19 years old) with (i) ICD-10 code for UC (K51.0–51.9) or CD (K50.0–50.9) and (ii) received biologics with anti-TNF-α agents (infliximab, adalimumab, and golimumab) or vedolizumab/ustekinumab from January 2007 to February 2021. We first excluded the patients (i) who did not have RID registration codes for

UC (V131) or CD (V130), and (ii) whose ICD-10 code for UC or CD was not in the principal or subsidiary diagnostic field. Then, to select patients with biologics-naïve IBD, those whose biologics were initiated before 2017 were excluded considering that the use of vedolizumab and ustekinumab was approved in South Korea in 2017(34). We further excluded the cases of which biologics started after December 2020 to secure at least 90 days of observation period. Of remaining patients, those who had medical comorbidity that can affect the development of serious infection or tuberculosis, such as organ transplantation were finally excluded. Finally, 12235 patients with biologics-naïve IBD who received anti-TNF-α agents or vedolizumab/ustekinumab from January 2017 to November 2020 were identified (Figure 1). This study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (IRB No.2022-0977). Informed consent was waived because the study used an existing database that was provided in a de-identified format.

The analysis of serious infection development

The first primary outcome of interest was the development of serious infections, defined as a diagnosis of infection requiring hospitalization or emergency department visit. The detailed diagnosis of serious infections was determined in accordance of previous study on the basis of ICD-10 code as all diagnostic fields of hospital admission or visit of emergency department., which categorized according to the site of infection; pulmonary, gastrointestinal, skin, urinary tract, ear/nose/throat, musculoskeletal, and other infections(31). Table 1 presents detailed diagnostic code of serious infection.

Table 1. ICD-10 codes included as any serious infections classified by infection sites.

	ICD-10

Pulmonary	
Pneumonia	A48.1, B01.2, B05.2, B25.0, J12-J18, J10-J11
other acute lower respiratory infections	A37, A42.0, B39-B40, B44, B58.3, B59, B95.3, J20-J22, U04
lung abscess	J85
Empyema	J86
Gastrointestinal	
intestinal infectious disease	A00-A08, K93.820
viral hepatitis	B15, B17, B25.1
Cholangitis	K80-K810, K830, K87.00, B25.8
liver abscess	K750
infectious esophagitis	B00.8(K23.80)
Skin and soft tissue	
erysipelas	A46
dermatophytosis and other superficial mycoses	B35-B36
cellulitis and abscess	L02-L03
herpes virus	B00.1-B00.2, B00.7, B00.9, B05.3-B05.9, B06.8-B06.9, B08-B09, A60
other local infections of skin, oral tissue, and subcutaneous tissue	A36.3, K11.3-K12.2, L00-L01, L04-L05, L08, L30.3, M72.6
Urinary tract and gynecological	
nephritis	N10
acute prostatitis and prostate abscess	N41.0, N41.2, N41.3
cystitis	N30.0
salpingitis and oophoritis	N70.0
endometritis	N71.0
cervicitis uteri	N72
syphilis	A50-A53, I98.0
gonorrhea	A54
chlamydia	A55-A56
orchitis and epididymitis	N45
other urinary tract infections	N39.0, N73.3, N77.1
ENT infections	
mastoiditis	H70
nasopharyngitis	A36.1
sinusitis	J01
pharyngitis	J02
pharyngeal, retropharyngeal, and parapharyngeal abscess	J36, J39.0-J39.1
tonsillitis	A36.0, J03
laryngitis and tracheitis	A36.2, J04-J05, J37
acute upper respiratory infections of multiple and unspecified sites	A36.8-A36.9, J06
infection of external ear and acute otitis media	H60.0-H60.3, H65.1-H65.2, H66, H68.0
Musculoskeletal infections	
infective arthritis	M00-M01
infective myositis	M60.0

osteomyelitis	M86
Others	
infection of the eye	B00.5, B30, H00-H01, H03.1, H06.1, H10.5, H10.8, H13.1, H19.1-H19.2
infection in the nervous system	A32.1, A39, A80-A89, B00.3-B00.4, B01.0-B01.1, B02.0-B02.2, B05.0-B05.1, B06.0, G00-G02, G04-G07
infection in prosthetic devices, implants, and grafts	T82.6-T82.7, T84.5-T84.7, T85.7
sepsis, SIRS of infectious origin and septic shock	A32.7, A40-A41, R57.2, R65.0-R65.1
certain bacterial disease	A20-A28, A32, A34-A35, A38, A42-A44, A48.0, A48.2-A49.9, B95.1, B95.2, B95.4-B95.8, B96-B97
spirochetal disease	A65-A69
rickettsiosis	A75-A79
viral infections	A90-A99, B25.2, B25.9, B26-B27; B33-B34
mycoses	B37-B49
protozoal disease	B50-B57, B58.1-B58.2, B58.8-B58.9, B60-B83
unspecified infectious disease	B99.9
acute infective pericarditis and endocarditis	I30.1, I33.0
mycobacterial infections	A15-A19, A31, K23.0, K67.3, K93.0, M01.1, M49.0, M90.0, N33.0, N74.0, N74.1

Abbreviations: ENT, ear, nose and throat; SIRS, systemic inflammatory response syndrome

The exposures of interest were the use of anti-TNF-α agents and vedolizumab/ustekinumab. As previous study demonstrated that the risk of serious infection related to the treatment of anti-TNF-α agents increased within the first 90 days of treatment initiation and subsequently decline(24), we excluded patients who had been recorded to have the history of serious infection within 90 days before the first prescription of biologics (Figure 1). Figure 2 presents detailed definition for serious infection outcome development attributing to biologics of the present study. In brief, after the initiation of biologics, patients were regarded to be continuously exposed from the index date, which was defined as the first date of prescription of the biologics. If the development of serious infection is noted, it was considered to be associated with the use of biologics until the 90 days after its discontinuation (Figure 2-A). Multiple events developments were separately counted as distinct events provided that the interval between outcome events (Figure 2-B) or the discontinuation period between biologics treatment was >90 days (Figure 2-C). Moreover, if biologics were switched (anti-TNF-α agents

to vedolizumab/ustekinumab or *vice versa*), the development of serious infection within 90 days after changing drugs was regarded to be associated with the former drugs (Figure 2-D). For the serious infection analysis, follow-up duration was determined as until (i) the 90 days after the discontinuation of biologics, or (ii) the 90 days after switching of biologics (anti-TNF-α agents to vedolizumab/ustekinumab or *vice versa*), or (iii) the end of the follow-up period was reached, whichever came first.

Figure 1. Flowchart of the study population

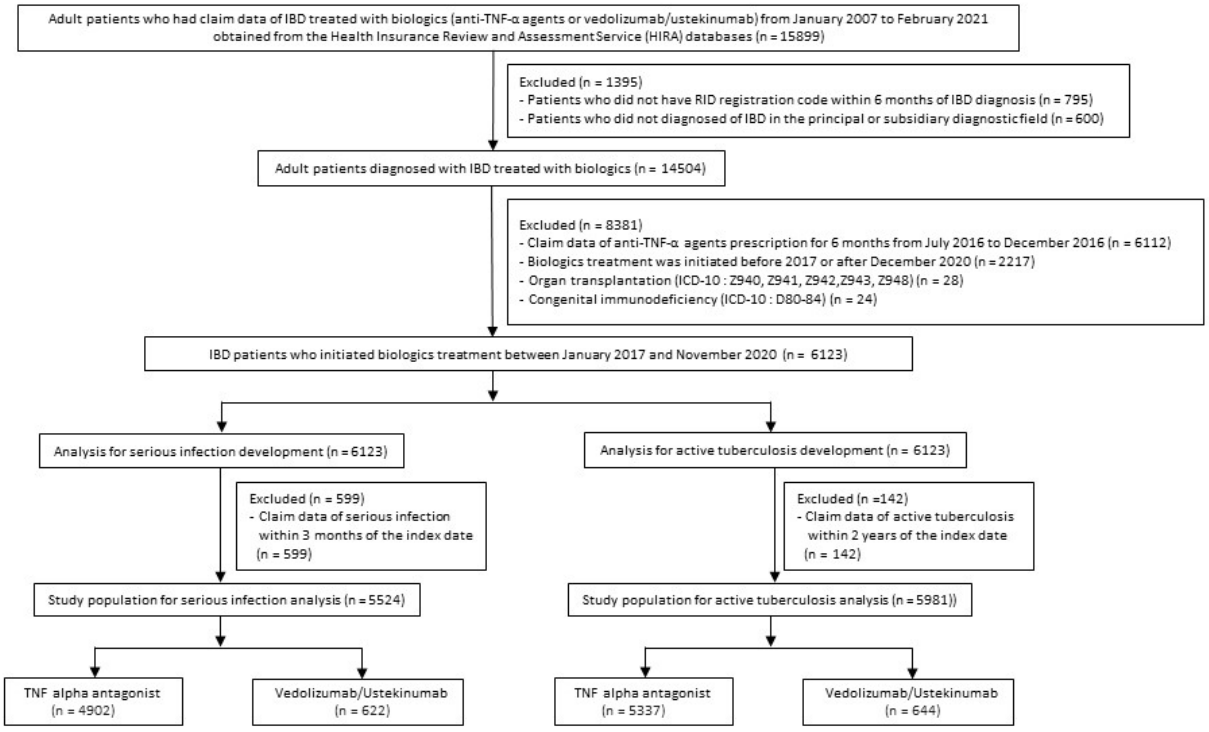


Figure 2-A,B,C. Study definition for serious infection development attributing to drug and follow-up duration in the patients treated with one type of biologics during study period.

