Effect of tumour necrosis factor-alpha inhibitors on renal function in patients with rheumatoid arthritis from the KOBIO registry from 2012 to 2016

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Abstract

Objective

The effect of biological disease-modifying anti-rheumatic drugs (bDMARDs) on renal function in patients with rheumatoid arthritis (RA) has not been well established. We assessed whether tumour necrosis factor (TNF) inhibitors could affect renal function in RA.

Methods

A total of 2110 patients with RA enrolled in the Korean College of Rheumatology Biologics (KOBIO) registry were analysed. All patients were taking bDMARDs or conventional synthetic DMARDs (csDMARDs). Renal function was evaluated by calculating the estimated glomerular filter rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation. Renal insufficiency was defined as eGFR <60 mL/min/1.73 m^2. Differences in eGFR changes between different types of DMARDs were assessed at each follow-up time using the generalised linear model (GLM) method. Risk factors for renal insufficiency were identified using binary logistic regression analysis.

Results

The changes of eGFR values in patients treated with TNF inhibitors were not significantly different from those with csDMARDs alone or non-TNF inhibitors in all RA patients regardless of renal function. Among patients with renal insufficiency, GLM analysis revealed that the changes of eGFR values by TNF inhibitors were also compatible to those treated with csDMARDs alone or non-TNF inhibitors. Older age (>55 years), longer disease duration (>5 years), and use of methotrexate were identified as clinical determinants for renal insufficiency.

Conclusion

TNF inhibitors did not influence the change of renal function during RA treatment. TNF inhibitors may be a safe treatment option irrespective of renal function.

Key words

rheumatoid arthritis, biological DMARD, TNF inhibitor, glomerular filtration rate

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that mainly affects the synovial joints, resulting in joint destruction, deformity, and functional disability (1). Renal disease is prevalent in patients with RA (2-4), although the precise prevalence of RA has not been determined. Increased mortality in patients with RA is associated with concurrent renal diseases (5-7). Impaired renal function in patients with RA is likely due to a chronic inflammatory response, anti-rheumatic drug toxicity, and renal involvement of RA itself (2-4).

Recently, biological disease-modifying anti-rheumatic drugs (bDMARDs) have emerged as the mainstay of RA treatment due to their clinical efficacy (8), together with conventional synthetic DMARDs (csDMARDs). Tumour necrosis factor-α (TNF-α) inhibitors such as infliximab and etanercept were first introduced to treat patients with RA. Despite the excellent therapeutic effect of TNF inhibitors, a growing body of evidence indicates that TNF inhibitors for rheumatic and autoimmune diseases are associated with the development of diverse autoimmune events including vasculitis, renal disorders, and interstitial lung diseases (9). Renal adverse effects of these bDMARDs were not reported in earlier randomised, double-blind, placebo-controlled studies in patients with RA treated with TNF inhibitors (10, 11). However, some studies have reported that biologic-related renal disorders such as RA-related nephropathy and de novo autoimmune renal diseases develop frequently, especially in patients treated with TNF inhibitors (12, 13). This finding implies that TNF inhibitors have a negative effect on renal function in patients with RA. However, biologic-related autoimmune glomerulonephritis was rare in patients with RA treated with abatacept and tocilizumab (14, 15). In contrast to these negative effects, biologics have been shown to restore renal function in patients with RA through their anti-inflammatory effects (16, 17). Another retrospective study found that biologic therapeutics for RA was not associated with deterioration of renal function (18).

Although few instances of biologic-related autoimmune renal disease have been reported, the possibility that biological agents cause renal function abnormalities such as increased estimated glomerular filter rate (eGFR) before the appearance of overt renal disease cannot be ruled out. Some studies evaluated whether bDMARDs induced changes of renal function based on serum creatinine or eGFR values in small-sized study population through retrospective analyses (16, 17, 19, 20). Few data have been reported regarding the effect of bDMARDs, especially TNF inhibitors, on renal function in large prospective studies of patients with RA. Thus, we investigated differences in renal function changes according to DMARD type (bDMARDs *vs*. csDMARDs) and bDMARD formula (TNF inhibitors *vs*. non-TNF inhibitors) based on eGFR values and identified clinical factors associated with renal impairment in patients with RA.

Subjects and methods

Study population

This study assessed data from the Korean College of Rheumatology Biologics (KOBIO) registry (ClinicalTrials.gov NCT01965132), a prospective nationwide biologics registry to evaluate the clinical manifestations and prevalence of biologic-related adverse effects in RA, ankylosing spondylitis, and psoriatic arthritis treated with bDMARDs. This registry was initially started after ethical approval by the Institutional Review Board of forty-four medical centres. In Korea, patients with RA receiving combination therapy with methotrexate and at least one other csDMARD who do not show adequate clinical response for at least 6 months can be treated with bDMARDs. Once patients began to receive any kind of bDMARD together with csDMARDs, they were enrolled in the KOBIO registry. These patients were defined as the 'bDMARD group' in this study. Simultaneously, patients treated with csDMARDs alone, *i.e*. the 'csDMARD group,' were also recruited as disease controls to identify differences in clinical characteristics between the bDMARD and csDMARD groups. The two groups were followed

up annually from baseline to the third follow-up period. All eligible patients with RA who met the 1987 American College of Rheumatology revised classification criteria for RA diagnosis (21) were enrolled in this registry. The protocol of this study was reviewed and then approved by the Institutional Review Board of Daegu Catholic University Medical Center (CR-12-161).

