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Original Article

ORIGINAL ARTICLE

Decreased chronic kidney disease in rheumatoid arthritis in the era of biologic disease-modifying anti-rheumatic drugs

Hironari Hanaoka, Jun Kikuchi, Kazuoto Hiramoto, Shuntaro Saito, Yasushi Kondo and Yuko Kaneko

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Correspondence to: Hironari Hanaoka; E-mail: hhanaoka@keio.jp

ABSTRACT

Background. We investigated the incidence of chronic kidney disease (CKD) progression and its factors relevant to patients with stable rheumatoid arthritis (RA).
Methods. We enrolled consecutive patients with RA who had initiated treatment with a biologic disease-modifying anti-rheumatic drug (bDMARD) at our institution and continued the same drug for >5 years between 2001 and 2016. Patients with CKD at bDMARD initiation were excluded. C-reactive protein (CRP) level, Clinical Disease Activity Index (CDAI) score and estimated glomerular filtration rate were measured every 6 months.
Results. We included 423 patients, with 196 on tumour necrosis factor inhibitors, 190 on tocilizumab and 37 on abatacept. Among these patients, 34 (8.0%) progressed to CKD within 5 years. The mean CRP level and CDAI score over 5 years were significantly lower in patients without CKD progression than in those with CKD progression ($P < .001$ and $P = .008$, respectively). Multivariable analysis revealed that age at bDMARD initiation [odds ratio (OR) 1.05, $P = .002$], non-steroidal anti-inflammatory drug use (OR 3.47, $P = .004$) and mean CRP >0.14 mg/dL (OR 5.89, $P = .015$) were independently associated with CKD progression, while tocilizumab use was associated with a decreased risk of CKD progression (OR 0.31, $P = .027$).
Conclusions. Controlling inflammation contributes to the inhibition of CKD progression in RA patients.

Keywords: biologics, chronic kidney disease, inflammation, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects the joints but also involves extra-articular organs [1]. Approximately one-fourth of patients with RA develop chronic kidney disease (CKD) [2, 3], a higher rate than that of healthy individuals [4]. The causes of kidney diseases in RA vary, but most cases can be categorized into two types: chronic inflammation, including secondary renal atherosclerosis and amyloidosis, and drug-induced kidney diseases. Previous studies have shown that elevated inflammatory markers, such as C-reactive protein (CRP), in the early clinical stage are associated with future CKD [5, 6]. In addition, many drugs used for the management of RA are cytotoxic, as represented by nonsteroidal anti-inflammatory drugs (NSAIDs).

The advent of biologic disease-modifying anti-rheumatic drugs (bDMARDs) has dramatically improved the management of RA, resulting in sustained remission or low disease activity in

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most patients [7–9]. Control of disease activity inhibits joint destruction, reduces physical impairment and suppresses inflammation. These benefits lead in turn to decreased use of drugs toxic to the kidney and a consequent lessening of the major causes of kidney disease in RA. In recent years, however, CKD status in RA patients has received little research attention.

The aim of this study was to investigate the recent incidence of CKD in patients with RA that was successfully controlled with bDMARDs and factors that influence CKD progression.

MATERIALS AND METHODS

Patient information and data collection

We enrolled patients diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (Supplementary data, Table S1) [10] and had continued treatment with a single bDMARD for >5 years at Keio University Hospital between 2000 and 2016. The treatment regimen was decided by the patients' attending physicians based on the latest recommendations for the management of RA through a shared decision-making process [11, 12]. Patients with CKD at bDMARD initiation were excluded. Clinical characteristics, including Clinical Disease Activity Index (CDAI) score [13], CRP, estimated glomerular filtration rate (eGFR), haemoglobin (Hb), low-density lipoprotein cholesterol (LDL-C) and haemoglobin A1c (HbA1c) levels were collected at baseline and every 6 months from bDMARD initiation for 5 years. The eGFR was calculated using the level of serum creatinine (SCr) and age using the Japanese coefficient-modified Modification of Diet in Renal Disease (MDRD) Study equation [14]. CKD was defined as two measurements of an eGFR level <60 mL/min/1.73 m^2 separated by >90 days. Furthermore, CKD progression was defined as the new appearance of CKD and >25% decrease in eGFR from baseline [15, 16]. We have additionally evaluated the annual incidence of CKD and average declines in eGFR (mL/min/1.73 m^2/year) for age groups ≤49, 50–59, 60–69 and ≥70 years. NSAIDs, anti-hypertensive drugs, statins and anti-diabetic drugs were regarded as regular medications when they were continued for >1 year.