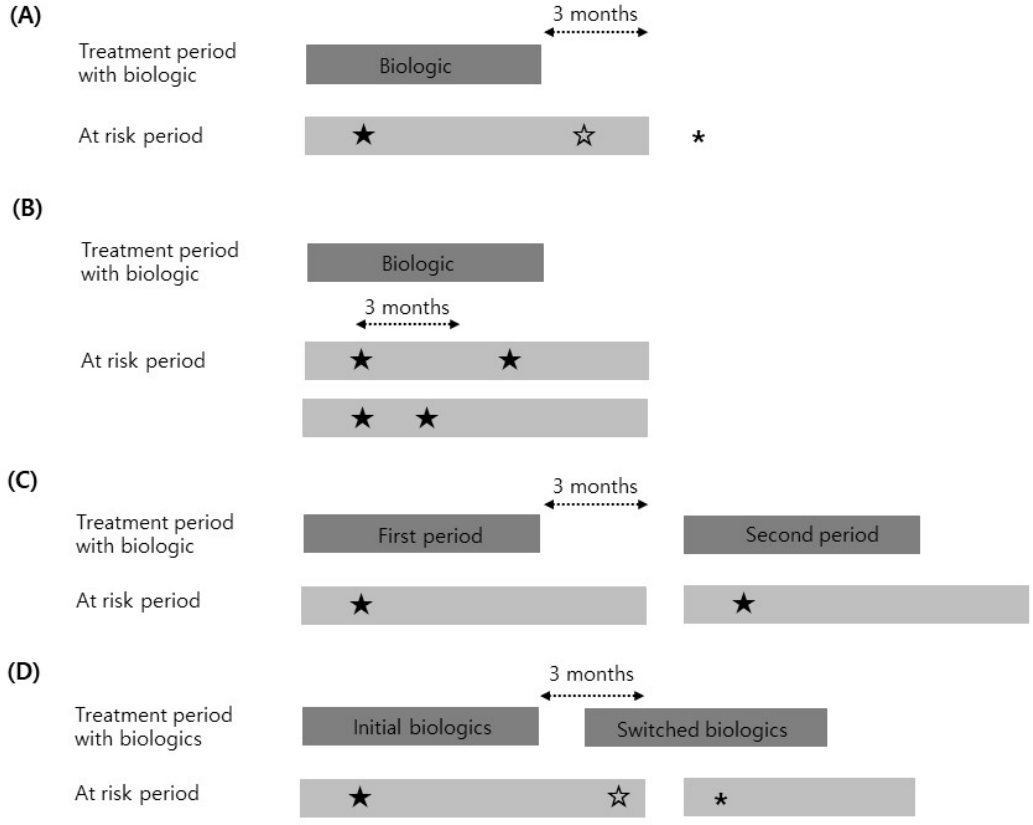
A. Development of outcome was regarded to be associated with the use of biologics if the outcome occurred during the biologics treatment (black star) or within 3 months after discontinuation of biologics (empty star). If the outcome developed 3 months after the

withdrawal of biologics, it was not included in the outcome analysis (asterisk), as the follow-up period was terminated at 3 months after the withdrawal of biologics.

B. In the case of multiple outcome development, if the interval between the outcome developments was >3 months, each event was counted as a separate outcome development (upper line). In contrast, if the interval between the multiple outcome developments was ≤3 months, only the first event was counted as a single outcome development (lower line).

C. For the case (i) of which biologics treatment was discontinued for >3 months, then resumed, and (ii) if the outcome development was noted in both treatment period, these events were separately counted as multiple outcome occurrence.

Figure 2-D. Study definition of serious infection analysis in patients whose biologics agent were switched during study period. Development of outcome was attributed to the use of initial biologics if it occurred during the use of biologics (black star). If the outcome developed during the use of switched biologics, it was considered to be associated with the influence of initial biologics if it developed within 3 months after discontinuation of initial biologic (empty star). The follow-up period was defined as up to 3 months after the discontinuation of the initial biologic. Therefore, events occurring in the period of the use of switched biologics were not included in the main analysis irrespective of the time of development (asterisk).



The analysis of active tuberculosis development

Another primary outcome was the development of active tuberculosis. Tuberculosis diagnosis was defined as the following: a patient with tuberculosis claims (ICD-10 codes A15–19) who had received a prescription for any antituberculosis drugs (isoniazid, rifamycin, ethambutol, pyrazinamide, prothionamide, cycloserine, para-aminosalicylic acid, levofloxacin or moxifloxacin, bedaquiline, linezolid, delamanid) at least once within 90 days from the time of diagnosis(35, 36). As the patients with active tuberculosis was usually treated with on the basis of outpatient department, the diagnosis of tuberculosis did not require hospitalization or emergency department visit.

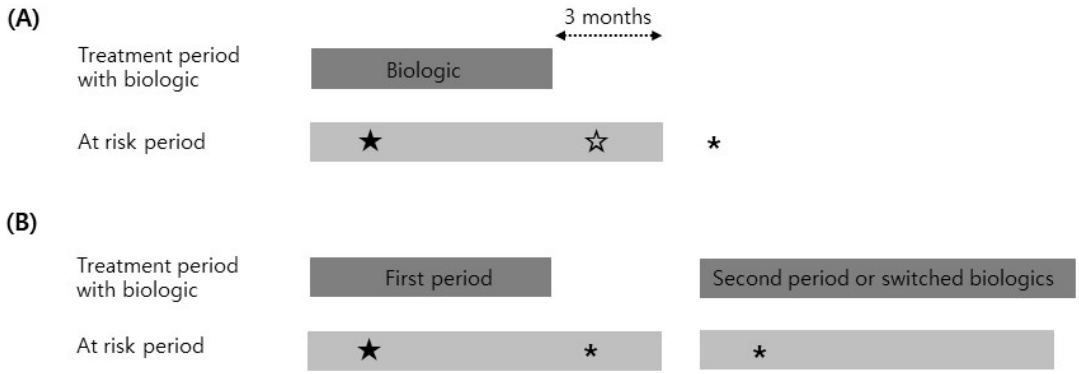
Previous history of tuberculosis is a significant risk factor for subsequent tuberculosis development(37, 38), and the likelihood of relapse significantly increases within the first 2 years after completion of tuberculosis treatment(39). Therefore, for the analysis of active tuberculosis development, we excluded those who had the history of active tuberculosis within 2 years before the first prescription date of biologics (Figure 1). Figure 3 shows detailed definition for active tuberculosis development attributing to biologics. Briefly, the tuberculosis was regarded to be related to the influence of biologics if the tuberculosis developed during the treatment with biologics or within 3 months of the discontinuation of biologics (Figure 3-A)(40, 41). In addition, only the first event was considered as study outcome development, while subsequent event(s) associated with initial or switched biologics were not included in our analysis (Figure 3-B).

For the active tuberculosis analysis, follow-up duration was defined as until (i) the study outcome occurred, (ii) the 90 days after the discontinuation or switching of biologics, or (iii) the end of the follow-up period was reached, whichever came first.

Figure 3-A, B. Study definition for active tuberculosis development attributing to drug and follow-up duration.

A. Development of active tuberculosis was determined to be related to the use of biologics if the outcome occurred during the biologics treatment (black star) or within 3 months after withdrawal of biologics (empty star). If the active tuberculosis occurred 3 months after the completion of biologics, it was not included in the outcome analysis (asterisk).

B. In the case of multiple outcome development, only the first event of active tuberculosis was counted as the single outcome associated with the prescribed biologics (black star), whereas the subsequent development of active tuberculosis was not included irrespective of whether it occurred during the use of initial or switched biologics (asterisk).