A total of 2110 patients with RA (658 patients on csDMARDs and 1452 patients on bDMARDs) were initially enrolled in this study (Fig. 1). All enrolled patients gave written informed consent at the time of recruitment into the KOBIO registry. The Institutional Review Board of each medical centre participating in this registry approved the protocol of this study. At baseline, 1410 patients in the bDMARD group and 636 patients in the csDMARD group were analysed at baseline. In the bDMARD group, 1089 patients at the first follow-up, 725 patients at the second follow-up, and 340 patients at the third follow-up were used for analysis. In the csDMARD group, 536 patients with RA at the first follow-up, 374 patients at the second follow-up, and 153 patients at the third follow-up were used for analysis. Patients were excluded from the analysis because of follow-up loss, transfer to a different hospital, stopping bDMARD therapy, study withdrawal, or death.

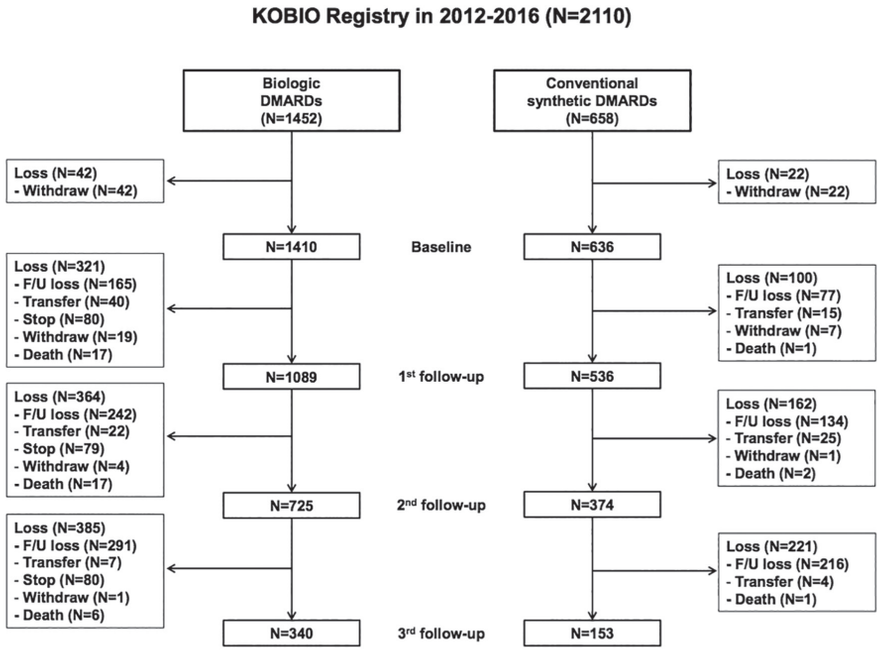


Fig. 1. Flow chart showing study design and study population at baseline and follow-up periods. DMARDs: disease-modifying anti-rheumatic drugs.

Collection of clinical information

The general characteristics collected at the time of enrolment in the KOBIO registry included age, sex, disease duration, marital status, cigarette smoking status, body weight (kg), height (cm), and body mass index (BMI, kg/m^2). Data for laboratory markers and clinical assessments related to RA, *e.g.* rheumatoid factor (RF) positivity status, anti-cyclic citrullinated peptide (CCP) antibody positivity status, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, swollen joint count (SJC), tender joint count (TJC), patient global assessment (PGA), and physician global assessment (PhGA) were collected. Based on these parameters, we calculated the 28-ESR disease activity score (DAS28-ESR) (22), the Simplified Disease Activity Index (SDAI) score (23), and the Clinical Disease Activity Index (CDAI) score (24). Data from the Routine Assessment of Patient Index Data 3 (RAPID3) questionnaire, a self-reported questionnaire of disease activity, were also collected (25). Patients were classified into two groups for baseline age (≤55/>55 years) and disease duration (≤5/>5 years) based on median values for determining clinical factors related to renal insufficiency. Patients were also divided into two groups based on DAS28-ESR score (≤5.1/>5.1) to identify patients with high disease activity (22).

We assessed the kinds of csDMARDs that patients were taking at the time of enrollment in both the csDMARD and bDMARD groups. csDMARDs included methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, tacrolimus, azathioprine, and cyclosporine. In addition, the use of corticosteroids was recorded. The use of bDMARDs including infliximab, infliximab biosimilars, etanercept, etanercept biosimilars, adalimumab, golimumab, rituximab, abatacept, tocillizumab, and tofacitinib was also recorded in all enrolled patients.

