Serum S100A12 May Be a Useful Biomarker of Disease Activity in Adult-onset Still's Disease

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ABSTRACT. ***Objective.*** S100A12 and soluble receptor for advanced glycation endproducts (sRAGE) have been suggested as biomarkers of disease activity in patients with systemic juvenile idiopathic arthritis. We investigated the clinical significance of these markers in adult-onset Still's disease (AOSD).

Methods. Blood samples were collected from 37 patients with active AOSD and 38 healthy controls (HC). Of the patients with AOSD, followup samples were collected from 19 patients after resolution of disease activity.

Results. Serum S100A12 (547.9 ± 148.4 ng/ml) in patients with AOSD was higher than those of HC (272.3 ± 133 ng/ml, $p < 0.001$). The sRAGE levels of AOSD (514.1 ± 273.6 pg/ml) were lower than those of HC (850.3 ± 405.8 pg/ml, $p < 0.001$). Serum S100A12 correlated with serum sRAGE ($r = –0.228$, $p = 0.049$). Serum S100A12 correlated with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and systemic score, whereas sRAGE did not correlate with any disease activity markers. In addition, the level of S100A12 was decreased after disease activity was resolved in followed-up patients with AOSD (505.7 ± 161.3 ng/ml vs 361.3 ± 162.5 ng/ml, $p = 0.01$). Further, the change of S100A12 was well correlated with that of ESR, CRP, and systemic score.

Conclusion. S100A12 levels showed strong correlations with known disease activity markers such as ESR, CRP, ferritin, and systemic score. In the followup patients with AOSD, most patients showed decreased S100A12 levels after resolution of disease activity. These results suggest that serum S100A12 can be a reliable clinical marker for monitoring disease activity and treatment response. (First Release Oct 1 2014; J Rheumatol 2014;41:2403–8; doi:10.3899/jrheum.140651)

Key Indexing Terms:
ADULT ONSET STILL'S DISEASE S100A12 DISEASE ACTIVITY
BIOMARKER SOLUBLE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS

Adult-onset Still's disease (AOSD) is an uncommon systemic inflammatory disorder of unknown etiology that was first described in 1971[1]. It is also known as the adult form of systemic juvenile idiopathic arthritis (JIA). Its clinical features include prolonged fever, arthritis, evanescent rash, elevated liver enzymes, lymphadenopathy, hepatosplenomegaly, and serositis[2]. However, the symptoms and laboratory findings of AOSD are not disease-specific; diagnosis and precise detection of disease activity is difficult[3,4,5]. For the diagnosis of AOSD, infections, neoplastic, and autoimmune disorders should be ruled out. The commonly used disease activity markers for AOSD are serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin, but these are not disease-specific markers. The etiology and pathogenesis of AOSD remain unclear, but many characteristic findings of AOSD and systemic JIA can be explained by proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, macrophage colony-stimulating factor, tumor necrosis factor-α, and IL-18[6]. IL-1 activity in systemic JIA is amplified by endogenous factors such as S100A8, S100A9, and S100A12. This signaling can induce increased production of proinflammatory cytokines such as IL-1β, which further increases production of S100 proteins[7,8]. Strikingly high levels of these S100 proteins are characteristics of active systemic JIA, and S100A8/A9 is also elevated in patients with AOSD[8,9,10].

S100A12 is an important ligand of the receptor for advanced glycation endproducts (RAGE)[11]. S100A12, also known as extracellular newly identified RAGE or calgranulin C, is a proinflammatory protein predominantly secreted by neutrophils[12,13]. S100A12 binding to RAGE activates intracellular signaling cascades, and the produc-

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tion and release of proinflammatory cytokines[14]. Moreover, S100A12 upregulates expression and affinity of the integrin receptor CD11b/CD18 on neutrophils and facilitates their adhesion to fibrinogen and to fibronectin, and the adhesion of monocytes to the endothelium *in vitro*[15,16]. The pathogenic relevance of these findings is supported by observation of a massive release and interaction of calgranulins with the endothelium in vasculitis and inflammatory arthritis[17,18,19]. Systemic JIA is associated with high concentration of S100A12[8,9].

