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ORIGINAL ARTICLE

Can serum granulocyte-macrophage colony-stimulating factor and CCL17 levels be a marker of disease activation in spondyloarthritis?

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ABSTRACT

Objectives: The aim of this cross-sectional study was to investigate if serum levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) and CC chemokine ligand 17 (CCL17) correlate with disease activity in axial spondyloarthritis (axSpA) and peripheral spondyloarthritis (pSpA) patients.

Patients and methods: The cross-sectional study was conducted with 80 individuals (48 females, 32 males; mean age: 47.7±11.5 years) between March 2021 and September 2021. Of the participants, 20 were axSpA, 20 were pSpA, and 20 were active rheumatoid arthritis patients, and the remaining 20 were healthy controls. Age, sex, body mass index, disease duration, comorbid diseases, smoking status, medical treatments, C-reactive protein (CRP) level and human leukocyte antigen B27 (HLA-B27) positivity were recorded. Serum GM-CSF and CCL17 levels were analyzed by ELISA. Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP) was used to evaluate the disease activity of patients with spondyloarthritis. Functional status of spondyloarthritis patients was evaluated by Bath Ankylosing Spondylitis Functional Index (BASFI).

Results: While the serum GM-CSF levels were similar in the axSpA and pSpA groups, they were significantly higher than the healthy control group (p=0.021 and p=0.009, respectively). There was a significant correlation between GM-CSF levels and ASDAS-CRP (r=0.545, p=0.013) and BASFI (r=0.546, p=0.013) in the axSpA group. In active axSpA patients, the cut-off value for GM-CSF was 15.89 pg/mL (sensitivity 50%, specificity 100%). No differences were detected in serum CCL17 levels among the groups.

Conclusion: The results suggest that serum GM-CSF levels may be used as a new marker for the evaluation of disease activity in axSpA, and GM-CSF might be a therapeutic target.

Keywords: Biomarkers, chemokine CCL17, GM-CSF, spondyloarthritis.

Spondyloarthritis (SpA) is classified as axial or peripheral according to the predominant clinical manifestations. While axial SpA (axSpA) manifests by sacroiliac joint and spine involvement, peripheral SpA (pSpA) is characterized by peripheral joint involvement, dactylitis, and enthesitis.[1] Enthesis areas are considered to be the starting point of SpA. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is one of the key cytokines of inflammation and new bone formation at enthesis sites.[2] CD4+ and CD8+ T lymphocytes producing GM-CSF were found in the blood and synovial fluid of patients with axSpA.[3] In addition, plasma GM-CSF levels were found to be high in inflammatory diseases, such as active rheumatoid arthritis (RA) and systemic lupus erythematosus; however, there was no such difference between the healthy subjects and the ankylosing spondylitis (AS) patients.[4,5]

Chemokine (C-C motif) ligand 17 (CCL17), also named TARC (thymus- and activation-regulated chemokine), is a proinflammatory chemokine whose production is increased by GM-CSF stimulation. Tumor necrosis factor (TNF) and

GM-CSF cause inflammatory pain via the CCL17. In recent studies, serum CCL17 levels have been found to be high in inflammatory diseases, such as AS and RA.[4,5]

Since frequently used acute phase reactants, such as erythrocyte sedimentation rate and C-reactive protein (CRP), often do not correlate with disease activity in SpA, there is a need for possible new laboratory markers. Serum GM-CSF and CCL17 levels were previously evaluated only in axSpA and not in pSpA. Hence, the aim of this study was to examine the correlation of serum GM-CSF and CCL17 levels with disease activity in patients with axSpA and pSpA.

PATIENTS AND METHODS

The cross-sectional study was conducted with 80 individuals (48 females, 32 males; mean age: 47.7±11.5 years). Of the participants, 20 were axSpA, 20 were pSpA, and 20 were active RA patients who were followed up in the rheumatology outpatient clinic of the Gazi University Medical Faculty Hospital between March 2021 and September 2021, and the remaining 20 individuals were healthy controls (HCs). SpA patients met the Assessment of Spondyloarthritis international Society (ASAS) criteria for predominantly axial and predominantly peripheral SpA.[1,6] Patients with RA fulfilled the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria.[7] Patients with active RA with a Disease activity score in 28 joints (DAS28) ≥3.2 were included as a positive control group, and healthy individuals were included as the negative control group.[8] Patients with acute infection, malignancy, and concomitant inflammatory rheumatic diseases other than RA, pregnant or breastfeeding women, and those under 18 years of age were excluded from the study.

