The Relationship Between Plasma sTRAIL Level and Disease Activity in Rheumatoid Arthritis

Romatoid Artritte Plazma sTRAIL Düzeyi ile Hastalık Aktivitesi İlişkisi

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Received \ Geliş tarihi : 17.01.2017
Accepted \ Kabul tarihi : 31.01.2017

ABSTRACT

Objective: The purpose of this study was to investigate the plasma soluble tumour necrosis factor related apoptosis-inducing ligand (sTRAIL) level in rheumatoid arthritis (RA) and to evaluate the relationship between sTRAIL and disease activity.

Material and Methods: 19 RA patients, and as a control group 31 primary Sjogren's syndrome (pSS) patients and 24 healthy subjects were included in the study. Disease activity of RA patients was calculated by the Disease Activity Score-28 (DAS-28). Plasma sTRAIL concentrations were measured by the enzyme linked immunosorbent assay (ELISA).

Results: Mean plasma sTRAIL concentration in RA patients (1751 ± 635 pg/ml) was higher than in disease control patients with pSS (1234 ± 625 pg/ml) and in healthy controls (1181 ± 304 pg/ml) (p=0.002). In RA patients, there was no correlation between mean DAS-28 score and plasma sTRAIL levels. And also, there was no correlation between sTRAIL levels and laboratory parameters indicating disease activity such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Conclusion: Plasma sTRAIL levels were significantly higher in RA regardless of disease activity. These findings suggest that sTRAIL may have an important role in the pathogenesis of rheumatoid arthritis.

Key Words: TNF-related apoptosis inducing ligand, Rheumatoid arthritis, Sjogren's syndrome

ÖZ

Amaç: Çalışmanın amacı romatoid artritte plazmada çözünmüş TNF ilişkili apoptoz tetikleyici ligand (sTRAIL) düzeyinin saptanması ve sTRAIL düzeyinin hastalık aktivitesi ile ilişkisinin araştırılmasıdır.

Gereç ve Yöntemler: 19 Romatoid artrit (RA) hastası ve kontrol grubu olarak belirlenen 31 primer Sjögren sendromu (pSS) hastası ile 24 sağlıklı kişi çalışmaya dahil edildi. RA hastalarının hastalık aktivitesi, hastalık aktivite skoru-28 (DAS-28) ile hesaplandı. Plazma sTRAIL düzeyi immunoenzimatik yöntem (ELISA) ile ölçüldü.

Bulgular: Ortalama sTRAIL düzeyi RA hastalarında (1751 ± 635 pg/ml), pSS hastaları (1234 ± 625 pg/ml) ve sağlıklı kontrol (1181 ± 304 pg/ml) grubundan daha yüksek olarak ölçüldü (p=0.002). RA hastalarında DAS-28 ve sTRAIL düzeyi arasında bir korelasyon saptanmadı. Ayrıca sTRAIL düzeyi ile hastalık aktivitesini gösteren ESR ve CRP arasında da korelasyon saptanmadı.

Sonuç: RA'li hastaların sTRAIL düzeyleri hastalık aktivitesinden bağımsız olarak anlamlı düzeyde artmaktadır. Bu bulgular sTRAIL'in RA patogenezinde önemli bir rol alabileceğini göstermektedir.

Anahtar Sözcükler: TNF ilişkili apoptoz tetikleyici ligand, Romatoid artrit, Sjögren sendromu

DOI: 10.17954/amj.2017.82

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder leading to joint injury and dysfunction due to chronic inflammation that primarily involves synovial joints, and is occasionally accompanied by extra-articular involvement. Its incidence is approximately 1% worldwide (1). Given the relative frequency, there is a need for better understanding of etiopathogenesis and treatment goals in RA. Although the etiopathogenesis has not been fully elucidated, it is thought that genetic factors' interplay with environmental factors have an important role in RA. In individuals thought to have a genetic predisposition, RA is characterized by synovial tissue hyperplasia and mononuclear cell infiltration as a result of some potential triggering factors. Synovial hyperplasia, the basis of RA pathology, develops due to imbalance between forces enhancing or reducing tissue cellularity. It is considered that inhibition of apoptosis accompanying cell proliferation, migration and retention may have a significant role in the explanation of increased synovial tissue cellularity (2).