RAGE serves as a pattern recognition receptor for several endogenous ligands that induce inflammation, and is mainly involved in the activation of endothelial cells and leukocytes[20,21]. The soluble forms of RAGE (sRAGE) correspond to the extracellular domain of circulating RAGE in humans[22]. The circulating proteins may act as decoys, thereby preventing binding of ligands with membrane-bound RAGE[23,24,25]. The proinflammatory effects of S100A12 can be inhibited *in vitro* by adding sRAGE[26]. Actually, sRAGE is negatively correlated with disease severity in various systemic conditions, such as coronary artery disease, systemic lupus erythematosus (SLE), atherosclerosis, and JIA[27,28,29,30]. Further, 1 study showed that the level of sRAGE correlated negatively with the level of S100A12 in patients with Kawasaki disease and controls[31].

Serum levels of S100A12 and sRAGE are prone to change and can be disease activity markers in systemic JIA[8,9,29]. However, to our knowledge, no study has addressed S100A12 and sRAGE in patients with AOSD[32]. Therefore, our study is the first to investigate the clinical significance of S100A12 related to IL-1β and sRAGE in Korean patients with AOSD with serial samplings.

MATERIALS AND METHODS

Subjects. Thirty-seven patients with active AOSD and 38 healthy controls (HC) were included in the study. Patients with AOSD were diagnosed according to Yamaguchi's criteria[33] after exclusion of infections and neoplastic and autoimmune disorders. HC without a history of rheumatic diseases were recruited through a public announcement. Serum samples were collected from patients with AOSD and the HC. Of the 37 patients with AOSD, 27 were in high disease activity before starting treatment at the time of sampling, and the other 10 patients were in flare among followup of AOSD at the time of sampling. Of the 37 patients with AOSD, followup samples were collected from 19 patients after resolution of disease activity. All blood samples were stored at –80°C immediately after collection.

Information on medical history, clinical symptoms, and findings of physical examinations were entered into a database when serum sampling was done. Each patient also underwent a series of laboratory tests, including complete blood count, ESR, CRP, rheumatoid factor (RF), antinuclear antibody (ANA), ferritin (normal 13–150 ng/ml for women and 30–400 ng/ml for men), liver function tests, and urinalysis. AOSD disease activity was evaluated as previously described[3], which assigns a score from 0 to 12 and adds 1 point for each of the following manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leukocytosis ≥ 15,000/mm^2, sore throat, myalgia, and abdominal pain. We defined resolution of disease activity of AOSD when the patient had no systemic symptoms, such as fever, pleuritis, pericarditis, and pneumonia. Our study was approved by the institutional review board of our hospital, and informed consent was received from all subjects.

S100A12 and sRAGE assay. Serum S100A12 levels were measured using commercial ELISA kits (CycLex Co.) according to the manufacturer's instructions. sRAGE levels were also determined using ELISA kits (R&D Systems) according to the manufacturer's instructions.

Statistical analyses. The data are shown as mean ± SD or median and interquartile range where appropriate. Differences in S100A12 and sRAGE levels were determined by independent Student t test. Differences in S100A12:sRAGE ratio levels were determined by a Mann-Whitney U test. The correlations between their levels and disease activity markers were evaluated with a Pearson correlation test or Spearman's correlation test. The Wilcoxon signed-rank test was also used to compare levels and disease activity markers in the patients who had followup sampling. The statistical analyses were performed using SPSS, version 12.0 (IBM SPSS). A p value < 0.05 was regarded as statistically significant.

RESULTS

Clinical characteristics of the patients. Table 1 summarizes the clinical characteristics of the 37 patients with AOSD and the 38 HC. The mean age of the patients with AOSD was 40.3 ± 13.7 years and women comprised 86.4%. There were no significant differences in age and sex between groups. The main clinical symptoms in patients with AOSD

Table 1. Clinical characteristics of patients. All values presented as n (%) or mean ± SD unless otherwise specified.