Study outcome

This study assessed changes in renal function, as assessed by GFR, during the study period. Among the methods for calculating eGFR based on serum creatinine, the Modification of Diet in Renal Disease (MDRD) equation is the most commonly used in subjects aged 18 and older (26). The MDRD equation for eGFR is GFR (mL/min/1.73 m^2) = 175 × (Serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female). Generally, chronic kidney disease refers to decreased GFR (<60 mL/min/1.73 m^2) for more than 3 months and one or more markers of kidney damage (27). eGFR was used as a proxy measurement for renal function because other data related to renal damage, including urine sediment abnormalities, abnormal histology, and structural abnormalities by imaging, were lacking. We defined renal insufficiency as eGFR <60 mL/min/1.73 m^2 in this study.

Statistical analysis

Descriptive data are reported as mean ± standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. Differences in characteristics of patients with RA on bDMARDs *versus* csDMARDs at baseline were assessed using Student's *t*-test for continuous variables and the chi-square test for categorical variables. Infliximab, infliximab biosimilar,

etanercept, etanercept biosimilar, adalimumab, and golimumab for TNF inhibitors and tocilizumab and abatacept for non-TNF inhibitors were classified for the statistical analysis. Differences in eGFR between two groups (bDMARD group *vs*. csDMARD group, csDMARD group *vs*. TNF inhibitors, and TNF inhibitors *vs*. non-TNF inhibitors) at baseline and over different follow-up periods were assessed by Student's *t*-test and the chi-square test. In addition, a generalised linear model was applied to identify differences in eGFR between two groups, considering time, group, and interaction of follow-up time and treatment group.

To identify risk factors related to renal insufficiency (<60 *vs*. ≥60 mL/min/1.73 m^2 [reference]), both crude and adjusted models were run using binary logistic regression analysis. First, we assessed the effect of TNF inhibitors on renal function in the crude model. Next, as potential confounders, baseline age (≤55/>55 years), sex (male/female), marital status (not married/married), RF status (negative/positive), anti-CCP antibody status (negative/positive), disease duration (≤5/>5 years), and DAS28-ESR score (≤5.1/>5.1) were included in the adjusted model 1. In addition, csDMARDs such as methotrexate, sulfasalazine, leflunomide, and tacrolimus were added for another adjusted analysis (adjusted model 2). Results are reported as odds ratio (OR) and 95% confidence interval (CI) for abnormal eGFR (<60 *vs*. ≥60 mL/min/1.73 m^2 [reference]). Two-sided significance levels (*p*-value <0.05) were used to assess statistical significance. All statistical analyses were performed using IBM SPSS Statistics 19 software (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics of enrolled patients

Of the 2110 patients with RA treated with csDMARDs with or without bDMARDs, they were divided into 1410 patients in the bDMARD group and 636 patients in the csDMARD group at baseline (Fig. 1). The baseline characteristics of the enrolled patients are shown in Table I. There were no dif-

Table I. Comparison of baseline characteristics in patients with rheumatoid arthritis according to DMARD treatment group.

