Original article

Serum sTREM-1 in adult-onset Still’s disease: a novel biomarker of disease activity and a potential predictor of the chronic course

Zhihong Wang1,*, Huihui Chi1,*, Yue Sun1,*, Jialin Teng1, Tienan Feng2, Honglei Liu1, Xiaobing Cheng1, Junna Ye1, Hui Shi1, Qiongyi Hu1, Jinchao Jia1, Tingting Liu1, Liyan Wan1, Zhuocho Zhou1, Xin Qiao1, Chengde Yang1 and Yutong Su1

Abstract

Objectives. Triggering receptor expressed on myeloid cells-1 (TREM-1) is an amplifier of inflammatory signals. Recently, a soluble form of TREM-1 (sTREM-1) was described. This study aimed to investigate the role of serum sTREM-1 in patients with adult-onset Still’s disease (AOSD).

Methods. Serum sTREM-1 levels were detected in 108 AOSD patients, 88 RA patients and 112 healthy controls (HC). The correlations of sTREM-1 with disease activity, clinical characteristics and laboratory parameters in AOSD patients were analysed by the Spearman correlation test. Risk factors for the chronic course of AOSD were evaluated by multivariate logistic regression analysis.

Results. AOSD patients had significantly higher serum sTREM-1 levels than RA patients and HC, and serum sTREM-1 levels were correlated with the systemic score, ferritin, leucocyte count, CRP, IL-1β and IL-6. The elevation in the initial sTREM-1 level by itself could discriminate patients developing the chronic course from patients developing the nonchronic course. Moreover, an elevated sTREM-1 level (> 526.4475 pg/ml) was an independent risk factor for the chronic course in active AOSD patients. Furthermore, interfering with TREM-1 engagement led to reductions in the secretion of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, in neutrophils and monocytes from active AOSD patients.

Conclusion. Serum sTREM-1 levels are correlated with disease activity, and an elevation in the initial serum sTREM-1 level is a potential predictor of the chronic course in AOSD patients, which currently provides the best predictive model for identifying patients prone to developing the chronic course of AOSD.

Key words: adult-onset Still’s disease, soluble triggering receptor expressed on myeloid cell-1, inflammation, biomarker, clinical course

Rheumatology key messages

- Serum sTREM-1 levels were correlated with disease activity in AOSD patients.
- Serum sTREM-1 is probably the best predictor of the chronic course in AOSD patients.
- Blocking TREM-1 reduced pro-inflammatory cytokine secretion in the peripheral neutrophils and monocytes of AOSD patients.

1Department of Rheumatology and Immunology, Ruijin Hospital, and 2Clinical Research Institute, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Submitted 14 November 2019; accepted 22 February 2020

Correspondence to: Yutong Su, Department of Rheumatology and Immunology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, No. 197 Rujin Second Road, Shanghai 200025, China. E-mail: suyt2015@163.com

*Zhihong Wang, Huihui Chi and Yue Sun contributed equally to this manuscript.
Introduction

Adult-onset Still’s disease (AOSD) is a rare, polygenic, systemic autoimmune inflammatory disease of unknown etiology [1]. The manifestation of AOSD includes high spiking fever, inflammatory arthralgia or arthritis, evanescent skin rash, sore throat, neutrophilic leucocytosis and abnormal liver function tests. The clinical presentation of AOSD is very heterogeneous, ranging from self-limited to chronic articular erosion or even life-threatening complications such as haemophagocytic lymphohistiocytosis (HLH) [2, 3]. After years of follow-up, the disease pattern of AOSD can be divided into systemic and chronic articular courses, or systemic monocyclic, polycyclic and chronic courses [1, 2, 4–7]. Due to the lack of disease-specific prognostic markers, prediction of disease patterns is thought to be currently impossible.

Accumulating evidence demonstrates that the activation of innate immune cells is the hallmark of the pathogenesis of AOSD. Environmental triggers such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) are recognized by specific Toll-like receptors (TLRs) in monocytes/macrophages and neutrophils, resulting in the activation of inflammasomes and overproduction of pro-inflammatory cytokines, including IL-1β, IL-6, IL-18, IL-8 and TNF-α [8, 9]. Multiple factors have been reported to contribute to the amplified inflammatory response, such as the endogenous TLR4 ligand S100A8/A9 [10], TLR7 signalling molecules [11] and neutrophil extracellular traps (NETs) [12].

