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JKAP correlates with lower disease risk and inflammation, and its increment during etanercept treatment associates with commendable treatment efficiency in rheumatoid arthritis patients

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Abstract. – OBJECTIVE: This study aimed to investigate the correlation of Jun N-terminal kinase pathway associated phosphatase (JKAP) with disease risk and inflammation, also to explore the association of its longitudinal change with etanercept (ETN) treatment efficiency in rheumatoid arthritis (RA) patients.

PATIENTS AND METHODS: A total of 107 active RA patients about to receive ETN treatment and 60 healthy controls (HCs) were enrolled in this study. Serum JKAP level was measured by enzyme-linked immunosorbent assay in RA patients (at week 0 (W0), W6, W12, and W24) and HCs (at recruitment). RA patients were categorized into W24 response patients and W24 non-response patients, or W24 remission patients and W24 non-remission patients, respectively, according to clinical response status or remission status at W24.

RESULTS: JKAP level was reduced in RA patients compared with HCs. In RA patients, decreased baseline JKAP was correlated with elevated C-reaction protein level and anti-citrullinated protein antibodies positive status. Moreover, JKAP level was increased during ETN treatment. Subgroup analyses revealed that JKAP level during ETN therapy was increased in W24 response patients, while no difference was discovered in JKAP level among different time points in W24 non-response patients. Meanwhile, JKAP level during ETN treatment was elevated in both W24 remission patients and W24 non-remission patients, however, its increment was more evident in W24 remission patients.

CONCLUSIONS: JKAP correlates with reduced disease risk and inflammation, and its increment during ETN treatment associates with commendable treatment efficiency in RA patients.

Key Words:
Rheumatoid arthritis, Jun N-terminal kinase pathway associated phosphatase (JKAP), Etanercept, Treatment response, Treatment remission.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by the immunological reaction against self-own antigens in various tissues types and mainly affects joints[1]. Notably, RA patients present with several typically clinical symptoms including swollen joints, pain and even disability[1]. In terms of pharmacological treatments, conventional disease-modifying antirheumatic drugs (cDMARDs) (such as methotrexate, leflunomide and sulfasalazine) are the first-line treatments for RA patients[2]. Furthermore, with the improvement in the pharmaceutical industry, biological DMARDs (such as tumour necrosis factor (TNF)-α inhibitors) are developed with beneficial clinical outcomes[2,3]. Etanercept (ETN), as a type of TNF-α inhibitor, is the most commonly used biological DMARDs in Chinese population[4]. ETN is reported to quickly reduce inflammation, lower disease activity and delay radiological progression in RA patients[1,3,4]. Although ETN has good clinical efficiency in RA patients, a small part of patients still experiences low treatment response[4]. Therefore, it is critical to discover candidate biomarkers for ETN treatment response in order to develop personalized treatment plans, thereby improving treatment efficiency in RA patients.

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Jun N-terminal kinase (JNK) pathway associated phosphatase (JKAP) has been reported to be involved in the inflammation process. For example, JKAP targets transcription factor Lck to inhibit T cell receptor (TCR) signaling pathway[5]. As to the role of JKAP in autoimmune diseases, JKAP suppresses $CD4^+$ T cell differentiation into Th 1/Th 17 cells in inflammatory bowel disease (IBD)[6]. Moreover, JKAP knockout mice show enhanced production of inflammatory cytokines (such as IL-4 and IFN-γ), which causes inflammation and leads to spontaneous autoimmunity in older age[5]. Regarding the clinical aspect, JKAP has been identified as a key biomarker for predicting the risks of systemic lupus erythematosus (SLE) nephritis and IBD[7,8]. Furthermore, over-expression of JKAP is related to encouraging clinical response to infliximab (IFX) (a type of TNF-α inhibitor) in IBD patients[6]. Based on those mentioned studies, we speculated that JKAP might be used as a potential predictive factor for TNF-α inhibitor (such as ETN) treatment efficiency in RA patients. However, no relevant study has been conducted yet.

Thus, the aim of this study was to investigate the association of JKAP with inflammation and disease activity in RA patients. More importantly, this study also intended to explore JKAP longitudinal change and its correlation with the treatment efficiency of ETN in RA patients.