Covariate

A number of covariates were extracted from HIRA data, including age, sex, the use of steroid or immunomodulatory drug, comorbidities, and Charlson comorbidity index (CCI). CCI was measured by using the ICD-10 code diagnoses for several major comorbidities, as previously defined(42). The presence of comorbidities and the measurement of CCI were assessed based on the time point within 1 year prior to the index date of diagnosis of IBD.

Statistical analysis

Categorical variables were compared with McNemar's test (2 categories) and Test of Marginal Homogeneity (3 categories), and continuous variables with Wilcoxon signed rank test. The

number of each episode of outcome of the development serious infection and active tuberculosis were counted, and then incidence rate (IR) per 100 person-year of exposure period were calculated for vedolizumab/ustekinumab versus anti-TNF-α agents. Rates of infections were calculated as exposure-adjusted incidence rates (rate per 100 PY = [number of patients experiencing an adverse event of interest / total patient exposure time in years] × 100). The relative risk (RR) of vedolizumab/ustekinumab compared to the use of anti-TNF-α agents were analyzed, and the 95% confidence interval (CI) were retrieved from Poisson regression based on the crude rates. Multivarible analysis using the Cox proportional hazards model was performed adjusted for covariates, such as age and sex. Statistical analyses were performed using SAS EG statistical software version 7.1 (SAS Institute, Cary, NC, USA) and R software version 3.5.1 (the R Foundation), and *P*-values <0.05 were considered statistically significant.

RESULTS

Study subjects for serious infection analysis

For the serious infection analysis, we selected 11,481 patients with biologics-naïve IBD after excluding 754 patients who had the history of serous infection (Figure 1).

Table 2 shows the baseline characteristics of study patients. Patients were predominantly male (68.5%) with a median age was 26.0 (interquartile range [IQR], 19.0–37.0) years. The diagnosis of CD and UC were made in 7649 (66.6%) and 3832 (33.4%), respectively. Anti-TNF-α agents were initiated in 10,849 (94.5%) patients (adalimuamb was most frequently presecribed drug [61.1%], followd by infliximab [34.7%] and golimumab [4.3%]), and the remaining 632 (5.5%) patients recevied vedolizumab (n = 292) or ustekinumab (n = 340). Statistical significance of

baseline characteristics was noted between two groups in term of type of IBD, the proportion of patients treated with steroid or thiopurine, and CCI, as Table 2 presents.

Table 2. Baseline characteristics of patients with inflammatory bowel disease according to the treated biologics for serious infection analysis

Characteristics	Total (n = 11481)	Anti-TNF-α agents (n = 10849)	Vedolizumab/ Ustekinumab (n = 632)	*P*-value
Age	26.0 (19.0–37.0)	26.0 (19.0–37.0)	26.0 (20.0–38.0)	0.097
Age >40 year	2345 (20.4%)	2210 (20.4%)	135 (21.4%)	0.548
Sex, male	7866 (68.5%)	7437 (68.6%)	429 (67.9%)	0.724
Type of IBD				0.019
Crohn's disease	7649 (66.6%)	7201 (66.4%)	448 (70.9%)	
Ulcerative disease	3832 (33.4%)	3648 (33.6%)	184 (29.1%)	
Corticosteroids*				<0.001
None	3965 (34.5%)	3773 (34.8%)	192 (30.4%)	
Low dose	773 (6.7%)	747 (6.9%)	26 (4.1%)	
High dose	6743 (58.7%)	6329 (58.3%)	414 (65.5%)	
Immunomodulatory drug				
Thiopurines	6910 (60.2%)	6500 (59.9%)	410 (64.9%)	0.013
Methotrexate	471 (4.1%)	446 (4.1%)	25 (4.0%)	0.848
Comorbidity				
Charlson Comorbidity Index				0.003
0	5510 (48.0%)	5243 (48.3%)	267 (42.2%)	
1	3576 (31.1%)	3364 (31.0%)	212 (33.5%)	
≥2	2395 (20.9%)	2242 (20.7%)	153 (24.2%)	
Hypertension	885 (7.7%)	829 (7.6%)	56 (8.9%)	0.264
Diabetes mellitus	793 (6.9%)	739 (6.8%)	54 (8.5%)	0.095
Malignancy	125 (1.1%)	107 (1.0%)	18 (2.8%)	<0.001
Chronic kidney disease	74 (0.6%)	71 (0.7%)	3 (0.5%)	0.799
Follow-up duration after biologics initiation, year	1.99 ± 1.36	2.05 ± 1.36	0.84 ± 0.68	<0.001

Data are presented as the number (%), mean ± standard deviation, and median (interquartile range).

Abbreviations: TNF, tumor necrosis factor; IBD, inflammatory bowel disease

*High dose defined as a dose ≥ 20mg prednisone or equivalent daily for ≥ 14days or cumulative dose ≥ 600mg of prednisone or equivalent

Serious infection development according to the biologics

Among the 10,849 patients received anti-TNF-α agents, the overall development of serious infection was noted in 1937 persons during the mean follow-up period of 2.05 ± 1.36 years, which corresponds to the incidence rate as 8.69 per 100 person-years. In addition, among the

patients who prescribed vedolizumab or ustekinumab, the serious infection developed in 38 patients during the mean follow-up period of 0.84 ± 0.68 years; the incidence rate of serious infection in the vedolizumab/ustekinumab groups was 7.13 per 100 person-years. Univariate analysis showed that the treatment with vedolizumab or ustekinumab was not associated with an increased risk of serious infection development compared with the use of anti-TNF-α agents (RR, 1.82; 95% CI, 0.59–1.13, $P = 0.225$) (Table 3). A number of covariates including age, sex, comorbidities, CCI, and the use of steroid were found to be associated with serious infection in univariate analyses, as shown in Table 4. After the adjustment of these confounding factors, no statistical difference of serious infection development was still noted; the adjusted RR of vedolizumab/ustekinumab for serious infection compared with anti-TNF-α agents was 0.80 (95% CI, 0.46–1.40, $P = 0.437$). Table 5 presents the detailed classification of serious infection according to the subgroup of infectious site.

Table 3. Risk of serious infection development of vedolizumab/ustekinumab compared to anti-TNF-α agents in patients with inflammatory bowel disease.

	Anti-TNF-α agents (n = 10849)*		**Vedolizumab/Ustekinumab (n = 632)†**					
	No. of episodes	IR/100 pys	No. of episodes	IR/100 pys	Relative risk (95% CI)	*P*-value	Adjusted relative risk‡ (95% CI)	*P*-value
Serious infections, overall	1937	8.69	38	7.13	0.82 (0.59–1.13)	0.225	0.80 (0.46–1.40)	0.437
Pulmonary	396	1.78	5	0.94	0.53 (0.16–1.76)	0.299	0.52 (0.16–1.67)	0.270
Gastrointestinal	391	1.75	8	1.50	0.85 (0.32–2.28)	0.754	0.83 (0.33–2.06)	0.686
Skin and soft tissue	296	1.33	9	1.69	1.27 (0.52–3.08)	0.596	1.25 (0.54–2.90)	0.602
Urinary tract	203	0.91	3	0.56	0.62 (0.14–2.82)	0.534	0.60 (0.12–3.00)	0.530
Eye/Nose/Throat	265	1.19	5	0.94	0.79 (0.26–2.40)	0.676	0.76 (0.25–2.29)	0.626
Musculoskeletal	20	0.09	1	0.19	2.09 (0.06–70.40)	0.681	2.05 (0.17–24.12)	0.570
Others	366	1.64	7	1.31	0.80 (0.21–2.97)	0.738	0.78 (0.23–2.62)	0.684

Abbreviations: TNF, tumor necrosis factor; IR, incidence rate; PY, person year; CI, confidence interval

*Sum of person-years of patients treated with anti-TNF-α agents was 22279.60.

†Sum of person-years of patients treated with vedolizumab/ustekinumab was 533.19.

‡Adjusted covariates included age, sex, Charlson comorbidity index, steroid use, and immunomodulatory drugs(thiopurines or methotrexate).

Table 4. Covariates associated with the development of serious infections in patients with inflammatory bowel disease treated with anti-TNF-α agents or vedolizumab/ustekinumab.