Triggering receptor expressed on myeloid cells-1 (TREM-1), a member of the immunoglobulin superfamily, is mainly expressed on neutrophils and monocytes and serves as a critical amplifier of inflammatory signalling by stimulating the production of pro-inflammatory chemokines and cytokines [13–16]. TREM-1 expression can be upregulated by pro-inflammatory cytokines and TLR ligands [17]. In addition to the membrane-bound form, a soluble form of TREM-1 (sTREM-1) has been detected in the blood [18]. sTREM-1 has been regarded as a useful diagnostic biomarker for severe sepsis and pneumonia [19, 20], as well as many noninfectious inflammatory diseases, such as RA [21], SLE [22], ankylosing spondylitis (AS) [23], IBD [24, 25] and FMF [26]. Given the crucial role of aberrant innate immune responses in the pathogenesis of AOSD, we sought to explore serum sTREM-1 levels in AOSD patients and evaluate the correlations of serum sTREM-1 with clinical features and its role in the pathogenesis of AOSD.

Methods

Patients and samples

This study included 108 AOSD patients (72 active and 36 inactive), 88 RA patients and 112 healthy controls (HC). The 72 active AOSD patients were consecutively recruited between August 2015 and December 2018 at the Department of Rheumatology and Immunology, Ruijin Hospital and were followed prospectively. Patients were diagnosed with AOSD according to Yamaguchi’s criteria [27] after infection, malignancy and other autoimmune diseases were excluded. RA was diagnosed according to the 2010 ACR classification criteria [28]. A total of 112 age- and sex-matched HC with no history of malignancy, autoimmune disease, or recent or chronic infection were also included.

Age, sex, disease duration, clinical features, laboratory markers and medication history were recorded. The laboratory markers included the complete blood count, ESR, CRP, ferritin, aspartate transaminase (AST) and alanine transaminase (ALT). Clinical and laboratory data were collected when blood samples were obtained. Fifteen blood samples were collected during the follow-up period after patients achieved remission. The disease activity of each AOSD patient was assessed using the Pouchot score [29]. Active AOSD was defined as presentation of two or more of the following diagnostic criteria of AOSD: fever ≥ 39°C, arthralgia/arthritis, typical rash, sore throat and leucocytosis including 80% or more granulocytes [30]. Inactive AOSD was defined as the complete disappearance of clinical symptoms, such as fever, evanescent rash, arthralgia/arthritis and sore throat, and the normalization of laboratory results, such as ESR, CRP and ferritin levels, for at least two consecutive months, regardless of therapy. The disease pattern of active AOSD patients was divided into three distinct types: monocyclic, polycyclic and chronic courses [1] over a 12-month follow-up period. The monocyclic and polycyclic courses were classified as the nonchronic course. This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Biological samples were acquired under approval by the Institutional Research Ethics Committee of Ruijin Hospital (ID: 2016–62), Shanghai, China. Informed consent was obtained from recruited subjects.

Peripheral blood neutrophil and monocyte isolation

Human blood collected from eight new-onset treatment-naïve patients was mixed with an equal volume of Polymorphprep™ (Axis-Shield, Dundee, UK) to sediment erythrocytes. Neutrophils were collected from the medium interface. CD14+ monocytes were purified from PBMCs by magnetic cell sorting using CD14 MicroBeads (Miltenyi Biotec, Bergisch Gladbach, Germany). The collected cells were used for cell cultures. Serum samples were stored at −80°C.

