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ORIGINAL ARTICLE

Comparison of creatine kinase elevation caused by Janus kinase inhibitors and interleukin-6 inhibitors in patients with rheumatoid arthritis: A propensity score-matched study

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ABSTRACT

Objectives: This study aimed to examine whether creatine kinase (CK) elevation occurs with interleukin (IL)-6 inhibitors, as in Janus kinase (JAK) inhibitors, which are reported to increase CK levels in rheumatoid arthritis.

Patients and methods: A multicenter database of JAK inhibitor and IL-6 inhibitor treatment was retrospectively searched between January 2016 to December 2022; 142 cases (117 females, 25 males, mean age: 63.8±13.0 years; range, 20 to 85 years), with 71 cases in each group, were extracted by propensity score matching using age, sex, body mass index, and CK at 0 weeks. The outlier rate was compared. Patients' background characteristics related to elevated CK levels at 24 weeks were investigated by univariate and multivariate analyses.

Results: Creatine kinase levels at 4 and 12 weeks were significantly higher with JAK inhibitors than with IL-6 inhibitors (four weeks, 72 *vs.* 87.5 IU/mL, p=0.016; 12 weeks, 71 *vs.* 95.5 IU/mL, p=0.028). The outlier rate (Grade 1) with JAK inhibitors increased significantly over time (0 weeks, 4.2%; four weeks, 18.1%; 12 weeks, 21.7%; 24 weeks, 18.3%; p=0.015), whereas that with IL-6 inhibitors increased slightly (0 weeks, 5.6%; four weeks, 9.2%; 12 weeks, 8.6%; 24 weeks, 8.5%; p=0.745), with a significant difference between the groups (p=0.035). No patients discontinued treatment due to myalgia or renal dysfunction. The factors significantly positively related to elevated CK levels at 24 weeks were male sex and creatinine. Those significantly negatively related were Steinbrocker stage and class, modified health assessment questionnaire scores, estimated glomerular filtration rate, and glucocorticoid dose.

Conclusion: Mild CK elevations with JAK inhibitors are not a particular clinical problem. CK elevation might be specific to JAK inhibitors.

Keywords: Creatine kinase, Il-6 inhibitor, JAK inhibitor, multicenter observational study, rheumatoid arthritis.

Cases of creatine kinase (CK) elevation caused by Janus kinase (JAK) inhibitor treatment for rheumatoid arthritis (RA) have been reported in various clinical trials. Tofacitinib relatively infrequently caused elevations above the reference level (7.6%),[1] whereas grade 2 or 3 CK elevation was reported with baricitinib.[2] Peficitinib also increased CK levels from 61.9 IU/L (0 weeks) to 80.1 IU/L (52 weeks) in a phase III randomized, double-blind, placebo-controlled trial (RAJ4).[3] For filgotinib, the rates were 34.0% in the FINCH1 study[4] and 32.0% in the FINCH3 study.[5] CK elevations were highest in the upadacitinib group compared to the methotrexate and adalimumab groups.[6] Whether the degree and frequency of CK elevation differ with selectivity is unclear since there are no studies of patients with comparable background characteristics. However,

CK elevation may not be related to JAK selectivity in various clinical trials.

In practice, CK is also mildly elevated in RA patients treated with JAK inhibitors, regardless of selectivity. However, this CK elevation is not an adverse event that would require discontinuation of JAK inhibitors but is in the category of abnormal laboratory data. The European Alliance of Associations for Rheumatology (EULAR) noted that elevations of CK are associated with JAK inhibitors; however, CK elevation has not been associated with clinical events in the points to consider for the treatment of immune-mediated inflammatory diseases with JAK inhibitors.[7]

On the other hand, the mechanism of JAK inhibitor-induced CK elevation is not well understood. Hypothetically, the involvement of oncostatin M and satellite cell function has been reported.[8-11] Oncostatin M is one of the inflammatory cytokines that inhibits myoblast differentiation by JAK1-STAT3 signaling.[9-11] JAK inhibitors increase muscle mass by blocking oncostatin M signaling. JAK-STAT signaling increases progressively with age and inhibits satellite cell function. In the presence of JAK or STAT inhibitors, satellite cell function is restored, and muscle regeneration is rescued. Self-renewal of muscle satellite cells by JAK inhibitors may be involved in CK elevation.[8] Interleukin (IL)-6 signals intracellularly via the JAK-STAT pathway, and IL-6 also inhibits muscle satellite cell function. If this effect is blocked by IL-6 inhibitors, it could stimulate self-renewal of muscle satellite cells and increase CK levels, similar to JAK inhibitors. However, CK elevations have not been reported with IL-6 inhibitors and are not seen clinically. The aim of this study was to examine whether the CK elevation is specific to JAK inhibitor therapy or also occurs with IL-6 inhibitor therapy by propensity score (PS) matching.

