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ORIGINAL RESEARCH

Drug Persistence and Incidence of Active Tuberculosis of Tumor Necrosis Factor Alpha Inhibitors Versus Tocilizumab as the First-Line Biological Treatment in Patients with Rheumatoid Arthritis: A Nationwide Population-Based Retrospective Cohort Analysis

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ABSTRACT

***Introduction*:** Drug persistence may be a surrogate marker that reflects both long-term efficacy and safety in clinical settings, and tuberculosis (TB) is considered as one of the most important opportunistic infections after the biological treatment in rheumatoid arthritis (RA). We aimed to compare drug persistence and incidence of TB between tumor necrosis factor alpha (TNFα) inhibitors and tocilizumab in patients with RA using data from the Korean Health Insurance Review and Assessment Service database.

***Methods*:** In this analysis, 5449 patients with RA who started TNFα inhibitors, such as adalimumab, etanercept, infliximab, and golimumab or tocilizumab, as the first-line biological therapy between January 2014 and December 2017 were analyzed and followed up until December 2019. Drug persistence was defined as the duration from initiation to first discontinuation, and TB was defined as the prescription of >2 anti-TB medications after the initiation of biologics.

Prior Presentation: Comparison of Drug Persistence and Incidence of Tuberculosis Between Tumor Necrosis Factor alpha Inhibitors and Tocilizumab as the First-line Biological Treatment in Patients with Rheumatoid Arthritis Using the Korean Health Insurance Review and Assessment Service Database—2022 ACR Meeting Abstract.

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***Results*:** TNFα inhibitors and tocilizumab were prescribed in 4202 (adalimumab, 1413; etanercept, 1100; infliximab, 769; golimumab 920) and 1247 patients with RA, respectively. During the analysis period, 2090 (49.7%) and 477 (38.3%) patients with RA discontinued TNFα inhibitors and tocilizumab, respectively, and 42 patients with RA developed TB (TNFα inhibitors, 33; tocilizumab, 9). After adjustment for confounding factors, TNFα inhibitors were significantly associated with a higher risk of discontinuation compared with tocilizumab (hazard ratio (HR) 1.63, $p<0.001$). In subgroup analysis, all types of TNFα inhibitors, except for infliximab, demonstrated a significantly lower persistence rate compared with tocilizumab. There was no significant difference in TB incidence between tocilizumab and TNFα inhibitors. In subgroup analysis, infliximab has a significantly higher risk of TB compared with tocilizumab (HR 2.84, $p=0.02$).

***Conclusion*:** In this analysis, tocilizumab had longer persistence than TNFα inhibitors with a similar incidence of TB. Our analysis has limitations: (1) The HIRA database lacks clinical details like disease activity and joint damage extent, potentially influencing the analysis results. (2) Reasons for discontinuing biological agents were not available. (3) TB diagnoses may be inaccurate because of missing microbiological results. (4) We did not analyze the impact of treating latent TB infection on TB development post-biological treatment, despite mandatory screening in Korea.

Keywords: Rheumatoid arthritis; Monoclonal antibodies; Treatment adherence and compliance; Mycobacterium infections

Key Summary Points

This study compared drug persistence and incidence of active tuberculosis (TB) between tumor necrosis factor alpha inhibitors and tocilizumab in patients with rheumatoid arthritis (RA).

Selecting medications with better long-term persistence and lower risk of adverse events may be more appropriate for optimizing clinical outcomes in patients with RA, who need to maintain lifelong therapy.

Tumor necrosis factor alpha inhibitors were significantly associated with a higher risk of discontinuation compared with tocilizumab whereas there was no significant difference in TB incidence between tocilizumab and tumor necrosis factor alpha inhibitors.

Tocilizumab may be a better therapeutic option for RA in terms of mediation persistence; however, the similar risk of TB between tocilizumab and TNFα inhibitors warrants caution.

INTRODUCTION

Rheumatoid arthritis (RA) has been considered incurable because of its characteristic progressive joint destruction caused by chronic and persistent synovitis and increased morbidity and mortality [1, 2]. Remission or low disease activity owing to the elimination of synovial inflammation using disease-modifying antirheumatic drugs (DMARDs) is the main goal of RA treatment. Conventional synthetic DMARDs (csDMARDs), such as methotrexate (MTX), are currently recommended as initial treatment [3, 4]; however, up to 60% of patients with RA do not achieve remission with these drugs alone [5, 6]. The development and introduction of biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), along with a better understanding of the molecular biology of the pathogenesis of RA, have led to dramatic improvements in RA treatment. Although the

biological targets and structures of bDMARDs and tsDMARDs differ, their therapeutic efficacies in RA are considered largely similar [7]. When a treatment target is not achieved despite csDMARD therapy, bDMARDs or tsDMARDs are recommended unless serious adverse effects occur [3, 4]. Since the initial use of anti-tumor necrosis factor alpha (TNFα) agents in the early 2000s, various non-TNFα inhibitors, such as tocilizumab and abatacept, and Janus kinase inhibitors, such as tofacitinib, baricitinib, and upadacitinib, have been approved as therapeutic agents for RA. Among them, TNFα inhibitors and tocilizumab are the most commonly used biological agents in Korea [8].