Patients and Methods

Participants

In this prospective study, a total of 107 active RA patients who intended to receive ETN treatment in our hospital were consecutively enrolled from January 2017 to December 2019. The inclusion criteria were: (1) diagnosed as RA based on clinical symptoms, laboratory examinations, ultrasonic or magnetic resonance imaging (MRI) examination according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA classification criteria[9]; (2) aged above 18 years old and less than 80 years old; (3) confirmed as active RA, which was defined as 28 joints disease activity score (DAS28)≥3.2; (4) had poor efficacy of a single drug or multi-drug treatment of cDMARDs; (5) about to initiate ETN treatment for 24 weeks; (6) could be followed up regularly. The exclusion criteria were: (1) severe joint damage; (2) severe infections; (3) history of malignancies or immunodeficiency diseases; (4) moderate to severe abnormalities of liver or renal function; (5) contraindication to ETN; (6) pregnant or lactating women. In addition, 100 healthy subjects who underwent healthy examinations in our hospital were recruited as healthy controls (HCs).

Ethics

This study was approved by the Institutional Review Board of our hospital. All procedures were performed according to the Declaration of Helsinki. The written informed consent was acquired from the participants before enrollment.

Data Collection

The clinical data before the initiation of ETN treatment (week 0, W0) were recorded, which included age, gender, body mass index (BMI), disease duration, history of biologics, history of cDMARDs, rheumatoid factor (RF) status, anti-citrullinated protein antibodies (ACPA) status, tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), DAS28 based on erythrocyte sedimentation rate ($DAS28_{ESR}$) score and health assessment questionnaire disability index (HAQ-DI) score.

Treatment and Assessment

All patients received ETN treatment as follows: subcutaneous injection of 50 mg ETN per week for 24 weeks or subcutaneous injection of 25 mg ETN twice a week for 24 weeks. During ETN treatment, other combined medications such as methotrexate (MTX) and leflunomide (LEF) were also recorded. After the initiation of ETN treatment, regular follow-up was performed for all patients. The clinical response and clinical remission of patients were assessed 6 weeks (W6), 12 weeks (W12) and 24 weeks (W24) after the initiation of ETN treatment, respectively. The clinical response was defined as a decrease of 1.2 points in the DAS28 score from baseline referring to the EULAR response criteria[10]. Clinical remission was defined as a DAS28 score<2.6 points referring to 2010 ACR/EULAR RA classification criteria[9]. According to the clinical response status or clinical remission status at W24, RA patients were termed as W24 response patients and W24 non-response patients, or W24 remission patients and W24 non-remission patients, respectively. For the RA

patients who withdrew from this study, the clinical response and clinical remission status were analyzed by using the last follow-up data.

Samples Collection

Peripheral blood (PB) of patients was collected at W0, W6, W12 and W24, and the serum was isolated from the PB by centrifugalizing. PB of HCs was collected when enrollment and the serum were isolated from the PB as the same method. The level of JKAP in serum was detected by enzyme-linked immunosorbent assay (ELISA), which was performed according to the manufacturer's protocol of the commercial human JKAP ELISA Kit (Shanghai Enzyme-linked Biotechnology Co., Ltd, Minhang District, Shanghai, China). For the RA patients who withdrew from this study, the JKAP level was analyzed using the last follow-up data.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD) or median value with interquartile range (IQR) based on their normality. Categorical variables were expressed as count with percentage. The comparison of JKAP between RA patients and HCs was determined by the Wilcoxon rank-sum test. The comparison of JKAP among W0, W6, W12 and W24 was determined by the Friedman test for repeated measures. The correlations of JKAP with continuous variables were determined by Spearman's rank correlation test. The correlation of JKAP with categorical variables was determined by the Wilcoxon rank-sum test. The receiver operating characteristic (ROC) curve was plotted. The area under the ROC curve (AUC), and sensitivity, as well as specificity at the best cut-off point in the ROC curve were used to assess the ability of JKAP in distinguishing RA patients from HCs. Statistical analysis was performed using SPSS version 24.0 (IBM, Armonk, NY, USA), and the figures were made using GraphPad Prism version 7.02 (GraphPad Software, San Diego, CA, USA). All tests were two-tailed. p-value <0.05 was considered as significant.