Characteristics	csDMARD group, n=636	bDMARD group, n=1410	*p*-value†
Age (years, mean ± SD)	57.2 ± 11.9	56.3 ± 13.2	0.107
≤55 (median)	256 (40.2)	626 (44.4)	0.080
>55	380 (59.8)	784 (55.6)	
Sex			
Male	89 (14.0)	228 (16.2)	0.208
Female	547 (86.0)	1182 (83.8)	
Marital status			
Not married (single, divorced, etc.)	45 (7.1)	145 (10.3)	0.021
Married	591 (92.9)	1265 (89.7)	
Cigarette smoking*			
Never smoker	49 (7.7)	120 (8.5)	0.053
Ex-smoker	55 (8.7)	82 (5.8)	
Current smoker	530 (83.6)	1208 (85.7)	
Body mass index (kg/m^2)*			
<18.5 (underweight)	47 (7.4)	131 (9.3)	0.317
18.5–22.9	307 (48.5)	694 (49.2)	
23.0–24.9 (overweight)	129 (20.4)	292 (20.7)	
≥25.0 (obese)	150 (23.7)	293 (20.8)	
Rheumatoid factor*			
Negative	517 (83.3)	1166 (85.5)	0.199
Positive	104 (16.7)	198 (14.5)	
Anti-CCP antibody*			
Negative	527 (82.9)	1179 (83.8)	0.599
Positive	109 (17.1)	228 (16.2)	
Disease duration (years, mean±SD)	9.3 ± 6.9	10.2 ± 7.8	0.022
≤5 (median)	240 (37.7)	503 (35.7)	0.369
>5	396 (62.3)	907 (64.3)	
DAS28-ESR (mean ± SD)	3.4 ± 1.3	5.7 ± 1.1	<0.001
≤5.1	574 (90.3)	403 (28.6)	< 0.001
>5.1 (high disease activity)	62 (9.7)	1007 (71.4)	
Swollen joint count (mean ± SD)	1.9 ± 3.5	6.9 ± 5.8	<0.001
Tender joint count (mean ± SD)	2.5 ± 4.5	8.9 ± 7.1	<0.001
Patient's GA (mean ± SD)	3.8 ± 2.3	7.0 ± 2.0	<0.001
Physician's GA (mean ± SD)	3.1 ± 1.9	6.5 ± 1.8	<0.001
ESR*			
Normal	285 (45.5)	140 (10.0)	<0.001
Abnormal	341 (54.5)	1260 (90.0)	
CRP*			
Normal	436 (69.8)	334 (23. 9)	<0.001
Abnormal	188 (30.1)	1064 (76.1)	
SDAI (mean ± SD)	11.3 ± 8.9	29.6 ± 11.9	<0.001
CDAI (mean ± SD)	10.6 ± 8.3	27.2 ± 11.1	<0.001
RAPID3 (mean ± SD)	8.3 ± 5.4	15.8 ± 5.7	<0.001
Conventional synthetic DMARDs			
Methotrexate	579 (91.0)	1325 (94.0)	0.016
Hydrochloroquine	448 (70.4)	909 (64.5)	0.008
Sulfasalazine	189 (29.7)	565 (40.1)	<0.001
Leflunomide	246 (38.7)	778 (55.2)	<0.001
Tacrolimus	102 (16.0)	402 (28.5)	<0.001
Azathioprine	4 (0.6)	21 (1.5)	0.101
Cyclosporine	17 (2. 7)	47 (3.3)	0.427
Corticosteroid	452 (71.1)	1215 (86.4)	<0.001
Biological DMARDs			
Etanercept		218 (15.5)	-
Etanercept biosimilar		1 (0.1)	-
Infliximab		45 (3.2)	-
Infliximab biosimilar		139 (9.9)	-
Adalimumab		278 (19.8)	-
Golimumab		105 (7.5)	-
Rituximab		18 (1.3)	-
Abatacept		191 (13.6)	-
Tocilizumab		395 (28.1)	-
Tofacitinib		17 (1.2)	-

Data was described as mean ± standard deviation and number (%).

DMARDs: disease-modifying anti-rheumatic drugs; CCP: cyclic citrullinated peptide; DAS: Disease Activity Score; GA: global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: simplified disease activity index; CDAI: clinical disease activity index; RAPID3: routine assessment of patient index data 3; SD: standard deviation.

*There are some missing data for each parameter (cigarette smoking (n=2), body mass index (n=3), rheumatoid factor (n=15), ESR (n=10), and CRP (n=12) for csDMARD group; rheumatoid factor (n=46), anti-CCP antibody (n=3), ESR (n=10), and CRP (n=12) for bDMARD group).

†Calculated by Student's *t*-test for continuous variables and chi-square test for categorical variables.

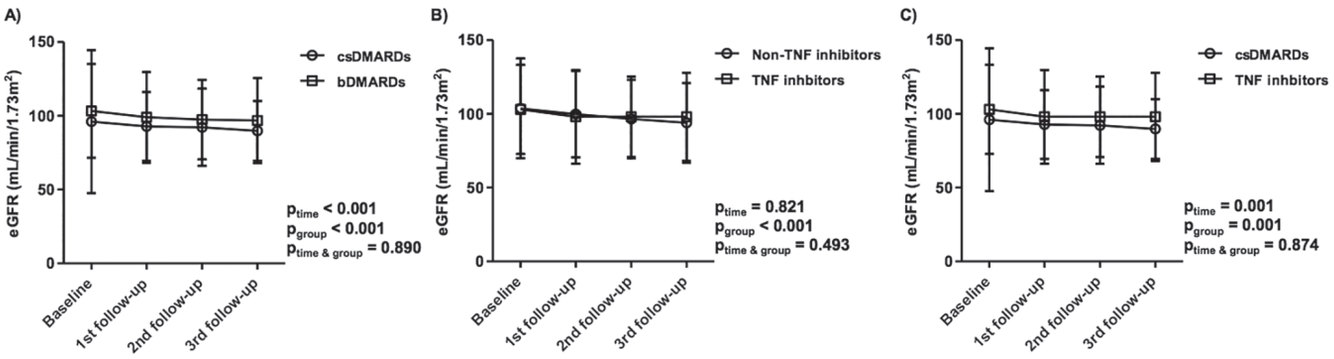


Fig. 2. Changes of estimated glomerular filtration rate based on types of DMARD over time in all patients. Data was described as mean and standard deviation. *p*-values were calculated by generalised linear model considering follow-up time, treatment group, or both.
eGFR: estimated glomerular filtration rate; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor.

ferences in age, sex, cigarette smoking status, BMI, RF positivity, or anti-CCP antibody positivity between the bDMARD and csDMARD groups. Compared to the csDMARD group, the bDMARD group had a higher percentage of non-married individuals, longer disease duration, and higher disease activity index scores (DAS28-ESR, SJC, TJC, PGA, PhGA, ESR, CRP, SDAI, CDAI, and RAPID3). Analysis of csDMARD use revealed that csDMARDs such as MTX, SSZ, leflunomide, and tacrolimus were more frequently used in the bDMARD group, as expected. Corticosteroid use was also prevalent in the bDMARD group. Among the bDMARDs, tocilizumab was most frequently used (28.1%), followed by adalimumab (19.8%), etanercept (15.5%), and abatacept (13.6%).

