Soluble Triggering Receptor Expressed on Myeloid Cell-1 (sTREM-1): A New Mediator Involved in Early Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To investigate the possible role of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in ankylosing spondylitis (AS).

Methods. Serum sTREM-1 levels were measured in 80 patients with AS and 30 healthy controls, and synovial fluid (SF) sTREM-1 levels were tested in 6 AS patients using ELISA. Demographic data were collected, and patient's disease activity (BASDAI), functional ability (BASFI), and global assessment (BAS-G) were evaluated. We also tested erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and IgA in these patients.

Results. Serum sTREM-1 levels were detectable (definition, ≥ 15 pg/ml) in 31.3% (25/80) of the AS patients, as compared to only 10% (3/30) of healthy controls (p = 0.027). SF sTREM-1 levels were detectable (≥ 15 pg/ml) in 83% (5/6) of the AS patients. The detectable rate of sTREM-1 in SF was significantly higher than in serum (p = 0.018). Disease duration was shorter in AS patients with "higher" serum sTREM-1 levels (≥ 30 pg/ml) versus those with "lower" levels (< 30 pg/ml) [mean (SD), 4.3 (3.7) vs 8.6 (7.8) yrs, p = 0.036], but the differences between these 2 groups of patients were not evident based on results of BASDAI, BASFI, BAS-G, ESR, CRP, or IgA levels. Of note, serum sTREM-1 levels inversely correlated with disease duration (r = –0.433, p = 0.03) in the 25 AS patients with detectable sTREM-1 levels.

Conclusion. sTREM-1 seems to be a new mediator involved in patients with AS, particularly in the early stages of disease. (First Release July 15 2008; J Rheumatol 2008;35:1846–8)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SERUM SYNOVIAL FLUID DISEASE DURATION
SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELL-1

Spondyloarthritis (SpA) is a family of chronic arthritis, characterized by inflammatory back pain, peripheral arthritis, and enthesitis. Ankylosing spondylitis (AS) is the prototype disease among this grouping of chronic arthritis. Although the etiology of SpA remains obscure, it has a strong association with HLA-B27. Intestinal bacteria are also important in the development of arthritis and colitis in the HLA-B27 transgenic rat[1]. The infiltration of SpA synovium by specific macrophages and neutrophils suggests that innate immunity plays a role in the pathogenesis of SpA[2-4].

The triggering receptor expressed on myeloid cell-1 (TREM-1) is a recently discovered member of the immunoglobulin superfamily, up-regulated on monocytes/macrophages and neutrophils in the presence of bacteria or fungus infection[5,6]. TREM-1 is a type of pattern recognition receptor, with innate immunity and ability to secrete proinflammatory mediators. Conversely, TREM-1 is only weakly expressed in samples with noninfectious inflammatory disorders, including psoriasis, ulcerative colitis, and immune-complex mediated vasculitis[6]. Soluble TREM-1 (sTREM-1), shed from activated phagocytes, can be measured in various body fluids, and helps in early identification of microorganism infection[7,8]. The role of sTREM-1 in SpA has not yet been studied. We investigated whether this new mediator is involved in AS.

MATERIALS AND METHODS

Patients. Blood samples were obtained from 80 Chinese patients with AS who fulfilled the 1984 modified New York criteria[9] (Table 1) and from 30 age and sex-matched Chinese healthy controls. Clinical and laboratory assessments were performed on the same day, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[10], Bath Ankylosing

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Spondylitis Functional Index (BASFI)[11], Bath Ankylosing Spondylitis Patient Global Score (BAS-G)[12], erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and IgA levels. Synovial fluid (SF) samples were collected from 6 AS patients with peripheral arthritis (knee), and 2 of the 6 patients contributed blood samples in this study.

Immunoassay of serum and SF levels of sTREM-1. Estimation of serum and SF concentrations of sTREM-1 was performed with commercial ELISA kits (R&D Systems, Minneapolis, MN, USA), and carried out in duplicate. The standard concentrations of sTREM-1 ranged from 15–4000 pg/ml. The serum or SF sTREM-1 levels < 15 pg/ml were regarded as undetectable.

Statistical analysis. Mann-Whitney U, Fisher's exact or Spearman's correlation test were used, as appropriate. P values < 0.05 were considered significant.

