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RESEARCH ARTICLE

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Mucosa-associated lymphoid tissue lymphoma translocation protein 1 in rheumatoid arthritis: Longitudinal change after treatment and correlation with treatment efficacy of tumor necrosis factor inhibitors

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Abstract

Background: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) correlates with treatment outcomes in inflammatory bowel disease and rheumatoid arthritis (RA). This study aimed to further evaluate the MALT1 longitudinal change and its relationship with tumor necrosis factor inhibitors (TNFi) response in RA patients.

Methods: Seventy-one RA patients receiving TNFi [etanercept ($n = 42$) or adalimumab ($n = 29$)] were enrolled. MALT1 was detected by RT-qPCR in peripheral blood samples of RA patients before treatment (W0), at week (W)4, W12, and W24 after treatment. RA patients were divided into response/non-response, remission/non-remission patients according to their treatment outcome at W24. Meanwhile, MALT1 was also detected by RT-qPCR in 30 osteoarthritis patients and 30 healthy controls (HCs).

Results: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 was elevated in RA patients compared with HCs (Z=−6.392, $p < 0.001$) and osteoarthritis patients ($Z = -5.020$, $p < 0.001$). In RA patients, MALT1 was positively correlated with C-reactive protein ($r_s = 0.347$, $p = 0.003$), but not other clinical characteristics, treatment history, or current TNFi category. Meanwhile, MALT1 decreased from W0 to W12 in total RA patients ($x^2 = 86.455$, $p < 0.001$), etanercept subgroup ($x^2 = 46.636$, $p < 0.001$), and adalimumab subgroup ($x^2 = 41.291$, $p < 0.001$). Moreover, MALT1 at W24 ($p = 0.012$) was decreased in response patients compared with non-response patients; MALT1 at W12 ($p = 0.027$) and W24 ($p = 0.010$) were reduced in remission patients than non-remission patients. In etanercept subgroup, MALT1 at W24 ($p = 0.013$) was decreased in response patients compared with non-response patients. In adalimumab subgroup, MALT1 at W24 ($p = 0.015$) was lower in remission patients than non-remission patients.

Feng Wang and Gaozhan Liu contributed equally to this work.

Conclusion: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 reduction after treatment is associated with response and remission to TNFi in RA patients.

KEYWORDS
disease characteristics, mucosa-associated lymphoid tissue lymphoma translocation protein 1, rheumatoid arthritis, treatment response and remission, tumor necrosis factor inhibitors

1 | INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease that affects approximately 1% of the entire human beings with the incidence ranging from 8 to 45 per 100,000 populations per year.[1,2] Clinically, RA not only causes swollen and tender joints, but also affects other systems or organs apart from the joints including skin, eyes, cardiovascular system, neuron system, etc.[3] Fortunately, with the induction of tumor necrosis factor (TNF) inhibitors, the most commonly used biologics, the treatment approaches of RA have been greatly enriched.[4–6] For RA patients who may not respond to conventional disease-modifying anti-rheumatoid drugs (cDMARDs), using TNF inhibitors is a promising option; meanwhile, it is also reported that using TNF inhibitors as the first-line therapy is a cost-effective strategy.[7–9] However, there are still some patients who may not response to TNF inhibitors. Therefore, it is necessary to explore potential biomarkers that may predict the treatment response to TNF inhibitors, thus improving the management of RA.

Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is a kind of paracaspase that exerts proteolysis effect.[10] According to previous studies, MALT1 is a vital regulator of immune diseases.[11–15] For instance, suppressing MALT1 represses osteoclast differentiation while alleviating pathologic bone erosion and synovitis in RA model mice.[11] Meanwhile, MALT1 knockdown inhibits the expression of pro-inflammatory cytokines and chemokines in human primary keratinocytes, thus regulating the progression of psoriasis.[12,13] Besides, inhibiting MALT1 also reduces the levels of inflammatory cytokines through suppressing nuclear factor-κB (NF-κB) pathway in inflammatory bowel disease or ankylosing spondylitis model mice.[14,15] Clinically, two very recent studies report that MALT1 is positively correlated with inflammation, disease activity, and clinical response in patients with inflammatory bowel disease or RA.[16,17] However, whether MALT1 could serve as a biomarker reflecting treatment response to TNF inhibitors in RA remains unclear.

