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Original Article

The association of anti-CD74 antibody with spondyloarthropathies

Seda Çolak[1], Tahsin Murat Turgay[2], Orhan Küçükşahin[2], Mustafa Türker Duman[3], Hülya Çetinkaya[4], Murat Toruner[4]

Abstract

Objective: The etiopathogenesis of spondyloarthropathies (SpA) is still unclear. Recently, anti-CD74 antibody has been suspected to play a role in SpA etiopathogenesis. This study aimed to examine the levels of anti-CD74 antibody in patients with SpA and investigate their association with disease activity.

Methods: This study was conducted using data from patients who were treated at the departments of rheumatology and gastroenterology between June 2013 and November 2013. The demographic and clinical characteristics of the participants and their serum IgG-type antibodies against anti-CD74 were analyzed.

Results: We analyzed 111 patients with ankylosing spondylitis (AS), 108 patients with inflammatory bowel disease (IBD), and 101 healthy controls. The rate of human leukocyte antigen–B27 positivity was 86.5% in patients with AS and 21.3% in patients with IBD. The mean levels of anti-CD74 antibodies in the AS, IBD, and control groups were 6.99±3.24 ng/mL, 6.25±3.34 ng/mL, and 7.83±4.72 ng/mL, respectively. Anti-CD74 levels were higher in healthy controls than in patients with IBD ($P = .009$). There was no significant difference in anti-CD74 levels between the AS and IBD groups and the AS and control groups. In addition, there was no correlation between anti-CD74 levels and disease activity.

Conclusion: This study could not find an association between anti-CD74 levels and SpA in Turkish patients.

Keywords: Anti-CD74 autoantibody, diagnosis, spondyloarthropathy

ORCID iDs of the authors:
S.Ç. 0000-0002-5703-6739;
T.M.T. 0000-0001-5302-4485;
O.K. 0000-0003-4530-2304;
M.T.D. 0000-0003-0093-2396;
H.Ç. 0000-0001-5788-1011;
M.T. 0000-0001-8873-7426.

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[1] Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey
[2] Department of Rheumatology, Ankara University School of Medicine, Ankara, Turkey
[3] Department of Immunology and Allergy Diseases, Ankara University School of Medicine, Ankara, Turkey
[4] Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey

Address for Correspondence: Seda Çolak; Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey

E-mail: sedayurumez@hotmail.com

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Introduction

Ankylosing spondylitis (AS) is a prototype of spondyloarthropathies (SpA), which are a group of chronic inflammatory arthritic diseases that may affect the spine and peripheral joints, with extra-articular manifestations. Another subtype of SpA is enteropathic arthritis, which is related to inflammatory bowel disease (IBD). IBD is known to be a chronic inflammatory disease of the gastrointestinal system that is marked by periods of remission and flare episodes.[1,2] Crohn's disease (CD) and ulcerative colitis (UC) are classified under IBD. Musculoskeletal system involvement is the most frequently seen extra-intestinal manifestation of IBD and may affect 2%-46% of patients.[3] The prevalence of AS and SpA in Turkey was reported to be 0.49% and 1.05%, respectively.[4,5]

Currently, the delay in diagnosis is one of the most important obstacles in the treatment of SpA. There are no sensitive or specific biomarkers that can be used for early diagnosis of SpA.[6] The human leukocyte antigen-B27 (HLA-B27), which is a surface antigen found in major histocompatibility complex (MHC) class I, is known to be the most sensitive biomarker. However, it can be seen in healthy populations at a rate of 10%, and its frequency varies across geographical regions and ethnic groups.[7,8] Thus, new biomarkers are needed for early diagnosis and to monitor the treatment response and prognosis of patients with SpA. In recent studies, autoantibodies against CD74 (anti-CD74) have been implicated in the pathogenesis of SpA.[9] CD74 is a transmembrane glycoprotein. It is also known as the gamma chain or invariant chain of MHC class II, and it inhibits the premature binding of peptides to MHC class II. It has 2 extracellular parts, thyroglobulin type 1 and *class II–associated invariant chain peptide* (CLIP).[10,11] The binding of CD74 and macrophage migration inhibitory factor activates nuclear factor kappa B, which leads to cell differentiation. CD74 plays a role in antigen presen-