Results

Study Flow

Totally, 129 active RA patients who intended to receive ETN treatment were invited to this study. Twenty-two patients were excluded (including 12 patients who were contradicting the inclusion criteria or met the exclusion criteria, and 10 patients who refused to participate in this study). Subsequently, the remaining 107 active RA patients were eligible for this study. However, 14 patients withdrew (including 6 patients who lost follow-up, 3 patients who had poor efficacy, 3 patients who were willing to discontinue the studied drug and 2 patients who had abnormal liver function). Finally, all 107 patients were included in the final analysis based on the intention-to-treat (ITT) principle with last observation carried forward (LOCF) method (Figure 1).

Baseline Characteristics

The analyzed RA patients had a mean age of 58.0±9.9 years, and there were 22 (20.6%) males, as well as 85 (79.4%) females (Table I). The median disease duration was 3.5 (1.9-6.6) years. Besides, 20 (18.7%) patients had a history of biologics and 107 (100.0%) patients had a history of cDMARDs. Meanwhile, there were 77 (72.0%) patients with RF positive status and 67 (62.6%) patients with APCA positive status. The median value of TJC and SJC was 7.0 (5.0-10.0) and 6.0 (4.0-8.0), respectively. In addition, the median ESR and CRP were 37.6 (21.9-54.7) mm/h and 31.6 (15.8-63.0) mg/L, respectively. Moreover, the

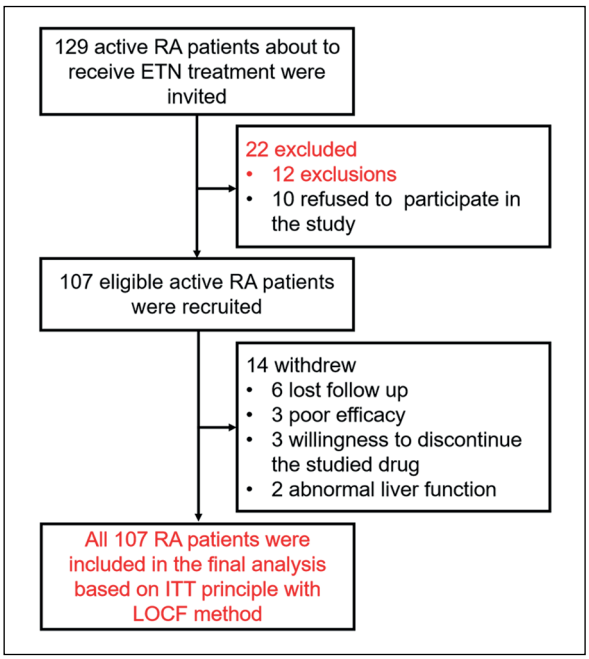


Figure 1. Study flow. RA: Rheumatoid arthritis; ETN: etanercept; ITT: Intention to treat; LOCF: last observation carried forward.

Table I. Clinical characteristics.

Items	RA patients (N = 107)
Age (years), mean±SD	58.0 ± 9.9
Gender, No. (%)	
Male	22 (20.6)
Female	85 (79.4)
BMI (kg/m^2), mean ± SD	22.8 ± 3.0
Disease duration (years), median (IQR)	3.5 (1.9-6.6)
History of biologics, No. (%)	
No	87 (81.3)
Yes	20 (18.7)
History of cDMARDs, No. (%)	
No	0 (0.0)
Yes	107 (100.0)
RF status, No. (%)	
Negative	30 (28.0)
Positive	77 (72.0)
ACPA status, No. (%)	
Negative	40 (37.4)
Positive	67 (62.6)
TJC, median (IQR)	7.0 (5.0-10.0)
SJC, median (IQR)	6.0 (4.0-8.0)
ESR (mm/h), median (IQR)	37.6 (21.9-54.7)
CRP (mg/L), median (IQR)	31.6 (15.8-63.0)
DAS28ESR score, mean ± SD	5.2 ± 0.7
HAQ-DI score, mean± SD	1.7 ± 0.3
Combined medications, No. (%)	
MTX	56 (52.3)
LEF	51 (47.7)

RA, rheumatoid arthritis; SD, standard deviation; BMI, body mass index; IQR, interquartile range; cDMARDs, conventional disease-modifying antirheumatic drugs; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; TJC, tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28ESR score, 28 joints disease activity score based on erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; MTX, methotrexate; LEF, leflunomide.

mean $DAS28_{ESR}$ and HAQ-DI scores were 5.2±0.7 and 1.7±0.3 respectively. Regarding combined medications, there were 56 (52.3%) patients receiving MTX treatment and 51 (47.7%) patients receiving LFX treatment. The detailed baseline clinical information was shown in Table I.