The current study aimed to assess the change in MALT1 after treatment and its relationship with response to TNF inhibitors in RA patients.

2 | METHODS

2.1 | Subjects

A total of 71 active RA patients treated with TNF inhibitors from February 2019 to January 2021 were included in this observational study. The inclusion criteria were as follows: (a) Diagnosis of RA in accordance with the American College of Rheumatology classification criteria for RA[18]; (b) 28-joint disease activity score with an erythrocyte sedimentation rate (DAS28 score (ESR)) more than 3.2; (c) over 18 years old; (d) were about to receive TNF inhibitor treatment; (e) volunteered to participate in the study. The exclusion criteria were as follows: (a) hypersensitive to TNF inhibitors used in the study; (b) presented with infection; (c) had a history of malignant tumor; (d) pregnancy or breast-feeding patient. Between February 2019 and January 2021, a total of 30 osteoarthritis (OA) patients were also enrolled in the study. The enrolled OA patients conformed to the following criteria: (a) Diagnosis of OA; (b) more than 18 years old; (c) volunteered to provide PB samples. Additionally, a total of 30 health controls (HCs) without any physical abnormalities were recruited during the same period. The exclusion criteria for RA patients were also suitable for OA patients and HCs, except allergic to TNF inhibitors. In order to eliminate the potential bias, the age and gender of OA patients as well as HCs were matched to RA patients. The age was limited within 45–70 years old, and the gender ratio was 4:1 (female vs. male). The study was permitted by the Ethics Committee of Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science. All patients signed informed consent.

2.2 | Collection of data and samples

Clinical characteristics were collected from all RA patients, including demographic characteristics, disease characteristics, and treatment information. Peripheral blood (PB) samples were collected from RA patients before treatment (W0, $N = 71$), from OA patients after enrollment ($N = 30$), and from HCs after recruitment ($N = 30$). Additionally, PB samples were also obtained from the RA patients at 4 weeks (W4, $n = 68$), 12 weeks (W12, $n = 61$), and 24 weeks (W24, $n = 55$) after treatment initiation.

2.3 | Examination of samples

After the collection of PB samples, peripheral blood mononuclear cells (PBMCs) were isolated to determine MALT1 expression by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Briefly, after extracted with a RNeasy Protect Mini Kit (Qiagen), total RNA was reversely transcribed into cDNA with a PrimeScript™ RT reagent Kit (Takara). Subsequently, qPCR was conducted using KOD SYBR® qPCR Mix (Toyobo). The primers used in

the current study were designed according to a previous study.[19] The relative expression of MALT1 was calculated by the $2^{-\Delta\Delta Ct}$ method with GAPDH as the internal reference.[20]

2.4 | Treatment and follow-up

All RA patients were treated with TNF inhibitors plus disease-modifying antirheumatic drug (DMARD), and TNF inhibitors included etanercept and adalimumab.[7] The patients treated with etanercept were considered as etanercept subgroup, and the patients treated with adalimumab were considered as adalimumab subgroup. Etanercept was administered subcutaneously at a dose of 50 mg every week; adalimumab was administered subcutaneously at a dose of 40 mg every 2 weeks. At W4, W12, and W24 after the initiation of treatment, the RA patients were followed up by clinic visit, and a total of 16 patients dropped out from the study early, including nine patients who switched to other therapies due to poor treatment efficacy, four patients postponed treatment due to abnormal liver function or infection at the injection site, and three patients who lost follow-up.

2.5 | Assessment of response and remission

At W4, W12, and W24 after treatment initiation, clinical response and clinical remission were assessed based on DAS28 score (ESR) according to RA response criteria.[21] For the patients who withdrew from the study early, clinical response and clinical remission were evaluated using the last observation carried forward (LOCF) method (DAS28 score (ESR) at the last follow-up were used as the values of each later missing visit) based on intention-to-treat (ITT) principle. Clinical response was considered if DAS28 score (ESR) decline over 1.2, and according to its realization at W24, the RA patients were divided into response patients and non-response patients. Clinical remission was considered if DAS28 score (ESR) lower than 2.6, and according to its realization at W24, the RA patients were classified as remission and non-remission patients.

