Serum S100A8/A9, But Not Follistatin-like Protein 1 and Interleukin 18, May Be a Useful Biomarker of Disease Activity in Adult-onset Still's Disease

HYOUN-AH KIM, JEONG-MI AN, JIN-YOUNG NAM, JA-YOUNG JEON, and CHANG-HEE SUH

ABSTRACT. ***Objective.*** S100A8/A9, follistatin-like protein 1, and interleukin 18 (IL-18) have been suggested as biomarkers of disease activity in patients with systemic juvenile idiopathic arthritis or adult-onset Still's disease (AOSD). We investigated the clinical significance of these factors in AOSD.

Methods. Blood samples were collected from 36 patients with AOSD, 40 patients with rheumatoid arthritis (RA), and 33 healthy controls. Of the patients with AOSD, followup samples were collected from 16 patients after resolution of disease activity.

Results. Serum levels of S100A8/A9 (11.77 ± 8.84 μg/ml) in AOSD patients were higher than those in RA patients (3.53 ± 3.43 μg/ml; $p < 0.001$) and controls (2.49 ± 1.83 μg/ml; $p < 0.001$). Follistatin-like protein 1 levels in AOSD were not different from those in RA and controls. IL-18 levels in AOSD (7560.3 ± 7577.6 pg/ml) were higher than those in RA (217.7 ± 292.1 pg/ml; $p < 0.001$) and controls (139.2 ± 86.2 pg/ml; $p < 0.001$). The sensitivity and specificity of IL-18 for diagnosing AOSD was highest with a cutoff value of 366.1 pg/ml. Serum S100A8/A9 correlated with leukocyte count, erythrocyte sedimentation rate, C-reactive protein, ferritin, and systemic disease score; however, IL-18 correlated only with ferritin and systemic disease score. S100A8/A9 was decreased after disease activity was resolved in followup of AOSD patients (9.96 ± 7.35 μg/ml in active AOSD vs 3.6 ± 4.77 μg/ml in resolved cases; $p = 0.001$). The change of S100A8/A9 was well correlated with that of systemic disease score.

Conclusion. The data suggest that serum S100A8/A9 may be a useful biomarker for evaluating disease activity in patients with AOSD. (J Rheumatol First Release June 1 2012; doi:10.3899/jrheum.120079)

Key Indexing Terms:

ADULT-ONSET STILL'S DISEASE | S100A8/A9 | FOLLISTATIN-LIKE PROTEIN 1
INTERLEUKIN 18 | BIOMARKER | DISEASE ACTIVITY

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology that is analogous to the systemic form of juvenile idiopathic arthritis (systemic JIA). AOSD is characterized by spiking fever, arthritis, evanescent rash, elevated liver enzymes, lymphadenopathy, hepatosplenomegaly, and serositis[1,2]. However, the spectrum of differential diagnoses is wide and includes infectious, neoplastic, and autoimmune disorders, which should be ruled out before the diagnosis of AOSD. Since the symptoms and laboratory results are not disease-specific, diagnosis of AOSD and accurate determination of disease activity is difficult[3,4,5,6]. The most commonly used biomarkers for AOSD have included the erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and ferritin, but these are nonspecific markers. Therefore, a simple biomarker that could be used to evaluate disease activity would be very useful.

S100A8 and S100A9 are 2 calcium-binding proteins that belong to the S100 family[7]. S100A8 and S100A9 form heterodimers that are the biologically relevant forms, and those are expressed by infiltrating monocytes and neutrophils, but not in quiescent resident macrophages and lymphocytes under inflammatory conditions[8,9,10,11]. S100A8/A9 can be detected in high levels in serum and body fluids in patients with different types of infectious, inflammatory, and malignant disorders[12,13]. Some studies showed that systemic JIA is associated with high concentrations of S100A8/A9[14,15]. One study reported that serum S100A8/A9 was increased in patients with AOSD and correlated with disease activity[16].

Follistatin-like protein 1, originally cloned from an osteoblast cell line as a transforming growth factor-ß (TGF-ß)-inducible gene, was found to be highly overexpressed in mouse paws during early arthritis[17,18]. Follistatin-like

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Supported by the Brain Korea 21 project for Ajou University School of Medicine.