JKAP Expression in RA Patients and HCs

JKAP level was reduced in RA patients compared to HCs (p<0.001) (Figure 2A). Besides, JKAP was able to distinguish RA patients from HCs (AUC of 0.896, 95% CI: 0.855-0.938) (Figure 2B). Its specificity was 89.0% and sensitivity was 77.6% at best cut-off point where the largest sum of specificity and sensitivity occurred (Figure 2B).

Correlation of JKAP with Clinical Characteristics in RA Patients

Regarding continuous variables, JKAP was negatively correlated with CRP level (r=-0.321, p=0.001), while no correlation was found in JKAP with age (r=0.007, p=0.940), BMI (r=-0.169, p=0.082), disease duration (r=-0.123, p=0.206), TJC (r=-0.117, p=0.231), SJC (r=-0.128, p=0.189), ESR (r=-0.120, p=0.217), $DAS28_{ESR}$ score (r=-0.145, p=0.137) or HAQ-DI score (r=-0.089, p=0.362) (Table II). As to categorical variables, JKAP level was decreased in ACPA positive patients compared with ACPA negative patients (38.0 (24.7-55.8) pg/mL *vs.* 47.7 (30.9-68.2) pg/mL, p=0.047) (Table III). However, no correlation was observed in JKAP with gender (p=0.493), history of biologics (p=0.876), RF status (p=0.089) or combined medications (p=0.371) (Table III).

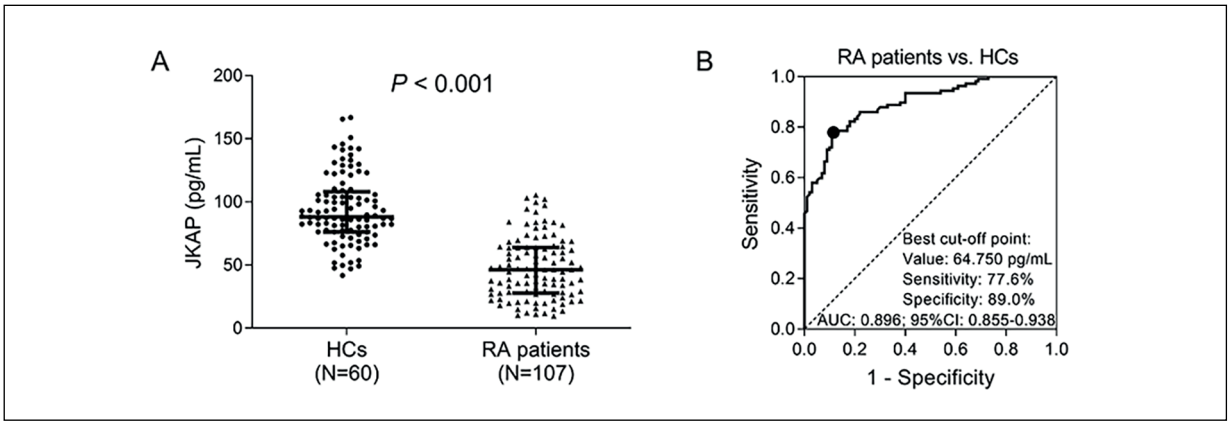
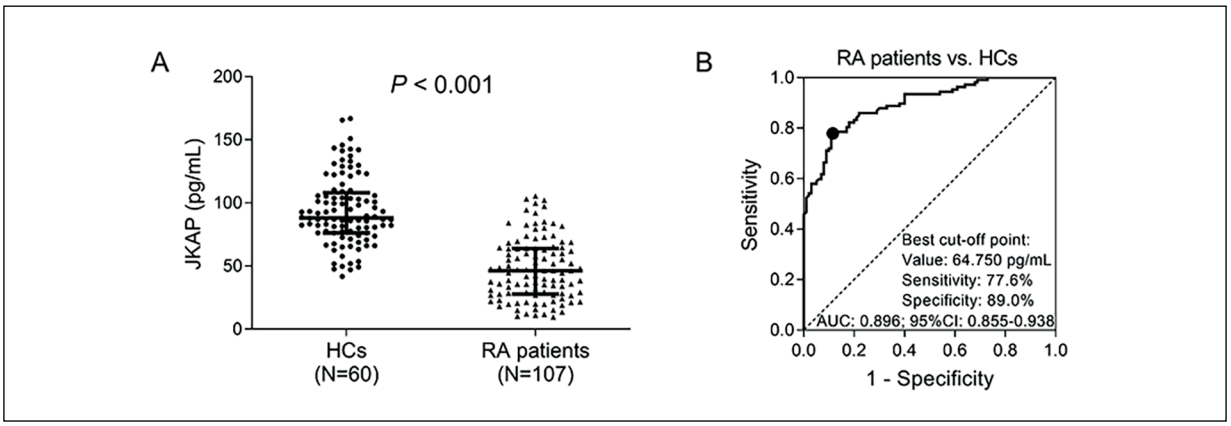