RESULTS

Serum levels of sTREM-1 in AS patients and healthy controls. Serum sTREM-1 levels were detectable (≥ 15 pg/ml) in 31.3% (25/80) of the AS patients, as compared to only 10% (3/30) of healthy controls (p = 0.027). The serum sTREM-1 levels in the 25 detectable AS patients were mean (SD), median (range), 538.8 (818.3), 128.5 (16.9–2815.8) pg/ml. The serum sTREM-1 levels in the 3 detectable healthy controls were 117.9, 139.6, and 341.6 pg/ml.

sTREM-1 were detectable (≥ 15 pg/ml) in 83% (5/6) of the SF samples, and the 5 detectable values were mean (SD), median (range), 68.5 (17.3), 60.2 (51.5–90.2) pg/ml. The SF sTREM-1 levels in the 2 AS patients with paired SF and serum samples were 51.5 pg/ml and 60.2 pg/ml, but their serum sTREM-1 levels were undetectable. The detectable rate of sTREM-1 in SF was significantly higher than in serum [83.3% (5/6) vs 31.3% (25/80), p = 0.018]. The median value of sTREM-1 in the 6 SF samples was also higher than the median value of sTREM-1 in the 80 serum samples (58.6 pg/ml vs < 15 pg/ml). However, the detectable rate of sTREM-1 in serum did not differ in AS patients with or without history of peripheral arthritis [25.5% (12/47) vs 39.3% (13/33), p = 0.255].

Table 1. Demographic and clinical characteristics of the 80 patients with AS. Values are mean (SD).

Characteristic	Patients with AS, n = 80
Age, yrs	32.8 (12.0)
Male/female	67/13
Disease duration, yrs	7.5 (7.2)
History of peripheral arthritis +/–	47/33
HLA-B27+	91% (73/80)
BASDAI	4.29 (2.19)
BASFI	2.24 (2.06)
ESR, mm/h	23.8 (22.8)
CRP, mg/dl	1.41 (1.63)
IgA, mg/dl	334.6 (139.8)

Clinical and laboratory variables in AS patients with "higher" versus "lower" serum sTREM-1 levels. Clinical and laboratory variables were compared between the AS patients with and without detectable serum sTREM-1 levels (≥ 15 pg/ml vs < 15 pg/ml) (Table 2). There were no significant differences observed in BASDAI (p = 0.458), BASFI (p = 0.655), BAS-G (p = 0.513), ESR (p = 0.087), CRP (p = 0.761), IgA (p = 0.788), or HLA-B27+ rate (p = 0.425). Between the 2 groups, each component of the BASDAI score also did not show significant differences (fatigue, spinal pain, peripheral joint, enthesitis, and morning stiffness). However, there was a trend to shorter disease duration in the AS patients with detectable serum sTREM-1 versus those without [Mean (SD), 5.4 (4.5) vs 8.4 (8.0) yrs, p = 0.208]. Of note, the difference in disease duration became significant if the "higher" serum sTREM-1 level cutoff value was set at 30 pg/ml [4.3 (3.7) vs 8.6 (7.8) yrs, p = 0.036; ≥ 30 pg/ml vs < 30 pg/ml], but the differences in BASDI (p = 0.619), BASFI (p = 0.726), BAS-G (p = 0.645), ESR (p = 0.094), CRP (p = 0.362), and IgA (p = 0.56) remained insignificant.

Correlations between clinical and laboratory variables in the 25 AS patients with detectable serum sTREM-1 levels. Interestingly, serum sTREM-1 levels inversely correlated with disease duration (r = –0.433, p = 0.03) in the 25 AS patients with detectable serum sTREM-1 levels (≥ 15 pg/ml) (Figure 1), but a significant correlation was not observed with BASDAI (r = 0.022, p = 0.984), BASFI (r = 0.026, p = 0.901), BAS-G (r = 0.045, p = 0.829), ESR (r = –0.067, p = 0.749), or CRP (r = –0.037, p = 0.859).

DISCUSSION

Our data demonstrate that the serum sTREM-1 levels were more frequently detectable (≥ 15 pg/ml) in AS patients than in

Table 2. Clinical variables in the 80 AS patients with different serum sTREM-1 levels. Values are mean (SD).