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Accepted for publication March 29, 2012.

protein 1 has been found in rheumatoid arthritis (RA) synovial tissue, and anti-follistatin-like protein 1 antibodies have been detected in the serum and synovial fluid of patients with RA[19,20]. Also, transfection of follistatin-like protein 1 into macrophages and fibroblasts led to upregulation of protein inflammatory cytokines that are believed to play central roles in chronic arthritis[19]. One study demonstrates that follistatin-like protein 1 may represent a useful biomarker of disease activity in systemic JIA[21].

Interleukin 18 (IL-18), originally described as interferon-γ-inducing factor, seems to bring on powerful Th1-promoting activities in synergy with IL-12[22]. Macrophages, Kupffer cells, keratinocytes, articular chondrocytes, synoviocytes, and osteoblasts are able to synthesize IL-18[23]. Many studies have revealed a broad spectrum of effects that implicate IL-18, a member of the IL-1 superfamily, as a pivotal regulator of chronic inflammation in human autoimmune diseases[24]. Serum levels of IL-18 were reported to be elevated in patients with active AOSD compared to those with other autoimmune diseases such as systemic lupus erythematosus (SLE), RA, and systemic sclerosis[25]. Serum IL-18 levels in the steroid nonresponders were significantly higher than in the steroid responders[26]. We previously reported elevated concentrations of IL-18 in patients with active and inactive AOSD[27].

It has been reported that the serum levels of S100A8/A9, follistatin-like protein 1, and IL-18 are elevated and could be disease activity markers in AOSD or systemic JIA. However, the sample sizes in those studies were small, and there has been no study regarding follistatin-like protein 1 in AOSD. Therefore, we have investigated the clinical significance of S100A8/A9, follistatin-like protein 1, and IL-18 in Korean patients with AOSD with serial samplings.

MATERIALS AND METHODS

Subjects. Thirty-six patients with AOSD, 40 patients with RA serving as disease controls, and 33 healthy controls were studied. Patients with AOSD were diagnosed according to the criteria of Yamaguchi, *et al*[28] after exclusion of common infections and hematological and autoimmune diseases. Patients with RA satisfied the American College of Rheumatology 1987 revised criteria for the classification of RA[29]. Serum samples were collected from patients and controls. Of the 36 patients with AOSD, followup samples were collected from 16 patients after resolution of disease activity. All blood samples were stored at –20°C immediately after collection.

Information on the medical history, clinical symptoms, and physical examinations was entered into a database when serum sampling was done. Each patient also underwent a series of laboratory tests, including complete blood count (CBC), ESR, CRP, rheumatoid factor, antinuclear antibody, 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 according to the systemic disease score method described by Pouchot, *et al*[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 arbitrarily defined resolution of disease activity of AOSD with a score of ≤ 2. This study was approved by the institutional review board of our hospital, and informed consent was received from all subjects.

S100A8/A9, follistatin-like protein 1, and IL-18 assay. Serum S100A8/A9 levels were measured using commercial ELISA kits (Buhlmann Laboratories, Schonenbuch, Switzerland) according to the manufacturer's instructions. Follistatin-like protein 1 levels were also determined using ELISA kits (USCN Life, Wuhan, China) according to the manufacturer's instructions. Serum IL-18 levels were measured using commercial ELISA kits (eBioscience, San Diego, CA, USA) according to the manufacturer's instructions.

Statistical analysis. Statistical analysis was performed using SPSS, version 12.0 (SPSS, Chicago, IL, USA). A p value < 0.05 was regarded as statistically significant. Data are shown as mean ± SD or median and interquartile range, where appropriate. Differences in S100A8/A9, follistatin-like protein 1, and IL-18 levels were determined by a Mann-Whitney U test. The ability of S100A8/A9, follistatin-like protein 1, IL-18, ferritin, and CRP to accurately diagnose AOSD was evaluated by a receiver-operating characteristics (ROC) analysis. The correlations between their levels and disease activity markers were evaluated with 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.

RESULTS

Clinical characteristics of patients. The mean age of the AOSD patients was 40.3 ± 13.6 years, and 81.6% were women. There were no significant differences in age and sex between groups (Table 1). The main clinical symptoms in patients with AOSD included high spiking fever (69.4%), rash (72.2%), sore throat (50%), arthritis (52.8%), and lymphadenopathy (36.1%).

