Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease

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Rheumatoid arthritis is associated with reduced kidney function, possibly due to chronic inflammation or the use of nephrotoxic therapies. However, little is known about the effects of using the newer novel non-nephrotoxic biologic agents on the risk of incident chronic kidney disease (CKD). To study this we used a cohort of 20,757 United States veterans diagnosed with rheumatoid arthritis with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73m^2 or more, recruited between October 2004 and September 2006, and followed through 2013. The associations of biologic use with incident CKD (eGFR under 60 with a decrease of at least 25% from baseline, and eGFR under 45 mL/min/1.73m^2) and change in eGFR (<-3, -3 to <0 [reference], and ≥0 mL/min/1.73m^2/year) were examined in propensity-matched patients based on their likelihood to initiate biologic treatment, using Cox models and multinomial logistic regression models, respectively. Among 20,757 patients, 4,617 started biologic therapy. In the propensity-matched cohort, patients treated (versus not treated) with biologic agents had a lower risk of incident CKD (hazard ratios 0.95, 95% confidence interval [0.82-1.10] and 0.71 [0.53-0.94] for decrease in eGFR under 60 and under 45 mL/min/1.73m^2, respectively) and progressive eGFR decline (multinomial odds ratios [95% CI] for eGFR slopes <-3 and ≥0 [versus -3 to <0] mL/min/1.73m^2/year, 0.67 [0.58-0.79] and 0.76 [0.69-0.83], respectively). A significant deceleration of eGFR decline was also observed after biologic administration in patients treated with biologics (-1.0 versus -0.4 [mL/min/1.73m^2/year] before and after biologic use). Thus, biologic agent administration was independently associated with lower risk of incident CKD and progressive eGFR decline.

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Rheumatoid arthritis (RA) has been associated with a variety of kidney disorders, such as secondary amyloidosis, glomerulonephritis, and drug-induced nephropathy, principally through chronic inflammation and/or exposure to nephrotoxic agents, and the prevalence of chronic kidney disease (CKD) in patients with RA has been reported to be higher than that in the general population.[1–3] A growing body of evidence has also shown the strong association between RA and a higher risk of cardiovascular events.[4–6] Because the systemic inflammation characteristic of RA plays a pivotal role in the development of atherosclerosis and subsequent cardiovascular disease, increasing attention has been paid to the management of cardiovascular risk factors in RA patients, with an enhanced focus on achieving remission early in the disease course with various anti-inflammatory therapeutic approaches using disease-modifying antirheumatic drugs (DMARDs) and biologic agents.[7] In addition, recent meta-analyses have identified the beneficial effect of tumor necrosis factor (TNF) inhibitors on cardiovascular risk in patients with RA,[8,9] which is also reflected in the current European League Against Rheumatism (EULAR) recommendations, suggesting that disease activity should be controlled optimally to lower cardiovascular risk in RA patients.[10] Considering these data and the possible biological link between systemic inflammation and CKD progression in patients with RA,[11] it is plausible that reducing their inflammatory burden with biologic treatment could also have favorable effects on renal function with the potential to slow kidney disease progression and to reduce the subsequent risk of incident CKD and end-stage renal disease.

In this study, we therefore hypothesized that patients with RA and normal kidney function who are treated with biologic agents are at a lower risk of incident kidney disease and are less likely to experience progressive decline of kidney function than those not receiving biologic treatment. To test these hypotheses, we investigated the association of biologic treatment with incident CKD and change in estimated glomerular filtration rate (eGFR) using a large nationally representative cohort of US veterans with RA and eGFR of ≥60 ml/min per 1.73 m^2.

RESULTS

Baseline characteristics overall and in patients categorized by biologic use are shown in Supplementary Table S1. The overall mean ± SD age at baseline was 63.2 ± 11.4 years; 91.7% of patients were male; 12.1% were African American; and 23.0% were diabetic. The mean baseline eGFR was 83.4 ± 14.8 ml/min per 1.73 m^2. During the follow-up period, 4617 patients (22.2%) started biologic therapy. Compared with RA patients without biologic treatment, those receiving biologic treatment were younger and less likely to be male and African American, had a higher baseline eGFR and per capita income and a lower prevalence of comorbidities except liver disease and HIV/AIDS, and were more likely to be service connected. They were also more likely to have RA-related articular procedures and to use nonbiologic DMARDs, nonsteroidal anti-inflammatory drugs, and glucocorticoids and less likely to use renin-angiotensin system inhibitors and statins. Baseline characteristics were well balanced between those with and without biologic use in the propensity-matched cohort (Table 1).