This study was approved by the ethics committee of Keio University School of Medicine. Since the study used a retrospective cohort design and no samples were taken other than for clinical use, written informed consent was not required under the guidelines of the Ministry of Health, Labour and Welfare of Japan.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD). The difference between the two groups was analysed using the *t*-test for continuous variables and chi-squared or Fisher's exact test for categorical variables. Cumulative CKD-free rates were calculated using the Kaplan–Meier method, with significant differences tested with the log-rank test. To identify independent factors, binary multivariable logistic regression analysis was performed using variables with a *P*-value <.01 on univariate analysis as covariates. A cut-off value to discriminate between the two groups was calculated using the receiver operating characteristics (ROC) curve. For propensity score matching, the propensity score was estimated using a multivariable logistic regression model with variables having a *P*-value <.05 in a previous multivariable analysis as covariates, in addition to the well-known key variables of age, disease duration, eGFR, methotrexate (MTX) use, glucocorticoid (GC) use, NSAID use, anti-hypertensive drug use, anti-diabetic drug use, rheumatoid factor (RF) positivity, anti-cyclic citrullinated protein (CCP) antibody positivity at baseline, mean Hb level, mean LDL-C level, average CDAI score and CRP level. Statistical significance was set at $P < .05$. All statistical analyses were performed using GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA) or JMP version 15.0 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics at biologic agent initiation

Among 2262 patients with RA who initiated bDMARD therapy in our hospital from 2001 to 2016, 1785 patients were excluded because they did not continue treatment with a single bDMARD for >5 years, while 54 patients were excluded because they already had CKD at bDMARD initiation. As a result, 423 patients were included in the study. Among them, 196 patients (46.3%) were treated with tumour necrosis factor (TNF) inhibitors, 190 (44.9%) with tocilizumab and 37 (8.7%) with abatacept. Patient characteristics by drug type are shown in Supplementary data, Table S2.

CKD progression and baseline characteristics

During the observation period, 34 patients (8.0%) developed CKD (Figure 1). Annual incidences of CKD were 0.99%, 3.36%, 5.50% and 8.66% and the changes in GFR were −2.59, −1.81, −1.93 and −2.77 mL/min/1.73 m^2/year for age groups ≤49, 50–59, 60–69 and ≥70 years, respectively. When divided into two groups based on CKD progression (Table 1), the patients in the CKD progression group were older (67.3 versus 54.0 years; $P < .001$), had a lower eGFR level (78.8 versus 86.6 mL/min/1.73 m^2; $P = .001$), had a higher CDAI score (21.7 versus 16.8%; $P = .029$) and had a lower anti-CCP titre (62.9 versus 139.9 IU/mL; $P = .023$) than those in the non-CKD progression group at bDMARD initiation. Tocilizumab was used less frequently in the CKD progression group (23.5% versus 46.9%; $P = .001$), whereas abatacept was used more frequently (20.6% versus 7.7%; $P = .002$).

CKD progression and RA activity

Disease activity of RA for 5 years was compared between the CKD progression and non-CKD progression groups. After bDMARD initiation, disease activity rapidly improved in both groups; nevertheless, average CRP levels (0.48 versus 0.24 mg/dL; $P < .001$) and CDAI scores (6.2 versus 4.7; $P = .008$) were significantly higher in the CKD progression than non-CKD progression group for 5 years (Table 1). At each of the 0.5-, 2.0-, 3.5-, 4.0-, 4.5-, and 5.0-year visits, significantly higher CRP levels were observed in the CKD group than in the non-CKD group (Figure 1A). In contrast, CDAI scores did not significantly differ at any visit (Figure 1B).