Serum S100A8/A9, follistatin-like protein 1, and IL-18 levels. Figure 1 shows S100A8/A9, follistatin-like protein 1, and IL-18 levels in patients with AOSD, patients with RA, and controls. S100A8/A9 levels in AOSD (11.77 ± 8.84 μg/ml) were higher than those in RA (3.53 ± 3.43 μg/ml; p < 0.001) and controls (2.49 ± 1.83 μg/ml; p < 0.001). IL-18 levels in AOSD (7560.3 ± 7577.6 pg/ml) were higher than those in RA (217.7 ± 292.1 pg/ml; p < 0.001) and controls (139.2 ± 86.2 pg/ml; p < 0.001). However, follistatin-like protein 1 levels in AOSD were not higher.

In the ROC analysis for S100A8/A9, follistatin-like protein 1, IL-18, CRP, and ferritin, the area under the curve (AUC) was 0.845 (95% CI 0.753–0.937, p < 0.001), 0.436 (95% CI 0.299–0.573, p = 0.527), 0.983 (95% CI 0.961–1.005, p < 0.001), 0.927 (95% CI 0.865–0.989, p < 0.001), and 0.828 (95% CI 0.723–0.933, p < 0.001), respectively (Figure 2). With a cutoff value of 366.1 pg/ml, the sensitivity and specificity of IL-18 was highest for diagnosis of AOSD (91.7% and 99.1%, respectively). Also, the sensitivity and specificity of S100A8/A9 were 69.4% and 98%, respectively (with a cutoff value of 4.55 μg/ml), and those of ferritin were 66.7% and 97% (cutoff value 237.3 ng/ml).

The comparisons of S100A8/A9, follistatin-like protein 1, and IL-18 levels according to the clinical manifestations of AOSD were evaluated. Serum S100A8/A9 levels were significantly higher in the AOSD patients with fever (p < 0.001), sore throat (p = 0.006), rash (p = 0.034), and splenomegaly (p = 0.019) compared to those without (data not shown). Serum IL-18 levels were significantly higher in the AOSD patients with fever (p < 0.001) and sore throat (p = 0.006; data not

Table 1. Clinical characteristics of patients. All values presented as number (%) or mean ± SD.

	AOSD, n = 36	RA, n = 40	Controls, n = 33
Age, yrs	40.3 ± 13.6	40.7 ± 12.5	38.5 ± 7.7
Female/male	31/5	35/5	31/2
Fever	25 (69.4)	0 (0)	
Sore throat	18 (50)	0 (0)	
Rash	26 (72.2)	0 (0)	
Lymphadenopathy	13 (36.1)	0 (0)	
Splenomegaly	10 (27.8)	0 (0)	
Hepatomegaly	6 (16.7)	0 (0)	
Pericarditis	4 (11.1)	0 (0)	
Pleuritis	4 (11.1)	0 (0)	
Arthralgia	31 (86.1)	40 (100)	
Arthritis	19 (52.8)	40 (100)	
Hemoglobin, g/dl	11.4 ± 1.6	12.0 ± 1.7	
Leukocytes, /μl	14,251 ± 5887	7074 ± 3229	
Platelets, × 10^3/μl	427.5 ± 788.6	312.4 ± 82.5	
Ferritin, ng/ml	4395.6 ± 496.7	64.5 ± 78	54.2 ± 58.4
ESR, mm/h	56.3 ± 37.4	29.6 ± 32.6	
CRP, mg/dl	9.03 ± 88.41	1.08 ± 1.7	0.09 ± 0.21
AST, mg/dl	91.2 ± 125.7	19.8 ± 5.7	
ALT, mg/dl	78.7 ± 111.5	20.6 ± 7.6	
ANA positivity	3 (8.3)	12 (30)	
RF positivity	5 (13.9)	28 (70)	
Systemic disease score	4.5 ± 2.34		
DAS-28	3.8 ± 1.41	4.3 ± 1.38	

AOSD: adult onset Still's disease; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AST: aspartate transaminase; ALT: alanine transaminase; ANA: antinuclear antibody; RF: rheumatoid factor; DAS-28: Disease Activity Score including 28 joints.

shown). However, serum follistatin-like protein 1 levels were not different.

Serum S100A8/A9, follistatin-like protein 1, and IL-18 levels and disease activity in patients with AOSD. Correlations between preexistent disease activity markers and serum S100A8/A9, follistatin-like protein 1, and IL-18 in patients with AOSD are shown in Table 2.