tation, release of pro-inflammatory cytokines, and differentiation of B cells. Thus, anti-CD74 may be a novel biomarker for the diagnosis of SpA.[12] Further studies are needed as data regarding the role of anti-CD74 in the pathogenesis of SpA are scarce and inconsistent. This study aimed to assess whether anti-CD74 can be used as a biomarker for patients with SpA, to evaluate the levels of anti-CD74 in patients with AS and IBD, and to examine the association between anti-CD74 and disease activity.

Methods

Patients and healthy controls

A total of 219 patients (111 with AS and 108 with IBD) who were treated in the departments of rheumatology and gastroenterology between June 2013 and November 2013 were included in this cross-sectional study. Of note, 101 consecutive healthy individuals who had no positive family history for SpA and who agreed to participate in the study were included as the control group. The study was approved by Ankara University, School of Medicine Local Ethical Committee (Approval date: June 24, 2013; Approval Number: 10-404-13) and was conducted in accordance with the principles of the Declaration of Helsinki. The exclusion criteria of the study were age <18 years, acute or chronic infection, malignancy, and pregnancy or up to 6 months postpartum. Patients with IBD were in remission. The control group included healthy individuals with no history of SpA in their family. Both verbal and written informed consents were obtained from all participants.

Diagnostic instruments

The Modified New York criteria and the Assessment of Spondyloarthritis International Society criteria were used to assess axial SpA.[13,14] The European Spondyloarthropathy Study Group criteria were used to diagnose enteropathic arthritis.[1]

Detection of anti-CD74 levels

The sera of participants were stored at -80°C for at least 6 months before the study. IgG-type autoantibodies against CD74 (Cusabio®, China) were detected using enzyme-linked immunosorbent assay (ELISA). The microplates in the kit were read spectrophotometrically at 450 nm in the EL 312 Microplate ELISA reader (BIOTEK, Inc, Missouri, Texas, USA). The optic density readings were converted to ng/mL using semi-logarithmic paper (Cusabio®, China). The minimum detectable value of anti-CD74 was 0.22 ng/mL.

Assessment of disease activity

The erythrocyte sedimentation rate and C-reactive protein (CRP) levels of all participants were measured. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), and Ankylosing Spondylitis Disease Activity Score (ASDAS) were used to evaluate spondyloarthropathy disease activity.[15-18]

Statistical analysis

Differences between the groups were assessed with a parametric test for normally distributed data (ASDAS and age) and non-parametric tests for non-normally distributed data. The chi-square test, Fisher's exact test, Mann-Whitney U test, and Spearman's correlation coefficient were used to examine correlations. *Post hoc comparisons were conducted using t-tests with the Bonferroni correction.* The SPSS version 15 (SPSS Inc.; Chicago, IL, USA) was used for analyses, and $P < .05$ was accepted as the level of statistical significance.

Results

A total of 219 patients (111 [50.7%] with AS and 108 [49.3%] with IBD) and 101 healthy controls were included in this study. In the IBD group, 67 patients (62%) were diagnosed with CD, whereas 41 (38%) were diagnosed with UC. The demographic and clinical characteristics of participants are shown in Table 1. In the AS group, the number of male patients was significantly higher than that in the IBD and control groups ($P < .05$). The mean age of individuals in the control group was lower than that of patients in the AS and IBD groups ($P < .05$). Of the 23 patients in the IBD group who were HLA-B27-positive, 15 (13.9%) and 8 (7.4%) had CD and UC diagnoses, respectively. Moreover, 7 (6.3%) patients with AS and 5 (12.8%) patients with enteropathic arthritis were in the first year of the disease. Between-group comparisons of disease activity revealed that BASMI scores were higher in patients with AS than in those with IBD ($P < .05$), as seen in Table 2.