Antagonist TREM-1 peptides

Antagonist TREM-1 peptides LP17 (LQVTDSGLYRCVYHPP) and the corresponding sequence-scrambled negative control peptides NC (EDSQCVIGLYQPPLQVY) were chemically synthesized with amidation at COOH terminus [31, 32]. The purity of the peptides was >98% as determined by HPLC.
Cell culture

Purified neutrophils or monocytes were cultured in RPMI 1640 medium (Life Technologies, New York, USA) supplemented with 100 µg/ml streptomycin (Beyotime, Shanghai, China), 100 U/ml penicillin (Beyotime, Shanghai, China) and 10% fetal bovine serum (Life Technologies, New York, USA) in a humidified atmosphere of 5% CO2 at 37°C. Neutrophils were seeded at 10^6 cells/well in a 24-well plate and pretreated with or without a synthesized human TREM-1 inhibitory peptide (LP17, 100 ng/ml) for 2 h, followed by stimulation with 1 µg/ml lipopolysaccharide (LPS; Sigma, St Louis, MO, USA) for 6 h. Monocytes were seeded at 2.5 x 10^4 cells/well in a 96-well plate and pretreated with or without LP17 for 2 h, followed by stimulation with LPS for 24 h. Culture supernatants were harvested and frozen at -80°C for cytokine analysis by ELISA.

Cytokine assessment

Serum sTREM-1 levels and cell culture supernatant cytokines were determined by ELISA following the manufacturer’s instructions. Serum sTREM-1 levels and cell culture supernatant TNF-α, IL-1β, IL-6 and IL-8 were accomplished using the ELISA kit (R&D Systems, Inc., Minneapolis, Canada). Serum TNF-α, IL-1β, IL-18, IL-6 and IL-10 levels were measured by the electrochemiluminescent assay (Meso Scale Discovery, MSD, Rockville, MD, USA).

Statistical analysis

Data are expressed as the mean (s.d.), number (percent-age) or median (interquartile range). The Spearman correlation test was used to assess relations between serum sTREM-1 levels and clinical or biological variables. The Mann–Whitney U test was used for comparisons between groups involving continuous data. Receiver operating characteristic curves were constructed to illustrate various cut-off values for sTREM-1 and other cytokines. Univariate and multivariate logistic regression analyses were employed to evaluate factors that could predict the chronic course of AOSD. Variables that were significant in the univariate analysis were included in the multivariate analysis. Statistical analysis was performed with IBM SPSS Statistics 25.0, and a two-tailed P-value < 0.05 was considered statistically significant.

Results

Serum sTREM-1 levels in AOSD patients

Our study comprised 108 patients with AOSD, of whom 72 had active disease and 36 had inactive disease, 88 patients with RA and 112 HC. There were no statistically significant differences among the groups with regard to demographic properties, such as age or sex. The clinical features, laboratory values and treatment of the AOSD patients at enrolment are summarized in Supplementary Table S1, available at Rheumatology online. Among the 72 active AOSD patients, 41 were treatment-naive new-onset patients, and 31 were under treatment, including 15 who were new-onset patients and 16 who had relapsed disease. The detailed treatment and disease status information for the 31 active AOSD patients at enrolment is summarized in Supplementary Table S2, available at Rheumatology online.

sTREM-1 levels were significantly higher in the patients with AOSD than in the RA patients (340.16 ± 253.88 vs 270.12 ± 187.63 pg/ml, respectively, P < 0.01) and HC (340.16 ± 253.88 vs 174.35 ± 85.21 pg/ml, respectively, P < 0.001; Fig. 1A). sTREM-1 levels were also higher in the RA patients than in the HC (270.12 ± 187.63 vs 174.35 ± 85.21 pg/ml, respectively, P < 0.001; Fig. 1A). In order to investigate whether sTREM-1 is related to disease activity in AOSD patients, we compared sTREM-1 levels between active and inactive AOSD patients. Our results showed that the active patients presented higher levels of sTREM-1 than the inactive patients (372.41 ± 283.71 vs 275.66 ± 165.36 pg/ml, respectively, P = 0.028; Fig. 1B), indicating that sTREM-1 was probably associated with the disease activity of AOSD. Moreover, we collected blood samples from 15 patients during follow-up, and serum sTREM-1 levels decreased after remission (Fig. 1C).