2.6 | Statistics

Statistical analyses and graph plotting were completed using SPSS V.24.0 (IBM Corp.) and GraphPad Prism V.6.01 (GraphPad Software Inc.), respectively. Difference in MALT1 expression between groups was compared using Mann–Whitney U test. The performance of MALT1 expression in differentiating subjects was analyzed using receiver operating characteristic (ROC) curves. The correlation of MALT1 expression with clinical characteristics was determined using Spearman's rank correlation test or Mann–Whitney U test. Change in MALT1 expression over time was determined using Friedman test. Comparison of MALT1 expression between response patients and non-response patients, as well as between remission patients and non-remission patients was analyzed using Mann–Whitney U test. p value < 0.05 was considered as statistically significant.

3 | RESULTS

3.1 | Baseline characteristics in RA patients

The enrolled RA patients included 13 (18.3%) males and 58 (81.7%) females with a mean age of 56.4 ± 8.9 years. Meanwhile, the median disease duration was 4.2 (2.7–6.8) years. Regarding disease characteristics, the median [interquartile range (IQR)] values of tender joint count (TJC) and swollen joint count (SJC) were 7.0 (4.0–10.0) and 6.0 (3.5–9.5), respectively; the median (IQR) levels of ESR and CRP were 32.9 (24.3–45.0) mm/h and 25.0 (13.1–38.5) mg/L, accordingly; the mean DAS28 and health assessment questionnaire-disability index (HAQ-DI) scores were 5.1 ± 0.7 and 1.1 ± 0.3, respectively. Besides, 42 (59.2%) patients were receiving etanercept plus DMARD and 29 (40.8%) patients were receiving adalimumab plus DMARD currently. More detailed characteristics of RA patients were presented in Table 1.

3.2 | MALT1 expression in RA patients, OA patients, and HCs

Mucosa-associated lymphoid tissue lymphoma translocation protein 1 in RA patients [median (IQR) level: 2.540 (1.900–3.430)] was elevated compared with HCs [median (IQR) level: 0.985 (0.703–1.500)] ($Z = -6.392$, $p < 0.001$) and OA patients [median (IQR) level: 1.310 (0.843–1.930)] ($Z = -5.020$, $p < 0.001$) (Figure 1A). Further ROC curve analyses revealed that MALT1 was valuable in discriminating RA patients from HCs [area under the curve (AUC): 0.904, 95% confidence interval (CI): 0.845–0.962]; it also presented good potential in discriminating RA patients from OA patients (AUC: 0.817, 95% CI: 0.728–0.907) (Figure 1B).

3.3 | Correlation of MALT1 with disease characteristics and treatment information in RA patients

Subsequently, the correlation analyses illustrated that MALT1 was positively correlated with CRP ($r_s = 0.347$, $p = 0.003$); however, MALT1 was not associated with disease duration, TJC, SJC, ESR, DAS28 score (ESR) or HAQ-DI score (all $p > 0.05$) (Figure 2A–G). Regarding the association of MALT1 with treatment information, it was revealed that MALT1 was associated with neither history of nonsteroidal anti-inflammatory drugs, glucocorticoid, DMARDs, biologics, nor current treatment (all $p > 0.05$) (Table 2).

TABLE 1 Clinical characteristics of RA patients

Items	RA patients (*N* = 71)
Age (years), mean ± SD	56.4 ± 8.9
Gender, *n* (%)	
Male	13 (18.3)
Female	58 (81.7)
BMI (kg/m^2), mean ± SD	22.9 ± 2.8
Disease duration (years), median (IQR)	4.2 (2.7–6.8)
History of NSAID, *n* (%)	63 (88.7)
History of GC, *n* (%)	68 (95.8)
History of DMARD, *n* (%)	68 (95.8)
History of Biologics, *n* (%)	17 (23.9)
RF positive, *n* (%)	57 (80.3)
ACPA positive, *n* (%)	50 (70.4)
TJC, median (IQR)	7.0 (4.0–10.0)
SJC, median (IQR)	6.0 (3.5–9.5)
ESR (mm/h), median (IQR)	32.9 (24.3–45.0)
CRP (mg/L), median (IQR)	25.0 (13.1–38.5)
DAS28 score (ESR), mean ± SD	5.1 ± 0.7
HAQ-DI score, mean ± SD	1.1 ± 0.3
Current treatment, *n* (%)	
Etanercept plus DMARD	42 (59.2)
Adalimumab plus DMARD	29 (40.8)