Characteristics	AOSD, n = 37	HC, n = 38
Age, yrs	40.3 ± 13.7	37.9 ± 7.5
Sex, female/male	32/5	36/2
Fever	35 (94.6)	—
Sore throat	21 (56.8)	—
Skin rash	29 (78.4)	—
Lymphadenopathy	16 (43.2)	—
Splenomegaly	14 (37.8)	—
Hepatomegaly	6 (16.2)	—
Pericarditis	7 (18.9)	—
Pleuritis	6 (16.2)	—
Arthralgia	36 (97.3)	—
Arthritis	23 (62.2)	—
Hemoglobin, g/dl	11.3 ± 1.8	—
Leukocyte, /μl	14,286 ± 4489	—
Platelet, × 10^3/μl	312.3 ± 112.1	—
Ferritin, ng/ml	4862 ± 9277.1	47.4 ± 54.7
ESR, mm/hr	69.2 ± 24.8	—
CRP, mg/dl	8.76 ± 5.34	0.09 ± 0.21
AST, mg/dl	82.8 ± 103.6	—
ALT, mg/dl	88.4 ± 110.4	—
ANA positivity	6 (16.2)	—
RF positivity	6 (16.2)	—
Systemic score	5.38 ± 1.36	—

Systemic score by Pouchot, *et al*[3] assigns a score from 0 to 12 and adds 1 point for each of the following manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leukocytosis ≥ 15,000/mm^2, sore throat, myalgia, and abdominal pain. AOSD: adult-onset Still's disease; HC: healthy control; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AST: aspartate transaminase; ALT: alanine transaminase; ANA: antinuclear antibody; RF: rheumatoid factor.

included high spiking fever (94.6%), skin rash (78.4%), arthritis (62.2%), sore throat (56.8%), and splenomegaly (37.8%). For RF-positive patients, the diagnosis of RA could be excluded according to the 1987 American College of Rheumatology (ACR) criteria[34]. For ANA-positive patients, the diagnosis of SLE could be excluded according to the 1982 ACR criteria[35].

Serum S100A12 and sRAGE levels. Figure 1 shows S100A12 and sRAGE levels in patients with AOSD and HC. The S100A12 levels of AOSD (547.9 ± 148.4 ng/ml) were higher than those of HC (272.3 ± 133 ng/ml, p < 0.001; Figure 1A). The sRAGE levels of AOSD (514.1 ± 273.6 pg/ml) were lower than those of HC (850.3 ± 405.8 pg/ml, p < 0.001; Figure 1B). Similarly, the S100A12:sRAGE ratio was significantly higher in patients with AOSD [0.99 (0.82–1.93)] compared with HC [0.33 (0.2–0.51), p < 0.001]. We compared the levels of S100A12, sRAGE, and S100A12:sRAGE between initial patients with active AOSD and flare during followup. The S100A12 levels of 27 initial patients with active AOSD (583.9 ± 141.8 ng/ml) were higher than those of 10 patients with flare (450.9 ± 125.2 ng/ml, p = 0.013). However, sRAGE and S100A12:sRAGE were not different between the groups. In patients with AOSD and HC, concentrations of S100A12 correlated negatively with the levels of sRAGE (r –0.228, p = 0.049; data not shown).