PATIENTS AND METHODS

In this retrospective study, data from patients in the Orthopedic Rheumatoid Arthritis Group database on anti-IL-6 receptor antagonists (IL-6 inhibitors) and JAK inhibitors were analyzed between January 2016 to December 2022. The Orthopedic Rheumatoid Arthritis Group maintains a research database of RA patients using biologics and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) at eight hospitals and one clinic. All patients fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria,[12] and all participants were over 20 years of age.

The effects of IL-6 inhibitors and JAK inhibitors on CK were compared in moderate and severe disease activity RA patients. The number of patients treated by IL-6 inhibitors (tocilizumab, n=61; sarilumab, n=52) and JAK inhibitors (tofacitinib, n=60; baricitinib, n=65; upadacitinib, n=30; peficitinib, n=7; filgotinib, n=6) was 113 and 168, respectively. The follow-up chart is shown in Figure 1. The number of patients who dropped out was 33 with IL-6 inhibitors and 65 with JAK inhibitors. The number of patients who could continue treatment and were followed for 24 weeks was 80 with IL-6 inhibitors and 103 with JAK inhibitors. A total of 71 cases in each treatment group were extracted by PS matching, adjusted by age, sex, body mass index, and CK at 0 weeks for a total of 142 participants (117 females, 25 males, mean age: 63.8±13.0 years; range, 20 to 85 years).

Each patient's physician decided the treatment strategy based on the treat-to-target concept during the follow-up period.[13] Laboratory examinations included CK, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), matrix metalloproteinase 3 (MMP3), erythrocyte sedimentation rate (ESR), rheumatoid factor, and anti-cyclic citrullinated peptide antibody. RA activity was measured as a disease activity score composite of the ESR and the 28-joint score (DAS28-ESR)[14] and the Simplified Disease Activity Index (SDAI).[15] Functional status was also measured in patients with RA based on the modified health assessment questionnaire (mHAQ) scores.[16] Disease staging was evaluated using Steinbrocker stage and class.[17]

Creatine kinase was evaluated at 0, 4, 12, and 24 weeks in both treatment groups. CK elevation was graded according to the Common Terminology Criteria for Adverse Events version 5.0.[18] Grade 0 was defined as below the upper limit of the standard value, Grade 1 as 1 to 2.5