ROC curves identified the cut-off levels of the mean CRP and CDAI scores to discriminate CKD-free status for 5 years as 0.14 mg/dL {area under the curve (AUC) 0.657 [95% confidence interval (CI) 0.457–0.771], $P = .002$} and 5.8 [AUC 0.600 (95% CI 0.412–0.682), $P = .016$], respectively (Supplementary data, Figure S1). From a total of 10 visits, visits where patients had a CRP level >0.14 mg/dL were significantly more frequent in the CKD progression than non-CKD progression group (4.0 versus 2.0; $P < .001$), as were visits where patients had a CDAI score >5.8 (7.0 versus 6.0; $P = .048$). When we divided patients into two groups using these cut-off values, CKD-free survival rates were significantly lower in the patients with CRP levels >0.14 mg/dL ($P = .014$) and CDAI scores >5.8 ($P = .029$) (Figure 2A, B).

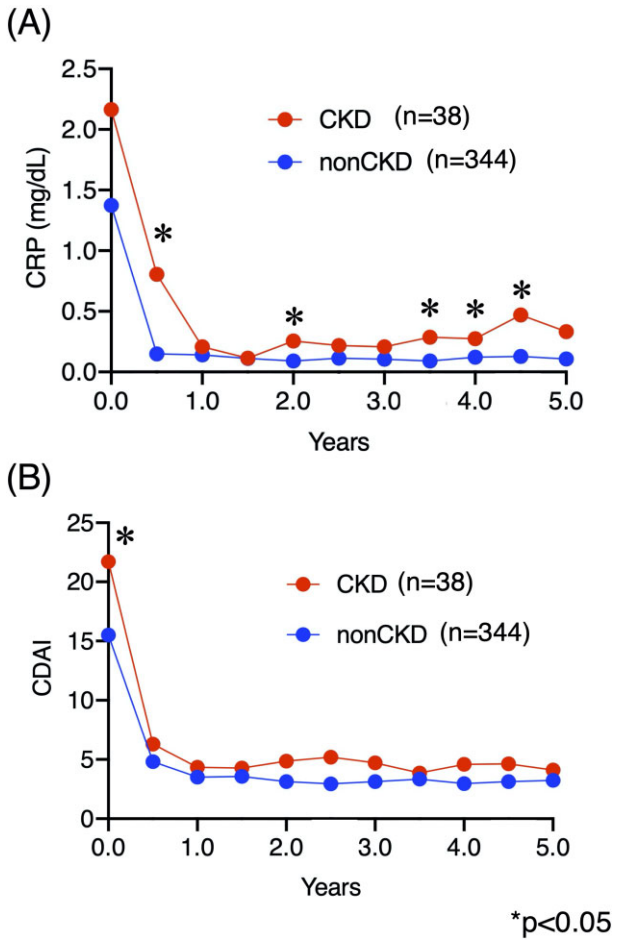

FIGURE 1: Changes in average CRP and CDAI scores on observation for 5 years. **(A)** A significantly higher level of CRP is observed at the 0.5-, 2.0-, 3.5-, 4.0-, 4.5- and 5.0-year visits in the CKD group than the non-CKD group (0.81 versus 0.17 mg/dL, 0.26 versus 0.09 mg/dL, 0.29 versus 0.08 mg/dL, 0.27 versus 0.12 mg/dL, 0.47 versus 0.11 mg/dL and 0.33 versus 0.11 mg/dL; $P < .001$, $P = .020$, $P < .001$, $P = .038$, $P = .001$ and $P = .014$, respectively). **(B)** CDAI scores did not significantly differ between the CKD and non-CKD groups after bDMARD initiation.