Covariates	Univariate analysis		
	Relative risk	95% CI	*P*-value
Age			
>40	2.11	1.78–2.49	<0.0001
Sex			
Female	1.43	1.21–1.70	<0.0001
Comorbidities			
Hypertension	2.44	1.96–3.04	<0.0001
Diabetes mellitus	2.59	2.08–3.24	<0.0001
Malignancy	2.64	1.55–4.49	<0.0001
Chronic kidney disease	3.46	1.96–6.12	<0.0001
Charlson Comorbidity Index			
0	1.00		
1	1.55	1.27–1.88	<0.0001
≥2	2.57	2.12–3.12	<0.0001
Steroid use*			
None	1.00		
Low dose	1.61	1.18–2.21	0.003
High dose	1.55	1.30–1.87	<0.0001
Immunosuppressants			
None	1.00		
Thiopurines or methotrexate	0.96	0.81–1.13	0.621

Abbreviations: TNF, tumor necrosis factor; CI, confidence interval

*High dose defined as a dose ≥ 20mg prednisone or equivalent daily for ≥ 14days or cumulative dose ≥ 600mg of prednisone or equivalent

Table 5. Risk of serious infection development of vedolizumab/ustekinumab compared with anti-TNF-α agents in patients with inflammatory bowel disease according to the site of infection.

	Anti-TNF-α agents (n = 10849)		Vedolizumab/Ustekinumab (n = 632)			
	No. of episodes	IR/100 pys	No. of episodes	IR/100 pys	Relative risk (95% CI)	*P*-value
Pulmonary	396	1.78	5	0.94	0.53 (0.16–1.76)	0.299
pneumonia	210	0.94	2	0.38	0.40 (0.06–2.73)	0.349
other acute lower respiratory infections	185	0.83	3	0.56	0.68 (0.17–2.64)	0.575
lung abscess	0	0.00	0	0.00	N/A	N/A

empyema	1	0.00	0	0.00	N/A	N/A
Gastrointestinal	391	1.75	8	1.50	0.85 (0.32–2.28)	0.754
intestinal infectious disease	162	0.73	3	0.56	0.77 (0.17–3.58)	0.743
viral hepatitis	15	0.07	1	0.19	2.79 (0.29–26.70)	0.374
cholangitis	209	0.94	4	0.75	0.80 (0.19–3.30)	0.757
liver abscess	3	0.01	0	0.00	N/A	N/A
infectious esophagitis	2	0.01	0	0.00	N/A	N/A
Skin and soft tissue	296	1.33	9	1.69	1.27 (0.52–3.08)	0.596
erysipelas	0	0.00	0	0.00	N/A	N/A
dermatophytosis and other superficial mycoses	27	0.12	0	0.00	N/A	N/A
cellulitis and abscess	119	0.53	6	1.13	2.11 (0.75–5.98)	0.162
herpes virus	26	0.12	2	0.38	3.21 (0.56–18.42)	0.190
other local infections of skin, oral tissue, and subcutaneous tissue	124	0.56	1	0.19	0.34 (0.03–4.51)	0.411
Urinary tract and gynecological	203	0.91	3	0.56	0.62 (0.14 - 2.82)	0.534
nephritis	46	0.21	0	0.00	N/A	N/A
acute prostatitis and prostate abscess	7	0.03	0	0.00	N/A	N/A
cystitis	27	0.12	0	0.00	N/A	N/A
salpingitis and oophoritis	0	0.00	0	0.00	N/A	N/A
endometritis	0	0.00	0	0.00	N/A	N/A
cervicitis uteri	8	0.04	0	0.00	N/A	N/A
syphilis	4	0.02	0	0.00	N/A	N/A
gonorrhea	0	0.00	0	0.00	N/A	N/A
chlamydia	0	0.00	0	0.00	N/A	N/A
orchitis and epididymitis	4	0.02	0	0.00	N/A	N/A
other urinary tract infections	107	0.48	3	0.56	1.17 (0.31–4.39)	0.814
ENT infections	265	1.19	5	0.94	0.79 (0.26–2.40)	0.676
mastoiditis	0	0.00	0	0.00	N/A	N/A
nasopharyngitis	0	0.00	0	0.00	N/A	N/A
sinusitis	30	0.13	1	0.19	1.39 (0.16–12.34)	0.766
pharyngitis	63	0.28	1	0.19	0.66 (0.07–6.15)	0.718
pharyngeal, retropharyngeal, and parapharyngeal abscess	12	0.05	0	0.00	N/A	N/A
tonsillitis	39	0.18	0	0.00	N/A	N/A
laryngitis and tracheitis	16	0.07	0	0.00	N/A	N/A
acute upper respiratory infections of multiple and unspecified sites	96	0.43	3	0.56	1.31 (0.34–4.97)	0.696
infection of external ear and acute otitis media	9	0.04	0	0.00	N/A	N/A
Musculoskeletal infections	20	0.09	1	0.19	2.09 (0.06–70.40)	0.681
infective arthritis	8	0.04	0	0.00	N/A	N/A

infective myositis	9	0.04	1	0.19	4.64 (0.27–80.85)	0.292
osteomyelitis	3	0.01	0	0.00	N/A	N/A
Others	366	1.64	7	1.31	0.80 (0.21–2.97)	0.738
infection of the eye	15	0.07	1	0.19	2.79 (0.45–17.19)	0.270
infection in the nervous system	24	0.11	2	0.38	3.48 (0.55–22.20)	0.187
infection in prosthetic devices, implants, and grafts	7	0.03	0	0.00	N/A	N/A
sepsis, SIRS of infectious origin and septic shock	63	0.28	1	0.19	0.66 (0.05–8.29)	0.750
certain bacterial disease	43	0.19	0	0.00	N/A	N/A
spirochetal disease	1	0.00	0	0.00	N/A	N/A
rickettsiosis	1	0.00	0	0.00	N/A	N/A
viral infections	79	0.35	0	0.00	N/A	N/A
mycoses	54	0.24	1	0.19	0.66 (0.05–8.29)	0.750
protozoal disease	5	0.02	1	0.19	8.36 (0.60–117.01)	0.115
unspecified infectious disease	0	0.00	0	0.00	N/A	N/A
acute infective pericarditis and endocarditis	1	0.00	0	0.00	N/A	N/A
mycobacterial infections	73	0.33	1	0.19	0.57 (0.01–40.57)	0.798

Abbreviations: TNF, tumor necrosis factor; IR, incidence rate; PY, person year; CI, confidence interval; ENT, ear, nose and throat; SIRS, systemic inflammatory response syndrome

*Sum of person-years of patients treated with anti-TNF-α agents was 22279.60.

†Sum of person-years of patients treated with vedolizumab/ustekinumab was 533.19.

Study subjects for active tuberculosis analysis

For the analysis of active tuberculosis development, 11,984 patients with biologics-naïve IBD were selected after excluding 251 patients with the history of active tuberculosis (Figure 1). Table 6 presents the baseline characteristics of study patients for active tuberculosis analysis. Their median age was 26.0 years (IQR, 19.0–38.0) years and males were predominant (68.3%). CD was diganosed in 65.7% of patients. Anti-TNF-α agents were selected as biologics therapy in 11,329 (94.5%) patients (most frequent prescirbed drug was adalimumab [61.7%], followd by infliximab [34.1%] and golimumab [4.2%]), and the remaining 655 (5.5%) patients recevied vedolizumab (n = 303) or ustekinumab (n = 352). Several characteristics such as type of IBD, the use of thiopurine, CCI showed statitical significant differences between two groups.

Table 6. Baseline characteristics of patients with inflammatory bowel disease according to the treated biologics for active tuberculosis analysis

Characteristics	Total (n = 11984)	Anti-TNF-α agents (n = 11329)	Vedolizumab/ Ustekinumab (n = 655)	*P*-value
Age	26.0 (19.0–38.0)	26.0 (19.0–38.0)	26.0 (20.0–38.0)	0.222
Age >40 year	2529 (21.1%)	2390 (21.1%)	139 (21.2%)	0.939
Sex, male	8191 (68.3%)	7750 (58.4%)	441 (67.3%)	0.563
Type of IBD				0.001
Crohn's disease	7868 (65.7%)	7400 (65.3%)	468 (71.5%)	
Ulcerative disease	4116 (34.3%)	3929 (34.7%)	187 (28.5%)	
Corticosteroids*				0.052
None	3966 (33.1%)	3772 (33.3%)	194 (29.6%)	
Low dose	791 (6.6%)	764 (6.7%)	27 (4.1%)	
High dose	7227 (60.3%)	6793 (60.0%)	434 (66.3%)	
Immunomodulatory drug				
Thiopurines	7223 (60.3%)	6799 (60.0%)	424 (64.7%)	0.016
Methotrexate	489 (4.1%)	462 (4.1%)	27 (4.1%)	0.956
Comorbidity				
Charlson Comorbidity Index				0.011
0	5610 (46.8%)	5338 (49.2%)	272 (51.5%)	
1	5320 (44.4%)	5008 (46.2%)	312 (47.6%)	
≥2	1054 (8.8%)	983 (9.1%)	71 (10.8%)	
Hypertension	961 (8.0%)	902 (8.3%)	59 (9.0%)	0.338
Diabetes mellitus	888 (7.4%)	835 (7.7%)	53 (8.1%)	0.493
Malignancy	137 (1.1%)	119 (1.1%)	18 (2.7%)	<0.001
Chronic kidney disease	75 (0.6%)	72 (0.7%)	3 (0.5%)	0.799
Follow-up duration after biologics initiation, year	1.96 ± 1.36	1.72 ± 0.75	0.83 ± 0.68	<0.001

Data are presented as the number (%), mean ± standard deviation, and median (interquartile range).