Correlations between sTREM-1 and disease activity score, laboratory values and inflammatory cytokines

To further investigate the relationship between serum sTREM-1 levels and AOSD disease activity, we performed a correlational analysis of serum sTREM-1 levels with the systemic score, laboratory values and inflammatory cytokines. The serum sTREM-1 levels showed a significant correlation with the AOSD systemic score (r = 0.231, P = 0.016; Fig. 2A). Moreover, sTREM-1 showed the highest correlation with leucocyte count (r = 0.611, P < 0.001; Fig. 2B), followed by CRP (r = 0.316, P = 0.010; Fig. 2C) and ferritin (r = 0.231, P = 0.047; Fig. 2D). However, serum sTREM-1 levels were not significantly correlated with ESR, ALT or AST (data not shown).

As cytokine storm plays an important role in the pathogenesis of AOSD, we analysed the correlations between sTREM-1 and inflammatory cytokines. Our results showed that serum sTREM-1 levels were positively correlated with the levels of serum IL-1β (r = 0.459, P < 0.001; Fig. 2E) and IL-6 (r = 0.337, P < 0.001; Fig. 2F). No significant correlations were found between serum sTREM-1 levels and TNF-α, IL-18 or IL-10 (data not shown).

We also analysed the associations between serum sTREM-1 levels and clinical manifestations in AOSD patients. The patients who had pneumonia or myalgia exhibited higher serum sTREM-1 levels than those who did not have these symptoms (see Supplementary Table S3, available at Rheumatology online).

Serum sTREM-1 is a potential predictor of the chronic course in AOSD patients.

Patients with the chronic course suffered from continuous systemic inflammation with intermittent flares,
which usually evolves into permanent joint deformation and has a poor prognosis, so we classified the active patients who had been followed for more than one year into two groups ($n=61$): chronic ($n=19$) and nonchronic ($n=42$) courses, and then evaluated serum sTREM-1 levels in these two patterns. As shown in Fig. 3A, serum sTREM-1 levels were significantly increased in the patients with the chronic course compared with those with the nonchronic course (417.84 ± 256.43 vs 267.75 ± 143.85 pg/ml, respectively, $P=0.002$). A previous study showed that patients with high levels of IL-18 tended to have the systemic course, while patients with low levels of IL-18 were more likely to develop the chronic arthritis course [6]. Consistent with the results, we also found that the serum IL-18 levels were higher in the patients with the nonchronic course, which mainly presented with systemic symptoms, while the AOSD patients with the chronic course had lower serum IL-18 levels (125.73 ± 172.95 vs 295.61 ± 244.21 ng/ml, respectively, $P=0.013$; Fig. 3B).

Furthermore, we explored the predictive value of initial serum sTREM-1 levels in distinguishing patients having an elevated risk of developing the chronic course by a receiver operating characteristic analysis. The area under the curve (AUC) was 0.747 (95% CI: 0.607, 0.887; $P=0.002$) when serum sTREM-1 levels were applied to differentiate the chronic course from the nonchronic course, and a cut-off value of 526.4475 pg/ml had a sensitivity of 47.4% and a specificity of 95.2% for the chronic course of AOSD. Meanwhile, the AUC was 0.699 when serum IL-18 levels were applied to differentiate the chronic course from the nonchronic course (Fig. 3C).

To test whether the initial sTREM-1 level is a risk factor for the chronic course, we performed logistic regression analysis. Univariate logistic regression analysis showed that initial serum sTREM-1 (>526.4475 pg/ml) and IL-18 (>105.5581 ng/ml) were significantly associated with the chronic course. Multivariate logistic regression analysis demonstrated that serum sTREM-1 (>526.4475 pg/ml) was an independent predictor of the
chronic course with an odds ratio (OR) of 22.809 (95% CI: 3.475, 149.691), while IL-18 was a negative predictor of the chronic course, with an OR of 0.145 (95% CI: 0.034, 0.615) (Table 1).

Blocking TREM-1 attenuates the secretion of inflammatory cytokines in the peripheral neutrophils and monocytes of AOSD patients.

TREM-1 has been reported to be an inflammatory amplifier that functions by enhancing the secretion of pro-inflammatory mediators, which prompted us to assess whether interfering with TREM-1 affects the secretion of inflammatory cytokines in neutrophils and monocytes. Treatment with LP17, an antagonistic peptide that blocks TREM-1 engagement, significantly reduced spontaneous and LPS-induced IL-1β (Fig. 4A), IL-6 (Fig. 4B) and IL-8 (Fig. 4D) secretion and LPS-induced TNF-α (Fig. 4C) secretion in the neutrophils of AOSD patients. In addition, the LP17 peptide significantly attenuated the increases in IL-1β (Fig. 5A), IL-6 (Fig. 5B) and TNF-α levels (Fig. 5C) following LPS stimulation in the monocytes of AOSD patients.