Other factors and CKD progression

NSAIDs and anti-hypertensive drugs were more frequently used in the CKD progression group than in the non-CKD progression group [35.3% versus 16.5% ($P = .010$) and 35.3% versus 13.1% ($P = .002$), respectively] (Table 1). There was no significant difference in the frequency of anti-diabetic drug use and anti-dyslipidaemia drug use between the two groups [5.9% versus 5.9% ($P = 1.000$) and 20.6% versus 11.8% ($P = .172$), respectively]. The mean levels of haemoglobin and LDL-C were lower in the CKD progression group [12.5 versus 13.8 mg/dL ($P < .001$) and 110.2 versus 136.2 mg/dL ($P = .001$), respectively].

Risk factors associated with CKD progression

We conducted multiple logistic regression analysis to identify risk factors associated with CKD progression using non-biologic agent covariates to exclude the effect of drugs (Table 2, model 1). The following were identified as independent factors associated with CKD progression: age at bDMARD initiation [odds ratio (OR) 1.05 (95% CI 0.99–1.06), $P = .002$], NSAID use [OR 3.47 (95% CI 1.01–11.99), $P = .004$] and a mean CRP level >0.14 mg/dL [OR 5.89 (95% CI 1.43–24.74), $P = .015$]. When we added tocilizumab and abatacept use in the logistic regression analysis, tocilizumab use [OR 0.31 (95% CI 0.11–0.89), $P = 0.027$] was identified as an independent factor instead of CRP level (Table 2, model 2).

We further investigated the effect of tocilizumab on the prevention of CKD progression. Since patient characteristics at the initiation of bDMARDs differed between tocilizumab users and non-users (Supplementary data, Table S3), we extracted 70 matched pairs for tocilizumab users and non-users using propensity score matching (Supplementary data, Table S4). We compared the CKD-free survival rate in all patients depending on tocilizumab use and found a significantly higher rate in patients who were treated with tocilizumab than those who were not ($P = .010$) (Figure 2C). After propensity score matching, the CKD-free survival rate was still significantly higher in patients treated with tocilizumab than in those not treated with tocilizumab ($P = .039$) (Figure 2D).

DISCUSSION

Our results demonstrated that 8.0% of patients with RA who initiated and continued bDMARD therapy for 5 years developed CKD. Our findings highlight the importance of preventing CKD progression by controlling disease activity, including intensive suppression of inflammation and the consequent reduction in NSAID use.

The association of RA with a variety of kidney disorders is mainly ascribable to chronic inflammation, drug exposure and toxicity [17]. Our results suggested a faster decline in eGFR in RA patients than in Japanese population. A study using annual checkup data from 120 727 Japanese patients [18] reported changes in GFR of −0.41, −0.31, −0.32 and −0.39 mL/min/1.73 m^2/year for age groups ≤49, 50–59, 60–69 and ≥70 years, respectively, which are smaller than our data (−2.89, −1.81, −1.93 and −2.77 mL/min/1.73 m^2/year for the same age groups, respectively). However, only a few studies have described the incidence of CKD in patients with RA [2–5]. A cross-sectional population-based cohort study of 102 patients with RA and without nephropathy demonstrated that 28% developed CKD within 15 years [3]. Hickson *et al.* [5] evaluated 813 RA patients and showed that the incidence of reduced kidney function (eGFR <60 mL/min/1.73 m^2) was higher in patients with RA than in those without RA (25.0% versus 20.0%; $P = .03$). This study enrolled RA patients who had been followed from 1980 to 2007. Since the first bDMARD for RA was approved in 1999 by the US Food and Drug Administration, most of the evaluated patients were unlikely to be treated with bDMARDs. Our finding that 8% of patients with RA treated with bDMARD therapy developed CKD suggests that the management of RA has dramatically improved through the years and that the development of CKD in these patients has decreased.