Figure 2. JKAP expression and its correlation with RA risk. **A,** Comparison of JKAP expression between RA patients and HCs; **B,** Predictive value of JKAP for RA risk by ROC curve. JKAP: JNK pathway-associated phosphatase; HCs: healthy controls; ROC: receiver's operating characteristic; AUC: area under the curve; CI: confidence interval.



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Correlation of JKAP with ETN Treatment Efficiency in RA Patients

JKAP level was higher in total patients over time (p<0.001) (Figure 3). There were 0 (0.0%), 33 (30.8%), 56 (52.3%) and 77 (72.0%) patients who realized clinical response at W0, W6, W12 and W24, respectively (Figure 4A). In W24 response patients, JKAP level was increased with study time (p<0.001) (Figure 4B). While in W24 non-response patients, no difference was observed in JKAP level among different time points (p=0.514) (Figure 4C).

Moreover, there were 0 (0.0%), 5 (4.7%), 18 (16.8%) and 34 (31.8%) patients who achieved clinical remission at W0, W6, W12 and W24, respectively (Figure 5A). Regarding the remission outcome, JKAP level was elevated in both W24 remission patients (p<0.001) (Figure 5B) and W24 non-remission patients (p=0.017) (Figure 5C) during ETN treatment, and the increment of JKAP level was more obvious in W24 remission patients.

Table II. Correlation of JKAP with continuous variables.

Items	JKAP level	
	p-value	Correlation coefficient (r)
Age	0.940	0.007
BMI	0.082	-0.169
Disease duration	0.206	-0.123
TJC	0.231	-0.117
SJC	0.189	-0.128
ESR	0.217	-0.120
CRP	0.001	-0.321
DAS28ESR score	0.137	-0.145
HAQ-DI score	0.362	-0.089

Correlation was determined by Spearman's rank correlation test. JKAP, JNK pathway-associated phosphatase; BMI, body mass index; TJC, tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28ESR score, 28 joints disease activity score based on erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index.

Table III. Correlation of JKAP with categorical variables.

Items	JKAP level (pg/mL)	*p*-value
Gender, median (IQR)		0.493
Male	39.3 (27.4-51.4)	
Female	48.1 (27.4-64.2)	
History of biologics, median (IQR)		0.876
No	44.8 (27.8-64.4)	
Yes	46.2 (29.1-58.7)	
RF status, median (IQR)		0.089
Negative	47.1 (30.0-64.5)	
Positive	35.1 (20.7-63.8)	
ACPA status, median (IQR)		0.047
Negative	47.7 (30.9-68.2)	
Positive	38.0 (24.7-55.8)	
Combined medications, median (IQR)		0.371
MTX	46.2 (26.9-59.5)	
LEF	44.8 (29.1-69.5)	

Correlation was determined by Wilcoxon rank sum test. JKAP, JNK pathway-associated phosphatase; IQR, interquartile range; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; MTX, methotrexate; LEF, leflunomide.

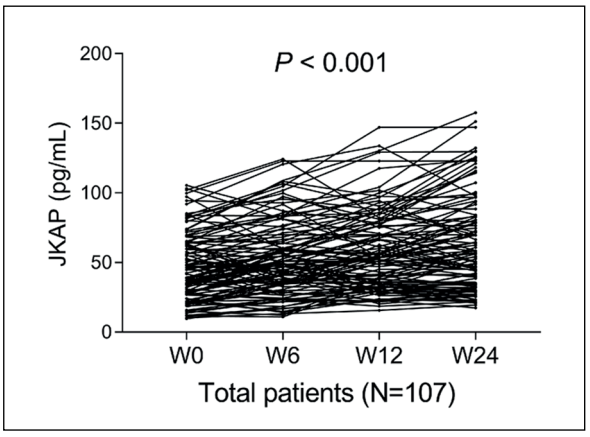

Figure 3. Longitudinal change of JKAP during ETN treatment in RA patients. JKAP: JNK pathway-associated phosphatase; RA: Rheumatoid arthritis.