Serum S100A8/A9 levels correlated with leukocyte count ($r = 0.425$, $p = 0.01$), ESR ($r = 0.557$, $p < 0.001$), CRP ($r = 0.785$, $p < 0.001$), ferritin ($r = 0.661$, $p < 0.001$), and systemic disease score ($r = 0.565$, $p < 0.001$). IL-18 levels correlated only with ferritin ($r = 0.448$, $p = 0.006$) and systemic disease score ($r = 0.396$, $p = 0.017$). However, no correlation was found between follistatin-like protein 1 and disease activity markers.

Changes of serum S100A8/A9, follistatin-like protein 1, and IL-18 levels in followup of patients with AOSD. Among patients with AOSD who have high disease activity before starting corticosteroids or immunosuppressive medications, 16 patients were followed throughout the resolution of disease activity with low- to moderate-dose corticosteroids (11.09 ± 10.99 mg/day prednisolone equivalent) and immunosuppressives such as methotrexate or azathioprine. Followup sera samples were collected from those patients with resolved AOSD.

In the patients with AOSD who had followup, serum S100A8/A9 levels were decreased after disease activity was resolved (9.96 ± 7.35 μg/ml in active AOSD vs 3.6 ± 4.77 μg/ml in resolved; $p = 0.001$; Figure 3). However, follistatin-like protein 1 and IL-18 levels were not different.

We evaluated the correlations between the change of disease activity markers and the change of systemic disease scores (Table 3). The change of systemic disease score was positively correlated with the change of ESR ($r = 0.532$, $p = 0.034$), CRP ($r = 0.728$, $p = 0.001$), ferritin ($r = 0.828$, $p < 0.001$), and S100A8/A9 ($r = 0.676$, $p = 0.011$). However, there was no correlation between the change of systemic disease score and the change of follistatin-like protein 1 or IL-18.

DISCUSSION

To examine clinical significance of serum S100A8/A9, follistatin-like protein 1, and IL-18, we measured these factors in patients with AOSD and compared them to those of patients with RA and normal controls. Also, we evaluated these levels as a biomarker for disease activity. Serum levels of S100A8/A9 and IL-18 of patients with AOSD were significantly higher than those of patients with RA and controls. When we evaluated sensitivity and specificity of these factors for diagnosing AOSD using ROC curves, IL-18 was found to have the highest sensitivity and specificity, with a cutoff value of 366.1 pg/ml. Serum S100A8/A9 correlated with leukocyte count, ESR, CRP, ferritin, and systemic disease score. In addi-