Abbreviations: ACPA, anti-citrullinated protein autoantibody; BMI, body mass index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; HAQ-DI, health assessment questionnaire-disability index; IQR, interquartile range; NSAID, non-steroid anti-inflammatory drugs; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count.

3.4 | MALT1 change after treatment in RA patients

In total RA patients, MALT1 presented a decreasing trend from W0 to W24 ($x^2 = 86.455$, $p < 0.001$) (Figure 3A). Meanwhile, in etanercept subgroup ($x^2 = 46.636$, $p < 0.001$) (Figure 3B) and adalimumab subgroup ($x^2 = 41.291$, $p < 0.001$) (Figure 3C), MALT1 also showed similar trends from W0 to W24.

3.5 | Association of MALT1 with response and remission in RA patients

In total RA patients, 43 (60.6%) and 21 (29.6%) patients achieved response and remission at W24, respectively (Figure 4A). In etanercept subgroup, there were 25 (59.5%) and 12 (28.6%) patients who realized response and remission at W24, accordingly (Figure 4B). In adalimumab subgroup, at W24, 18 (62.1%) and 9 (31.0%) patients reached response and remission, respectively (Figure 4C). Meanwhile, the number of patients who achieved response or remission at W0, W4, and W12 is shown in detail in Figure 4A–C.

Further comparison analyses disclosed that in total RA patients, MALT1 at W24 ($p = 0.012$) was decreased in response patients compared with non-response patients (Figure 5A); meanwhile, MALT1 at W12 ($p = 0.027$) and W24 ($p = 0.010$) were reduced in remission patients compared with non-remission patients (Figure 5B). In etanercept subgroup, only MALT1 at W24 ($p = 0.013$) was decreased in response patients compared with non-response patients (Figure 5C); whereas it remained similar between remission and non-remission patients (all $p > 0.05$) (Figure 5D). In adalimumab subgroup, MALT1 was not changed between response and non-response patients (all $p > 0.05$) (Figure 5E); however, MALT1 at W24 ($p = 0.015$) was lower in remission patients compared with non-remission patients (Figure 5F). Besides, MALT1 was decreased in both responders ($p < 0.001$) and non-responders ($p = 0.008$) (Figure S1A–B).

4 | DISCUSSION

Mucosa-associated lymphoid tissue lymphoma translocation protein 1 is reported to modulate the progression of immune diseases through multiple approaches. For instance, as mentioned above, MALT1 inhibition or knockdown reduces the level of pro-inflammatory cytokines in psoriasis, inflammatory bowel disease, and ankylosing spondylitis.[12,14,15] Meanwhile, suppressing MALT1 directly relieves bone erosion and synovitis in RA.[11] Moreover, MALT1 increases the population of T helper (Th) 17 in inflammatory bowel disease model mice, while Th 17 is one of the key regulators of inflammatory bowel disease.[22,23] However, the clinical