One interesting finding of our study is that mean CRP levels in the CKD progression group were higher than those in the non-CKD progression group. This is consistent with the notion that persistent inflammation is associated with CKD progression [19, 20]. Elevated erythrocyte sedimentation rate was independently associated with reduced kidney function at a hazard ratio of 1.08 per 10 mm/h increase in 813 patients with RA [5]. Furthermore, persistent CRP levels >3.0 mg/dL early in the clinical course were an independent predictor of CKD incidence in 345 patients with RA [6]. Our study also showed that among

Table 1. Clinical characteristics at bDMARD initiation in patients with or without CKD progression

Clinical characteristics	CKD progression (+) ($n = 34$)	CKD progression (−) ($n = 388$)	*P*-value
Age (years)	67.3 ± 11.3	54.0 ± 13.7	<.001
Female, *n* (%)	28 (82.4)	332 (85.6)	.614
Duration from RA diagnosis to DMARD therapy initiation (months)	105.1 ± 112.6	85.0 ± 92.3	.234
SS, *n* (%)	1 (2.9)	25 (6.4)	.382
eGFR (mL/min/1.73 m^2)	78.8 ± 12.4	86.6 ± 17.3	.001
Hb level (g/dL)	11.4 ± 1.7	13.5 ± 1.4	.102
HbA1c (%)	5.9 ± 1.8	5.9 ± 0.8	.825
LDL-C level (mg/dL)	109.4 ± 2.2	131.0 ± 33.9	.932
CRP level (mg/dL)	1.75 ± 2.08	1.49 ± 2.37	.541
CDAI score	21.7 ± 12.1	16.8 ± 12.2	.029
RF, *n* (%)	23 (67.7)	292 (75.3)	.312
RF titre (U/mL)	118.1 ± 179.1	96.3 ± 128.2	.355
Anti-CCP, *n* (%)	24 (70.6)	294 (75.7)	.534
Anti-CCP titre (IU/mL)	62.9 ± 100.3	139.9 ± 193.8	.023
ANA, *n* (%)	22 (64.7)	260 (67.0)	.788
Anti-SSA, *n* (%)	17 (8.7)	40 (10.3)	.588
Treatment			
TNFi, *n* (%)	20 (58.8)	176 (45.3)	.151
Tocilizumab, *n* (%)	8 (23.5)	182 (46.9)	.001
Abatacept, (%)	7 (20.6)	30 (7.7)	.002
MTX, *n* (%)	27 (79.4)	306 (78.9)	
MTX dose (mg/week)	8.0 ± 2.4	8.7 ± 3.7	.301
GC, *n* (%)	8 (23.5)	94 (24.2)	
GC dose (mg/day)	5.6 ± 2.1	5.1 ± 3.6	.751
Tacrolimus, *n* (%)	5 (14.7)	34 (8.7)	.226
NSAIDs, *n* (%)	12 (35.3)	64 (16.5)	.010
Anti-diabetic drugs, *n* (%)	2 (5.9)	23 (5.9)	
Anti-hypertensive drugs, *n* (%)	12 (35.3)	51 (13.1)	.002
Anti-dyslipidaemia drugs, *n* (%)	7 (20.6)	46 (11.8)	.172
Values during observation[a]			
Laboratory findings			
Hb level (g/dL)	12.5 ± 1.7	13.8 ± 1.0	.001
HbA1c (%)	6.0 ± 0.9	5.7 ± 0.4	.778
LDL-C level (mg/dL)	110.2 ± 38.1	136.2 ± 21.9	.001
CRP level (mg/dL)	0.48 ± 0.49	0.24 ± 0.29	<.001
Disease activity			
CDAI score	6.2 ± 4.1	4.7 ± 3.0	.008
Treatment			
Maximum MTX dose (mg/week)	8.0 ± 2.4	8.8 ± 3.7	.301
MTX dose at final visit (mg/week)	2.6 ± 3.0	3.8 ± 3.7	.116
Maximum GC dose (mg/day)	5.6 ± 2.1	5.1 ± 3.6	.751
GC dose at final visit (mg/day)	0.4 ± 0.8	1.2 ± 2.0	.270

Values are presented as mean ± SD unless stated otherwise. SS, Sjögren syndrome; ANA, anti-nuclear antibody; TNFi, anti-tumour necrosis factor inhibitor; GC, glucocorticoid.