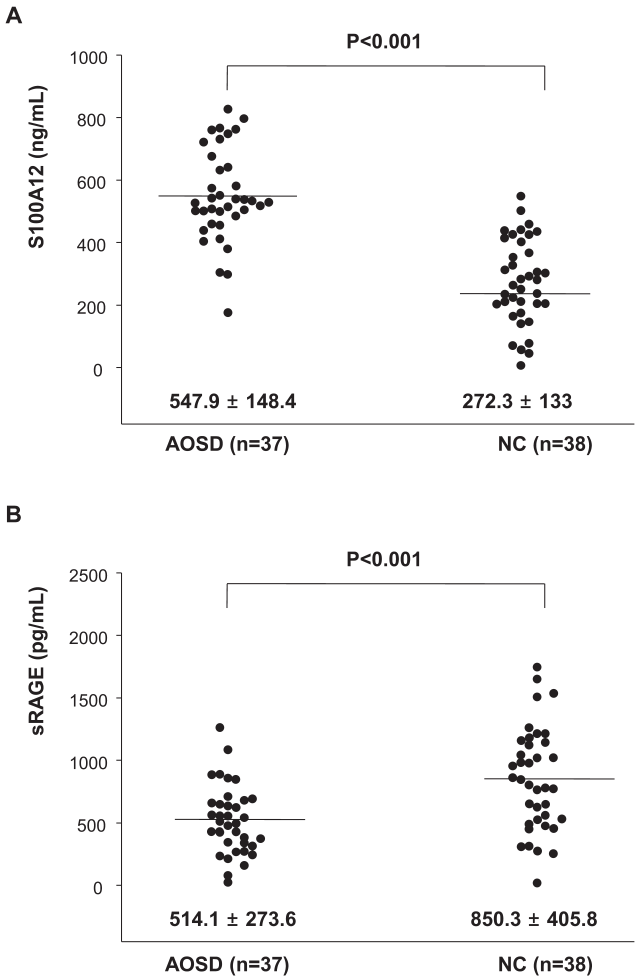

Figure 1. A. The levels of S100A12 and (B) soluble receptor for advanced glycation endproducts (sRAGE) in 37 patients with AOSD and 38 NC. Independent Student t test was used to perform the statistical analysis. AOSD: adult-onset Still's disease; NC: normal controls.

Serum S100A12 or sRAGE levels and disease activity in patients with AOSD. The correlations between preexistent disease activity markers and serum S100A12 or sRAGE in patients with AOSD are shown in Table 2. Serum S100A12 levels correlated with ESR (r 0.38, p = 0.02), CRP (r 0.358, p = 0.03), ferritin (r 0.396, p = 0.015), and systemic score (r 0.419, p = 0.01). However, no correlation was found between sRAGE and disease activity markers.

We evaluated correlations between steroid initial dosing, cumulative steroid dosing, or other medications [methotrexate (MTX), azathioprine (AZA), or biologics] and S100A12 in patients with AOSD. However, there were no significant findings. S100A12 was not correlated with the initial steroid dose (r –0.07, p = 0.679) or the cumulative steroid dose (r –0.249, p = 0.137). The S100A12 level was not different between the patients treated with MTX and those without (p = 0.479). The S100A12 level was not different between the patients treated with biologics and those without (p = 0.423; data not shown).

Change of serum S100A12 levels and sRAGE levels in the followup patients with AOSD. Among patients with AOSD with high disease activity, 19 patients were followed up in the resolution of disease activity with low- to moderate-dose corticosteroids and immunosuppressive agents, including MTX or AZA. Followup sera were collected from those resolved patients with AOSD. In the patients with AOSD who had followup, serum S100A12 levels were decreased

Table 2. Correlation between disease activity markers and systemic score in 37 patients with AOSD. These data were assessed using a Spearman correlation.

Disease Activity Markers	Correlation Coefficient (p value) S100A12	sRAGE
Systemic score	**0.419 (0.01)**	0.221 (0.188)
Leukocyte	0.147 (0.386)	0.163 (0.336)
ESR	**0.38 (0.02)**	0.09 (0.597)
CRP	**0.358 (0.03)**	0.03 (0.858)
Ferritin	**0.396 (0.015)**	0.15 (0.376)

All significant data are in bold face. Systemic score by Pouchot, *et al*[3] assigns a score from 0 to 12 and adds 1 point for each of the following manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leukocytosis ≥ 15,000/mm^2, sore throat, myalgia, and abdominal pain. AOSD: adult-onset Still's disease; sRAGE: soluble receptor for advanced glycation endproducts; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

after activity was resolved (505.7 ± 161.3 ng/ml vs 361.3 ± 162.5 ng/ml, p = 0.01; Figure 2A). However, sRAGE levels were not different (Figure 2B). S100A12:sRAGE was not changed after activity was resolved [0.93 (0.3–1.9) vs 1.25 (0.56–4.6), p = 0.573]. We evaluated the correlation between the change of S100A12 and the change of disease activity markers (Table 3). The change of S100A12 was positively correlated with the change of ESR (r 0.485, p = 0.035), CRP (r 0.498, p = 0.03), and systemic score (r 0.585, p = 0.009). However, the change of sRAGE was negatively correlated only with the change of CRP (r –0.472, p = 0.041).