Programmed cell death, apoptosis, occurs via 2 different pathways including the intrinsic pathway promoted and regulated by Bcl-2 protein family (3) and the extrinsic pathway promoted by death receptors (4). CD95/Fas/Apo1, tumor necrosis factor receptor (TNFR) and tumor necrosis factor (TNF)-related apoptosis inducing ligand receptors (TRAIL-Rs) are well-defined death receptors (5). TRAIL is a novel type II membrane protein that is highly analogous to members of the TNF super family and CD95/Fas/apo-1 ligand. TRAIL has 2 forms including a membrane protein (mTRAIL) and soluble protein (sTRAIL) (6).

In recent years, it is thought that apoptosis mediated by TRAIL, a member of TNF super family, plays an important role in autoimmune processes. It is well known that TRAIL expression is enhanced in T cells and, as a result, monocyte apoptosis is increased in patients with SLE (7), whereas TRAIL-R1 is increased in ductal cells by IFN-g stimulation and these cells become susceptible to apoptosis in Sjogren's syndrome (8). It has been observed that the soluble TRAIL level is significantly higher in some neoplastic (9), infectious (10), and autoimmune diseases such as SLE (11-13) and ankylosing spondylitis (14,15).

In a rat model of rheumatoid arthritis developed by Song K. et al., it was shown that TRAIL inhibition by recombinant sDR5 led exacerbation of arthritis that was alleviated by injection of recombinant TRAIL to the joint with arthritis (16). This finding has led the emergence of the idea that TRAIL is a potent inhibitor for autoimmune arthritis, promoting studies investigating TRAIL and TRAIL-R in RA (17-20). Although sTRAIL has less potential activity than mTRAIL, it can exert an apoptotic effect similar to mTRAIL. The sTRAIL levels were studied in RA patients and found to be higher than those in patients with osteoarthritis (21).

In this study, it was aimed to determine the plasma sTRAIL level in RA patients and to investigate the relationship between the plasma sTRAIL level and disease activity, disease duration and acute phase proteins.

MATERIAL and METHODS

The study included 19 patients (aged 27-58 years; mean age: 45.4 ± 10.5 years) who presented to the rheumatology outpatient clinic and were diagnosed as RA according to American College of Rheumatology (ACR) classification criteria (1987) between January and June 2009 (22). As control group, 31 patients with primary Sjogren's syndrome (pSS) (aged 18-77 years; mean age: 46.4 ± 13.9 years) according to the American-European Consensus criteria (2002) (23) and 24 healthy individuals (aged 27-60 years; mean age: 39.0 ± 9.3 years) were included. Patients with active or chronic infection, chronic liver or kidney disease, sarcoidosis, or primary immune deficiency were excluded. Complete blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were routinely studied in all patients. Disease activity was calculated by the tender and swollen joint count, ESR value and Disease Activity Score-28 (DAS28) score rated on the Visual Analog Scale (VAS) (24). Disease activity determined by DAS28 was classified as follows: remission, <2.6; mild or moderate active, 2.6-5.1; and severe>5.1.

The study was approved by the Local Ethics Committee. All participants gave written informed consent before participation.

Method

Blood samples drawn were centrifuged at 2500 rpm for 7 minutes in a BECKMAN COULTER Allegra X-22R centrifuge device. The plasma obtained was stored at -80°C. ELISA analyses were performed using the BIOTEK ELx800 device and 50 µl biotinylated anti-TRAIL antibody (Human soluble TRAIL/APO/2L ELISA KIT).