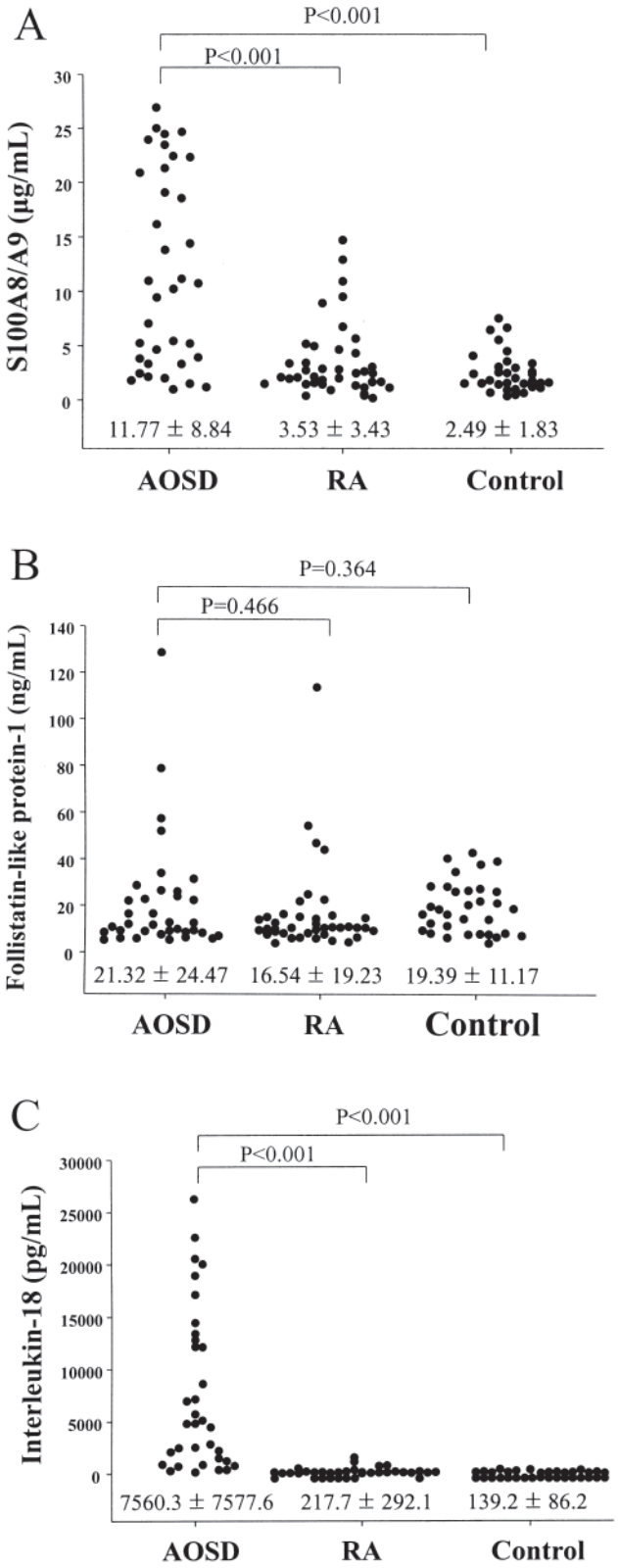

Figure 1. The levels of S100A8/A9 (A), follistatin-like protein 1 (B), and interleukin-18 (C) in 36 adult-onset Still's disease (AOSD), 40 rheumatoid arthritis (RA) patients, and 33 healthy controls. Data are expressed as the mean ± SD. A Mann-Whitney test was used to perform the statistical analysis.

tion, serum S100A8/A9 was decreased when disease activity resolved in the followup patients with AOSD. Further, the changes of serum S100A8/A9 levels were correlated with the changes of systemic disease scores in the followup AOSD patients.

Many features of AOSD and systemic JIA seem to be explained by the known effects of proinflammatory cytokines such as IL-1, IL-6, macrophage colony-stimulating factor, tumor necrosis factor-α (TNF-α), and IL-18. In particular, IL-1, a protein with pleiotropic effects, upregulates its own transcription as well as that of IL-6[30]. IL-1 stimulates the destruction of cartilage and bone; for example, by inducing follistatin-like protein 1, an inflammatory product of joint matrix cells[21,30]. In addition, IL-1 activity in systemic JIA is amplified by endogenous factors such as S100A8, S100A9, and S100A12 that are themselves produced in excess. This signaling can lead to increased production of proinflammatory cytokines including IL-1ß, which in turn, further increases production of S100[14,31]. Therefore, we evaluated the endogenous factors related to IL-1 such as S100A8/A9, follistatin-like protein 1, and IL-18, in serum samples from patients with AOSD as a disease activity marker.

S100 proteins, which mediate inflammatory responses and are involved in the recruitment of inflammatory cells to sites of injury, have been suggested to form "damage-associated molecular patterns"[32,33]. S100 proteins form a family with more than 20 members including 3 that are linked to innate immune functions by their expression by myeloid cells: S100A8, S100A9, and S100A12. Recently, S100A8/A9 has been shown to be the endogenous ligand of Toll-like receptor-4, to play an important role in innate immunity, and to be associated with human sepsis and endotoxemia[11,13]. This signaling leads to increased production of proinflammatory cytokines such as IL-1ß, which in turn further increases production of S100 proteins[30].

One study showed that serum S100A8/A9 levels were significantly elevated in patients with active systemic JIA compared to those in healthy controls, patients with systemic infections, and patients with leukemia[14]. Additionally, S100A8/A9 distinguished systemic-onset JIA from infections with a specificity of 95%, in contrast to CRP levels. Recently, S100A8/A9 was evaluated as a marker for disease activity in AOSD[16]. Serum S100A8/A9 was increased in patients with AOSD, in close correlation with disease activity.

In our study, serum S100A8/A9 levels of patients with AOSD were significantly higher than in patients with RA and controls. In addition, serum S100A8/A9 levels showed strong correlations with known disease activity markers such as leukocyte count, ESR, CRP, ferritin, and systemic disease score. Further, in followup of patients with AOSD, most patients had significantly decreased S100A8/A9 levels after resolution of disease activity, and the changes of serum S100A8/A9 levels were correlated with the changes of systemic disease scores. These results suggest that serum