Drug persistence may be a surrogate marker that reflects both long-term efficacy and safety in clinical settings [9]. Thus, selecting medications with better long-term persistence may be more appropriate for optimizing clinical outcomes in patients with chronic diseases, such as RA, who need to maintain lifelong therapy. Hence, considerable studies have been conducted to explore drug persistence of biological agents in patients with RA to date, but there is a paucity of data comparing the persistence rate between TNFα inhibitors and tocilizumab in Korea. Despite the remarkable therapeutic benefits of bDMARDs and tsDMARDs in RA treatment, the use of these medications is accompanied by a wide range of side effects, among which primary and opportunistic infections impose significant concern owing to their ability to compromise the host immune defense. In particular, TNFα plays an important role in the prevention of reactivation of latent tuberculosis (TB); thus, anti-TNFα drug use is associated with an approximately four- to eightfold increased risk of active TB [10]. bDMARDs other than TNFα inhibitors and tsDMARDs seem to have a lower risk of TB compared with TNFα inhibitors, but real-world data comparing the risk of TB between TNFα inhibitors and other treatments are limited, as pointed out by Evangelatos et al. [10]. In the present analysis, we aimed to compare drug persistence and incidence of TB between TNFα inhibitors and tocilizumab in Korean patients with RA using a nationwide claims database.

Our analysis has some limitations. First, the Korean Health Insurance Review and Assessment Service (HIRA) database used in this analysis does not provide clinical information, including disease activity, RA-associated autoantibodies, symptom duration, and extent of joint destruction, which could potentially influence the analysis results. In addition, we could not obtain data regarding the reasons for discontinuation of biological agents. Second, as the microbiological results of TB diagnoses are not available in the HIRA database, the identification of TB cases in our analysis may not be accurate. Third, we did not analyze the effect of treatment of latent TB infection on the development of TB after biological treatment. Preventive therapy by screening for latent TB infection prior to the initiation of biological treatments is mandatory in Korea, and Shin et al. reported that chemotherapy for latent TB infection could reduce the incidence of TB after biologics therapy in Korean patients with RA [11]. Fourth, we did not collect data regarding the number of concomitant csDMARDs and the mean dose of GCs in patients with RA receiving TNFα inhibitors or tocilizumab and the proportion of patients on TNFα inhibitors or tocilizumab who were taking these medications as monotherapy. Fifth, we did not calculate the 5-year persistence rate in patients with RA.

METHODS

Data Source and Study Design and Population

We conducted a nationwide, population-based, retrospective cohort analysis using data from the HIRA claims database. Nearly the entire Korean population (97%) is enrolled in the Korean National Health Insurance Service (NHIS) program, which reimburses approximately 70–95% of the total medical expenses, except for some medical services, such as cosmetic surgery or unproven treatments [12]. Healthcare providers submit all medical claims for both outpatient visits and inpatient care to HIRA, which announces the results of the review to the NHIS [12]. Thus, HIRA contains clinical data, such

as demographics, diagnoses, tests, prescription records, procedures, and operations; however, the results of medical tests and treatment outcomes are not recorded [12]. The HIRA database uses the seventh edition of the Korean Classification of Diseases (KCD-7), which is a modified version of the tenth edition of the International Classification of Diseases (ICD-10). Patients with RA aged ≥ 18 years who newly started TNFα inhibitors or tocilizumab as the first-line biological treatment owing to inadequate response to csDMARDs, such as MTX, between January 2014 and December 2017 were analyzed. TNFα inhibitors included adalimumab, etanercept, golimumab, and infliximab that were available during the analysis period in Korea. The index date was defined as the date of initiation of TNFα inhibitors or tocilizumab treatment, and patients with RA having relevant diagnostic codes (ICD-10 code M05 or M06, KCD-7 code M05 or M06) before the index date were selected. The following patients were excluded from this analysis: (1) patients with RA aged < 18 years; (2) patients receiving TNFα inhibitors, tocilizumab, other bDMARDs, such as abatacept and rituximab, or tsDMARDs, such as tofacitinib and baricitinib, within 6 months prior to the index date; (3) patients diagnosed with active TB within 6 months prior to the index date; and (4) patients with concomitant diagnosis of ankylosing spondylitis (ICD-10 code M45, KCD-7 code M45), psoriatic arthritis (ICD-10 code M07, KCD-7 code M07), psoriasis (ICD-10 code L40, KCD-7 code L40), Crohn's disease (ICD-10 code K50, KCD-7 code K50), or ulcerative colitis (ICD-10 code K51, KCD-7 code K51). Figure 1 shows the flowchart of the inclusion and exclusion criteria of the study subjects. All study patients were followed up until December 2019 for the occurrence of study outcomes, such as drug persistence and active TB. This study was approved by the Research and Ethical Review Board of Pusan National University Hospital, which waived the requirement for informed consent because of the retrospective study design and anonymity of the extracted data (IRB no. 2007-032-093). The present study was funded by JW Pharmaceutical.