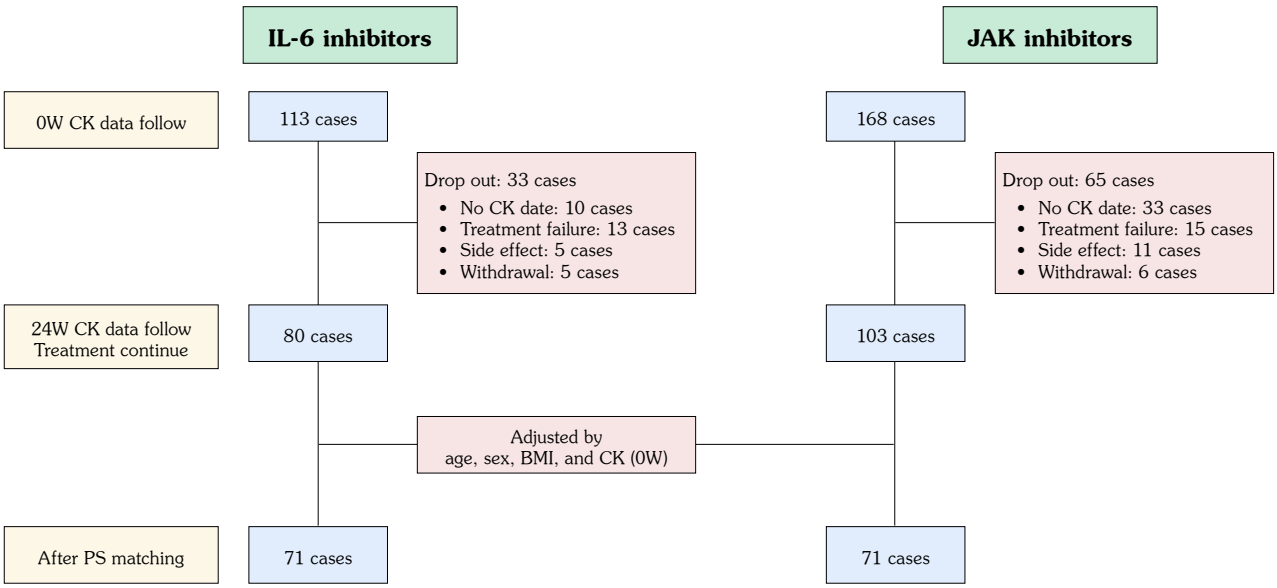

Figure 1. The flowchart of the study and the reasons for dropout in the IL-6 inhibitor and JAK inhibitor groups.
IL-6: Interleukin-6; JAK: Janus kinase; W: Week; CK: Creatine kinase; PS: Propensity score; BMI: Body mass index.

times, Grade 2 as 2.5 to 5 times, Grade 3 as 5 to 10 times, and Grade 4 as over 10 times. The outlier rate of CK elevation was evaluated using this grading system. CK levels differed by sex and facility. Considering this, grading of elevated CK levels was performed.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Data were presented as mean ± standard deviation values for those with a normal distribution or as median (25^{th}, 75^{th} percentiles) values for nonnormally distributed data. The difference between the two groups was analyzed using Student's t-test or the Mann-Whitney U test for continuous data and Fisher exact test for categorical data. The outlier rate of CK elevation between the two groups and the time courses were analyzed using Fisher exact test. Correlations between elevated CK levels at 24 weeks and patients' background characteristics at the time of starting treatment were investigated using univariate analysis by Spearman's correlation coefficient and multivariate analysis adjusted by sex (male) and CK level at 0 weeks. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

Baseline demographics and characteristics of all patients and those treated with IL-6 inhibitors or JAK inhibitors are shown in Table 1. The median disease duration was 14.1 years. Steinbrocker stages III or IV were present in 61.3%, with classes II or III in 71.4%. The median CRP and MMP3 were 1.29 mg/dL and 210.3 ng/mL, respectively. The mean DAS28-ESR was 5.03±1.40, and the median SDAI was 21.6. The methotrexate usage rate was 55.6%, and the mean dosage was 10.6±3.5 mg/week. On the other hand, the glucocorticoid usage rate was 37.3%, and the mean dosage was 4.8±2.8 mg/day. There were no significant differences in baseline demographics and characteristics between the two groups due to the adjustments in PS matching.

The time-dependent changes in CK levels in the IL-6 inhibitor group and the JAK inhibitor group are shown in Figure 2. There was no difference in CK levels at 0 weeks between the IL-6 inhibitor group and the JAK inhibitor group (56 *vs.* 57 IU/mL, p=0.886). On the other hand, CK levels at 4 and 12 weeks were significantly higher in the JAK inhibitor group than in the IL-6 inhibitor group (four weeks, 72 *vs.* 87.5 IU/mL, p=0.016; 12 weeks, 71 *vs.*

Table 1. Baseline demographics and characteristics of RA patients with IL-6 inhibitors and JAK inhibitors

	All RA patients (n=142)				IL-6 inhibitors (n=71)				JAK inhibitors (n=71)				
	%	Mean±SD	Median	25th-75th percentile	%	Mean±SD	Median	25th-75th percentile	%	Mean±SD	Median	25th-75th percentile	*p*
Women (%)	82.4				81.7				83.1				1.000***
Age (year)			66.5	54.0-74.0			67.0	56.0-74.0			66.0	53.0-74.0	0.943**
Disease duration (year)			14.1	5.0-24.3			11.3	3.4-21.4			15.0	7.6-25.7	0.106**
Steinbrocker stage I II III IV	 27 28 37 50				 15 13 17 26				 12 15 20 24				0.737***
Steinbrocker class 1 2 3 4	 44 61 39 0				 20 30 21 0				 22 31 18 0				0.602***
BMI (kg/m^2)		22.5±3.7				22.5±3.7				22.5±3.8			0.999*
ACPA positive (%)	81.0				83.1				78.9				0.817***
RF positive (%)	79.6				81.8				77.4				0.797***
CRP (mg/dL)			1.29	0.38-3.28			1.34	0.42-3.45			1.23	0.34-2.98	0.673**
MMP3 (ng/mL)			210.3	108.4-359.3			224.2	115.3-382.3			193.6	100.1-334.6	0.549**
DAS28-ESR		5.03±1.40				5.00±1.36				5.06±1.45			0.797*
SDAI			21.6	13.1-30.1			21.9	13.6-30.1			21.0	12.9-30.0	0.989**
mHAQ			0.625	0.125-1.125			0.5	0.125-1.125			0.625	0.125-1.250	0.419**
CK (IU/mL)			57	40-84			56	38-84			57	43-87	0.886**
eGFR (mL/min/1.73 m^2)			72.0	59.2-88.1			71.4	54.4-89.1			75.1	60.8-88.3	0.638**
MTX (rate) (mg/W)	55.6	10.6±3.5			50.7	10.2±3.7			60.5	10.9±3.4			0.311***
GC (rate) (mg/D)	37.3	4.8±2.8			36.6	5.3±3.0			38.0	4.3±2.6			1.000***