**Discussion**

TREM-1 is an important signalling receptor expressed on the majority of innate immune cells that acts to
amplify inflammation. TREM-1 signalling pathways contribute to the pathologies of infectious diseases and noninfectious inflammatory diseases; however, the role of sTREM-1 in AOSD is undetermined. In this study, we showed for the first time that the levels of sTREM-1 were positively correlated with disease activity. Moreover, an elevated sTREM-1 level at initial visits was independently associated with the chronic course of AOSD.

In this study, sTREM-1 levels were increased in AOSD patients and correlated with laboratory values and the levels of pro-inflammatory cytokines, including IL-1β and IL-6, indicating that sTREM-1 contributed to the inflammatory process in AOSD. The activation of monocytes and neutrophils is central to AOSD with the characteristic of cytokine storm. Considering that sTREM-1 is derived from proteolytic cleavage or membrane shedding of surface-expressed TREM-1 [33] and that stimulation of neutrophils or monocytes with microbial products induced the release of sTREM-1 into culture supernatants, we speculated that the elevated sTREM-1 levels in the serum could be derived from activated neutrophils or monocytes in patients with AOSD; at the same time, increased serum sTREM-1 levels might partially reflect the activation of neutrophils or monocytes during the progression of AOSD. Although the function of sTREM-1 remains unclear, sTREM-1 is thought to negatively regulate TREM-1 signalling by neutralizing the TREM-1-mediated inflammatory response. Axel Bouchon reported that sTREM-1 conferred protection against endotoxic shock in mice [16]. As a result, sTREM-1 may act as an anti-inflammatory mediator in AOSD.

Serum sTREM-1 (A) and IL-18 (B) levels in AOSD patients with the chronic course (n=19) or nonchronic course (n=42). (C) Receiver operating characteristic curves of sTREM-1 and IL-18 in differentiating the chronic course and nonchronic courses in AOSD patients. The area under the curve (AUC) was 0.747 (95% CI: 0.607, 0.887, P =0.002) for sTREM-1 and 0.699 (95% CI: 0.562, 0.836, P =0.013) for IL-18. AOSD, adult-onset Still’s disease. The data represent the mean (s.d.). *P <0.05. ** P <0.01.

Table 1: Multiple logistic regression analysis of factors contributing to the chronic course of AOSD

| Predictor | P-value | Odds ratio (95% CI) |
|-----------|---------|---------------------|
| Univariate analysis |         |                     |
| sTREM-1 > 526.4475 pg/ml | 0.001 | 18.000 (3.349, 96.734) |
| IL-18 > 105.5581 ng/ml | 0.005 | 0.185 (0.057, 0.599) |
| IL-1β > 0.1265 pg/ml | 0.053 | 3.178 (0.987, 10.228) |
| IL-6 > 7.6369 pg/ml | 0.175 | 2.175 (0.707, 6.693) |
| TNF-α > 3.6443 pg/ml | 0.059 | 0.294 (0.082, 1.049) |
| Multivariate analysis |         |                     |
| sTREM-1 > 526.4475 pg/ml | 0.001 | 22.809 (3.475, 149.691) |
| IL-18 > 105.5581 ng/ml | 0.009 | 0.145 (0.034, 0.615) |

To date, sTREM-1 has been reported to be a potential biomarker in several diseases. sTREM-1 in bronchoalveolar lavage fluids may help clinicians diagnose patients with bacterial or fungal pneumonia [20]. In addition, serum sTREM-1 may be a novel biomarker for early RA, disease activity and the response to DMARD treatment [21]. A correlation between sTREM-1 and disease activity has also been demonstrated in IBDs [25]. Moreover, low TREM-1 expression in whole blood predicts good responses to anti-TNF therapy in IBD [34, 35]. Similarly, our study showed that serum sTREM-1 levels in AOSD patients were closely correlated with markers of disease activity including the systemic score, CRP, leucocyte count and ferritin, which suggests that sTREM-1 may serve as a potential biomarker in AOSD.