Among those with AS, axial involvement was observed in 95 (85.6%) patients, axial and peripheral involvement in 8 (7.2%) patients, and non-radiographic axial SpA in 8 (7.2%) patients. Moreover, 68 (63%) patients with IBD had no musculoskeletal involvement. However, musculoskeletal involvement was detected in 40 patients (37%) with IBD. More specifically, axial involvement was seen in 11 (10.2%) patients with IBD, peripheral involvement in 5 (4.6%) patients, axial and peripheral involvement in 5 (4.6%) patients, and non-radiographic axial SpA in 19 (17.6%) patients. Peripheral involvement was higher among patients with IBD, but the difference was not statistically significant ($P = .06$).

There was a significant main effect of CD74 mean scores ($F [3, 142]=3.280$, $P = .021$). Post hoc comparisons conducted with the Bonferroni corrected t-tests indicated that the mean score for enteropathic arthritis (5.79±3.28 ng/mL) was significantly different from that of the control group (7.83±4.73 ng/mL). However, no significant differences were observed in other groups.

Table 1. Demographic and clinical characteristics of the study groups.

	AS (n=111)	IBD (n=108)	HC (n=101)
Women/men, n (%)	23 (20.7)/ 88 (79.3)[a]	52 (48.1)/ 56 (51.9)	55 (54.5)/ 46 (45.5)
Age, mean±SD (minimum-maximum)	43.17±11.96 (18-76)	39.5±11.5 (19-70)	32.5±8.2[a] (18-57)
Smokers, n (%)	46 (41.4)[a]	31 (28.7)	
HLA-B27 positivity, n (%)	96 (86.5)[a]	23 (21.3)	
Anterior uveitis, n (%)	30 (27)[a]	2 (1.9)	
SpA in the first-degree relatives, n (%)	54 (48.6)[a]	24 (22.2)	
Anti-TNF-α use, n (%)	82 (62.1)	50 (37.9)	

AS: ankylosing spondylitis; IBD: inflammatory bowel disease; HC: healthy controls; SpA: spondyloarthropathy; TNF: tumor necrosis factor; HLA-B27: human leukocyte antigen-B27; SD: standard deviation.
[a]$P < .05$.

Main Points

- Etiopathogenesis of spondyloarthropathies is not well known.
- In a study conducted in Turkish patients, anti-CD74 was not found to be associated with spodyloarthropathy.
- The role of CD74 in the pathogenesis of spondyloarthropathy is still inconsistent.

Table 2. Disease activity evaluation of patients with spondyloarthritis.

	Ankylosing spondylitis	Enteropathic arthritis
BASDAI, 0-10 nVAS	3.27±1.84	2.53±1.71
BASFI, 0-10 nVAS	1.92±1.41	1.24±1.28
BASMI, 0-10	4.55±2.51[a]	1.69±2.46
ASDAS-CRP	1.94±0.77	1.79±0.77
CRP, mg/dL	12.09±17.27	10.77±14.99
ESR, mm/h	23.74±20.49	21.54±21.53

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analog scale.
[a]$P < .05$.
Variables are shown in mean±standard deviation.

Table 3. The correlation between anti-CD74 levels and disease activity.

	Anti-CD74 levels	
Disease activity scores	r	*P*
BASDAI	0.060	.472
BASFI	-0.049	.559
BASMI	0.116	.167
ASDAS-CRP	-0.122	.143

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein.

The levels of anti-CD74 were 6.99±3.24 ng/mL in the AS group, 6.52±3.38 ng/mL in the IBD group without arthritis, 5.79±3.28 ng/mL in the enteropathic arthritis group, and 7.83±4.73 ng/mL in the control group. The levels of anti-CD74 in the control group were significantly higher than those in the IBD group ($P = .009$). However, no other statistically significant between-group differences in anti-CD74 levels were found.