RA: Rheumatoid arthritis; IL-6: Interleukin-6; JAK: Janus kinase; SD: Standard deviation; BMI: Body mass index; ACPA: Anti-cyclic citrullinated peptide antibody; RF: Rheumatoid factor; CRP: C-reactive protein; MMP3: Matrix metalloproteinase 3; DAS28: Disease activity score 28; ESR: Erythrocyte sedimentation rate; SDAI: Simplified disease activity index; mHAQ: Modified health assessment questionnaire; CK: Creatine kinase; eGFR: Estimated glomerular filtration rate; MTX: Methotrexate; GC: Glucocorticoid; * Continuous variables were analyzed using an unpaired Student's t-test; ** Mann-Whitney U-test; *** Categorical variables were analyzed using Fisher's exact test.

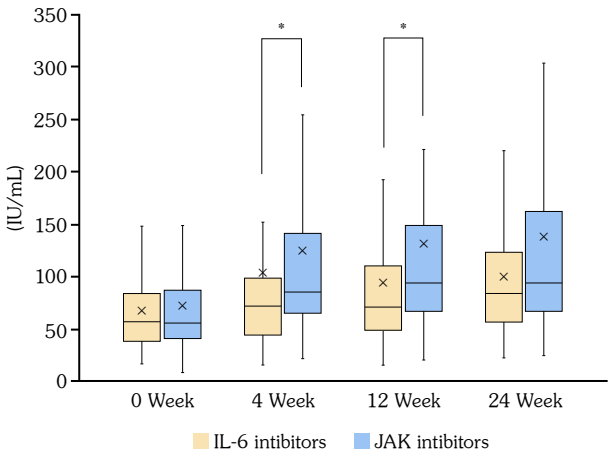

Figure 2. Time-dependent changes in CK levels in the IL-6 inhibitor group and the JAK inhibitor group. The box plot shows comparisons of the groups. The CK levels at four weeks and 24 weeks are significantly higher in the JAK inhibitor group than in the IL-6 inhibitor group. Statistical analysis was performed by the Mann-Whitney U test.

IU: International units; IL-6: Interleukin-6; CK: Creatine kinase; JAK: Janus kinase; * p<0.05 compared with the CK level of the IL-6 inhibitor group.

95.5 IU/mL, p=0.028). CK at 24 weeks tended to be higher in the JAK inhibitor group than in the IL-6 inhibitor group (84 *vs.* 95.5 IU/mL, p=0.058).

The outlier rates of over Grade 1 and Grade 2 for the IL-6 inhibitor group and the JAK inhibitor group are shown in Figure 3. The outlier rate of over Grade 1 for the JAK inhibitor group increased significantly from 4.2% at 0 weeks to 18.1% at four weeks (p=0.012), and it remained higher at 12 weeks (21.7%) and 24 weeks (18.3%) than at 0 weeks (p=0.002 and p=0.015, respectively). On the other hand, the outlier rate of over Grade 1 for the IL-6 inhibitor group was not significantly increased at four (9.2%), 12 (8.6%), and 24 (58.5%) weeks compared to 0 weeks (5.6%; p=0.519, p=0.532, and p=0.745, respectively). The outlier rate of over Grade 1 at 12 weeks was significantly higher in the JAK inhibitor group than in the IL-6 inhibitor group (Figure 3a). The outlier rates of over Grade 2 in both groups were not significantly different at all time points (Figure 3b).

Table 2 shows the relationships between CK elevation at 24 weeks and patients' background characteristics on univariate and multivariate analyses. CK elevation at 24 weeks was significantly positively correlated with CK, sex (male), and creatinine, and it was negatively correlated with Steinbrocker stage and class, mHAQ, eGFR, and glucocorticoid dose on univariate analysis. However, no significant factors were identified on multivariate analysis.