Statistical analysis

Statistical analyses were performed by using SPSS for Windows version 14.0. For categorical variables, the chi-square test was used to compare descriptive statistics and groups. Numerical data were presented as mean ± SD. For comparisons between three groups, the ANOVA test was used to compare parametric variables with a normal distribution whereas the Kruskal-Wallis test was used to compare parametric variables with a skewed distribution. Student's t test and Mann-Whitney U test were used for

binary comparisons. Spearman's or Pearson's correlation test was used to assess relationships among variables. A p value<0.01 was considered to be statistically significant.

RESULTS

The study included 19 patients with RA as the study group and 31 patients with pSS and 24 healthy individuals as the control group. No significant differences were detected between the RA and pSS groups regarding ESR, CRP, hemoglobin, leukocyte count, lymphocyte percentage and platelet count. Table I presents the clinical characteristics of the RA patients.

Mean sTRAIL level (mean ±SD) was 1751±635 pg/mL in the RA group, 1234±525 pg/mL in the pSS group and 1181±304 pg/mL in healthy controls. The level of sTRAIL was significantly higher in the RA group than those in the pSS group and healthy controls (p=0.002). No significant difference was detected between the pSS group and healthy controls (p>0.01).

Table I: Clinical characteristics of RA patients.

	RA (n=19)
Mean DAS-28	3.7 ± 1.6
DAS-28 score (n)	
<2.6	6
2.6 - 5.1	8
>5.1	5
Treatments, n (%)	
Corticosteroid	12 (63.0)
Methotrexate	14 (73.6)
Sulfasalazine	10 (52.6)
Hydroxychloroquine	5 (26.3)
Leflunomide	4 (21.0)
Anti-TNF	6 (31.6)

RA: Rheumatoid arthritis, **DAS-28:** Disease Activity Score-28, **TNF:** Tumor necrosis factor

No correlation was detected between leukocyte and lymphocyte counts, ESR, CRP value and plasma sTRAIL levels of the RA and control groups. sTRAIL levels were found to be 1658.4 pg/mL in one RA patient with neutropenia while 825.6 pg/mL and 904.6 pg/mL in 2 pSS patients with neutropenia, indicating lower sTRAIL levels than the mean value of the relevant groups. There was no patient with lymphopenia in the RA group while there were 2 patients with lymphopenia in the pSS group. The mean plasma sTRAIL level was 904.6 pg/mL (lower than group average) in one of these patients and 1548.3 pg/mL (higher than group average) in the other patient.

When the relationship between sTRAIL and disease activity was assessed, no correlation was detected between the plasma sTRAIL value and mean DAS28 score (p=0.26; r-0.28). When stratified according to DAS28 score, it was found that the mean sTRAIL level was 1925±704 pg/mL in patients with DAS28 score <2.6 but 1690±521 pg/mL and 1739 ± 776 pg/mL in patients with a DAS28 score of 2.6-5.1 and those with a DAS28 score >5.1, respectively. No significant difference was detected in the mean sTRAIL levels between groups (Table II).

Mean sTRAIL level was 1671±433 pg/ml and 1789±709 pg/mL in patients who had received or not received an anti-TNF agent, respectively. Although the mean sTRAIL level was slightly higher in patients who had not received an anti-TNF agent, the difference did not reach statistical significance.

DISCUSSION

The synovium in RA is characterized by synovial cell hyperplasia caused by lymphocyte and macrophage infiltration, monocyte migration and proliferation of fibroblasts and/or decreased macrophage and fibroblast apoptosis (25).

There are some in vivo and in vitro studies that demonstrate the relationship between mTRAIL and sTRAIL, considered to be involved in apoptosis, and autoimmune

Table II: Demographic and clinical characteristics of RA patients according to disease activity score.