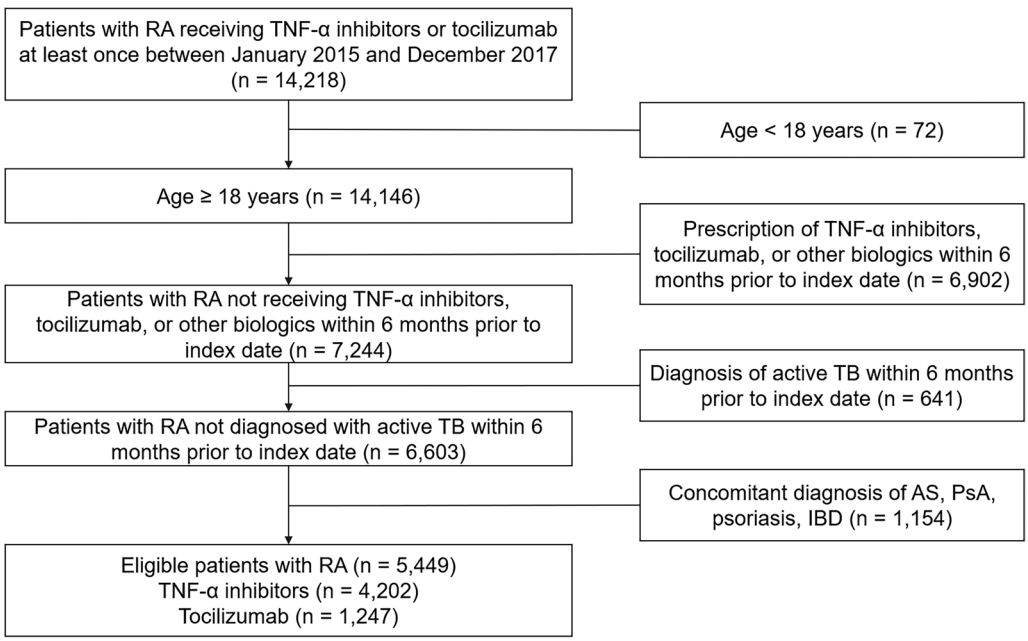

Fig. 1 Flowchart of the present analysis. *RA* rheumatoid arthritis, *TNFα* tumor necrosis factor alpha, *TB* tuberculosis, *AS* ankylosing spondylitis, *PsA* psoriatic arthritis

Study Outcomes

Drug persistence was defined as the time from initiation (index date) to discontinuation of TNFα inhibitors or tocilizumab treatment. The "discontinuation" included as follows: (1) stopping index TNFα inhibitors or tocilizumab that was defined as no claim for these medications after the last prescription, (2) restarting index TNFα inhibitors or tocilizumab > 90 days (treatment gap) after the last prescription, and (3) switching to the other bDMARDs, such as TNFα inhibitors, tocilizumab, abatacept, and tocilizumab, or tsDMARDs, such as tofacitinib and baricitinib. The HIRA considers bDMARDs to be uninterrupted if they are re-prescribed within 90 days of their last prescription, but bDMARDs are discontinued by the HIRA if they are re-prescribed > 90 days after their last prescription. In addition, the reimbursement criteria for re-prescribed bDMARDs differ depending on whether the bDMARDs are re-prescribed ≤ 90 or > 90 days after the last prescription in Korea. Considering the HIRA reimbursement regulations, we assumed that it was appropriate to set the treatment gap to 90 days.

Active TB caused by TNFα inhibitors or tocilizumab was defined as taking > 2 anti-TB medications for TB diagnosis (ICD-10 codes A15, A16, A17, A18, A19, P370, O980, B200, U880, and U843 and KCD-7 codes A15, A16, A17, A18, A19, P370, O980, B200, U880, and U881) from the index date to > 2 anti-TB medications within 3 months after the discontinuation of TNFα inhibitors or tocilizumab [13]. Because triple or quadruple therapy is the standard treatment for active TB, active TB should be defined as cases in which > 2 anti-TB medications are prescribed [13]. In addition, it would be reasonable to assume receiving "latent TB prophylaxis" rather than active TB if ≤ 2 anti-TB medications had been prescribed prior to the index date, because standard treatments for latent TB infection in Korea include rifampicin for 4 months, isoniazid and rifampicin for 3 months, and isoniazid for 9 months.

Covariates

The following demographic and clinical data were obtained from the HIRA database: sex, age, index year, medical institution, concomitant csDMARDs and medications, and Charlson comorbidity index (CCI) score. Medical institutions were categorized as tertiary hospitals, secondary hospitals, primary hospitals, and clinics/others. Concomitant csDMARDs and medications included MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF), bucillamine (BUC), tacrolimus (TAC), glucocorticoids (GCs), and non-steroidal anti-inflammatory drugs (NSAIDs). Although BUC and TAC are not universally recognized as true DMARDs, they are recommended for RA in Korea. Based on the diagnostic codes within 12 months before the index date, the CCI score was calculated as the sum of relevant comorbidities, as previously described [14].

Statistical Analyses

Categorical variables are presented as numbers (percentages), and numerical variables are expressed as means ± standard deviations or medians (interquartile ranges), as appropriate. Baseline characteristics were compared using the chi-squared or Fisher's exact test for categorical variables and Student's *t* test or Mann–Whitney *U* test for numerical variables, as appropriate. Drug persistence and TB-free survival were estimated using the Kaplan–Meier method and compared using the log-rank test. To assess the associated factors for non-persistence to index bDMARDs and the occurrence of active TB, we used multivariate Cox proportional hazards regression models adjusting for variables that differed between the TNFα inhibitor and tocilizumab groups and clinically relevant variables, such as CCI score. The results of Cox regression models are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). In subgroup analysis, drug persistence and occurrence of active TB were compared among tocilizumab and individual TNFα inhibitors, such as adalimumab, etanercept, golimumab, and infliximab, using the Kaplan–Meier method along