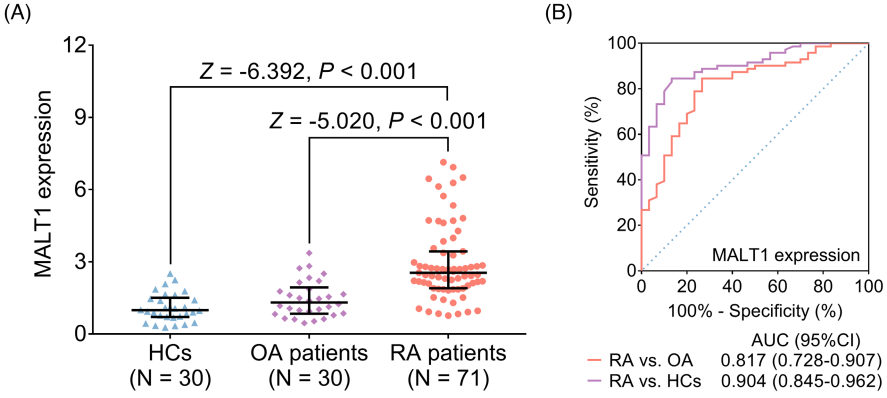

FIGURE 1 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 expression. Comparison of MALT1 in RA patients versus OA patients, and in RA patients versus HCs (A); ROC curve analysis (B)