The clinical course of AOSD is highly diverse and currently impossible to predict. A previous study revealed that AOSD with chronic articular involvement had distinct cytokine and immunogenetic profiles [7]. The systemic pattern favours the IL-1β, IL-18 and IFN-γ, whereas IL-6, TNF-α and IL-8 predominate in the chronic articular pattern [6, 9, 36]. In addition, the presence of erosive arthritis is associated with low levels of ferritin and IL-18 at initial treatment [6]. In line with a previous study, we confirmed that the initial serum IL-18 level was lower in patients developing the chronic course than in nonchronic patients. However, no significant difference was found in serum ferritin levels between these two groups of patients (data not shown). Moreover, chronic AOSD patients are often less responsive to steroid therapy, requiring early administration of...
methotrexate or ciclosporin in order to improve their prognosis. Hence, early prediction and timely recognition of patients with the chronic course are important. However, identifying the classification of clinical patterns of AOSD is often lagging as it tends to depend on the long-term follow-up observation in clinical practice. Our data are the first to show that serum sTREM-1 levels at initial visits could be a desirable model to predict the chronic course of AOSD. Additionally, a serum sTREM-1 level higher than 526.4475 pg/ml was an independent risk factor for the chronic course by multivariate logistic regression analysis. Thus, our findings shed light on the early identification of patients prone to developing the chronic course of AOSD.

Inhibiting TREM-1 signalling has been reported to be a potential therapeutic approach to prevent the overactivation of inflammatory responses in several infectious and noninfectious diseases. TREM-1 blockade using the extracellular domain of TREM-1 fusion IgG or synthetic TREM-1 antagonistic peptide LP17 ameliorated the clinical manifestations of collagen-induced arthritis (CIA) [37]. In addition, pharmacological inhibition of TREM-1 using LR12, a synthetic inhibitory peptide, protected mice during septic shock in vitro and in vivo [38], and the LR12 peptide is now under clinical trials in septic patients (www.clinicaltrials.gov, NCT03158948). Consistent with the previous studies, our results demonstrated that blockade of TREM-1 with LP17 significantly reduced the spontaneous secretion of IL-1β, IL-6 and IL-8 in the neutrophils of AOSD patients, indicating the involvement of TREM-1 in the inflammatory response. Moreover, treatment with LP17 also reduced excessive pro-inflammatory cytokine secretion under LPS stimulation in neutrophils and monocytes, suggesting that LP17 is useful for
inflammation control and functions by inhibiting the TREM-1 inflammatory amplification loop, which provides a potential strategy for AOSD therapy.

To date, the natural ligand of TREM-1 has not yet been fully identified; however, high mobility group box 1 (HMGB1) is regarded as a TREM-1 ligand. Wu and colleagues found a direct interaction between TREM-1 and HMGB1 by immunoprecipitation and cross-linking assays [39]. Elevated HMGB1 expression has been reported in AOSD patients compared with HC and correlated with the systemic score [40]. Therefore, we proposed that HMGB1 may be involved in the activation of TREM-1 in AOSD patients. Nevertheless, the precise mechanism involving TREM-1 in the pathogenesis of AOSD requires further investigation.

It is important to acknowledge that there are some limitations to our study. Even though there was no significant difference in the levels of sTREM-1 between active AOSD patients with or without treatment (data not shown), a study that includes more treatment-naive AOSD patients compared with other groups would be more convincing. In addition, a longitudinal study of sTREM-1 in AOSD with a large sample size is also needed in the future.

In conclusion, our study for the first time shows that serum sTREM-1 is a potential disease activity biomarker and a possible predictor of the chronic course of AOSD, which makes it possible to predict the prognosis of AOSD at initial visits. More importantly, blocking of TREM-1 may serve as a promising therapeutic approach to prevent the inflammatory progression of AOSD.