Table 1 Baseline characteristics of patients with rheumatoid arthritis

	All patients with RA (*n* = 5449)	TNFα inhibitors (*n* = 4202)	Tocilizumab (*n* = 1247)	*p* value
Female, *n* (%)	4423 (81.2)	3382 (80.5)	1041 (83.5)	0.018
Age, years, mean ± SD	53.4 ± 13.4	53.1 ± 13.5	54.5 ± 12.9	0.001
Index year				
2014, *n* (%)	1744 (32)	1419 (33.8)	325 (26.1)	< 0.001
2015, *n* (%)	1244 (22.8)	958 (22.8)	286 (22.9)	
2016, *n* (%)	1254 (23)	936 (22.3)	318 (25.5)	
2017, *n* (%)	1207 (22.2)	889 (21.2)	318 (25.5)	
Medical institution				
Tertiary hospital, *n* (%)	3414 (62.7)	2519 (59.9)	895 (71.8)	< 0.001
Secondary hospital, *n* (%)	1519 (27.9)	1213 (28.9)	306 (24.5)	
Primary hospital, *n* (%)	349 (6.4)	312 (7.4)	37 (3)	
Clinic and others, *n* (%)	167 (3.1)	158 (3.8)	9 (0.7)	
csDMARDs				
MTX, *n* (%)	4512 (82.8)	3579 (85.2)	933 (74.8)	< 0.001
SSZ, *n* (%)	953 (17.5)	777 (18.5)	176 (14.1)	< 0.001
HCQ, *n* (%)	1655 (30.4)	1279 (30.4)	376 (30.2)	0.847
LEF, *n* (%)	1607 (29.5)	1198 (28.5)	409 (32.8)	0.004
Other medications				
BUC, *n* (%)	124 (2.3)	79 (1.9)	45 (3.6)	< 0.001
TAC, *n* (%)	851 (15.6)	594 (14.1)	257 (20.6)	< 0.001
GCs, *n* (%)	4686 (86)	3581 (85.2)	1105 (88.6)	< 0.001
NSAIDs, *n* (%)	5326 (97.7)	4123 (98.1)	1203 (96.5)	< 0.001
CCI, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.974
Type of TNFα inhibitors				
Adalimumab, *n* (%)		1413 (33.6)	–	
Etanercept, *n* (%)		1100 (26.2)	–	
Golimumab, *n* (%)		920 (21.9)	–	
Infliximab, *n* (%)		769 (18.3)	–	

RA rheumatoid arthritis, *TNFα* tumor necrosis factor alpha, *SD* standard deviation, *csDMARDs* conventional synthetic disease-modifying drugs, *MTX* methotrexate, *SSZ* sulfasalazine, *HCQ* hydroxychloroquine, *LEF* leflunomide, *BUC* bucillamine, *TAC* tacrolimus, *GCs* glucocorticoids, *NSAIDs* non-steroidal anti-inflammatory drugs, *CCI* Charlson comorbidity index, *IQR* interquartile range

with log-rank test and Cox regression models. Statistical significance was defined as a two-sided p value < 0.05, and all statistical analyses were performed using SAS version 9.4 (SAS Inst., Cary, NC, USA).

RESULTS

During the analysis period, we identified 5449 patients with RA treated with TNFα inhibitors (n = 4202) or tocilizumab (n = 1247). Table 1 shows the baseline demographic and clinical characteristics of the patients. Most patients with RA were female (81.2%), with a mean age of 53.4 years. The most commonly prescribed csDMARD was MTX, followed by HCQ, LEF, and SSZ. Most patients with RA received GCs and NSAIDs. In the TNFα inhibitor-treated group, adalimumab, etanercept, golimumab, and infliximab were prescribed in 1413 (33.6%), 1100 (26.2%), 920 (21.9%), and 769 (18.3%) patients, respectively. Compared with those receiving TNFα inhibitors, patients with RA receiving tocilizumab were more likely to be female and older. The distribution of index years and medical institutions differed significantly between the TNFα inhibitor- and tocilizumab-treated patients. LEF, BUC, TAC, and GCs were more frequently prescribed in the tocilizumab-treated group than in the TNFα inhibitor-treated group, whereas MTX, SSZ, and NSAIDs were more frequently prescribed in the TNFα inhibitor-treated group than in the tocilizumab-treated group. The frequency of HCQ use did not significantly differ between the two groups.

During the analysis period, 2090 (49.7%) and 477 (38.3%) patients with RA discontinued TNFα inhibitors and tocilizumab, respectively. In the Kaplan–Meier analysis, TNFα inhibitors showed significantly worse drug persistence than tocilizumab (log-rank test, p < 0.001) (Fig. 2). In the TNFα inhibitors group, bDMARDs were discontinued in 700 (49.5%), 620 (56.4%), 452 (49.1%), and 318 (41.4%) patients treated with adalimumab, etanercept, golimumab, and infliximab, respectively. In subgroup analysis, a significant difference in drug persistence among individual type of TNFα inhibitors and tocilizumab was observed (log-rank test, p < 0.001, Supplementary Fig. 1).

Factors associated with bDMARD discontinuation in patients with RA analyzed using Cox