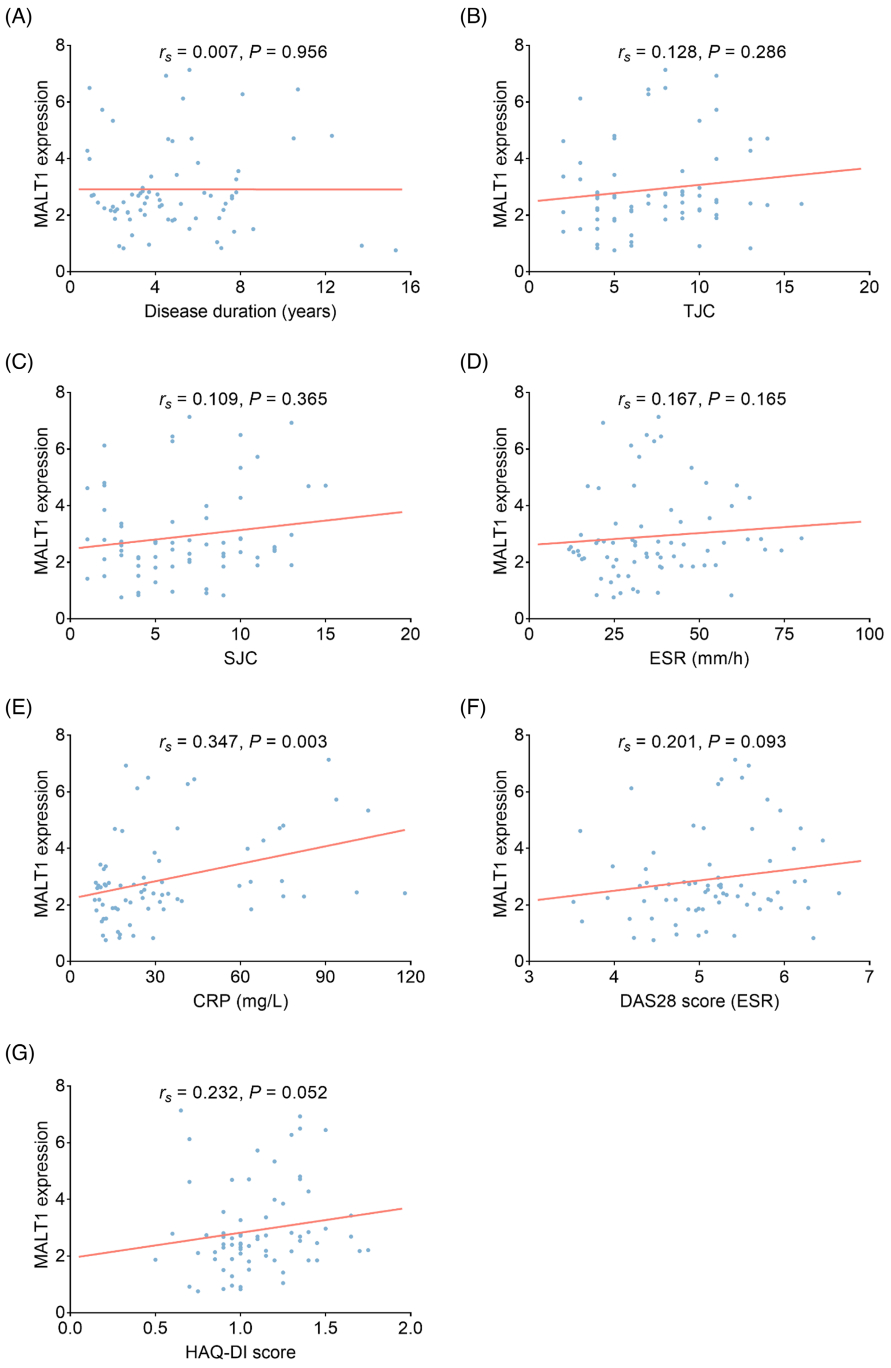

FIGURE 2 Correlation of MALT1 with disease characteristics of RA patients. Correlation of MALT1 with disease duration (A), TJC (B), SJC (C), ESR (D), CRP (E), DAS28 score (ESR) (F), and HAQ-DI score (G)

implication of MALT1 in immune diseases is not totally clear. In the current study, it was observed that MALT1 was elevated in RA patients compared to HCs and OA patients. These findings could be explained by the fact that high level of MALT1 promotes synovitis, thus inducing RA[11]; elevated MALT1 might also promote the differentiation of Th 17, thus resulting in the pathogenesis of RA.[13,22] Therefore, MALT1 was elevated in RA patients compared to HCs and OA patients. Besides, the ROC curve analysis revealed that MALT1 possessed good potential in discriminating RA patients from HCs and OA patients, which indicated that MALT1 could be used for the diagnosis of RA. However, further studies should be conducted to verify that.

Regarding the role of MALT1 as the indicator of inflammation and disease activity in immune diseases, two very recent studies suggest that MALT1 is positively correlated with inflammation and disease activity in patients with inflammatory bowel disease or RA.[16,17] In the present study, it was observed that MALT1 was only positively correlated with CRP in RA patients, which was partly in line with a previous study.[17] The possible explanation could be that: high expression of MALT1 might activate the NF-κB pathway, a key pathway that regulates pro-inflammatory cytokines,[14,15,24] to increase inflammation in RA patients. However, we did not observe the statistical significance in the correlation of MALT1 with disease activity in RA, which was different from the previous study.[17] A possible

TABLE 2 Correlation of MALT1 expression with treatments

Items	MALT1 expression, median (IQR)	Z	p Value
History of NSAID			
No	2.295 (1.863–2.775)	−0.509	0.611
Yes	2.600 (2.010–3.560)		
History of GC			
No	2.300 (1.565–3.290)	−0.572	0.568
Yes	2.570 (1.955–3.400)		
History of DMARD			
No	3.990 (3.050–4.860)	−1.000	0.317
Yes	2.500 (1.895–3.320)		
History of biologics			
No	2.455 (1.983–3.045)	−0.552	0.581
Yes	2.790 (1.700–4.450)		
Current treatment			
Etanercept plus DMARD	2.530 (1.880–3.633)	−0.152	0.879
Adalimumab plus DMARD	2.540 (2.100–3.200)		

Abbreviations: DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; IQR, interquartile range; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; NSAID, nonsteroidal anti-inflammatory drug.

explanation for this difference might be that the sample size of this study was relatively small, which resulted in low statistical power.

Apart from the correlation of MALT1 with inflammation and disease activity, previous studies also report that MALT1 is decreased after treatment in patients with inflammatory bowel disease or RA.[16,17] However, the study conducted on inflammatory bowel disease does not mention the specific treatment of the patients; whereas, in the study conducted in RA, some of the patients receive cDMARDs and the other patients receive biologics with or without cDMARDs.[16,17] Until present, the association of MALT1 with treatment response in RA patients who receive TNF inhibitors is largely unclear. In the current study, it was observed that MALT1 was decreased after treatment, which was in line with previous studies.[16,17] Meanwhile, MALT1 at W24 was lower in patients who achieved response or remission compared to those who did not achieve response or remission. A possible explanation might be that: in patients who achieved response or remission to TNF inhibitors, the inflammation level was lower compared to those who did not achieve response or remission; meanwhile, since MALT1 is able to regulate the release of pro-inflammatory cytokine,[14,15] it might reflect the level of inflammation in RA patients. Therefore, MALT1 was lower in those who achieve response or remission to TNF inhibitors. Moreover, subgroup analyses revealed that, although the trend was similar to that in total RA patients, statistical significance was only observed in the difference of