Comparison of changes in eGFR values between different two treatment groups among all patients

eGFR values were compared at baseline, the first follow-up, the second follow-up, and the third follow-up. eGFR values were higher in the bDMARD group than the csDMARD group ($p<0.001$ at baseline, $p<0.001$ at 1st follow-up, $p=0.002$ at 2nd follow-up, and $p=0.009$ at 3rd follow-up). Generalised linear model analysis showed that there was no significant difference in eGFR changes considering interaction of follow-up time and treatment group ($p=0.890$), although the significant differences in eGFR changes considering either time or treatment group were noted ($p<0.001$ for both) (Fig. 2A).

Table II. Comparison of proportions in renal insufficiency based on estimated glomerular filtration rate (<60 *vs.* ≥60 mL/min/1.73m²) according to types of DMARDs.

Type of DMARDs	eGFR	Baseline	1st follow-up	2nd follow-up	3rd follow-up
csDMARD group*	≥60	572 (94.9)	457 (94.6)	315 (92.7)	133 (94.3)
	<60	31 (5.1)	26 (5.4)	25 (7.3)	8 (5.7)
bDMARD group*	≥60	1217 (93.7)	945 (93.4)	643 (93.2)	291 (91.2)
	<60	82 (6.3)	67 (6.6)	47 (6.8)	28 (8.8)
p-value †		0.314	0.358	0.744	0.253
Non-TNF inhibitors‡	≥60	517 (93.7)	397 (93.0)	243 (92.8)	94 (92.2)
	<60	35 (6.3)	30 (7.0)	19 (7.2)	8 (7.8)
TNF inhibitors‡	≥60	700 (93.7)	548 (93.7)	400 (93.5)	197 (90. 8)
	<60	47 (6.3)	37 (6.3)	28 (6.5)	20 (9.2)
p-value†		0.262	0.632	0.624	0.845
csDMARD group*	≥60	572 (94.9)	457 (94.6)	315 (92.7)	133 (94.3)
	<60	31 (5.1)	26 (5.4)	25 (7.3)	8 (5.7)
TNF inhibitors‡	≥60	700 (93.7)	548 (93.7)	400 (93.5)	197 (90. 8)
	<60	47 (6.3)	37 (6.3)	28 (6.5)	20 (9.2)
p-value †		0.368	0.516	0.660	0.052

Data was described as number and percentage (%).
eGFR: estimated glomerular filtration rate; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biological disease modifying anti-rheumatic drugs.
*We analysed 1299 patients, 1022 patients, 690 patients, and 319 patients for bDMARD group and 603 patients, 483 patients, 340 patients, and 141 patients for csDMARD group at baseline, the 1st follow-up, the 2nd follow-up, and the 3rd follow-up, respectively, because some patients had no serum creatinine at each assessment time. †Calculated by chi-square test. ‡TNF inhibitors include infliximab, infliximab biosimilar, etanercept, etanercept biosimilar, adalimumab, and golimumab and non-TNF inhibitors include tocilizumab and abatacept.

The frequency of renal insufficiency, defined as eGFR <60 mL/min/1.73 m², was next compared between the bDMARD and csDMARD groups at each follow-up (Table II). The numbers of patients with impaired renal function were similar between the bDMARD and csDMARD groups at baseline, the first follow-up, the second follow-up, and the third follow-up ($p>0.05$ for all). In the comparison of changes in renal function between patients treated with TNF inhibitors and patients treated with non-TNF inhibitors, generalised linear model analysis revealed that the changes in eGFR values were not significant between two treatment groups considering both follow-up time and treatment group ($p=0.493$) (Fig. 2B). eGFR values were significantly different between patients treated with TNF inhibitors and non-TNF inhibitors ($p<0.001$), whereas eGFR changes were not significantly different for any of the follow-up time points ($p=0.821$). Comparison of frequencies of impaired renal function revealed no significant difference at any follow-up