Study conception and design: Y.Su, C.Y., Y.Sun, Z.W., H.C.; acquisition of data: H.L., X.C., J.Y., H.S., Q.H., J.J., T.L., L.W., Z.Z., X.Q.; drafting and revising...
the article: Y.Su, C.Y., Y.Sun, Z.W., H.C.; analysis and interpretation of data: Y.Su, Z.W., H.C., T.F., J.T.

Acknowledgements

An innovative research team of high-level local universities in Shanghai, all authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Y.Su had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: This work was supported by the National Natural Science Foundation of China (81801600, 81601400); the Shanghai Sailing Program (18YF1414500); Shanghai Jiao Tong University Medicine-Engineering Cross-disciplinary Research Foundation (YQ2016QN62); the Guangci Distinguished Young Scholars Training Program (GCQN-2017-B04).

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1. Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still’s disease. Nat Rev Rheumatol 2018;14:603–18.
2. Gerfaud-Valentin M, Jamillon Y, Iwaz J, Seve P. Adult-onset Still’s disease. Autoimmun Rev 2014;13:708–22.
3. Cush JJ, Medsger TA Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still’s disease. Clinical course and outcome. Arthritis Rheum 1987;30:186–94.
4. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still’s disease. Ann Rheum Dis 2006;65:564–72.
5. Franchini S, Dagna L, Salvo F et al. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still’s disease. Arthritis Rheum 2010;62:2530–5.
6. Ichida H, Kawaguchi Y, Sugiuira T et al. Clinical manifestations of adult-onset Still’s disease presenting with erosive arthritis: association with low levels of ferritin and interleukin-18. Arthritis Care Res 2014;66:642–6.
7. Fuji T, Noyama T, Yasuoka H et al. Cytokine and immunogenetic profiles in Japanese patients with adult Still’s disease. Association with chronic articular disease. Rheumatology 2001;40:1398–404.
8. Maria AT, Le Quellec A, Jorgensen C et al. Adult onset Still’s disease (AOSD) in the era of biologic therapies: dichotomous view for cytokine and clinical expressions. Autoimmun Rev 2014;13:1149–59.
9. Jamilloux Y, Gerfaud-Valentim M, Martinon F et al. Pathogenesis of adult-onset Still’s disease: new insights from the juvenile counterpart. Immunol Res 2015;61:53–62.
10. Kim HA, Han JH, Kim WJ et al. TLR4 endogenous ligand S100A8/A9 levels in adult-onset still’s disease and their association with disease activity and clinical manifestations. Int J Mol Sci 2016;17:1342.
11. Chen DY, Lin CC, Chen YM, Lan JL et al. Involvement of TLR7 MyD88-dependent signaling pathway in the pathogenesis of adult-onset Still’s disease. Arthritis Res Ther 2013;15:R39.
12. Hu Q, Shi H, Zeng T et al. Increased neutrophil extracellular traps activate NLRP3 and inflammatory macrophages in adult-onset Still’s disease. Arthritis Res Ther 2019;21:9.
13. Colonna M. TREMs in the immune system and beyond. Nat Rev Immunol 2003;3:445–53.
14. Klesney-Tait J, Turnbull IR, Colonna M. The TREM receptor family and signal integration. Nat Immunol 2006;7:1266–73.
15. Bouchon A, Dietrich J, Colonna M. Cutting edge: inflammatory responses can be triggered by TREM-1, a novel receptor expressed on neutrophils and monocytes. J Immunol 2000;164:4991–5.
16. Bouchon A, Facchetti F, Weigand MA, Colonna M. TREM-1 amplifies inflammation and is a crucial mediator of septic shock. Nature 2001;410:1103–7.
17. Tesseract AS, Cerwenka A. The TREM-1/DAPI pathway. Immunol Lett 2008;116:111–6.
18. Gibot S, Kolopp-Sarda MN, Bene MC et al. A soluble form of the triggering receptor expressed on myeloid cells-1 modulates the inflammatory response in murine sepsis. J Exp Med 2004;200:1419–26.
19. Gibot S, Kolopp-Sarda MN, Bene MC et al. Plasma level of a triggering receptor expressed on myeloid cells-1: its diagnostic accuracy in patients with suspected sepsis. Ann Int Med 2004;141:9–15.
20. Gibot S, Cravoisy A, Levy B et al. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 2004;350:451–8.
21. Molad Y, Ofer-Shiber S, Pokroy-Shapira E et al. Soluble triggering receptor expressed on myeloid cells-1 is a biomarker of anti-CCP-positive, early rheumatoid arthritis. Eur J Clin Invest 2015;45:557–64.
22. Bassouyi IH, Fawzi S, Gheita TA et al. Clinical association of a soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in patients with systemic lupus erythematosus. Immunol Invest 2017;46:38–47.
23. Chen CH, Liao HT, Chen HA et al. Soluble triggering receptor expressed on myeloid cell-1 (sTREM-1): a new mediator involved in early ankylosing spondylitis. J Rheumatol 2008;35:1846–8.
24. Park JJ, Cheon JH, Kim BY et al. Correlation of serum-soluble triggering receptor expressed on myeloid cells-1 with clinical disease activity in inflammatory bowel disease. Dig Dis Sci 2009;54:1525–31.
25. Jung YS, Park JJ, Kim SW, Hong SP, Kim TI et al. Correlation between soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) expression and
endoscopic activity in inflammatory bowel diseases. Dig Liver Dis 2012;44:897–903.