Clinical and demographic data such as age, sex, smoking status, body mass index, comorbid diseases, disease duration, and medical treatments were recorded. CRP and, when available, human leukocyte antigen B27 (HLA-B27) results were recorded. The disease activity of SpA patients was evaluated with Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP), and the functional status was evaluated with Bath Ankylosing Spondylitis Functional Index (BASFI).[9,10] An ASDAS-CRP ≥1.3 was interpreted as active disease.

Blood samples were taken into test tubes with serum separators for the measurement of serum CCL17 and GM-CSF levels. After 30 min at room temperature, the blood was centrifuged for 10 min at 3,000 rpm. Sera were placed in new Eppendorf tubes and stored at –80°C until analysis.

Commercial ELISA (enzyme-linked immunosorbent assay) kits were used in accordance with the manufacturers' instructions. The assays were performed in 96-well plates, and the results were presented as picograms per milliliter. The collected samples from each of the groups were analyzed on the same day on two ELISA plates. Washing procedures were performed with a BioTek brand washing device (ELx50 Bioelisa Washer; BioTek Instruments, Inc., Winooski, VT, USA), and absorbance readings were performed with a BioTek brand reader (ELx800 UV Universal Microplate Reader; BioTek Instruments, Inc., Winooski, VT, USA).

The ELISA kits used were USCN Granulocyte Macrophage Colony Stimulating Factor 2 and USCN Thymus Activation Regulated Chemokine (Wuhan USCN Business Co., Ltd., Wuhan, China). Intra-assay coefficient of variation was <8% and inter-assay coefficient of variation was <10% for both kits.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Compliance of numerical data with normal distribution was evaluated by visual (histogram and detrended Q-Q charts) and analytical (Kolmogorov-Smirnov test) methods. Normally distributed numerical data were presented as mean ± standard deviation, and nonnormally distributed numerical data were presented as median (min-max). Categorical variables were presented as numbers and percentages. The relations between normally distributed numerical data were determined by the independent samples t-test, one-way analysis of variance, multivariate analysis of variance, and Pearson correlation coefficient. Relations between nonnormally distributed numerical

data were determined by the Mann-Whitney U test, Kruskal-Wallis analysis of variance, and Spearman correlation coefficient. Relationships between categorical data were evaluated with the chi-square test and Fisher exact chi-square test. Tukey test and Bonferroni correction were performed during the analyses to determine the group difference. Receiver operating characteristic (ROC) analysis was performed using the ASDAS-CRP activity (inactive-active) variable for the optimal GM-CSF cut-off value. The cut-off value was determined from the maximized sum of sensitivity and specificity. The level of statistical significance was set at $p<0.05$.

RESULTS

The clinical and demographic data of the study population are shown in Table 1. Group characteristics differed in mean age (higher in RA than in axSpA; 54.15±9.05 *vs.* 44.95±10.97), sex (more males in axSpA than in pSpA and RA; 16 *vs.* 7 and 1, respectively), body mass index (higher in RA than in axSpA; 30.93±3.24 *vs.* 26.90±4.51), disease duration (longer in axSpA than in pSpA; 144 months [3-408] *vs.* 36 months [2-384]), psoriasis (more frequent in pSpA than in the other three groups; 9 *vs.* 1 [axSpA], 0 [RA], 0 [HC]), smoking (more frequent in axSpA than in RA; 12 *vs.* 1), bDMARD (biological disease-modifying anti rheumatic drug) use (more frequent in axSpA than in pSpA; pSpA group, two patients on anti-interleukin (IL)-17; axSpA group, 11 patients on anti-TNF; RA group, three patients on anti TNF, two patients on anti-CD20), CRP >5 mg/L (higher in the other three groups compared to HCs) and ASDAS-CRP ≥1.3 (more frequent in pSpA than in axSpA; 18 *vs.* 12). While the serum GM-CSF levels were similar in the axSpA and pSpA groups, they were significantly higher than in the HC group ($p=0.021$ and $p=0.009$, respectively). No differences were detected in serum CCL17 levels