Abbreviations: TNF, tumor necrosis factor; IBD, inflammatory bowel disease

*High dose defined as a dose ≥ 20mg prednisone or equivalent daily for ≥ 14days or cumulative dose ≥ 600mg of prednisone or equivalent

Analysis of actuve tuberculosis development

During the mean 1.72 ± 0.75 years of follow-up period, 102 patient developed active tuberculosis of 11,329 patients treated with anti-TNF-α agents. In addition, the development of active tuberculosis was noted in 2 patients of 655 patietns received vedolizumab/ustekinumab during the mean follow-up duration of 0.83 ± 0.68 years. The incidence rate of active tuberculosis was 0.45 per 1,00 PYs and 0.37 per 1,00 PYs, respectively. The univariate analysis

revealed that the risk of active tuberculosis was not different according to the treated biologics; the RR of vedolizumab/ustekinumab compared with anti-TNF-α agents was 0.54 (95% CI, 0.13–2.19, $P = 0.387$) (Table 7). Table 8 shows that baseline characteristics of 2 patient who develop active tuberculosis during the treatment with vedolizumab/ustekinumab in detail.

Table 7. Risk of tuberculosis development of vedolizumab/ustekinumab compared to anti-TNF-α agents in patients with inflammatory bowel disease.

	Anti-TNF-α agents (n = 11329)*		**Vedolizumab/Ustekinumab (n = 655)†**			
	No. of episodes	IR/100 pys	No. of episodes	IR/100 pys	Relative risk (95% CI)	*P*-value
Mycobacterium tuberculosis infection, overall	102	0.45	2	0.37	0.54 (0.13–2.19)	0.387
Pulmonary tuberculosis	77	0.34	2	0.37	0.73 (0.18–2.99)	0.664
Extrapulmonary tuberculosis	25	0.11	0	0.00	N/A	N/A

Abbreviations: TNF, tumor necrosis factor; IR, incidence rate; PY, person year; CI, confidence interval

*Sum of person-years of patients treated with anti-TNF-α agents was 22863.90.

†Sum of person-years of patients treated with vedolizumab/ustekinumab was 544.54.

Table 8. Characteristics of two patients who developed active tuberculosis during the vedolizumab/ustekinumab treatment

	Case1	Case2
Age, year	72	19
Sex	male	female
Site of tuberculosis	Pulmonary tuberculosis	Pulmonary tuberculosis
TB diagnosis time after biologics use, day	97	311
Type of inflammatory bowel disease	Crohn's disease	Ulcerative disease
Steroid	yes	yes
Immunomodulatory drug		
Thiopurines	yes	no
Methotrexate	no	no
Comorbidities		
CCI, mean	3	0
Hypertension	yes	no
Diabetes mellitus	no	no
Malignancy	yes	no
Chronic kidney disease	no	no

Abbreviations: TB, tuberculosis; CCI, charlson comorbidity index

Primary outcomes excluding previous anti-TNF-α agents users

To minimize the effect of previous anti- TNF-α agents, patients with claim data of anti-TNF-α agents prescription within 6 months before 2017 were excluded, and additional analysis was performed for development of serious infection and active tuberculosis (Figure 1).

Analysis of serious infection development

Of the 14504 patients with IBD who received biologics treatment, 8381 patients who were previously treated with anti-TNF- α agents for 6 months from July 2016 to December 2016 were excluded, and finally 6123 patients were selected for the serious infection analysis. Table 9 shows baseline characteristics of patients with IBD without prior use of anti-TNF-α agents.

The median age was 27.0 (IQR, 21.0—41.0) years and 69.3% were male. The diagnosis of CD and UC were made in 3339 (60.4%) and 2185 (39.6%) respectively. For 4902 patients who were treated with the anti-TNF-α agents, the development of overall serious infection occurred in 718 patients during the mean follow-up period of 1.55 ± 1.05 years. This corresponds to the incidence rate as 9.43 per 100 person-years. In addition, among the 622 patients who were prescribed vedolizumab or ustekinumab, the serious infection developed in 36 patients during the mean follow-up period of 0.84 ± 0.69 years, which corresponds to the incidence rate as 6.87 per 100 person-years. The unadjusted RR was 0.73 (95% CI, 0.40—1.34, P = 0.308), numerically lower than that of aforementioned results, and RR in the multivariate analysis after adjustment of the confounding factors was 0.81 (95% CI, 0.46—1.44, P = 0.478), showing similar results to the previous results that included the previous anti-TNF-α agents users (Table 10). Table 11 presents the detailed classification of serious infection according to the subgroup of infectious site excluding patients with the anti-TNF-α agents users.

Table 9. Baseline characteristics of patients with inflammatory bowel disease without prior use of anti-tumor necrosis factor alpha agents within 6 months before 2017 according to the treated biologics for serious infection analysis

Characteristics	Total (n = 5524)	Anti-TNF-α agents (n = 4902)	Vedolizumab/ Ustekinumab (n = 622)	*P*-value
Age	27.0 (21.0–41.0)	28.0 (21.0–40.0)	26.0 (20.0–38.0)	0.230
Age >40 year	1349 (24.4%)	1214 (24.8%)	135 (21.7%)	0.094
Sex, male	3830 (69.3%)	3405 (69.5%)	425 (68.3%)	0.564
Type of IBD				<0.001
Crohn's disease	3339 (60.4%)	2897 (59.1%)	442 (71.1%)	
Ulcerative disease	2185 (39.6%)	2005 (40.9%)	180 (28.9%)	
Corticosteroids*				<0.001
None	1063 (19.2%)	873 (17.8%)	190 (30.5%)	
Low dose	215 (3.9%)	189 (3.9%)	26 (4.2%)	
High dose	4246 (76.9%)	3840 (78.3%)	406 (65.3%)	

Immunomodulatory drug				
Thiopurines	3967 (71.8%)	3562 (72.7%)	405 (65.1%)	<0.001
Methotrexate	191 (3.5%)	166 (3.4 %)	25 (4.0%)	0.416
Comorbidity				
Charlson Comorbidity Index				0.757
0	2361 (42.7%)	2097 (42.8%)	264 (42.4%)	
1	1772 (32.1%)	1565 (31.9%)	207 (33.3%)	
≥2	1391 (25.2%)	1240 (25.3%)	151 (24.3%)	
Hypertension	517 (9.4%)	461 (9.4%)	56 (9.0%)	0.746
Diabetes mellitus	460 (8.3%)	406 (8.3%)	54 (8.7%)	0.734
Malignancy	68 (1.2%)	50 (1.0%)	18 (2.9%)	<0.001
Chronic kidney disease	31 (0.6%)	28 (0.6%)	3 (0.5%)	>0.999
Follow-up duration after biologics initiation, year	1.55 ± 1.05	1.55 ± 1.05	0.84 ± 0.69	<0.001

Data are presented as the number (%), mean ± standard deviation, and median (interquartile range).

Abbreviations: TNF, tumor necrosis factor; IBD, inflammatory bowel disease

*High dose defined as a dose ≥ 20mg prednisone or equivalent daily for ≥ 14days or cumulative dose ≥ 600mg of prednisone or equivalent

Table 10. Risk of serious infection development of vedolizumab/ustekinumab compared to anti-TNF-α agents in patients with inflammatory bowel disease without prior use of anti-tumor necrosis factor alpha agents 6 months before 2017.