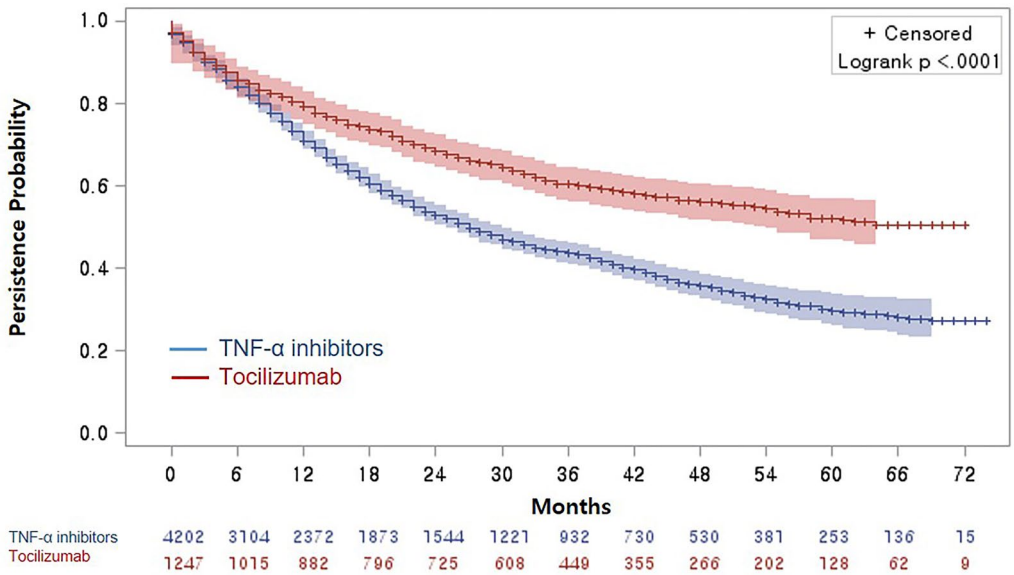

Fig. 2 Drug persistence of tumor necrosis factor alpha inhibitors and tocilizumab in patients with rheumatoid arthritis. *TNFα* tumor necrosis factor alpha

Table 2 Associated factor for the risk of biological agents discontinuation in patients with rheumatoid arthritis

	Univariable model		Multivariable model[a]		Multivariable model[b]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Biological agents (TNFα inhibitors vs tocilizumab)						
TNFα inhibitors	1.7 (1.53–1.87)	< 0.001	1.63 (1.47–1.8)	< 0.001	–	–
Tocilizumab	Ref		Ref		–	–
Biological agents (type of TNFα inhibitors vs tocilizumab)						
Adalimumab	1.96 (1.74–2.21)	< 0.001	–	–	2.15 (1.86–2.49)	< 0.001
Etanercept	1.75 (1.56–1.97)	< 0.001	–	–	2.4 (2.07–2.79)	< 0.001
Golimumab	1.28 (1.11–1.47)	0.001	–	–	1.84 (1.56–2.17)	< 0.001
Infliximab	1.69 (1.49–1.93)	< 0.001	–	–	1.19 (0.98–1.45)	0.069
Tocilizumab	Ref		–	–	Ref	
Age, years	1.01(1.01–1.01)	< 0.001	1.01 (1.01–1.01)	< 0.001	1 (0.99–1.01)	0.479
Sex						
Male	1.17 (1.06–1.29)	0.001	1.15 (1.05–1.27)	0.004	1.17 (1.04–1.32)	0.01
Female	Ref		Ref		Ref	
Index year						
2014	1.23 (1.1–1.38)	< 0.001	1.22 (1.09–1.37)	0.001	1.06 (0.92–1.23)	0.421
2015	1.11 (0.99–1.26)	0.086	1.1 (0.97–1.25)	0.127	1.06 (0.91–1.23)	0.48
2016	1.06 (0.94–1.2)	0.364	1.05 (0.92–1.19)	0.483	1.02 (0.88–1.19)	0.787
2017	Ref		Ref		Ref	
Medical institution						
Secondary hospital, *n* (%)	1.2 (1.1–1.31)	< 0.001	1.15 (1.06–1.26)	0.002	1.06 (0.95–1.18)	0.33
Primary hospital, *n* (%)	1.45 (1.25–1.68)	< 0.001	1.24 (1.07–1.5)	0.006	1.13 (0.93–1.37)	0.221
Clinic and others, *n* (%)	1.38 (1.09–1.75)	0.007	1.38 (1.08–1.75)	0.009	1.05 (0.76–1.45)	0.753
Tertiary hospital, *n* (%)	Ref		Ref		Ref	
csDMARDs						
MTX	0.88 (0.8–0.98)	0.016	0.84 (0.75–0.93)	0.001	0.9 (0.78–1.03)	0.129
SSZ	1.04 (0.94–1.15)	0.472	0.94 (0.85–1.05)	0.276	0.98 (0.86–1.11)	0.695
LEF	0.84 (0.77–0.91)	< 0.001	0.82 (0.75–0.9)	< 0.001	0.84 (0.75–0.95)	0.003
Other medications						
BUC	1.03 (0.81–1.31)	0.81	0.99 (0.78–1.26)	0.922	1.02 (0.77–1.35)	0.913
TAC	0.81 (0.72–0.9)	< 0.001	0.79 (0.71–0.89)	< 0.001	0.84 (0.73–0.96)	0.011
GCs	0.75 (0.68–0.83)	< 0.001	0.79 (0.71–0.88)	< 0.001	0.82 (0.71–0.93)	0.003

Table 2 continued

	Univariable model		Multivariable model[a]		Multivariable model[b]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
NSAIDs	0.83 (0.64–1.06)	0.133	0.92(0.7–1.2)	0.538	0.83 (0.6–1.15)	0.258
CCI	1.04 (1.01–1.07)	0.003	1.01 (0.99–1.04)	0.355	1 (0.96–1.03)	0.853

HR hazard ratio, *CI* confidence interval, *TNFα* tumor necrosis factor alpha, *csDMARDs* conventional synthetic disease-modifying drugs, *MTX* methotrexate, *SSZ* sulfasalazine, *HCQ* hydroxychloroquine, *LEF* leflunomide, *BUC* bucillamine, *TAC* tacrolimus, *GCs* glucocorticoids, *NSAIDs* non-steroidal anti-inflammatory drugs, CCI Charlson comorbidity index, *Ref* reference