Table 1. Demographic and clinical data of patients and healthy controls

Characteristics	pSpA group (n=20)	axSpA group (n=20)	RA group (n=20)	Healthy controls (n=20)	*p*
Age (year) (mean±SD)	45.95±13.37	44.95±10.97	54.15±9.05	45.70±10.44	**0.033**
Sex Male n (%)	7 (35)	16 (80)	1 (5)	8 (40)	**0.001**
BMI (mean±SD)	28.66±4.72	26.90±4.51	30.93±3.24	28.80±3.77	**0.027**
Disease duration (month) median (min-max)	36 (2-384)	144 (3-408)	108 (4-324)	-	**0.008**
Psoriasis n (%)	9 (45)	1 (5)	0 (0)	0 (0)	**0.001**
IBD n (%)	1 (5)	1 (5)	0 (0)	0 (0)	1.000
Uveitis n (%)	1 (5)	1 (5)	0 (0)	0 (0)	1.000
GM-CSF (pg/mL) median (min-max)	14.58 (10.89-19.84)	14.57 (10.89-21.42)	13.53 (9.84-33.52)	11.16 (8.26-45.11)	**0.006**
CCL17 (pg/mL) median (min-max)	620.51 (349.38-1495.29)	812.33 (163.68-1208.33)	707.17 (467.05-2185.43)	606.48 (219.44-939.04)	0.046
Smoking status (ever) n (%)	5 (25)	12 (60)	1 (5)	6 (30)	**0.009**
Current bDMARDs n (%)	2 (10)	11 (55)	5 (25)	0 (0)	**0.001**
CRP (>5 mg/L) n (%)	14 (70)	11 (55)	15 (75)	0 (0)	**0.001**
HLA B27 positivity n (%)	8 (72.7)	9 (75)	-	-	1,000
ASDAS-CRP (≥1.3) n (%)	18 (90)	12 (60)	-	-	**0.028**
BASFI median (min-max)	1.70 (0-8.90)	0.55 (0-5.00)	-	-	0.055

pSpA: Peripheral spondyloarthritis; axSpA: Axial spondyloarthritis; RA: Rheumatoid arthritis; BMI: Body mass index; IBD: Inflammatory bowel disease; GM-CSF: Granulocyte-macrophage colony-stimulating factor; CCL17: Chemokine (C-C motif) ligand 17 (CCL17); bDMARDs, biological disease-modifying antirheumatic drugs; CRP: C-reactive protein; HLA-B27: Human leucocyte antigen B27; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index.

Table 2. Relationship of GM-CSF and CCL17 levels with clinical and demographic data

	pSpA						axSpA					
	GM-CSF			CCL17			GM-CSF			CCL17		
	Median	Min-Max	*p*	Median	Min-Max	*p*	Median	Min-Max	*p*	Median	Min-Max	*p*
Sex			0.282			0.251			0.538			0.299
Male	13.53	11.95-17.21		757.95	357.05-1495.29		14.84	10.89-21.42		824.94	163.68-1208.33	
Female	15.11	10.89-19.84		548.96	349.38-1055.37		14.05	13.00-14.57		730.03	474.73-856.42	
Psoriasis			0.939			0.342			0.099			0.795
Yes	15.11	10.89-19.84		592.43	349.38-1055.37		21.42	21.42-21.42		757.95	757.95-757.95	
No	14.05	11.95-17.21		648.60	413.31-1495.29		14.57	10.89-19.84		821.16	163.68-1208.33	
Smoking			0.483			0.343			0.447			0.188
Yes	16.16	10.89-17.21		661.35	357.05-1055.37		14.58	10.89-21.42		873.98	420.98-1208.33	
No	15.11	12.47-19.84		568.14	349.38-961.45		14.57	11.94-16.15		747.80	163.68-1038.15	
bDMARDs			0.526			0.450			0.209			0.518
Yes	15.11	10.89-19.84		589.87	349.38-1495.29		14.57	10.89-21.42		821.16	474.73-1128.66	
No	13.79	13.53-14.05		747.81	737.66-757.95		13.52	11.42-18.78		712.26	163.68-1208.33	
HLA-B27			0.348			0.683			0.926			0.405
Positive	13.26	11.95-17.21		662.49	357.05-961.45		14.05	10.89-19.84		821.16	163.68-1128.66	
Negative	15.63	14.05-17.21		648.60	441.46-1495.29		14.57	11.42-16.15		747.80	420.98-828.72	
ASDAS-CRP			0.751			1.000			**0.027**			0.643
Inactive	14.32	13.53-15.11		643.22	528.49-757.95		12.73	10.89-15.63		856.36	420.98-1208.33	
Active	14.58	10.89-19.84		620.51	349.38-1495.29		15.36	12.47-21.42		780.72	163.68-1177.07	

GM-CSF: Granulocyte-macrophage colony-stimulating factor; CCL17: C-C motif chemokine ligand 17; pSpA: Peripheral spondyloarthritis; axSpA: Axial spondyloarthritis; bDMARDs: Biological disease-modifying anti-rheumatic drugs; HLA-B27: Human leukocyte antigen B27; ASDAS: Ankylosing Spondylitis Disease Activity Score.