	Anti-TNF-α agents (n = 4902)*		**Vedolizumab/Ustekinumab (n = 622)†**					
	No. of episodes	IR/100 pys	No. of episodes	IR/100 pys	Relative risk (95% CI)	*P*-value	Adjusted relative risk‡ (95% CI)	*P*-value
Serious infections, overall	718	9.43	36	6.87	0.73 (0.40–1.34)	0.308	0.81 (0.46–1.44)	0.478
Pulmonary	135	1.77	4	0.76	0.43 (0.10–1.85)	0.256	0.47 (0.11–1.98)	0.302
Gastrointestinal	165	2.17	8	1.53	0.70 (0.27–1.85)	0.476	0.83 (0.33–2.07)	0.688
Skin and soft tissue	104	1.37	9	1.72	1.26 (0.53–3.01)	0.607	1.43 (0.63–3.25)	0.391
Urinary tract	63	0.83	2	0.38	0.46 (0.07–2.92)	0.411	0.50 (0.07–3.72)	0.497
Eye/Nose/Throat	80	1.05	5	0.95	0.91 (0.30–2.76)	0.865	0.94 (0.31–2.87)	0.912
Musculoskeletal	3	0.04	1	0.19	4.84 (0.76–30.70)	0.094	4.24 (1.16–15.43)	0.029
Others	168	2.21	7	1.34	0.61 (0.15–2.37)	0.471	0.66 (0.19–2.31)	0.516

Abbreviations: TNF, tumor necrosis factor; IR, incidence rate; PY, person year; CI, confidence interval

*Sum of person-years of patients treated with anti-TNF-α agents was 7613.75

†Sum of person-years of patients treated with vedolizumab/ustekinumab was 524.17

‡Adjusted covariates included age, sex, Charlson comorbidity index, steroid use, and immunomodulatory drugs(thiopurines or methotrexate).

Table 11. Risk of serious infection development of vedolizumab/ustekinumab compared with anti-TNF-α agents in patients with inflammatory bowel disease without prior use of anti-tumor necrosis factor alpha agents within 6 months before 2017 according to the site of infection.

	Anti-TNF-α agents (n = 10849)		Vedolizumab/Ustekinumab (n = 632)			
	No. of episodes	IR/100 pys	No. of episodes	IR/100 pys	Relative risk (95% CI)	*P*-value
Pulmonary	135	1.77	4	0.76	0.43 (0.10–1.85)	0.256
pneumonia	70	0.92	2	0.38	0.41 (0.05–3.74)	0.433
other acute lower respiratory infections	65	0.85	2	0.38	0.45 (0.09–2.34)	0.340
lung abscess	0	0.00	0	0.00	N/A	N/A
empyema	0	0.00	0	0.00	N/A	N/A
Gastrointestinal	165	2.17	8	1.53	0.70 (0.27–1.85)	0.476
intestinal infectious disease	65	0.85	3	0.57	0.67 (0.15–2.96)	0.598
viral hepatitis	3	0.04	1	0.19	4.84 (0.34–68.45)	0.243
cholangitis	95	1.25	4	0.76	0.61 (0.15–2.45)	0.487
liver abscess	1	0.01	0	0.00	N/A	N/A
infectious esophagitis	1	0.01	0	0.00	N/A	N/A
Skin and soft tissue	104	1.37	9	1.72	1.26 (0.53–3.01)	0.607
erysipelas	0	0.00	0	0.00	N/A	N/A
dermatophytosis and other superficial mycoses	9	0.12	0	0.00	N/A	N/A
cellulitis and abscess	37	0.49	6	1.14	2.36 (0.75–7.38)	0.142
herpes virus	9	0.12	2	0.38	3.23 (0.42–24.69)	0.259
other local infections of skin, oral tissue, and subcutaneous tissue	49	0.64	1	0.19	0.30 (0.02–3.73)	0.347
Urinary tract and gynecological	63	0.83	2	0.38	0.46 (0.07 - 2.92)	0.411
nephritis	15	0.20	0	0.00	N/A	N/A
acute prostatitis and prostate abscess	3	0.04	0	0.00	N/A	N/A
cystitis	10	0.13	0	0.00	N/A	N/A
salpingitis and oophoritis	0	0.00	0	0.00	N/A	N/A
endometritis	0	0.00	0	0.00	N/A	N/A
cervicitis uteri	3	0.04	0	0.00	N/A	N/A
syphilis	1	0.01	0	0.00	N/A	N/A
gonorrhea	0	0.00	0	0.00	N/A	N/A
chlamydia	0	0.00	0	0.00	N/A	N/A
orchitis and epididymitis	1	0.01	0	0.00	N/A	N/A
other urinary tract infections	30	0.39	2	0.38	0.97 (0.21–4.41)	0.967
ENT infections	80	1.05	5	0.95	0.91 (0.30–2.76)	0.865
mastoiditis	0	0.00	0	0.00	N/A	N/A

nasopharyngitis	0	0.00	0	0.00	N/A	N/A
sinusitis	6	0.08	1	0.19	2.42 (0.26–22.14)	0.434
pharyngitis	15	0.20	1	0.19	0.97 (0.09–10.58)	0.979
pharyngeal, retropharyngeal, and parapharyngeal abscess	5	0.07	0	0.00	N/A	N/A
tonsillitis	12	0.16	0	0.00	N/A	N/A
laryngitis and tracheitis	5	0.07	0	0.00	N/A	N/A
acute upper respiratory infections of multiple and unspecified sites	36	0.47	3	0.57	1.21 (0.31–4.76)	0.784
infection of external ear and acute otitis media	1	0.01	0	0.00	N/A	N/A
Musculoskeletal infections	3	0.04	1	0.19	4.84 (0.76–30.70)	0.094
infective arthritis	0	0	0	0.00	N/A	N/A
infective myositis	3	0.04	1	0.19	4.84 (0.76–30.70)	0.094
osteomyelitis	0	0	0	0.00	N/A	N/A
Others	168	2.21	7	1.34	0.61 (0.15–2.37)	0.471
infection of the eye	5	0.07	1	0.19	2.91 (0.36–23.28)	0.315
infection in the nervous system	8	0.11	2	0.38	3.63 (0.49–26.74)	0.206
infection in prosthetic devices, implants, and grafts	2	0.03	0	0.00	N/A	N/A
sepsis, SIRS of infectious origin and septic shock	25	0.33	1	0.19	0.58 (0.06–6.04)	0.649
certain bacterial disease	19	0.25	0	0.00	N/A	N/A
spirochetal disease	0	0	0	0.00	N/A	N/A
rickettsiosis	1	0.01	0	0.00	N/A	N/A
viral infections	42	0.55	0	0.00	N/A	N/A
mycoses	20	0.26	1	0.19	0.73 (0.05–11.50)	0.821
protozoal disease	2	0.03	1	0.19	7.26 (0.85–61.79)	0.070
unspecified infectious disease	0	0	0	0.00	N/A	N/A
acute infective pericarditis and endocarditis	1	0.01	0	0.00	N/A	N/A
mycobacterial infections	43	0.56	1	0.19	0.34 (0.00–23.27)	0.615

Analysis of active tuberculosis development

For the analysis for the active tuberculosis development, of the 12235 patients who received biologics treatment between January 2017 November 2020, 5733 patients who were treated anti-TNF-α agents were excluded, and 5981 patients were selected for active tuberculosis analysis (Figure 1). Table 12 shows the baseline characteristics of patients without prior use of anti-TNF-α agents. The mean age was 28.0 (IQR, 21.0—41.0) years, and males were predominant (68.9%). The CD and UC were diagnosed in 3524 (58.8%), and 2457 (41.1%)

respectively. For 5337 patients who were treated with the anti-TNF-α agents, the active tuberculosis developed in 71 patients during the mean follow-up period of 1.53 ± 1.05 years. This corresponds to the incidence rate as 0.87 per 1,00 PYs. In addition, of the 644 patients who received vedolizumab, the active tuberculosis developed in 2 patients during the mean follow-up period of 0.83 ± 0.68 years, which corresponds to the incidence rate as 0.37 per 1,00 PYs. In the univariate analysis, the RR of vedolizumab/ustekinumab compared with anti-TNF-α agents was 0.31 (95%CI, 0.07—1.26, P = 0.101), lower than that of aforementioned results that included the previous anti-TNF-α agents users (Table 13).

Table 12. Baseline characteristics of patients with inflammatory bowel disease without prior use of anti-tumor necrosis factor alpha agents within 6 months of the study date according to the treated biologics for active tuberculosis analysis

Characteristics	Total (n = 5981)	Anti-TNF-α agents (n = 5337)	Vedolizumab/ Ustekinumab (n = 644)	*P*-value
Age	28.0 (21.0–41.0)	28.0 (21.0–41.0)	26.0 (20.0–38.0)	0.041
Age >40 year	1532 (25.6%)	1393 (26.1%)	139 (21.6%)	
Sex, male	4123 (68.9%)	3687 (69.1%)	436 (67.7%)	0.474
Type of IBD				<0.001
Crohn's disease	3524 (58.9%)	3063 (57.4%)	461 (71.6%)	
Ulcerative disease	2457 (41.1%)	2274 (42.6%)	183 (28.4%)	
Corticosteroids*				<0.001
None	1069 (17.9%)	877 (16.4%)	192 (29.8%)	
Low dose	228 (3.8%)	201 (3.8%)	27 (4.2%)	
High dose	4684 (78.3%)	4259 (79.8%)	425 (66.0%)	
Immunomodulatory drug				
Thiopurines	4276 (71.5%)	3858(72.3%)	418 (64.9%)	<0.001
Methotrexate	200 (3.3%)	173 (3.2%)	27 (4.2%)	0.205
Comorbidity				
Charlson Comorbidity Index				0.500
0	2455 (41.0%)	2187 (41.0%)	268 (41.6%)	
1	1928 (32.2%)	1712 (32.1%)	216 (33.5%)	
≥2	1598 (26.7%)	1438 (26.9%)	160 (24.8%)	
Hypertension	585 (9.8%)	526 (9.9%)	59 (9.2%)	0.575
Diabetes mellitus	545(9.1%)	492 (9.2%)	53 (8.2%)	0.410
Malignancy	76 (1.3%)	58 (1.1%)	18 (2.8%)	<0.001

Chronic kidney disease	34 (0.6%)	31 (0.6%)	3 (0.5%)	>0.999
Follow-up duration after biologics initiation, year	1.45 ± 1.04	1.53 ± 1.05	0.83 ± 0.68	<0.001

Data are presented as the number (%), mean ± standard deviation, and median (interquartile range).