Clinical Variables	Serum sTREM-1 ≥ 15 pg/ml n = 25 (A)	Serum sTREM-1 < 15 pg/ml† n = 55 (B)	p A vs B	Serum sTREM-1 ≥ 30 pg/ml n = 21 (C)	Serum sTREM-1 < 30 pg/ml n = 59 (D)	p C vs D
Disease duration, yrs	5.4 (4.5)	8.4 (8.0)	0.208	4.3 (3.7)	8.6 (7.8)	0.036*
BASDAI	3.96 (1.48)	4.43 (2.45)	0.458	4.0 (1.5)	4.39 (2.39)	0.619
BASFI	1.95 (1.81)	2.37 (2.17)	0.655	2.0 (1.91)	2.32 (2.12)	0.726
BAS-G	4.51 (2.30)	5.0 (3.17)	0.513	4.58 (2.34)	4.94 (3.11)	0.645
ESR, mm/h	17.1 (15.8)	26.9 (24.9)	0.087	16.86 (16.4)	26.36 (24.31)	0.094
CRP, mg/dl	1.36 (1.68)	1.44 (1.62)	0.761	1.52 (1.78)	1.37 (1.58)	0.362
IgA, mg/dl	311.5 (115.9)	245.3 (24.9)	0.788	305.6 (124.6)	345.1 (144.5)	0.56

† Undetectable. * Statistically significant. p values by Mann-Whitney U test.

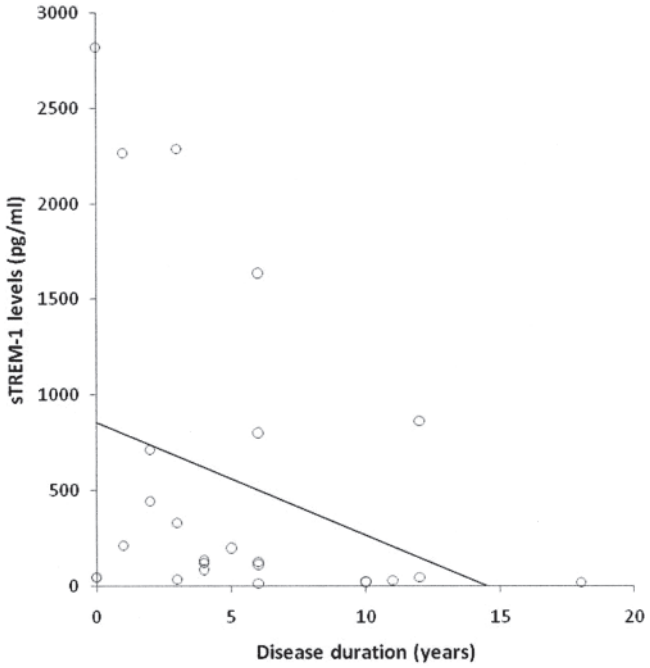

Figure 1. Correlation of serum sTREM-1 levels and disease duration in 25 AS patients with detectable serum sTREM-1 levels (≥ 15 pg/ml) (r = –0.433, p = 0.03).

healthy controls, indicating that this new mediator was increasingly expressed in the serum of AS patients. A previous study showed that normal subjects generally lack serum sTREM-1 expression, with 15•1 pg/ml in all the 10 healthy volunteers[13].

SF levels of sTREM-1 could be detected in the majority of the AS patients (5/6), and were higher than sTREM-1 in serum (25/80) (p = 0.011). The median value of sTREM-1 in the 6 SF samples was also higher than the median value of sTREM-1 in the 80 serum samples (58.6 pg/ml vs < 15 pg/ml). In the 2 AS patients with both SF and serum samples, the SF sTREM-1 levels were higher than their serum sTREM-1 levels. Nevertheless, the peripheral joint component of the BASDAI score did not show a significant difference between AS patients with and without detectable serum sTREM-1 levels. Inflamed joints may be one of the sources of sTREM-1, and this requires a large survey of SF samples for further evaluation.

Our results also showed that disease duration was shorter in the AS patients with "higher" (≥ 30 pg/ml) versus those with "lower" (< 30 pg/ml) serum sTREM-1 levels. However, disease activity, functional ability, patient global assessment, and acute phase reactants did not show significant differences. Further, in the 25 AS patients with detectable sTREM-1 levels, serum sTREM-1 levels inversely correlated with disease duration (r = –0.433, p = 0.03). Overall, serum sTREM-1 levels seemed to be more frequently detectable in AS patients at an early stage of disease. Recent studies showed that synovium in patients with spondyloarthritis was infiltrated with specific macrophage and polymorphonuclear leukocytes[2-4]. Macrophages were also found to be one of the most frequent cells in early and active sacroiliitis[14]. The sTREM-1, shedding from these early infiltrating phagocytes, may participate in the disease process of spondyloarthritis.

In conclusion, the findings of increasingly detectable rates of sTREM-1 in serum and SF of patients with AS, and the higher serum sTREM-1 levels in the AS patients with shorter disease duration suggest that this new mediator may be involved in AS, particularly in the early stages of disease.

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