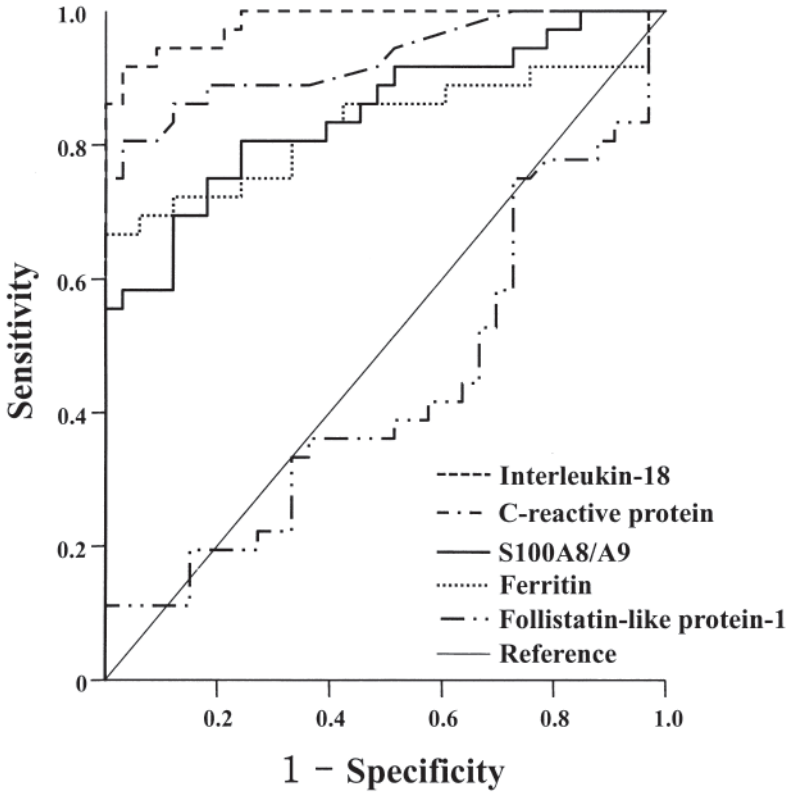

Figure 2. The receiver-operating characteristic (ROC) curves for S100A8/A9, follistatin-like protein 1, interleukin-18 (IL-18), C-reactive protein (CRP), and ferritin levels in adult-onset Still's disease and controls. The ROC curve values were 0.983 for IL-18 (95% CI 0.961-1.005; $p < 0.001$), 0.927 for CRP (95% CI 0.865-0.989, $p < 0.001$), 0.845 for S100A8/A9 (95% CI 0.753-0.937; $p < 0.001$), 0.828 for ferritin (95% CI 0.723-0.933; $p < 0.001$), and 0.436 for follistatin-like protein 1 (95% CI 0.299-0.573; $p = 0.527$).

Table 2. Correlation between disease activity markers and systemic disease score in 36 patients with adult-onset Still's disease.

Disease Activity Markers	Correlation Coefficient, r (p value) S100A8/A9	Follistatin-like Protein 1	Interleukin 18
Systemic disease score*	0.565 (< 0.001)	0.129 (0.454)	0.396 (0.017)
Leukocytes	0.425 (0.01)	0.151 (0.381)	0.301 (0.075)
ESR	0.557 (< 0.001)	0.135 (0.243)	0.205 (0.23)
CRP	0.785 (< 0.001)	0.111 (0.341)	0.243 (0.153)
Ferritin	0.661 (< 0.001)	0.258 (0.129)	0.448 (0.006)

Data were assessed by Spearman correlation. * Systemic disease 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. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

S100A8/A9 can provide reliable clinical information for monitoring the disease activity and treatment response.

One study analyzed gene expression in the mouse model of collagen-induced arthritis, discovering that a poorly characterized gene, follistatin-like protein 1, originally cloned from an osteoblast cell line as a TGF-ß-inducible gene, was highly overexpressed in mouse paws during early arthritis, especially at the interface of synovial pannus and eroding bone[17,18]. Overexpression of follistatin-like protein 1 in mouse paws by gene transfer resulted in severe arthritis, while neutralization of follistatin-like protein 1 suppressed arthritis[19]. In addition, transfection of follistatin-like protein 1 into macrophages and fibroblasts led to the upregulation of proinflammatory cytokines that are believed to play central roles in chronic