Abbreviations: TNF, tumor necrosis factor; IBD, inflammatory bowel disease

*High dose defined as a dose ≥ 20mg prednisone or equivalent daily for ≥ 14days or cumulative dose ≥ 600mg of prednisone or equivalent

Table 13. Risk of tuberculosis development of vedolizumab/ustekinumab compared to anti-TNF-α agents in patients with inflammatory bowel disease without prior use of anti-tumor necrosis factor alpha agents within 6 months before 2017.

	Anti-TNF-α agents (n =5337)*		**Vedolizumab/Ustekinumab (n =644)†**			
	No. of episodes	IR/100 pys	No. of episodes	IR/100 pys	Relative risk (95% CI)	*P*-value
Mycobacterium tuberculosis infection, overall	71	0.87	2	0.37	0.31 (0.07–1.26)	0.101
Pulmonary tuberculosis	52	0.64	2	0.37	0.43 (0.10–1.76)	0.238
Extrapulmonary tuberculosis	19	0.23	0	0.00	N/A	N/A

Abbreviations: TNF, tumor necrosis factor; IR, incidence rate; PY, person year; CI, confidence interval

*Sum of person-years of patients treated with anti-TNF-α agents was 8155.87

†Sum of person-years of patients treated with vedolizumab/ustekinumab was 535.22

DISCUSSION

Vedolizumab and ustekinumab have recently been widely used for the treatment of IBD, with similar therapeutic efficacy compared with anti-TNF-α agents(43). However, the studies comparing vedolizumab/ustekinumab and anti-TNF-α agents in terms of serious infection and active tuberculosis development is limited, particularly for Asian population. In the present study, we analyzed whether there is a difference in the serious infection and active tuberculosis development between the use of vedolizumab/ustekinumab and anti-TNF-α agents through the population-based cohort analysis of patients with biologics-naïve IBD in South Korea by analyzing nationwide administrative claim data. To our knowledge, this is the first study to analyze this issue for the patients with IBD. The key findings were as follows: (1) there was no difference of incidence of serious infection in the patients with biologics-naïve IBD treated with vedolizumab/ustekinumab compared to those received anti-TNF-α agents, and (2) the risk of tuberculosis development was also similar irrespective of treatment with vedolizumab/ustekinumab or anti-TNF-α agents.

A number of previous studies reported the rate of serious infection between the anti-TNF-α agents and vedolizumab or ustekinumab. Singh et al. found that vedolizumab was related to lower risk of serious infections development than anti-TNF-α agents in patients with UC, whereas the indifferent risk was noted in those with CD, after analyzing US administrative claims database(31). Recently, study assessing US Medicare administrative claims cohort of 1632 patients with old age also found that treatment with vedolizumab had a lower risk of infections requiring hospitalization compared with anti-TNF-α agents(44). Another study analyzing a national commercial health insurance plan in the United States from 2008 to 2019 showed that the use of ustekinumab led to significant lower risk of infection(30). In contrast, the serious infection risk was similar between the use of vedolizumab/ustekinumab and anti-

TNF-α agents in our study subjects, of which finding were consistent with the retrospective study conducted in Italy(45) and recent meta-analysis reporting that a comparable rate of serious infection development between infliximab and vedolizumab in patients with IBD(46).

As TNF plays an pivotal role in the formation and maintenance of the integrity of the granuloma(25), there is an increased risk of active tuberculosis development after the use of anti-TNF-α agents which is in proportion to the tuberculosis burden of each country(47). Since the recent incidence of tuberculosis is intermediate in South Korea (36/100,000 per year in 2021(48), patients with IBD in South Korea treated with anti-TNF-α agents have a high risk of developing tuberculosis compared with those in western countries(49),(50). In contrast, as the action mechanism of ustekinumab is indirectly related to the inhibition of TNF and the drug target of vedolizumab is not associated with TNF(51), the risk of tuberculosis development with these drugs appear to be theoretically low than anti-TNF-α agents. While previous studies also reported that the risk of active tuberculosis is considerably low in patients with IBD received vedolizumab/ustekinumab(29, 52, 53), the rate of active tuberculosis development was similar between vedolizumab/ustekinumab and anti-TNF-α agents in our study cohort. Given that immunosuppressive agents such as steroid or azathioprine can substantially increase the risk of active tuberculosis(54), the cause of active tuberculosis could be related to immunosuppressive agents other than vedolizumab/ustekinumab in our patients.

The present study had several limitations. First, the number of patients treated with vedolizumab/ustekinumab was limited compared with those received anti-TNF-α agents, and the follow-up duration after the treatment of biologics was relatively short in the present study. This was because we selected only new users of biologics to exclude the effect of previous biologics treatment on the outcome, and it was only after 2017 when vedolizumab/ustekinumab has been approved for the treatment of IBD in South Korea(34). Moreover, we could not assess

unobserved confounders, particularly those related to treatment selection by attending physician, although we included steroid or other immune-modulators to adjust surrogate of disease activity. Third, as the present study was an administrative claims database study, subjective or objective disease activity of IBD was not evaluated. Finally, as the detailed microbiological data was not available in claims databases, we adopted ICD-10 code for the serious infection or active tuberculosis development. However, the definition of hospitalization-requiring serious infections or active tuberculosis development has been well validated in previous studies(31, 55).

Conclusion

We found that the treatment of vedolizumab/ustekinumab resulted in the similar rate of serious infection requiring hospitalization compared with anti-TNF-α agents in the patients with biologics-naïve IBD. Additionally, a comparable rate of active tuberculosis development was also noted between the use of vedolizumab/ustekinumab and anti-TNF-α agents.

References

1. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. World J Gastroenterol. 2014;20(1):91-9.
2. Wright RD, Cooper D. Glycobiology of leukocyte trafficking in inflammation. Glycobiology. 2014;24(12):1242-51.
3. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res. 2014;7:113-20.
4. Nawroth PP, Stern DM. Modulation of endothelial cell hemostatic properties by tumor necrosis factor. J Exp Med. 1986;163(3):740-5.
5. Juillerat P, Grueber MM, Ruetsch R, Santi G, Vuillèmoz M, Michetti P. Positioning biologics in the treatment of IBD: A practical guide - Which mechanism of action for whom? Curr Res Pharmacol Drug Discov. 2022;3:100104.
6. Shi HY, Ng SC. The state of the art on treatment of Crohn's disease. J Gastroenterol. 2018;53(9):989-98.
7. Banerjee R, Ali RAR, Wei SC, Adsul S. Biologics for the Management of Inflammatory Bowel Disease: A Review in Tuberculosis-Endemic Countries. Gut Liver. 2020;14(6):685-98.
8. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.
9. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201-14.
10. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375(20):1946-60.
11. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711-21.
12. Arseneau KO, Cominelli F. Targeting leukocyte trafficking for the treatment of inflammatory bowel disease. Clin Pharmacol Ther. 2015;97(1):22-8.
13. Smith MA, Mohammad RA. Vedolizumab: an α4β7 integrin inhibitor for inflammatory bowel diseases. Ann Pharmacother. 2014;48(12):1629-35.
14. Luzentales-Simpson M, Pang YCF, Zhang A, Sousa JA, Sly LM. Vedolizumab: Potential Mechanisms of Action for Reducing Pathological Inflammation in Inflammatory Bowel Diseases. Front Cell Dev Biol. 2021;9:612830.
15. Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. Drugs. 2005;65(16):2253-86.
16. Verstockt B, Salas A, Sands BE, Abraham C, Leibovitzh H, Neurath MF, et al. IL-12 and IL-23 pathway inhibition in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2023.
17. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov. 2012;11(10):763-76.
18. . !!! INVALID CITATION !!! 2-4.
19. D'Haens G, Reinisch W, Colombel JF, Panes J, Ghosh S, Prantera C, et al. Five-year Safety Data From ENCORE, a European Observational Safety Registry for Adults With Crohn's Disease Treated With Infliximab [Remicade®] or Conventional Therapy. J Crohns