DISCUSSION

To evaluate the clinical usefulness of serum S100A12 and sRAGE, we studied these factors in patients with AOSD and compared them with those of HC. Moreover, we also studied these levels as a biomarker for checking disease activity. To the best of our knowledge, the present study is the first to show elevated S100A12 levels with low concentration of circulating sRAGE in patients with AOSD. Further, serum S100A12 correlated with several inflammatory markers and systemic score, and serum S100A12 was decreased when the disease activity resolved in the followup patients with AOSD.

The activities of S100A12 include chemotactic activity and activation of intracellular signaling cascades leading to cytokine production and induction of oxidative stress[36]. S100A12 is overexpressed in several inflammatory diseases, such as inflammatory bowel diseases, vasculitis, JIA, rheumatoid and psoriatic arthritis, and asthma[8,9,17,18,19,29,37,38]. Additionally, S100A12 distinguished systemic onset JIA from infections with a high specificity of 94%[8].

In our study, serum S100A12 levels of patients with AOSD were significantly higher than those of HC, and serum S100A12 levels strongly correlated with known disease activity markers, such as ESR, CRP, and ferritin, and with systemic score. Further, most followup patients with AOSD had significantly decreased S100A12 levels after resolution of disease activity, and the changes of serum S100A12 levels were correlated with the changes of ESR, CRP, and systemic scores. These results strongly suggest that serum S100A12 has an important role in pathogenesis of AOSD, and can be a good marker for monitoring disease activity and evaluating treatment response.

Soluble RAGE corresponds to the extracellular domain of RAGE lacking cytosolic and transmembrane domains. Consequently, sRAGE can act as a decoy molecule by binding S100A12, thereby preventing ligation with membrane RAGE[23]. Levels of sRAGE are reduced in various types of autoimmune diseases, such as SLE, RA, and JIA[8,28,29,39]. One study evaluated serum S100A12 and sRAGE with patients with Kawasaki disease, and suggested

Table 3. Correlation between the changes of disease activity markers and the changes of systemic score in followup patients with AOSD. These data were assessed using a Spearman correlation.

Clinical Features	Correlation Coefficient (p value)	
	Δ S100A12	Δ sRAGE
Δ systemic score	**0.585 (0.009)**	–0.367 (0.122)
Δ leukocyte	–0.116 (0.637)	–0.156 (0.523)
Δ ESR	**0.485 (0.035)**	0.114 (0.642)
Δ CRP	**0.498 (0.03)**	**–0.472 (0.041)**
Δ ferritin	0.367 (0.123)	–0.037 (0.881)

All significant data are in bold face. Systemic score by Pouchot *et al*[3] assigns a score from 0 to 12 and adds 1 point for each of the following manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leukocytosis ≥ 15,000/mm^2, sore throat, myalgia, and abdominal pain. AOSD: adult-onset Still's disease; sRAGE: soluble receptor for advanced glycation endproducts; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