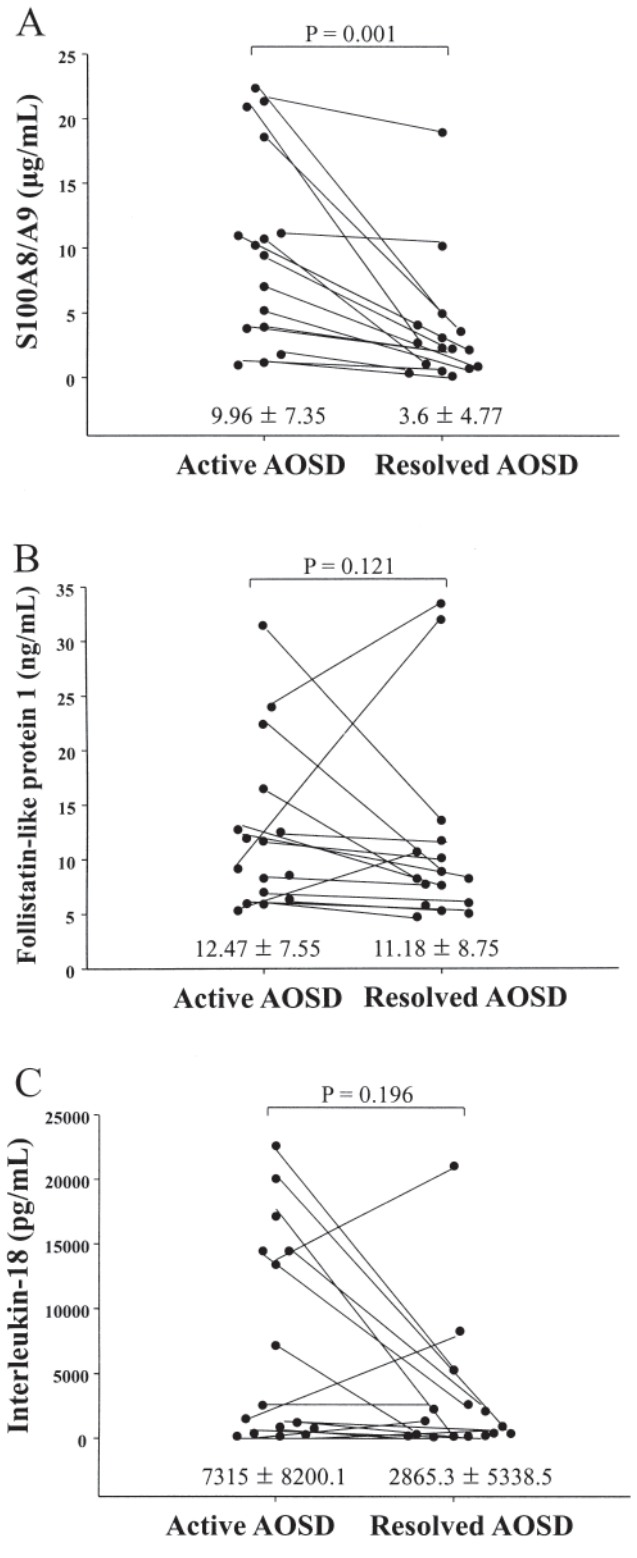

Figure 3. The levels of S100A8/A9 (A), follistatin-like protein 1 (B), and interleukin-18 (C) in 16 patients with adult-onset Still's disease (AOSD) according to disease activity. Data are expressed as the mean ± SD. A Wilcoxon signed-rank test was used to perform the statistical analysis.

Table 3. Correlation between changes of disease activity markers and changes of systemic disease score in followup of patients with adult-onset Still's disease.

Clinical Feature	Correlation Coefficient, r (p value) Delta Systemic Disease Score*
Delta hemoglobin	0.052 (0.848)
Delta leukocytes	0.098 (0.719)
Delta platelets	–0.237 (0.378)
Delta ESR	0.532 (0.034)
Delta CRP	0.728 (0.001)
Delta ferritin	0.828 (< 0.001)
Delta S100A8/A9	0.676 (0.011)
Delta follistatin-like protein 1	–0.076 (0.779)
Delta interleukin 18	0.018 (0.948)

Data were assessed by Spearman correlation. * Systemic disease 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. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

arthritis, including IL-1ß and TNF-α. Further, induction of follistatin-like protein 1 requires nuclear factor-κB. These data supported the idea that follistatin-like protein 1 is a novel proinflammatory molecule with a previously unrecognized role in inflammation[19,34]. Recently, a study reported that serum and synovial fluid samples from children with systemic JIA had elevated concentrations of follistatin-like protein 1. In addition, the elevation in serum follistatin-like protein 1 concentrations correlated closely with elevations in the ESR and platelet count[21]. Therefore, the investigators suggested that follistatin-like protein 1 may represent a useful biomarker of disease activity in systemic JIA.