Colitis. 2017;11(6):680-9.
20. D'Haens G, Reinisch W, Panaccione R, Satsangi J, Petersson J, Bereswill M, et al. Lymphoma Risk and Overall Safety Profile of Adalimumab in Patients With Crohn's Disease With up to 6 Years of Follow-Up in the Pyramid Registry. Am J Gastroenterol. 2018;113(6):872-82.
21. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol. 2013;108(8):1268-76.
22. Holmer A, Singh S. Overall and comparative safety of biologic and immunosuppressive therapy in inflammatory bowel diseases. Expert Rev Clin Immunol. 2019;15(9):969-79.
23. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol. 2012;107(9):1409-22.
24. Nyboe Andersen N, Pasternak B, Friis-Møller N, Andersson M, Jess T. Association between tumour necrosis factor-α inhibitors and risk of serious infections in people with inflammatory bowel disease: nationwide Danish cohort study. Bmj. 2015;350:h2809.
25. Shim TS. Diagnosis and Treatment of Latent Tuberculosis Infection due to Initiation of Anti-TNF Therapy. Tuberc Respir Dis (Seoul). 2014;76(6):261-8.
26. Dobler CC. Biologic Agents and Tuberculosis. Microbiol Spectr. 2016;4(6).
27. Colombel JF, Sands BE, Rutgeerts P, Sandborn W, Danese S, D'Haens G, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017;66(5):839-51.
28. Sandborn WJ, Feagan BG, Danese S, O'Brien CD, Ott E, Marano C, et al. Safety of Ustekinumab in Inflammatory Bowel Disease: Pooled Safety Analysis of Results from Phase 2/3 Studies. Inflamm Bowel Dis. 2021;27(7):994-1007.
29. Choi MG, Ye BD, Yang SK, Shim TS, Jo KW, Park SH. The Risk of Tuberculosis in Patients With Inflammatory Bowel Disease Treated With Vedolizumab or Ustekinumab in Korea. J Korean Med Sci. 2022;37(14):e107.
30. Cheng D, Kochar BD, Cai T, Ananthakrishnan AN. Risk of Infections With Ustekinumab and Tofacitinib Compared to Tumor Necrosis Factor α Antagonists in Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2022.
31. Singh S, Heien HC, Herrin J, Dulai PS, Sangaralingham L, Shah ND, et al. Comparative Risk of Serious Infections With Tumor Necrosis Factor α Antagonists vs Vedolizumab in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2022;20(2):e74-e88.
32. Kim HK, Song SO, Noh J, Jeong IK, Lee BW. Data Configuration and Publication Trends for the Korean National Health Insurance and Health Insurance Review & Assessment Database. Diabetes Metab J. 2020;44(5):671-8.
33. Ahn HJ, Kim YJ, Lee HS, Park JH, Hwang SW, Yang DH, et al. High Risk of Fractures Within 7 Years of Diagnosis in Asian Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2022;20(5):e1022-e39.
34. Jung YS. Trends in Healthcare Costs for Inflammatory Bowel Disease in South Korea. Gut Liver. 2020;14(1):3-4.
35. Bae S, Kim YJ, Kim MJ, Kim JH, Yun SC, Jung J, et al. Risk of tuberculosis in patients with cancer treated with immune checkpoint inhibitors: a nationwide observational study. J Immunother Cancer. 2021;9(9).
36. Kim MC, Yun SC, Lee SO, Choi SH, Kim YS, Woo JH, et al. Association between Tuberculosis, Statin Use, and Diabetes: A Propensity Score-Matched Analysis. Am J Trop Med

Hyg. 2019;101(2):350-6.
37. Hermans SM, Zinyakatira N, Caldwell J, Cobelens FGJ, Boulle A, Wood R. High Rates of Recurrent Tuberculosis Disease: A Population-level Cohort Study. Clin Infect Dis. 2021;72(11):1919-26.
38. Verver S, Warren RM, Beyers N, Richardson M, van der Spuy GD, Borgdorff MW, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. Am J Respir Crit Care Med. 2005;171(12):1430-5.
39. Luzze H, Johnson DF, Dickman K, Mayanja-Kizza H, Okwera A, Eisenach K, et al. Relapse more common than reinfection in recurrent tuberculosis 1-2 years post treatment in urban Uganda. Int J Tuberc Lung Dis. 2013;17(3):361-7.
40. Yoo JW, Jo KW, Kang BH, Kim MY, Yoo B, Lee CK, et al. Mycobacterial diseases developed during anti-tumour necrosis factor-α therapy. Eur Respir J. 2014;44(5):1289-95.
41. Lee SK, Kim SY, Kim EY, Jung JY, Park MS, Kim YS, et al. Mycobacterial infections in patients treated with tumor necrosis factor antagonists in South Korea. Lung. 2013;191(5):565-71.
42. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004;57(12):1288-94.
43. Bressler B, Yarur A, Silverberg MS, Bassel M, Bellaguarda E, Fourment C, et al. Vedolizumab and Anti-Tumour Necrosis Factor α Real-World Outcomes in Biologic-Naïve Inflammatory Bowel Disease Patients: Results from the EVOLVE Study. J Crohns Colitis. 2021;15(10):1694-706.
44. Kochar B, Pate V, Kappelman MD, Long MD, Ananthakrishnan AN, Chan AT, et al. Vedolizumab Is Associated With a Lower Risk of Serious Infections Than Anti-Tumor Necrosis Factor Agents in Older Adults. Clin Gastroenterol Hepatol. 2022;20(6):1299-305.e5.
45. Innocenti T, Roselli J, Lynch EN, Apolito P, Parisio L, Bagnoli S, et al. Infectious risk of vedolizumab compared with other biological agents in the treatment of inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2021;33(1S Suppl 1):e574-e9.
46. Peyrin-Biroulet L, Arkkila P, Armuzzi A, Danese S, Guardiola J, Jahnsen J, et al. Comparative efficacy and safety of infliximab and vedolizumab therapy in patients with inflammatory bowel disease: a systematic review and meta-analysis. BMC Gastroenterol. 2022;22(1):291.
47. Kedia S, Mouli VP, Kamat N, Sankar J, Ananthakrishnan A, Makharia G, et al. Risk of Tuberculosis in Patients With Inflammatory Bowel Disease on Infliximab or Adalimumab Is Dependent on the Local Disease Burden of Tuberculosis: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2020;115(3):340-9.
48. Annual Report on the Notified Tuberculosis in Korea. Cheongju, Korea: Korea Disease Control and Prevention Agency; 2021.
49. Kang J, Jeong DH, Han M, Yang SK, Byeon JS, Ye BD, et al. Incidence of Active Tuberculosis within One Year after Tumor Necrosis Factor Inhibitor Treatment according to Latent Tuberculosis Infection Status in Patients with Inflammatory Bowel Disease. J Korean Med Sci. 2018;33(47):e292.
50. Lee JY, Oh K, Hong HS, Kim K, Hong SW, Park JH, et al. Risk and characteristics of tuberculosis after anti-tumor necrosis factor therapy for inflammatory bowel disease: a hospital-based cohort study from Korea. BMC Gastroenterol. 2021;21(1):390.
51. Neurath MF. Current and emerging therapeutic targets for IBD. Nat Rev Gastroenterol Hepatol. 2017;14(5):269-78.
52. Ng SC, Hilmi IN, Blake A, Bhayat F, Adsul S, Khan QR, et al. Low Frequency of

Opportunistic Infections in Patients Receiving Vedolizumab in Clinical Trials and Post-Marketing Setting. Inflamm Bowel Dis. 2018;24(11):2431-41.
53. Sandborn WJ, Rutgeerts P, Gasink C, Jacobstein D, Zou B, Johanns J, et al. Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. Aliment Pharmacol Ther. 2018;48(1):65-77.
54. Hong SN, Kim HJ, Kim KH, Han SJ, Ahn IM, Ahn HS. Risk of incident Mycobacterium tuberculosis infection in patients with inflammatory bowel disease: a nationwide population-based study in South Korea. Aliment Pharmacol Ther. 2017;45(2):253-63.
55. Kang HY, Yoo H, Park W, Go U, Jeong E, Jung KS, et al. Tuberculosis Notification Completeness and Timeliness in the Republic of Korea During 2012-2014. Osong Public Health Res Perspect. 2016;7(5):320-6.