26 Gorlier C, Sellam J, Laurans L et al. In familial Mediterranean fever, soluble TREM-1 plasma level is higher in case of amyloidosis. Innate Immun 2019;25:487–90.

27 Yamaguchi M, Ohta A, Tsunematsu T et al. Preliminary criteria for classification of adult Still’s disease. J Rheumatol 1992;19:424–30.

28 Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.

29 Pouchot J, Sampalis JS, Beaudet F et al. Adult Still’s disease: manifestations, disease course, and outcome in 62 patients. Medicine 1991;70:118–36.

30 Park JH, Kim HS, Lee JS et al. Natural killer cell cytolytic function in Korean patients with adult-onset Still’s disease. J Rheumatol 2012;39:2000–7.

31 Schenk M, Bouchon A, Seibold F, Mueller C. TREM-1-expressing intestinal macrophages crucially amplify chronic inflammation in experimental colitis and inflammatory bowel diseases. J Clin Invest 2007;117:3097–106.

32 Tammaro A, Derive M, Gibot S et al. TREM-1 and its potential ligands in non-infectious diseases: from biology to clinical perspectives. Pharmacol Ther 2017;177:81–95.

33 Gomez-Pina V, Soares-Schanoski A, Rodriguez-Rojas A et al. Metalloproteinases shed TREM-1 ectodomain from lipopolysaccharide-stimulated human monocytes. J Immunol 2007;179:4065–73.

34 Gaujoux R, Starosvetsky E, Maimon N et al. Cell-centred meta-analysis reveals baseline predictors of anti-TNFalpha non-response in biopsy and blood of patients with IBD. Gut 2019;68:604–14.

35 Verstockt B, Verstockt S, Dehairs J et al. Low TREM1 expression in whole blood predicts anti-TNF response in inflammatory bowel disease. EBioMedicine 2019;40:733–42.

36 Shimizu M, Yokoyama T, Yamada K et al. Distinct cytokine profiles of systemic-onset juvenile idiopathic arthritis-associated macrophage activation syndrome with particular emphasis on the role of interleukin-18 in its pathogenesis. Rheumatology 2010;49:1645–53.

37 Murakami Y, Akahoshi T, Aoki N et al. Intervention of an inflammation amplifier, triggering receptor expressed on myeloid cells 1, for treatment of autoimmune arthritis. Arthritis Rheum 2009;60:1615–23.

38 Jolly L, Carrasco K, Derive M et al. Targeted endothelial gene deletion of triggering receptor expressed on myeloid cells-1 protects mice during septic shock. Cardiovasc Res 2018;114:907–18.

39 Wu J, Li J, Salcedo R et al. The proinflammatory myeloid cell receptor TREM-1 controls Kupffer cell activation and development of hepatocellular carcinoma. Cancer Res 2012;72:3977–86.

40 Jung JY, Suh CH, Sohn S, Nam JY, Kim HA. Elevated high-mobility group B1 levels in active adult-onset Still’s disease associated with systemic score and skin rash. Clin Rheumatol 2016;35:1937–42.