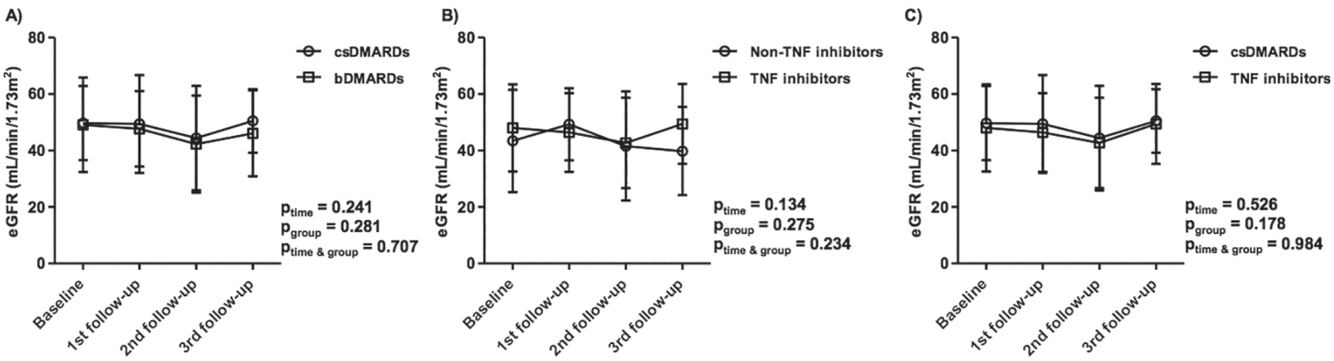


Fig. 3. Changes of estimated glomerular filtration rate based on types of DMARD over time in patients with renal insufficiency. Data was described as mean and standard deviation. *p*-values were calculated by generalised linear model considering follow-up time, treatment group, or both. eGFR: estimated glomerular filtration rate; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor.

time point (Table II). In addition, the eGFR changes were not significantly different among four TNF inhibitors, when follow-up time and each TNF inhibitor were considered together (Supplementary Fig. 1).

In the comparison of eGFR changes between csDMARD group and TNF inhibitors, no significant differences of eGFR changes between them were noted considering both follow-up time and treatment group (p=0.874) (Fig. 2C). There were similar frequencies of renal insufficiency between two groups (Table II). These findings suggest that TNF inhibitors were not responsible for worsening renal function in RA patients.

Comparison of changes in renal function between different two treatment groups among patients with renal insufficiency

Among patients with renal insufficiency, the changes in eGFR considering both follow-up time and treatment group were not significantly different between each two treatment group (p=0.707 for csDMARD group *vs*. bDMARD group, p=0.234 for TNF inhibitors *vs*. non-TNF inhibitors, and p=0.984 for csDMARD group *vs*. TNF inhibitors) (Fig. 3). Even in patients with renal insufficiency, TNF inhibitors did not additional decrease of eGFR during RA treatment.

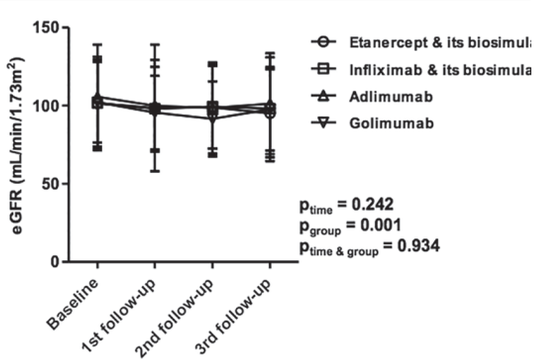
Determination of clinical factors associated with impaired renal function

Among the patients treated with bDMARDs, we found that patients treated with TNF inhibitors had no effect on the presence of renal insufficiency (OR=0.992, 95% CI 0.631–1.559) (Table III). Next, the association was assessed using covariates. In the adjusted model 1, elderly patients and patients with longer disease duration were found to have increased risk for impaired renal function (OR=8.637, 95% CI 3.891– 19.172 and OR=1.863, 95% CI 1.059–3.278, respectively). After adjusting for clinical covariates and csDMARDs, some clinical parameters such as age, disease duration,

Table III. Risk factor for renal insufficiency based on estimated glomerular filtration rate (<60 *vs*. ≥60 mL/min/1.73m² [reference]) using binary logistic regression.

Variables	OR (95% CI)		
	Crude model	Adjusted model 1	Adjusted model 2
TNF inhibitors (yes *vs*. no)	0.992 (0.631, 1.559)	1.122 (0.704, 1.791)	1.149 (0.712, 1.852)
Baseline age (>55 *vs*. ≤55 years)		8.637 (3.891, 19.172)	8.527 (3.801, 19.126)
Sex (female *vs*. male)		1.247 (0.638, 2.440)	1.197 (0.604, 2.372)
Marital status (married *vs*. not married)		0.685 (0.221, 2.118)	0.611 (0.195, 1.911)
RF (positive vs. negative)		0.793 (0.173, 3.646)	0.613 (0.127, 2.972)
Anti-CCP antibody (positive *vs*. negative)		1.383 (0.770, 2.482)	1.387 (0.763, 2.521)
Disease duration (>5 *vs*. ≤5 years)		1.863 (1.059, 3.278)	1.905 (1.072, 3.386)
DAS28-ESR (>5.1 *vs*. ≤5.1)		0.777 (0.472, 1.277)	0.773 (0.465, 1.284)
Methotrexate			5.278 (2.745, 10.149)
Sulfasalazine			1.151 (0.708, 1.871)
Leflunomide			0.929 (0.574, 1.504)
Tacrolimus			1.249 (0.730, 2.136)

Data was described as odds ratio (OR) and 95% confidence interval (CI).
TNF: tumour necrosis factor; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DAS: disease activity score; ESR: erythrocyte sediment rate; OR: odds ratio; CI: confidence interval.