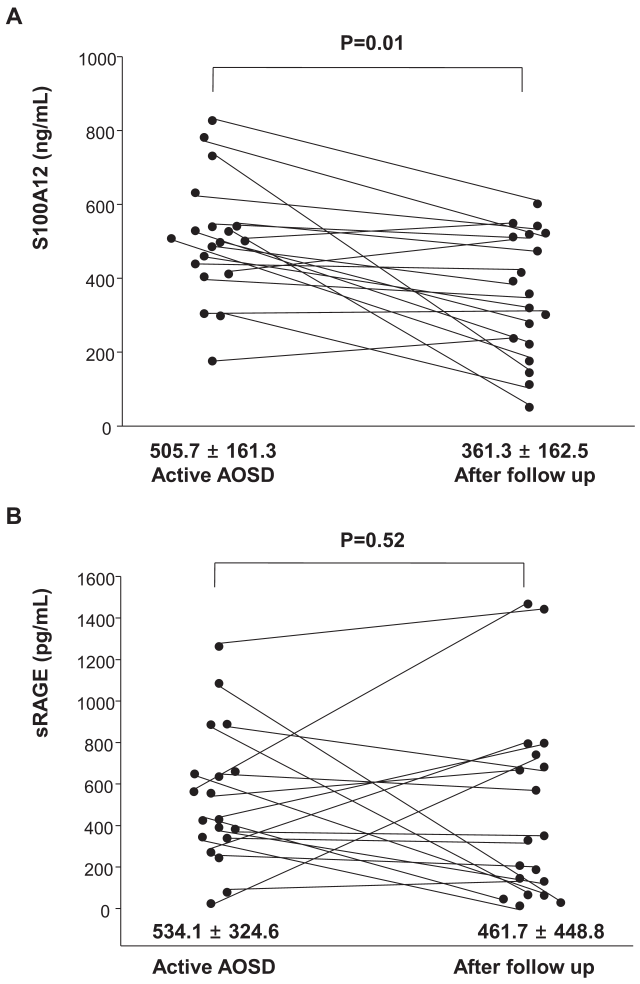

Figure 2. A. The levels of S100A12 and (B) soluble receptor for advanced glycation endproducts (sRAGE) in 19 patients with AOSD according to disease activity. Wilcoxon signed-rank test was used to perform the statistical analysis. AOSD: adult-onset Still's disease.

that S100A12:sRAGE ratio might help to detect patients with Kawasaki disease who are at risk of being unresponsive to intravenous immunoglobulin therapy[8]. The authors also evaluated 15 patients with systemic JIA, and reported decreased sRAGE and elevated S100A12:sRAGE ratio compared to healthy controls.

In our study, we evaluated the levels of sRAGE and S100A12:sRAGE ratio for disease activity markers in patients with AOSD. The sRAGE levels of AOSD were lower than those of HC. Further, the S100A12:sRAGE ratio levels of AOSD were lower than those of HC. However, no correlation was found between sRAGE and disease activity markers such as ESR, CRP, ferritin, and systemic score in patients with AOSD. Moreover, there were no changes of sRAGE correlated with the changes of other disease activity markers except for CRP. Only the change of CRP was negatively correlated with the change of sRAGE. S100A12:sRAGE was also not changed after activity was resolved. These results suggest that sRAGE and S100A12:sRAGE could not be a reliable biomarker for evaluating disease activity in patients with AOSD, although sRAGE would play a role in initial disease activity of AOSD.

S100A12 showed strong correlations with known disease activity markers with followup samples. To the best of our knowledge, ours is the first study describing the relationship between S100A12 or sRAGE levels and conventional inflammatory markers in patients with AOSD. These results suggest that S100A12, a marker of neutrophil activation, is highly overexpressed in patients with AOSD, and could play an important role in AOSD pathogenesis. However, it is not clear why serum sRAGE, soluble form of S100A12 receptor, are decreased in patients with AOSD without any correlation with known disease activity markers. These findings suggested that sRAGE could be a contributing factor in the pathogenesis of AOSD or a secondary decrease attributable to inflammation. However, we did not compare these markers with other febrile disorders and had a relatively small sample size in followup samples. Therefore, further studies involving a larger sample size are required for evaluating the usefulness of these markers in patients with AOSD and treatment response with control groups of other febrile disorders such as sepsis.

Serum S100A12 levels of patients with AOSD were significantly higher than those of HC. The sRAGE levels of patients with AOSD were significantly lower than those of HC. S100A12 levels showed strong correlations with known disease activity markers such as ESR, CRP, ferritin, and systemic score. Most followup patients with AOSD showed decreased S100A12 levels after resolution of disease activity. These results suggest that serum S100A12 could have an important role in AOSD pathogenesis, and could be a reliable clinical marker for monitoring disease activity and treatment response.

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