DAS28	<2.6	2.6 -5.1	>5.1	p
Age (years)	40.3 ± 10.9	47.0 ± 6.7	46.6 ± 14	NS
Disease duration (months)	128 ± 103.1	113.1 ± 106	154.6 ± 126	NS
ESR (mm/hr)	25 ± 7.5	28.9 ± 17.3	76 ± 2.9	0.001
CRP (mg/dl)	0.60 ± 0.25	0.64 ± 0.82	1.96 ± 1.66	NS
Lymphocyte (mm^3)	2471 ± 790	2217 ± 608	2070 ± 425	NS
sTRAIL (pg/ml)	1925 ± 704	1690 ± 521	1739 ± 776	NS

DAS-28: Disease Activity Score-28, **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein, **sTRAIL:** Soluble tumor necrosis factor (TNF)-related apoptosis inducing ligand

disorders other than cancer. In a study by Yang ZX et al., serum sTRAIL levels were found to be significantly higher in patients with ankylosing spondylitis than those in RA patients and healthy controls but no significant difference was found between the RA group and healthy controls. As a reason for this finding, it is thought that sTRAIL might have largely passed to the synovial fluid and might be associated with apoptosis of synovial fibroblasts (14). In another study, sTRAIL level measured in RA synovial fluid was found to be significantly higher than that measured in osteoarthritis synovial fluid (19). Lub-de Hooge et al. found significantly higher sTRAIL level in SLE patients than those in RA patients and healthy controls but no significant difference between RA patients and healthy controls (11). In contrast to above-mentioned studies, we found that plasma sTRAIL levels were significantly higher in RA patients than those in pSS patients and healthy controls.

Hematological abnormalities such as leucopenia (<4000/mm^3) and lymphopenia (<1000/mm^3) can be seen in some autoimmune diseases such as SLE and pSS. Although there is a limited number of studies, it seems that there may be a relationship between sTRAIL level and these hematological abnormalities (7,11). In our study, no significant correlation was detected between sTRAIL levels and leukocyte and lymphocyte counts in RA and pSS patients. sTRAIL levels in one RA patient and in 2 pSS patients were lower than the mean values of the relevant groups. Lymphopenia was detected in 2 pSS patients; however, the sTRAIL level was lower than the group average in one while higher in the other. Considering the small sample size, it would be inaccurate to draw conclusions about relationship between plasma sTRAIL and leukocyte and lymphocyte counts in this study.

In autoimmune diseases such as RA or SLE, information on disease activity is of important for monitoring the therapeutic process and determining the prognosis. Thus, several disease activity scores (e.g. DAS28) including clinical and laboratory findings have been developed in order to use in the follow-up of such diseases (24). In studies on patients with SLE (11,12) and psoriatic arthritis (26), it was found that sTRAIL levels were higher than in healthy controls but there was no correlation between disease activity and sTRAIL levels. When we assessed the relationships between disease activity and sTRAIL levels, we found no significant correlation between sTRAIL level and the tender and swollen joint count, ESR, CRP and DAS28 score. These results suggest that TRAIL and sTRAIL may be involved in the pathogenesis ofthe disease but amount of sTRAIL secreted into the circulation is not a determinant of disease activity.

The interplay between TRAIL-TRAILR1 receptor, FAS-FAS ligand and TNF-TNFR is strongly related to caspase-8 activation that is involved in the stimulation of apoptotic processes. It is thought that FAS-related apoptotic cell death could be responsible for the synovial hyperplasia in RA, and that the anti-TNF agents exerting their effects by binding soluble TNF-α or binding to TNF receptors can provide clinical benefit by affecting this mechanism (27). However, there are studies indicating that the anti-TNF agents are not effective on lymphocyte and synovial cell apoptosis (28-30). Although there is no controlled study that shows the effects of the anti-TNF agents on the serum sTRAIL level and mTRAIL expression, it was shown that the serum TRAIL level was not affected from infliximab infusion in a study conducted on AS patients receiving infliximab therapy (31). In our study, no significant difference was detected in sTRAIL levels of patients receiving or not receiving anti-TNF therapy. However, this result should be interpreted cautiously due to the smaller number of patients receiving anti-TNF therapy. We think that further studies with larger sample sizes are needed.

In conclusion, we detected that plasma sTRAIL levels were significantly higher in RA patients than those in pSS patients and healthy controls regardless of disease activity. These findings suggest that sTRAIL may have an important role in the pathogenesis of rheumatoid arthritis but has no influence on disease severity.

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