Supplementary Fig. 1. Comparison of eGFR values of four different types of TNF inhibitors during RA therapy.

and methotrexate were identified as risk factors related to renal insufficiency (OR=8.527, 95% CI 3.801–19.126, OR=1.905, 95% CI 1.072–3.386, and OR=5.278, 95% CI 2.745–10.149, respectively).

Discussion

Concerns have recently been heightened regarding the possibility of developing impaired renal function during bDMARD therapy for RA. Earlier clinical trials of bDMARD therapy in patients with RA did not report any biologic-related renal adverse effects (10, 11). Various bDMARDs with different mechanisms of action have been introduced in the management of RA, including TNF-α inhibitors, interleukin-6 receptor antagonist (tocilumab), CTLA4-Ig (abatacept), and anti-CD20 monoclonal antibody (rituximab). Since bDMARDs have become more frequently used in clinical practice, evidence for bDMARD-related renal dysfunction or damage such as glomerulonephritis has accumulated (12-15). Regarding the development of bDMARD-related renal disorders, TNF inhibitors such as infliximab, etanercept, and adalimumab have been reported to be more frequently associated with renal abnormalities (12, 13). In contrast, glomerulonephritis was rarely noted in patients using other formulated bDMARDs such as tocilizumab and abatacept (14, 15). This finding suggests that bDMARDs might be related to renal function deterioration. However, insufficient data are available to determine whether bDMARDs, especially TNF inhibitors, induce renal functional abnormalities during RA treatment.

As reported in previous studies, bDMARDs (especially TNF inhibitors) can induce drug-related autoimmune glomerulonephritis. With the initiation of TNF inhibitors in patients with no previous renal involvement, clinical and laboratory abnormalities of newly developed nephropathy were reported to be markedly improved by withdrawal of TNF inhibitors or addition of immunosuppressive agents in most of the treated patients (12, 13). Based on this evidence, TNF inhibitors might worsen renal function or overt renal disorders. While the precise mechanism by which TNF inhibitors contribute to the development of autoimmunity or lupus-like features, including glomerulonephritis, has been not clearly determined, a few reasonable hypotheses have been supported by experimental evidence. One hypothesis is that binding of infliximab to TNF-α on the cell surface causes cellular apoptosis, leading to the release of nucleosomal autoantigens that induce anti-dsDNA antibodies in genetically susceptible patients (28). In addition, the administration of recombinant TNF-α delayed the progression of lupus nephritis in lupus-prone NZB/NZW F1 (B/W) mice by regulating the cellular immune response (29). As other immunologic evidence, inhibition of endogenous TNF was shown to enhance IFN-α release by immature pDCs exposed to influenza virus (30). This finding suggests a protective role of TNF-α in the development of autoimmune-related inflammatory responses. However, other studies have demonstrated that TNF can deteriorate the inflammatory response. TNF-α induces renal damage, partly due to elevated expression of TNF-α signaling adaptors such as TNF-α, TRADD, and TRAF-2 and partly due to recruitment of immune cells into the kidney, then leading to cell death and inflammation (31). Liu *et al*. demonstrated that TNF-α induces apoptosis signaling kinase-1 (ASK-1)-interacting protein expression, thereby promoting activation of ASK-1 via binding of TNF-α and TNF receptor 1 (TNFR1) (32). A consensus has not yet been reached regarding the role of TNF in the regulation of renal function. Considering the fact that immunopathogenic renal injury has been observed to develop after anti-TNF therapy, it is plausible to conclude that anti-TNF treatment might decrease renal function.

Few long-term follow-up studies have evaluated renal function in patients with RA treated with bDMARDs. In the present study, we prospectively evaluated changes in eGFR calculated by the MDRD equation in patients with RA treated with bDMARDs and compared them to those in patients receiving csDMARDs alone during the third follow-up period. We found that the eGFR values in the two treatment groups tended to gradually decrease over time; this decrease was statistically significant. In contrast, two retrospective studies have shown that renal function (as assessed by serum creatinine and eGFR) was better in patients treated with TNF inhibitors than in patients treated with csDMARDs alone (16, 17). In the present study, the prevalence of patients with renal impairment (eGFR <60 ml/min/m^2) was estimated as 5.1% and 6.3% in the csDMARD and bDMARD groups, respectively; these prevalences are lower than those reported in earlier studies (4, 18). In addition, there was no statistically significant difference in the proportions in patients with renal impairment during the follow-up period between the csDMARD and bDMARD groups. We found that the eGFR change between the two DMARD groups was not different considering the two covariates of both follow-up time and treatment group in the generalised linear model, as shown in Figure 2. Our results suggest that bDMARD therapy might not be responsible for the changes in eGFR in patients with RA.