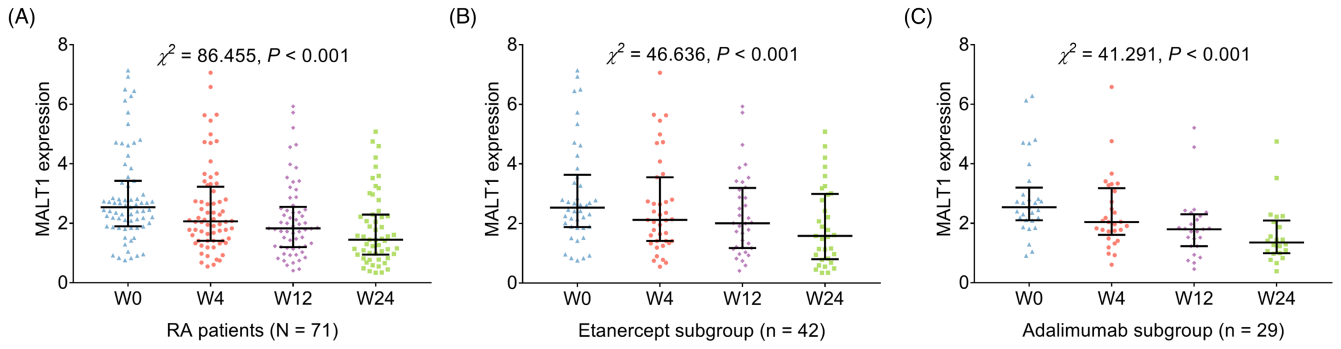

FIGURE 3 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 change after treatment in RA patients. MALT1 expression at W0, W4, W12, and W24 in total RA patients (A), etanercept subgroup (B), and adalimumab subgroup (C)

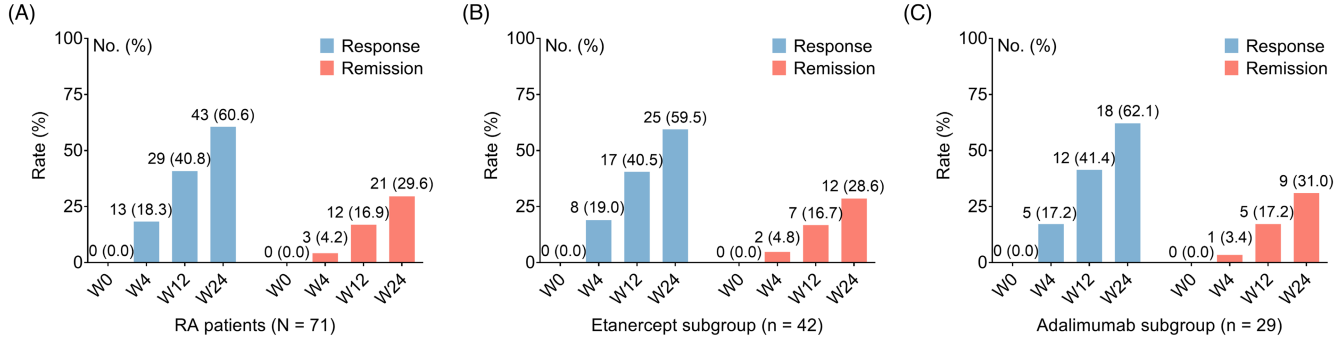

FIGURE 4 Response or remission in RA patients. Rate of response and remission patients at W0, W4, W12, and W24 in total RA patients (A), etanercept subgroup (B), and adalimumab subgroup (C)