Table 3. Correlation of GM-CSF and CCL17 levels with clinical and demographic data

	pSpA		axSpA	
Characteristics	GMCSF	CCL17	GMCSF	CCL17
Age				
r	-0.213	0.474	-0.104	0.084
p	0.368	0.055	0.663	0.724
BMI				
r	-0.187	-0.108	-0.120	-0.415
p	0.430	0.650	0.613	0.069
Disease duration				
r	0.060	-0.012	-0.020	-0.370
p	0.802	0.960	0.934	0.108
CRP				
r	-0.076	-0.144	0.006	0.323
p	0.751	0.544	0.979	0.165
ASDAS-CRP				
r	0.088	-0.014	0.545	0.007
p	0.713	0.955	**0.013**	0.977
BASFI				
r	-0.117	0.186	0.546	-0.143
p	0.623	0.433	**0.013**	0.548

pSpA: Peripheral spondyloarthritis; axSpA: Axial spondyloarthritis; GM-CSF: Granulocyte-macrophage colony-stimulating factor; CCL17: C-C motif chemokine ligand 17; BMI: Body mass index; CRP: C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; r: Pearson or spearman's correlation test.

among the groups.

When the relationship between GM-CSF and CCL17 levels, as well as clinical and demographic data, were evaluated, there was a statistically significant relevance between active disease (ASDAS-CRP ≥1.3) and GM-CSF levels only in the axSpA group (p=0.027) (Table 2). There was a significant correlation between GM-CSF levels and ASDAS-CRP (r=0.545, p=0.013) and BASFI (r=0.546, p=0.013) in the axSpA group (Table 3).

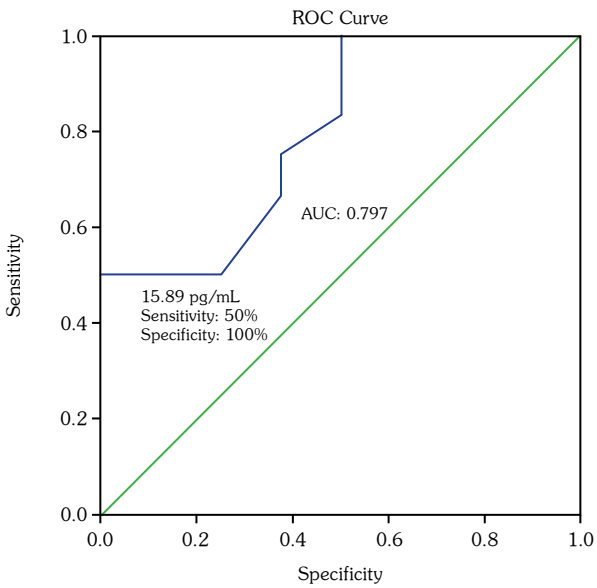

Figure 1. Receiver operating characteristic (ROC) curve for GM-CSF measurements in active axSpA patients.

ROC: Receiver operating characteristic; AUC: Area under the curve; GM-CSF: Granulocyte-macrophage colony-stimulating factor; axSpA: Axial spondyloarthritis.

In active axSpA patients, the cut-off value for GM-CSF was 15.89 pg/mL (sensitivity 50%, specificity 100%, positive predictive value 100%, and negative predictive value 35.71%). The area under the curve in ROC analysis was 79.7% (95% confidence interval 59.6-99.8%), with a standard error of 10.3% (Figure 1).