In our study, although a few patients with AOSD had elevated serum levels of follistatin-like protein 1, there were no significant differences of the levels between patients with AOSD and patients with RA or controls. In addition, serum follistatin-like protein 1 levels did not show any correlations with known disease activity markers such as ESR, CRP, and systemic disease score and any significant change according to disease activity. These results suggest that follistatin-like protein 1 is not a useful biomarker for evaluating disease activity in patients with AOSD.

IL-18 was originally described as an interferon-γ-inducing factor mainly produced by activated macrophage. IL-18 stimulates a variety of inflammatory responses, enhances proliferation and activity of T cells and natural killer cells, and shifts the Th cell balance toward the Th1 response[35,36]. Some reports have shown that serum IL-18 levels are highly elevated in patients with AOSD or systemic JIA[23,25,26,27,37,38]. Serum levels of IL-18 were reported to be elevated in patients with active AOSD compared to those with SLE, RA, JIA, systemic sclerosis, polymyositis or dermatomyositis, Sjögren's syndrome, and infection. Further, reports described increased

IL-18 mRNA expression in blood monocytes and T cells and increased IL-18 bioactivity in sera of patients with active AOSD, and serum IL-18 levels gradually normalized after the disease was successfully controlled[25]. One study reported increased levels of serum IL-18 in systemic and chronic articular AOSD, even in remission, but correlation with disease activity was noted only in chronic articular AOSD[39]. Previously, we reported elevated concentrations of IL-18 in patients with active and inactive AOSD compared to normal controls, but there was no significant difference between the active and the inactive disease states[27]. Further, in patients with active disease, serum IL-18 levels showed significant correlation with ferritin levels.

In our current study, serum IL-18 levels of patients with AOSD were significantly higher than those of patients with RA and controls. In the ROC analysis, the AUC of IL-18 (0.983) was greater than that for CRP (0.927) and S100A8/A9 (0.845) and the sensitivity and specificity of IL-18 (cutoff value, 366.1 pg/ml) were 91.7% and 99.1%, respectively, which was more sensitive and specific than CRP and S100A8/B9. In addition, IL-18 levels showed correlations with ferritin and systemic disease score. However, in the followup of patients with AOSD, some did not have decreased IL-18 levels after resolution of disease activity. These results were consistent with previous reports[27,39].

Laboratory markers of active disease in AOSD include ESR, CRP, and ferritin, but these markers do not discriminate AOSD from other inflammatory conditions. Also, the initial differential diagnosis of AOSD can be difficult, and it remains a significant clinical challenge to differentiate AOSD from other causes of fever, such as malignancy and infection. In this study, we showed highest sensitivity and specificity of IL-18 for diagnosing AOSD. Also, S100A8/A9 showed strong correlations with known disease activity markers with followup samples. However, we did not compare these markers in samples from febrile disorders, and had relative small followup sample sizes. Therefore, further studies with larger sample sizes would be needed for evaluating specificity of these markers in patients with AOSD and treatment response in control groups with febrile disorders.

Serum S100A8/A9 and IL-18 levels of patients with AOSD were significantly higher than those of patients with RA and normal controls. The sensitivity and specificity of IL-18 for diagnosing AOSD was highest with a cutoff value of 366.1 pg/ml. S100A8/A9 levels showed strong correlations with known disease activity markers such as leukocyte count, ESR, CRP, ferritin, and systemic disease score. In the followup of patients with AOSD, most patients had decreased S100A8/A9 levels after resolution of disease activity. Our results suggest that serum S100A8/A9 can be a reliable clinical marker for monitoring disease activity and treatment response.

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Correction

Serum S100A8/A9, But Not Follistatin-like Protein 1 and Interleukin 18, May Be a Useful Biomarker of Disease Activity in Adult-onset Still's Disease

Kim H-A, An J-M, Nam J-Y, Jeon J-Y, Suh C-H. Serum S100A8/A9, but not follistatin-like protein 1 and interleukin 18, may be a useful biomarker of disease activity in adult-onset Still's disease. J Rheumatol 2012;39:1399-406. The study described in this article was supported by the new faculty research fund of Ajou University School of Medicine, Suwon, Korea. That information was not available at the time of publication.

doi:10.3899/jrheum.120079.C1