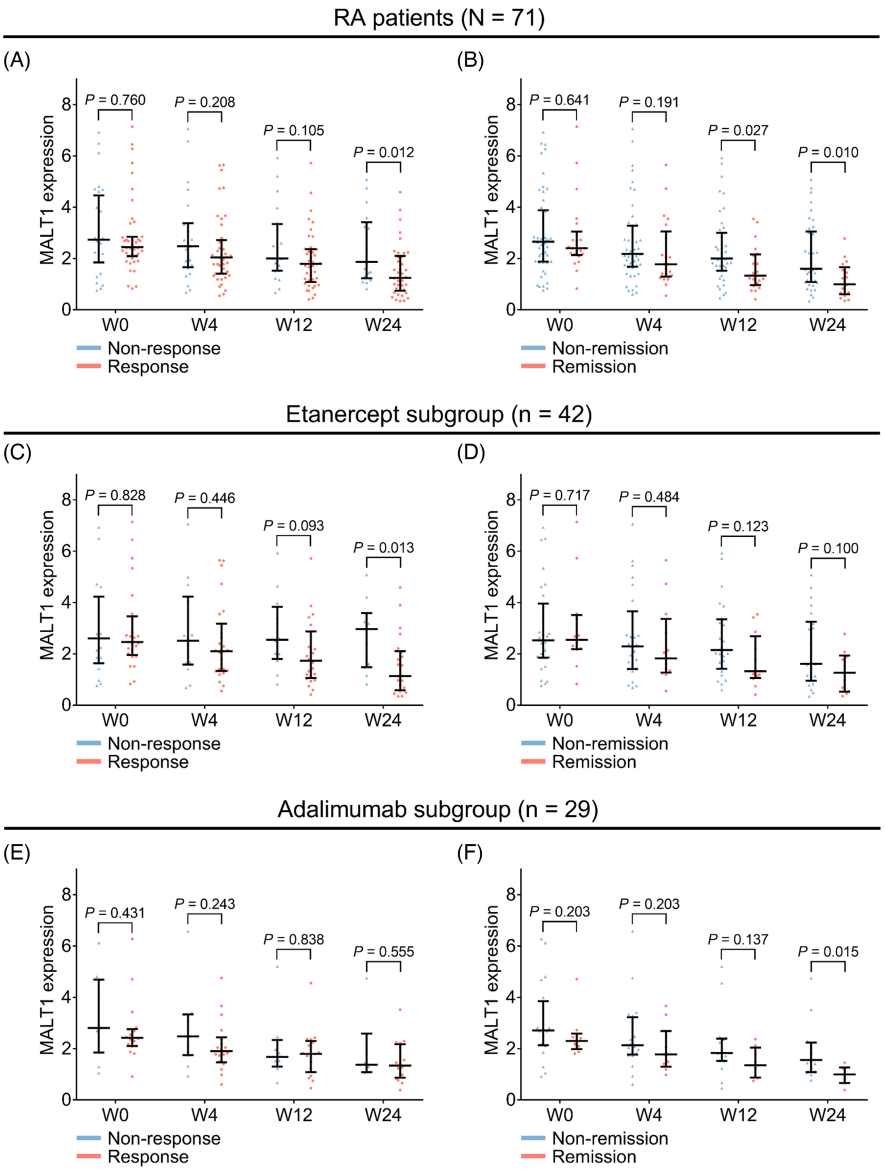

FIGURE 5 Correlation of MALT1 with response or remission in RA patients. Correlation of MALT1 with response (A), as well as remission (B) in total RA patients; Correlation of MALT1 with response (C), as well as remission (D) in etanercept subgroup; Correlation of MALT1 with response (E), as well as remission (F) in adalimumab subgroup

MALT1 at W24 between response and non-response patients in etanercept subgroup, and between remission and non-remission patients in adalimumab subgroup. An explanation might be that the small sample size led to low statistical power.

Although several interesting results were revealed, there existed several limitations in this study. First, as mentioned earlier, the sample size of this study was relatively small, which led to low statistical power. Therefore, further studies with larger sample sizes could be conducted to further verify the clinical role of MALT1 in RA. Second, TNF inhibitors were the most commonly used biologics in our center; whereas the association of MALT1 with the efficacy of other kinds of biologics, such as Janus kinase (JAK) inhibitors, could be investigated further. Third, the molecular mechanism of MALT1 implicated in the treatment of RA by TNF inhibitors was not explored in the current study.

To be conclusive, MALT1 continuously decreases with the treatment of TNF inhibitors, whose reduction was associated with favorable treatment outcomes in RA patients.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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