[a]Values from the baseline to the last observation.

bDMARDs, use of tocilizumab, an interleukin-6 (IL-6) inhibitor, was an independent factor favourable to CKD progression. Together, these findings suggest that intensive suppression of CRP levels with IL-6 inhibition may be beneficial in terms of CKD progression.

Another mechanism of IL-6 inhibition that favours the suppression of CKD progression is the contribution of IL-6 to renal injury in glomerulonephritis and other forms of renal disease [21]. IL-6 enhances the signalling response of tubular epithelial cells to pro-fibrotic cytokines, such as transforming growth factor β [22]. IL-6-deficient mice show less kidney-associated inflammation [23]. IL-6 inhibition in Castleman's disease improves urinary sediment and stabilizes renal function [24, 25]. Furthermore, the effect of tocilizumab in improving anaemia induced by chronic inflammation also contributes to the inhibition of CKD progression [26, 27]. These findings suggest a direct effect of IL-6 inhibition on renal injury.

It is not surprising that NSAID use was an independent factor associated with CKD progression in our study. NSAIDs inhibit cyclooxygenase 1 and 2 (COX-1 and COX-2) isoenzymes. COX-1 mainly functions to control renal haemodynamics, while COX-2 primarily affects salt and water excretion [28]. Accordingly, blocking either or both of these enzymes can result in renal dysfunction [29]. The association between NSAID use and CKD progression has been proven clinically in a large cohort of 10 184 patients [30]. Our study suggests that disease control and suppression of inflammation in RA are also important to prevent CKD progression, because these lead to a reduction in NSAID use.