[a]Multivariable model includes biological agents (TNFα inhibitors vs tocilizumab), age, sex, index years, medical institution, csDMARDs, other medications, and CCI

[b]Multivariable model includes biological agents (type of TNFα inhibitors vs tocilizumab), age, sex, index years, medical institution, csDMARDs, other medications, and CCI

proportional hazards regression models are presented in Table 2. In the univariate Cox regression model, TNFα inhibitors, older age, male sex, index year 2014, medical institutions other than tertiary hospitals, and CCI score were significantly associated with a higher risk of nonpersistence, whereas MTX, LEF, TAC, and GCs showed a significant association with a lower risk of nonpersistence. After adjustment for confounding factors, TNFα inhibitors had significantly higher hazards for bDMARD discontinuation compared with tocilizumab (HR 1.63, 95% CI 1.47–1.8, $p<0.001$). Multivariate Cox regression models showed that older age, male sex, index year 2014, and bDMARD prescription at secondary hospitals, primary hospitals, and clinics/others were independently associated with a higher risk of bDMARD discontinuation and that the concomitant use of MTX, LEF, TAC, and GCs was independently associated with a lower risk of bDMARD discontinuation. In subgroup analysis, adalimumab (HR 2.15, 95% CI 1.86–2.49, $p<0.001$), etanercept (HR 2.4, 95% CI 2.07–2.79, $p<0.001$), and golimumab (HR 1.84, 95% CI 1.56–2.17, $p<0.001$) showed a significantly worse drug persistence compared with tocilizumab. Infliximab tended to be more associated with a higher risk of nonpersistence compared with tocilizumab, but it did not reach statistical significance (HR 1.19, 95% CI 0.98–1.45, $p=0.069$).

During the follow-up period, 33 (0.8%) and 9 (0.7%) cases of active TB were observed in the TNFα inhibitor- and tocilizumab-treated groups, respectively. The incidence rates of active TB in patients with RA treated with TNFα inhibitors and tocilizumab were 459 per 100,000 person-years (PY) and 305 per 100,000 PY, respectively. No significant differences in TB-free survival between the two groups were observed (log-rank test, $p=0.399$). In the TNFα inhibitor-treated group, active TB developed in 12 (0.9%), 2 (0.2%), 5 (0.5%), and 14 (1.8%) patients with RA receiving adalimumab, etanercept, golimumab, and infliximab, respectively. Moreover, the incidence rates of active TB in adalimumab-, etanercept-, golimumab-, and infliximab-treated patients with RA were 514, 109, 322, and 961 per 100,000 PY, respectively. In subgroup analysis, a significant difference in TB-free survival among patients treated with adalimumab, etanercept, golimumab, infliximab, and tocilizumab was observed (log-rank test, $p=0.002$).

Table 3 shows the results of the Cox proportional hazards regression models that analyzed the risk factors for TB in patients with RA. After adjustment for confounding factors, there was no significant difference in the risk of the development of active TB between the use of TNFα inhibitors and tocilizumab. Meanwhile, in subgroup analysis, infliximab treatment was significantly associated with a higher risk of the occurrence of active TB compared with tocilizumab treatment (HR 2.84, 95% CI 1.18–6.84, $p=0.02$). The use of etanercept tended to show a lower risk of the incidence of active TB (HR 0.26,

Table 3 Risk factors for the development of tuberculosis in patients with rheumatoid arthritis

	Univariable model		Multivariable model[a]		Multivariable model[b]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Biological agents (TNFα inhibitors vs tocilizumab)						
TNFα inhibitors	1.37 (0.66–2.87)	0.401	1.3 (0.61–2.78)	0.501	–	–
Tocilizumab	Ref		Ref		–	–
Biological agents (type of TNFα inhibitors vs tocilizumab)						
Adalimumab	1.5 (0.63–3.57)	0.358	–	–	1.62 (0.67–3.93)	0.287
Etanercept	0.32 (0.07–1.48)	0.145	–	–	0.26 (0.05–1.23)	0.089
Golimumab	0.95 (0.32–2.83)	0.922	–	–	0.84 (0.27–2.59)	0.758
Infliximab	3.07 (1.33–7.1)	0.009	–	–	2.84 (1.18–6.84)	0.02
Tocilizumab	Ref		–	–	Ref	
Age, years	1.09 (1.06–1.12)	< 0.001	1.09 (1.05–1.12)	< 0.001	1.09 (1.06–1.12)	< 0.001
Sex						
Male	1.83 (0.94–3.58)	0.076	1.53 (0.77–3.01)	0.222	1.58 (0.8–3.13)	0.19
Female	Ref		Ref		Ref	
Index year						
2014	1.15 (0.5–2.62)	0.758	1.34 (0.57–3.18)	0.501	1.26 (0.53–2.98)	0.613
2015	0.71 (0.26–1.93)	0.505	0.71 (0.26–1.93)	0.502	0.63 (0.23–1.7)	0.33
2016	1.08 (0.45–2.62)	0.862	1.01 (0.41–2.46)	0.989	0.94 (0.39–2.32)	0.9
2017	Ref		Ref		Ref	
Medical institution						
Secondary hospital, *n* (%)	1.08 (0.53–2.22)	0.83	0.91 (0.44–1.87)	0.792	1.01 (0.48–2.12)	0.98
Primary hospital, *n* (%)	1.72 (0.6–4.94)	0.315	1.44 (0.47–4.41)	0.526	1.4 (0.45–4.43)	0.563
Clinic and others, *n* (%)	2.22 (0.53–9.36)	0.279	2.53 (0.58–11.17)	0.219	3.36 (0.75–15.12)	0.115
Tertiary hospital, *n* (%)	Ref		Ref		Ref	
csDMARDs						
MTX	0.71 (0.34–1.47)	0.352	0.89 (0.42–1.91)	0.773	0.78 (0.36–1.67)	0.518
SSZ	1.64 (0.83–1.54)	0.158	1.63 (0.8–3.34)	0.18	1.84 (0.89–3.81)	0.1
LEF	1.6 (0.86–2.96)	0.137	1.61 (0.84–3.11)	0.154	1.33 (0.68–2.59)	0.402
Other medications						
BUC	0.94 (0.13–6.8)	0.947	0.86 (0.12–6.32)	0.879	1.15 (0.15–8.66)	0.891
TAC	0.55 (0.2–1.54)	0.254	0.66 (0.23–1.89)	0.436	0.74 (0.26–2.15)	0.587
GCs	0.77 (0.34–1.74)	0.532	0.7 (0.3–1.63)	0.41	0.68 (0.29–1.59)	0.374