Discussion

Based on these above-mentioned results, we found that (a) JKAP level was reduced in RA patients compared to HCs and it was able to differentiate RA patients from HCs; (b) reduced JKAP expression was related to elevated CRP and ACPA positive status in RA patients; (c) the increment of JKAP expression was related to clinical response and clinical remission during ETN treatment in RA patients.

JKAP, which is also named as dual-specificity phosphatase-22 (DUSP22), is an atypical DUSP due to lack of regulatory domain[11]. JKAP has been identified as a scaffold protein in apoptosis signal-regulating kinase 1 (ASK1) – mitogen-activated protein kinase kinase 7 (MKK7) – JNK1/2 pathway to regulate cell apoptosis in the human embryonic kidney (HEK) 293 cells[12]. Moreover, JKAP dephosphorylates focal adhesion kinase, thereby leading to decreased cell migration activity in H1299 cells[13]. It has been illustrated that JKAP participates in inflammation processes. For example, JKAP suppresses TCR signaling by the inactivation of transcription factor Lck, thereby resulting in enhanced T cell response and increased production of pro-inflammatory cytokines[5]. Meanwhile, JKAP inhibits T cell proliferation and differentiation in IBD[6]. Moreover, JKAP suppresses IL-6 induced signal transducer and activator of transcription 3 (STAT3) signaling to reduce the genetic production of inflammatory cytokines in mouse GC-1 cells and Hepa 1-6 cells[14]. Taken together, JKAP is highly involved in inflammation processes.

Apart from that JKAP is strongly involved in inflammation processes *in vivo* and *in vitro*, its reduced expression in patients with various inflammation-related diseases has been observed. From the existing evidence, JKAP level is decreased in SLE nephritis patients and IBD patients when compared with HCs[6,7,15]. Meanwhile, down-regulation of JKAP level is correlated with elevated sepsis risk and IBD risk[8,15]. However, the role of JKAP in RA patients remains unclear. In our study, we found that JKAP level was lower in RA patients compared to HCs and it was able to differentiate RA patients from HCs. The possible reasons were: down-regulation of JKAP might inhibit TCR signaling to suppress $CD4^+$ T cell proliferation, thereby developed an insufficient T cell-mediated immune response and eventually led to higher RA risk[5,6]. Therefore, down-regulation of JKAP was found in RA patients and it was correlated with increased RA risk.

The correlation of JKAP with inflammation and disease activity in some inflammation-relat-

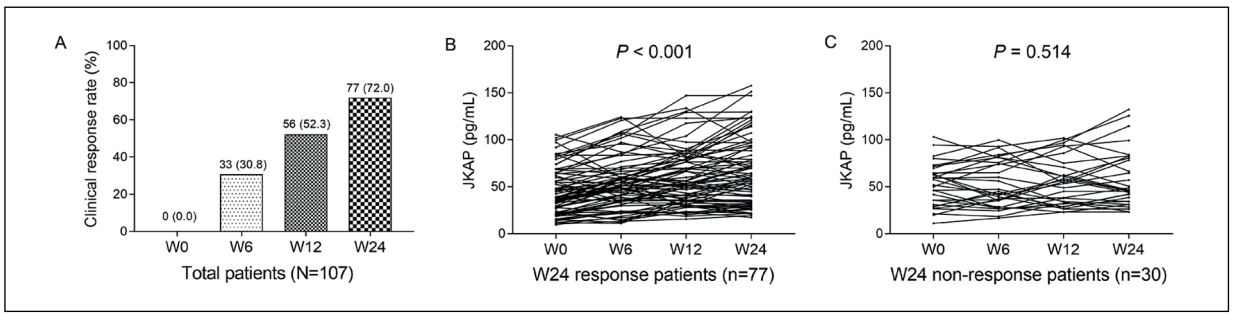

Figure 4. Correlation of longitudinal JKAP change with treatment response in RA patients. **A,** Clinical response rate at different times in total patients; **B,** Comparison of JKAP level at different times in W24 response patients; **C,** Comparison of JKAP level at different times in W24 non-response patients. JKAP: JNK pathway-associated phosphatase; W24: Week 24; RA: Rheumatoid arthritis.