DISCUSSION

Comparing CK level changes over time, adjusted for background factors by PS matching, between JAK inhibitors and IL-6 inhibitors shows

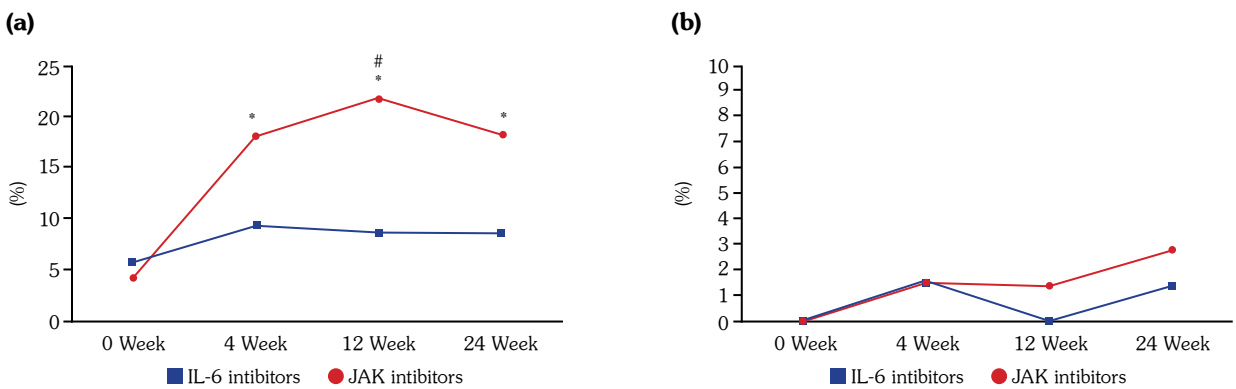

Figure 3. The outlier rate of over Grade 1 **(a)** and Grade 2 **(b)** for the IL-6 inhibitor group and the JAK inhibitor group. The outlier rate of over Grade 1 at 12 weeks is significantly higher for the JAK inhibitor group than for the IL-6 inhibitor group (a). The outlier rates of over Grade 2 in both groups are not significantly different at all time points. Data are shown as mean outlier rates. Statistical analysis was performed by Fisher exact test.

IL-6: Interleukin-6; JAK: Janus kinase; CK: Creatine kinase; * p<0.05 compared with the outlier rate of over Grade 1 at 0 weeks. # p<0.05 compared with the outlier rate of over Grade 1 for the IL-6 inhibitor group at 12 weeks.

Table 2. Uni- and multivariate analyses of factors related to CK elevation at 24 weeks

	Univariate		Multivariate		
	R value	*p* value	β value	95% CI	*p* value
CK (IU/mL)	0.639	<0.001	-	-	-
Sex Male	0.339	<0.001	-	-	-
Steinbrocker stage	–0.192	0.027	–0.086	–17.1-4.1	0.226
Steinbrocker class	–0.218	0.014	0.005	–1.9-15.0	0.938
mHAQ	–0.205	0.018	–0.065	–0.37-1.4	0.369
Creatinine (mg/dL)	0.289	<0.001	0.030	–24.8-39.4	0.0653
eGFR (mL/min/1.73 m^2)	–0.178	0.034	–0.074	–0.62-0.19	0.295
Glucocorticoid dose (mg)	–0.273	0.048	–0.089	–8.3-2.8	0.329

CK: Creatine kinase; CI: Confidence interval; mHAQ: Modified health assessment questionnaire; eGFR: Estimated glomerular filtration rate; Univariate analysis by Spearman's correlation coefficient and multivariate analysis adjusted by gender (male) and CK at 0 weeks.

that CK elevation is a unique effect of JAK inhibitors, not IL-6 inhibitors. However, most of the JAK inhibitor-induced CK elevations were Grade 1, and there were no clinically relevant elevations that required withdrawal.

Creatine kinase levels were significantly elevated over time in the JAK inhibitor group compared to the IL-6 inhibitor group, with a difference in the outlier rate of over Grade 1. If the CK elevation is an indirect effect of decreased disease activity, improved quality of life, or increased activity, CK should be elevated not only in the JAK inhibitor group but also in the IL-6 inhibitor group. However, since the CK level was only slightly elevated with IL-6 inhibitors, it is possible that the CK elevation is due to a direct blocking of JAK-STAT signaling.