In the present study, we first assessed whether TNF inhibitors increased the risk of renal impairment compared to non-TNF inhibitors including abatacept and tocilizumab. Although the TNF and non-TNF inhibitor groups showed gradually decreased eGFR from baseline to the third follow-up, there was no significant difference in eGFR change between the TNF inhibitor and non-TNF inhibitor groups, as shown in Figure 2. The prevalence of renal impairment (eGFR <60 ml/min/m^2) was also not significantly different between the two treatment groups during the follow-up periods (Table II). Regarding the assessment of risk factors for renal impairment, the use of TNF inhibitors was not shown to increase the risk of renal impairment (OR=0.992, 95% CI 0.631–1.559). Our data are consistent with those of previous studies concluding that TNF inhibitors including infliximab, etanercept, and adalimumab may be safe for treatment of patients with or without renal impairment or chronic kidney disease (16, 17, 20).

Although TNF inhibitor-related glomerulonephritis has been reported (12, 13), few studies have examined the risk of renal impairment associated with each TNF inhibitor type. Among the 29 patients with newly developed biologic-induced autoimmune renal disorders, etanercept (15 cases, 51.7%) was the most frequent biologic, followed by adalimumab (9 cases, 31.0%) and infliximab (3 cases, 10.3%) among the TNF inhibitors (12). In contrast, etanercept tended to decrease serum creatinine after 6 months of treatment (albeit without statistical significance), whereas the serum creatinine level was increased after adalimumab and infliximab therapy (16). In the present study, eGFR values during the follow-up period did not differ among the four TNF inhibitors (Supplementary Fig. 1). In addition, no TNF inhibitor increased the risk of renal impairment in logistic regression analysis. This finding should be confirmed through immunologic investigation and clinical studies with large sample sizes.

It is important to assess whether TNF inhibitors are safe therapeutic drugs in patients with renal impairment. An earlier retrospective study analysed 11 patients with renal insufficiency (serum creatinine ≥1.1 mg/dl) who were treated with TNF inhibitors such as infliximab, etanercept, and adalimumab for changes in renal function over a follow-up period of 24 months (19). Serum creatinine levels did not increase significantly, although they did tend to increase in some patients. Similarly, a retrospective analysis of 39 patients with RA with renal insufficiency (eGFR <60 ml/min/m^2 as calculated by the Cockcroft-Gault formula) treated with adalimumab revealed that eGFR values did not worsen over the follow-up period (20). Furthermore, another study that enrolled patients with CKD (eGFR <60 ml/min/m^2) concluded that TNF inhibitors might improve renal function due to the positive annual eGFR change compared to patients without anti-TNF therapy (95% CI 0.001–0.487, p=0.019) (17). This finding might be in part due to the beneficial effect of anti-inflammatory drugs on inflammatory responses in kidney tissue, which stabilise renal function (33, 34). In the present study, we also noted that renal function did not worsen significantly during the follow-up period in patients with eGFR <60 ml/min/m^2. Considering the previous data for patients with renal dysfunction, TNF therapy might be safely used in the treatment of RA with renal insufficiency.

There are some limitations and strengths of this study. First, we assessed renal function using only the MDRD equation, which is based on serum creatinine, and defined renal impairment as eGFR <60 ml/min/m^2. However, chronic renal disease is generally defined as eGFR <60 ml/min/m^2 for at least 3 months, in addition to the presence of renal functional and structural abnormalities (27). Unfortunately, data for pathologic abnormalities and urinary markers were not fully included in this registry. Therefore, the prevalence and risk of renal impairment could not be fully evaluated in this study. Nevertheless, it will be useful to compare the results of our study with those of other studies, because other studies also used similar criteria for renal disease (17, 18, 20). This study also has several strengths that overcome its weaknesses. For instance, previous studies investigating the association between TNF inhibitors and renal dysfunction were mainly retrospective analyses with small sample sizes (17, 20). However, the present study provides more reliable results and analysed a wider range of data to determine the effect of bDMARDs on renal function, because our data were prospectively collected from a nationwide registry in Korea.

In conclusion, we did not find any significantly different changes in eGFR values between patients treated with csDMARD group and bDMARD group during the 3-year follow-up period. Of particular note, TNF inhibitors did not affect changes in renal function during RA treatment. Analysis of clinical determinants for renal impairment revealed that csDMARDs such as methotrexate, baseline age, and longer disease duration might be responsible for the increased risk of renal impairment in patients with RA. This study suggests that TNF inhibitors can be used to treat RA without affecting renal function.

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