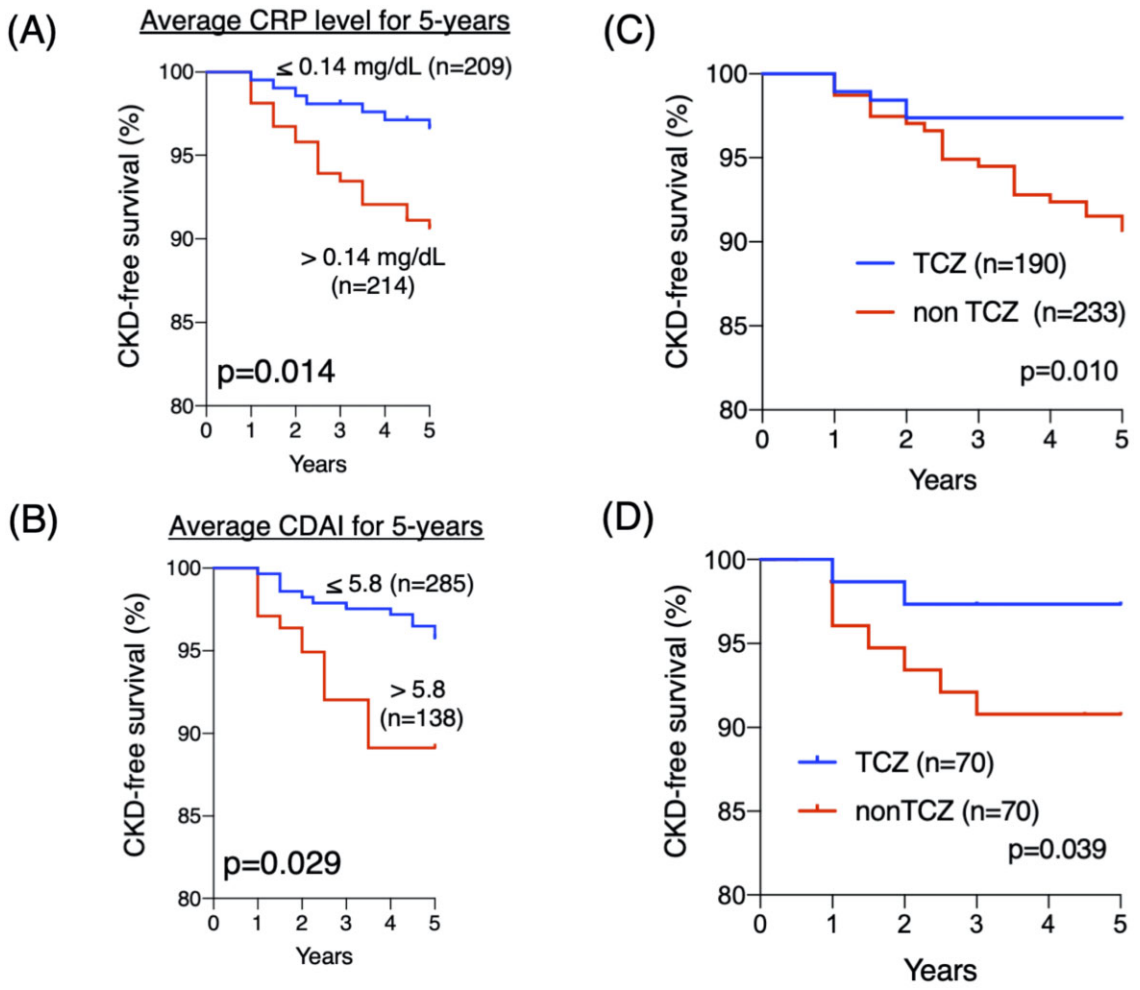

FIGURE 2: Cumulative CKD-free rate by cut-off levels discriminating CKD progression and cumulative CKD-free rate with tocilizumab use. Patients were divided into two groups based on the cut-off levels obtained from ROC curve analysis for CKD progression and cumulative CKD-free rates were compared in terms of **(A)** average CRP level and **(B)** average CDAI. **(C)** The cumulative CKD-free rates for tocilizumab users and non-tocilizumab users in full population. **(D)** After propensity matching, patients were divided into two groups by use of tocilizumab and the cumulative CKD-free rate was compared.

Table 2. Multivariate analysis for factors associated with CKD progression

	Model 1 (without biologics use)		Model 2 (with biologics use)	
Factor	OR (95% CI)	P-value	OR (95% CI)	P-value
Age at bDMARD initiation	1.05 (0.99–1.06)	.002	1.01 (0.98–1.03)	<.001
Female	1.00 (0.87–1.11)	.342	0.99 (0.88–1.25)	.531
eGFR level at bDMARD initiation	1.01 (0.97–1.04)	.412	1.01 (0.99–1.03)	.411
Mean Hb level	0.89 (0.77–1.60)	.215	1.18 (0.89–1.71)	.254
Mean LDL level	0.98 (0.96–1.02)	.435	0.97 (0.97–1.10)	.546
NSAID use	3.47 (1.01–11.99)	.004	4.11 (1.57–10.74)	.004
Anti-hypertensive drug use	2.42 (0.77–7.76)	.127	2.22 (0.91–5.35)	.077
Mean CRP level >0.14 mg/dL	5.89 (1.43–24.74)	.015	2.23 (0.90–5.48)	.082
Mean CDAI score >5.8	1.11 (0.40–3.35)	.924	1.57 (0.67–3.58)	.359
Tocilizumab use			0.31 (0.11–0.89)	.027
Abatacept use			1.34 (0.45–3.64)	.582

Our study has some limitations. First, it was conducted under a retrospective design at a single centre. This may have resulted in a degree of selection bias. Second, the interval of clinical data collection was every 6 months, and changes occurring within the 6-month period were sometimes unclear. Third, CKD was defined by the level of eGFR, lacking albuminuria assessment. Since albuminuria is a key parameter predisposing to CKD progression, the prevalence and risk of CKD may have been underestimated in this study. Our findings should therefore be confirmed in a multicentre prospective study with a longer follow-up period with albuminuria assessment.

In conclusion, CKD progression has decreased in the bDMARD era. Disease control, through inflammation management and reduced NSAID use, is important to the prevention of CKD. Further, the use of tocilizumab may suppress the effect of IL-6 on renal injury and reduce disease progression.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

None declared.

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