The mechanism by which JAK inhibitors increase CK levels is not clear. One hypothesis is the involvement of muscle satellite cell self-renewal. Since IL-6 inhibits muscle satellite cell self-repair via JAK-STAT signaling, IL-6 inhibitors and JAK inhibitors may inhibit this effect, resulting in muscle recovery and an increase in CK.

However, because CK is not elevated with IL-6 inhibitors but only with JAK inhibitors, another mechanism may be involved. One reported candidate is the involvement of oncostatin M, one of the inflammatory cytokines that inhibits myoblast differentiation by JAK1-STAT3 signaling.[9-11] This mechanism is also noted in the EULAR points to consider for treatment with JAK inhibitors.[7] Future studies are needed to investigate the association between muscle mass

Table 3. Creatine kinase among JAK inhibitors

	Tofacitinib (n=42)		Baricitinib (n=25)		Upadacitinib (n=4)		
	Median	25^{th}-75^{th} percentile	Median	25^{th}-75^{th} percentile	Median	25^{th}-75^{th} percentile	*p* value*
0 weeks (IU/mL)	53.0	40.0-92.0	62.5	51.0-81.5	60.0	47.5-60.5	0.991
4 weeks (IU/mL)	85.0	63.0-141.0	96.5	73.0-143.0	84.0	79.5-130.5	0.103
12 weeks (IU/mL)	94.0	62.0-158.0	93.0	73.0-133.0	94.0	93.5-142.0	0.171
24 weeks (IU/mL)	98.0	64.0-155.0	90.5	81.0-167.0	194.0	136.5-201.5	0.185

JAK: Janus kinase; * Continuous variables were analyzed using an Kruskal-Wallis test

and CK under biologic and targeted synthetic DMARD therapy.

Baseline CK, male sex, and creatinine were significantly positively correlated with the CK level at 24 weeks. Since these factors are proportional to muscle mass, baseline muscle mass may have affected the CK level at 24 weeks. With regard to muscle mass and CK, CK has been reported to be associated with the appendicular skeletal mass index and sarcopenia in osteoarthritis patients.[19] On the other hand, Steinbrocker stage and class, mHAQ, eGFR, and glucocorticoid dose showed significant negative correlations. Patients with high Steinbrocker stage and class and high mHAQ may be less likely to have elevated CK levels due to lower activity and less muscle mass. The CK level may be less likely to increase in patients taking high doses of glucocorticoid due to the muscle loss effect of glucocorticoids. In addition, patients with low eGFR may have elevated CK levels due to decreased renal function.[20]

Creatine kinase elevations have been reported in clinical trials of each JAK inhibitor.[1-6,21] Their selectivity may be irrelevant since mild CK elevation is a common phenomenon with JAK inhibitors. In the present study, there was no significant difference in CK elevation among the different JAK inhibitors tofacitinib (n=42), baricitinib (n=25), and upadacitinib (n=4; Table 3).

The EULAR points to consider for treatment with JAK inhibitors noted that creatinine increases have also been observed but without organ dysfunction or other clinical sequelae in conditions such as hypertension.[7] In the present study, the degree of CK elevation was mild, and there were no cases of renal impairment or myalgia due to high CK levels. Mild elevations in CK with JAK inhibitors are not a particular clinical problem.

The present study has several limitations that need to be considered. First, patients who had discontinued JAK inhibitor or inhibitor therapy by 24 weeks were not included in the study and, therefore, could not be studied. However, no patients discontinued treatment due to CK elevations and related side effects. Second, the influence of muscle mass and daily activity level, which might have an impact on the CK level, was not eliminated. Third, the mechanism by which JAK inhibitors increase CK levels is not clear. Fourth, CK isozyme levels were not measured. However, patients with myocardial infarction or progressive muscle dystrophy were not included.

In conclusion, the present study showed that CK elevation was greater at four weeks and 12 weeks and was maintained until 24 weeks with JAK inhibitors compared to IL-6 inhibitors in RA patients with adjustment for background characteristics by PS matching. The slight CK elevation might be specific to JAK inhibitors, but the mechanism is not clear and needs to be clarified in the future.

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Ethics Committee Approval: The study protocol was approved by the Osaka Metropolitan University Ethics Committee (date: 21.06.2021, no: 2021-096). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study design, data collection, data analysis, drafting the manuscript: M.T.; Drafting the manuscript and data collection: T.O., K.M., Y.Y.; Data collection: K.O., K.M., S.A., T.I.; Drafting the manuscript: K.I.; Drafting the manuscript and data analysis: T.K.

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