Table 3 continued

	Univariable model		Multivariable model[a]		Multivariable model[b]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
NSAIDs	NA	NA	NA	NA	NA	NA
CCI	1.35 (1.16–1.58)	< 0.001	1.14 (0.95–1.36)	0.152	1.14 (0.96–1.36)	0.133

HR hazard ratio, *CI* confidence interval, *TNFα* tumor necrosis factor alpha, *csDMARDs* conventional synthetic disease-modifying drugs, *MTX* methotrexate, *SSZ* sulfasalazine, *HCQ* hydroxychloroquine, *LEF* leflunomide, *BUC* bucillamine, *TAC* tacrolimus, *GCs* glucocorticoids, *NSAIDs* non-steroidal anti-inflammatory drugs, *CCI* Charlson comorbidity index, *Ref* reference

[a]Multivariable model includes biological agents (TNFα inhibitors vs tocilizumab), age, sex, index years, medical institution, csDMARDs, other medications, and CCI

[b]Multivariable model includes biological agents (type of TNFα inhibitors vs tocilizumab), age, sex, index years, medical institution, csDMARDs, other medications, and CCI

95% CI 0.05–1.23, $p=0.089$) compared with the use of tocilizumab. In addition, older age and higher CCI score were significantly associated with a higher risk of active TB in the multivariate Cox regression model.

DISCUSSION

Our analysis showed that tocilizumab exhibited greater drug persistence while maintaining a comparable risk of TB compared with TNFα inhibitors in patients with RA, which was determined by a comprehensive analysis of a nationwide claims database in Korea. In subgroup analysis, all types of TNFα inhibitors, except infliximab, demonstrated a significantly lower persistence rate compared with tocilizumab, whereas a notable higher risk of active TB incidence was associated with infliximab compared with tocilizumab and other TNFα inhibitors, except for infliximab. Furthermore, nearly half of the patients with RA discontinued either tocilizumab or TNFα inhibitors during the follow-up period, and the incidence rate of active TB in patients with RA receiving either tocilizumab or TNFα inhibitors was >300 per 100,000 PY in Korea.

Data regarding the comparison of drug persistence between TNFα inhibitors and non-TNFα inhibitor biologics as first-line biological therapy may provide valuable insights into determining which option can provide better outcomes, considering that drug persistence may be a relevant indicator for both efficacy and safety of medications. In Korea, the use of non-TNFα inhibitors, such as tocilizumab and abatacept, has been rapidly increased since 2012 [15], and tocilizumab is more frequently prescribed than abatacept for patients with RA [8]. Our analysis found that tocilizumab showed a significantly better persistence compared with the overall group of four TNFα inhibitors in patients with RA. Similarly, Lauper et al. reported that tocilizumab demonstrated greater drug persistence than TNFα inhibitors in a European RA cohort [16]. In addition, our analysis along with previous studies [17–19] showed that tocilizumab had a superior persistence rate even compared with individual anti-TNFα agents as the first-line biological therapy in patients with RA. Our analysis showed that three types of TNFα inhibitors, except infliximab, were associated with worse persistence compared with tocilizumab. Hishitani et al. demonstrated that tocilizumab had a higher drug retention rate compared with infliximab and adalimumab, but not etanercept, in 11,505 European patients with RA [17] and Ebina et al. reported better drug retention of tocilizumab compared with infliximab in 1037 Japanese patients with RA [18]. Dos Santos et al. concluded that tocilizumab, abatacept, etanercept, and golimumab had a significantly higher persistence, and infliximab showed a significantly lower persistence compared with