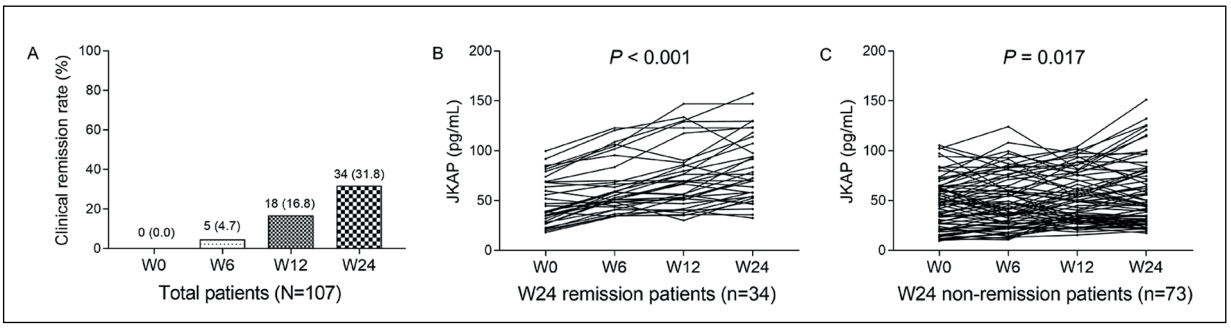

Figure 5. Correlation of longitudinal JKAP change with treatment remission in RA patients. **A,** Clinical remission rate at different times in total patients; **B,** Comparison of JKAP level at different times in W24 remission patients. **C,** Comparison of JKAP level at different times in W24 non-remission patients. JKAP: JNK pathway-associated phosphatase; W24: Week 24; RA: Rheumatoid arthritis.

ed diseases has been illustrated. Regarding inflammation, JKAP is negatively correlated with CRP level in sepsis patients[8]. Moreover, JKAP is inversely related to the production of pro-inflammatory cytokines (including IL-17 and TNF-α) in IBD patients[6]. As to disease activity, previous studies reveal that down-regulation of JKAP is related to advanced disease activity in IBD patients reflected by CDAI score and Mayo index, and higher disease activity in SLE patients based on the SLE disease activity index[6,7]. In our study, we found that reduced JKAP was correlated to elevated CRP level and ACPA positive status in RA patients. These results could be explained by the following reasons: (a) JKAP might suppress multiple inflammation-related signaling pathways (including IL-6/LIF/STAT3 signaling pathway) to decrease the production of pro-inflammatory cytokines, subsequently resulted in reduced inflammation in RA patients[14]; (b) down-regulation of JKAP might enhance T cell-mediated immune response, thus led to increased inflammation in RA patients[5]. Taken together, JKAP was negatively related to inflammation in RA patients.

The correlation of JKAP expression with TNF-α inhibitor treatment response has been explored in previous studies. For instance, the increment of JKAP level is associated with improved TNF-α inhibitor treatment response in IBD patients[6]. In our study, we discovered that JKAP level was elevated during ETN treatment, and the increase of JKAP level was related to enhanced ETN treatment efficiency in RA patients. The possible reasons were listed as follows: (a) JKAP was negatively correlated with inflammatory level as discussed earlier, and the rapid increase of JKAP level suggested the reduction of inflammation during ETN treatment, thus an increment of JKAP level was related to better treatment efficiency in RA patients[6,15,16]; (b) JKAP might activate several signaling pathways (such as TCR-mediated signaling pathway and IL-6/LIF/STAT3 signaling pathway) to directly influence the treatment efficiency in RA patients. However, no study underlines the detailed pharmacological mechanism regarding the correlation of JKAP with TNF-α inhibitor, thus further relevant study is needed.

There were some limitations in this study, which should be clarified. First, this was a single-center study with a relatively small sample size, so further multi-center study with a larger sample size was needed. Second, the detailed molecular mechanism of JKAP in RA was not explored. Thus, further molecular experiments were needed. Thirdly, we only recruited RA patients who intended to receive ETN therapy, therefore further study investigating the correlation of JKAP with the clinical efficiency of other TNF-α inhibitors was necessary.

Conclusions

We found that JKAP correlates with reduced disease risk and inflammation, and its increment during ETN treatment correlates with commendable treatment efficiency in RA patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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