Factors associated with initial biologic treatment

Among 4617 RA patients treated with biologics in the overall cohort, 2779 (60.2%) were treated with etanercept, followed by adalimumab (21.4%), infliximab (9.6%), abatacept (4.1%), and other biologics (Supplementary Table S2). The timing of biologics initiation over time was depicted in a

Table 1 | Baseline patient characteristics by biologic use in the propensity-matched cohort

Characteristics	Biologic use		Standardized difference
	No (*N* = 4041)	Yes (*N* = 4041)	
Age, yr, mean ± SD	61.6 ± 10.5	61.1 ± 9.8	−0.042
eGFR, ml/min per 1.73 m^2, mean ± SD	85.9 ± 14.4	86.6 ± 14.4	0.045
Past slope of eGFR, ml/min per 1.73 m^2 per year, mean ± SD	−1.0 ± 2.4	−1.0 ± 2.3	0.050
Male	3625 (89.7)	3597 (89.0)	−0.023
African American	467 (11.6)	453 (11.2)	−0.011
Hypertension	2326 (57.6)	2250 (55.7)	−0.038
Diabetes mellitus	770 (19.1)	751 (18.6)	−0.012
Coronary heart disease	434 (10.7)	414 (10.2)	−0.016
Congestive heart failure	137 (3.4)	124 (3.1)	−0.018
Cerebrovascular disease	186 (4.6)	176 (4.4)	−0.012
Peripheral arterial disease	202 (5.0)	197 (4.9)	−0.006
Chronic lung disease	905 (22.4)	875 (21.7)	−0.018
Dementia	5 (0.1)	7 (0.2)	0.013
Liver disease	46 (1.1)	40 (1.0)	−0.015
Malignancies	284 (7.0)	281 (7.0)	−0.003
HIV/AIDS	2 (0.05)	5 (0.1)	0.025
Depression	417 (10.3)	408 (10.1)	−0.007
Married	1655 (41.0)	1650 (40.8)	−0.003
Service connected	1940 (48.0)	1997 (49.4)	0.028
Median (IQR) per capita income, US$	23,765 (12,718–33,864)	24,708 (13,155–33,910)	0.0004
Living in area with high housing stress	1341 (33.2)	1327 (32.8)	−0.007
Living in area with low education	477 (11.8)	461 (11.4)	−0.012
Living in area with low employment	414 (10.2)	398 (9.8)	−0.013
Living in area of persistent poverty	225 (5.6)	219 (5.4)	−0.013
BMI, kg/m^2, mean ± SD	29.0 ± 5.6	29.1 ± 5.5	0.013
Systolic BP, mm Hg, mean ± SD	133 ± 18	133 ± 18	0.001
Serum albumin, g/dl, mean ± SD	4.0 ± 0.4	4.0 ± 0.4	0.002
Articular procedures per year, mean ± SD	0.2 ± 0.5	0.2 ± 0.4	0.050
RASi use	1688 (41.8)	1691 (41.8)	0.002
Statin use	1536 (38.0)	1536 (38.0)	0.0001
Methotrexate use	2256 (55.8)	2291 (56.7)	0.018
Hydroxychloroquine use	1363 (33.7)	1357 (33.6)	−0.003
Sulfasalazine use	928 (23.0)	987 (24.4)	0.034
Leflunomide use	350 (8.7)	452 (11.2)	0.085
Other nonbiologic DMARD use	197 (4.9)	202 (5.0)	0.085
NSAID use	2711 (67.1)	2740 (67.8)	0.015
Glucocorticoid use	2325 (57.5)	2381 (58.9)	0.028

BMI, body mass index; BP, blood pressure; DMARD, disease-modifying antirheumatic drug; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; RASi, renin-angiotensin system inhibitor.
Values are *N* (%) unless otherwise indicated.