adalimumab in an analysis of 66,787 Brazilian patients with RA who initiated their first biological therapy [19]. Similarly, Park et al. evaluated data on 2713 Korean patients with RA who started bDMARDs between December 2013 and December 2014 and reported no differences in drug retention between tocilizumab and infliximab (reference bDMARDs) [8]. In addition, Park et al. demonstrated a significantly lower persistence of adalimumab and etanercept compared with the reference infliximab [8]. Although their study and our analysis used different reference drugs, the overall results regarding the comparison of persistence among bDMARDs seemed to be nearly identical. We believe that our analysis provides more comprehensive information than the study conducted by Park et al. because of our analysis of a larger cohort of patients over a longer period. Moreover, because the NHIS reimbursement criteria for the initiation and maintenance of bDMARDs, which were previously based on active joint counts and acute phase reactant (APR) levels, were revised to be based on a disease activity score of 28 in January 2014 in Korea [20], it is inappropriate to analyze patients with RA who initiated bDMARDs before that date and those who initiated them together, as in the study conducted by Park et al. This is because changes in reimbursement criteria can have a significant influence on drug persistence. Taken together, the various studies conducted in different countries, including our analysis, suggest a superior drug persistence of tocilizumab as the first-line biological therapy for RA compared with TNFα inhibitors. In addition, among TNFα inhibitors, infliximab showed better persistence compared to other drugs in our data, although the exact reason is unclear. It is speculated that infliximab was administered intravenously, unlike other drugs which were administered subcutaneously, may have influenced this finding. Of interest, the index year of 2014 was significantly associated with a lower drug persistence. Since the end of 2013, tocilizumab has become available in Korea, which has expanded the availability of a greater number of bDMARDs, potentially leading to more medication switching and subsequent lower drug persistence rates.

According to real-world data, the persistence of biological agents in RA can be affected by various factors beyond efficacy and safety, including previous biological treatments, comedications, and baseline disease activity [21]. Thus, although biological treatments with different mechanisms of action have demonstrated similar efficacy in clinical trials, differences in persistence have been reported among different classes of bDMARDs in our data and previous studies [8, 17–19], although conflicting data also exist [22, 23]. The exact reasons for this finding remain unclear; however, the pharmacological characteristics of tocilizumab can be considered a potential cause. Owing to its direct ability to reduce APR levels unlike TNFα inhibitors, the therapeutic effect of tocilizumab may be exaggerated when disease activity is measured using tools that incorporate APR, such as DAS28. In particular, according to the reimbursement criteria in Korea, if the DAS28 decreases by > 1.2 compared with baseline after 6 months of treatment with biological agents, the medication can be maintained; otherwise, it should be switched to another biological agent or discontinued. This may have caused the difference in drug persistence between tocilizumab and TNFα inhibitors in our data; however, further studies are required to confirm this assumption.

Our analysis found a similar risk of TB occurrence between tocilizumab and TNFα inhibitors, except for infliximab, in Korean patients with RA. In line with our result, Jung et al. also reported that except for infliximab, there was no difference in TB risk among anti-TNFα agents and tocilizumab in Korean patients with RA [24]. These findings are unexpected because the frequency of TB after tocilizumab treatment is considerably low, especially in countries with low TB incidence, whereas TNFα inhibitors, especially monoclonal antibodies, are associated with increased risk of reactivation of latent TB infection [10, 25–29]. The exact reasons for the comparable risk of TB between tocilizumab and TNFα inhibitors in our analysis are not yet fully understood, and the following factors may potentially affect this result. First, the risk of TB after biological treatment in patients with RA is largely influenced by the incidence and prevalence of TB in each country. Previous studies on TB risk following tocilizumab therapy were primarily conducted in countries with low TB

incidence rates, such as the UK [25] and Japan [26]. However, this analysis was conducted in South Korea, which has the highest TB incidence among the Organization for Economic Cooperation and Development countries [30]. Second, we could not fully adjust for potential confounding factors for the development of active TB, such as nutritional status, alcohol consumption, smoking, and history of latent TB infection, which may have affected our results. Third, the low number of TB cases in our RA cohort may have resulted in insufficient statistical power. Thus, further prospective studies or clinical trials investigating the comparison of TB incidence among TNFα inhibitors and non-TNFα inhibitors are necessary.

Our analysis has some limitations. First, the HIRA database used in this analysis does not provide clinical information, including disease activity, RA-associated autoantibodies, symptom duration, and extent of joint destruction, which could potentially influence the analysis results. In addition, we could not obtain data regarding the reasons for discontinuation of biological agents. Second, as the microbiological results of TB diagnoses are not available in the HIRA database, the identification of TB cases in our analysis may not be accurate. Third, we did not analyze the effect of treatment of latent TB infection on the development of TB after biological treatment. Preventive therapy by screening for latent TB infection prior to the initiation of biological treatments is mandatory in Korea, and Shin et al. reported that chemotherapy for latent TB infection could reduce the incidence of TB after biologics therapy in Korean patients with RA [11].

CONCLUSIONS

The present analysis observed that Korean patients with RA had a higher drug persistence rate with tocilizumab compared with TNFα inhibitors, but there was no significant difference in TB incidence between these two classes of drugs. The results of our analysis could suggest that tocilizumab may be a better option in some patients but clearly there are patients who obtain long-term benefits from both options (tocilizumab and TNFα inhibitors). However, the similarity of the occurrence of TB in both modes of action highlights the need to monitor for the occurrence of TB no matter which mode of action is employed. We believe that our findings provide valuable insights for rheumatologists in making decisions on which biological agent to select as the first-line treatment for patients with RA.

Author Contributions. Min Wook So: study design, data collection and analysis, and writing of the manuscript; A-Ran Kim: data interpretation and revision of manuscript; Seung-Geun Lee: study design, data analysis and interpretation, writing of the manuscript, and coordination of the entire study.

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Data Availability. The data that support the findings will be available in HIRA open database at https://opendata.hira.or.kr/home.do following an embargo from the date of publication to allow for commercialization of research finding.

Declarations

Conflict of Interest. Min Wook So, A-Ran Kim, and Seung-Geun Lee have declared no conflicts of interest.

Ethical Approval. This study was approved by the Research and Ethical Review Board of Pusan National University Hospital, which waived the requirement for informed consent because of the retrospective study design and anonymity of the extracted data (IRB no. 2007-032-093).

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