DISCUSSION

In our study, serum GM-CSF levels were significantly higher in the axSpA and pSpA groups compared to HCs, and it was associated with disease activity and functional status only in the axSpA group. According to study findings, GM-CSF can be used as a disease activation biomarker in axSpA and also might be a therapeutic target. There was no difference

in serum CCL17 levels in pairwise comparisons between groups. Serum CCL17 levels were higher in the axSpA group than in the pSpA group. However, this difference was not statistically significant. Furthermore, serum CCL17 levels were not associated with disease activity. Previous studies have shown that the GM-CSF/CCL17 pathway plays an important role in AS;[3-5] however, to the best of our knowledge, previous studies did not examine this pathway in pSpA patients, and its association with disease activity was not evaluated. This study is the first to evaluate serum levels of GM-CSF and CCL17 according to the SpA type and its relationship with disease activation. Previously, Al-Mossawi et al.[3] have demonstrated that GM-CSF-producing lymphocytes are abundant in the blood and the synovial fluid of the patients with axSpA, and the GM-CSF/CCL17 pathway is important in the pathogenesis. While there are studies in the literature showing that serum GM-CSF levels are high in active RA, there are also studies, such as our study, in which no difference was detected in serum GM-CSF levels. Since the local effects of GM-CSF in synovial tissue are predominant in RA, serum GM-CSF levels may not have differed in the RA group.[4-5,11-13]

Ankylosing Spondylitis Disease Activity Score (ASDAS) is very specific and sensitive for detecting patients with high disease activity and low functional status. BASFI and ASDAS are strongly correlated when assessing AS severity.[14] In our study, we observed that the serum GM-CSF level was significantly correlated with disease activity and BASFI in axSpA patients.

In our study, the cut-off serum GM-CSF value by ROC analysis for active disease in axSpA was 15.89 pg/mL, with 100% specificity. The fact that the specificity is 100% suggests that measuring serum GM-CSF levels can be a prominent option in the evaluation of disease activity in axSpA.

The CCL17 levels are high in diseases where T helper 2 cells are dominant, such as atopic dermatitis.[15] Studies on serum CCL17 levels in AS have conflicting results. While Duftner et al.[16] showed no difference in CCL17 levels between AS and HCs, Shi et al.[5] and Wang et al.[17] found that CCL17 levels were higher in AS compared to HCs. Wang et al.,[17] however, found no correlation between CCL 17 levels and disease activity indices in AS. In our study, we did not detect any difference in serum CCL17 levels among the groups. Since we divided the patients into two groups, axSpA and pSpA, in our study, the relatively small number of patients in the groups may not have been enough to reveal the difference in serum CCL17 levels among the groups. Additionally, the reason for not achieving a significant difference in CCL levels between active and inactive pSpA patients may be the imbalance in the number of patients between the comparison arms (n=2/18). Previous studies have shown that anti-TNF therapy reduces serum CCL17 levels in AS.[5,16] In our study, there were more patients on anti-TNF therapy in the axSpA group than in the pSpA and RA groups (11 *vs.* 0 and 3, respectively), which may have resulted in finding reduced serum CCL17 levels in axSpA. This effect may have prevented the difference in the axSpA group compared to the other groups. Although not statistically significant, serum CCL17 levels were higher in the axSpA group than in the pSpA group. This finding suggests that different pathways may be present in the formation of SpA types, as in the lipopolysaccharide-dependent and -independent models described by Shi et al.[5]

In our study, the disease duration was significantly longer in axSpA patients than in the pSpA group. In an animal experiment, it was shown that TNF is influential only in the early stages of arthritic pain and disease progression and that CCL17 is the main active cytokine throughout the entire disease course.[18] Considering that CCL17 is more prominent in chronic conditions, although not statistically significant, the disease duration might have been influential for the numerical difference in serum CCL17.

This study has some limitations. The sample size of the study groups was relatively small. Serial measurements could not be performed before and after medical treatment. The groups were not homogenous for disease duration, sex, age, and medical treatments. Due to the limited budget of the research, this study was conducted with 80 ELISA kits. Consequently, the sample could not be calculated size before the study. However, post hoc power analysis of the study was 60%.

In conclusion, serum GM-CSF levels were high in both axSpA and pSpA and were correlated with disease activity only in axSpA. Measurement

of serum GM-CSF levels can be a crucial option in the evaluation of disease activity in axSpA. Moreover, GM-CSF might be a therapeutic target.

Ethics Committee Approval: The study protocol was approved by the Gazi University Clinical Research Ethics Committee (date: 19.04.2021, no: 2021/409). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Were responsible for data acquisition: R.K.U., A.K., S.B., İ.M.Ç., Z.G., A.S.D., F.N.G.; Analyzed the data: E.N.Y.Ö.; Wrote the manuscript: R.K.U., S.B., İ.M.Ç., Z.G., A.S.D., F.N.G.; All authors critically revised the manuscript and approved the final version. All authors were responsible for the study design.

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