Anti-CD74 was not significantly higher in patients with HLA-B27 positivity ($P = .648$). There was no relationship between BASFI, BASDAI, BASMI, and ASDAS-CRP scores and levels of CD74 ($P = .559$, $P = .472$, $P = .167$, and $P = .143$, respectively) (Table 3). Similarly, no significant relationship was found between the levels of CRP and anti-CD74 ($P = .143$).

Discussion

To the best of our knowledge, this is the first study to compare the anti-CD74 levels in patients with AS and IBD and healthy individuals and to evaluate the association between levels of anti-CD74 and disease activity in Turkey. In this study, HLA-B27 positivity was found to be 86.5% in the AS group. This value is slightly higher than those reported in previous studies, which showed positivity rates of 70%-80%.[5,19]

In this study, anti-CD74 levels were not higher in patients with SpA than in healthy individuals. Baraliakos et al[20] have shown that anti-CD74 antibodies against the CLIP part of the protein were detected in 85.1% of patients with axial SpA and 7.8% patients with no SpA. They have also reported that antibodies against CLIP were sensitive and specific in patients with axial SpA. Baerlecken and Nothdorft[21] have found that 69% of patients with axial SpA and 65% patients with peripheral SpA had positive autoantibodies against CD74. In the same study, anti-CD74 positivity was detected in only 5% of healthy controls. Riechers et al[22] have assessed the IgA and IgG autoantibodies against CD74 in patients with early axial SpA and found the sensitivity of IgA and IgG to be 47% and 17%, respectively. The positive likelihood ratios of IgA anti-CD74 antibodies, IgG anti-CD74 antibodies, and HLA-B27 were reported to be 10, 3.6, and 8.1 respectively. A recent study has found similar results that support the conclusion that anti-CD74 may be a marker for early axial SpA.[23] However, a recent study from China has indicated that anti-CD74 is not a good biomarker for SpA. They found no correlation between anti-CD74 levels and disease activity in patients with SpA.[24] There was also no association between disease activity and anti-CD74 levels in this study. Similarly, Baraliakos et al[20] and Baerlecken and Nothdorft[21] have found no association between disease activity and clinical characteristics of patients.

Anti-CD74 levels may decrease during the course of the disease.[25] A recent study has shown that in the first year of the disease, anti-CD74 was present in 97% of patients.[21] In contrast, Baraliakos et al[20] have shown that there was no difference between the early and advanced stages of the disease in terms of the presence of autoantibodies against CLIP. According to another study, levels of both IgG and IgA autoantibodies against CD74 were higher in patients with AS than in healthy controls, but there was no statistically significant difference in the early stages of the disease. In this study, only 7 (6.3%) patients with AS were in the first year of the disease.[26]

In this study, more patients in the AS group were treated with anti-TNF-α drugs than in the IBD group. It is not clear whether anti-TNF-α treatment influences the levels of anti-CD74, but Baerlecken and Nothdorft[21] have found no association between the treatment modality and autoantibody levels.

Some limitations of this study should be noted. First, only the IgG anti-CD74 antibody was investigated. The diversity of methods used to conduct laboratory analyses may partly explain why the results that are different from those of this study have been reported. Second, the ELISA kit used in this study evaluates soluble anti-CD74 levels that may degrade after prolonged exposure of the sera. Whole anti-CD74 levels should be measured to achieve higher test sensitivity. Finally, recent studies have investigated that anti-CD74 is more effective in the early stages of the disease. There were an insufficient number of patients in the first year of the disease. The number of patients in the early stages of the disease should be increased in further studies.

Based on the results of this study, we conclude that the levels of autoantibodies against CD74 are not useful in the diagnosis and measurement of disease activity in patients with SpA. New biomarkers are required for the diagnosis of SpA. Further studies should be conducted in different geographical regions and with different ethnic groups to clarify the role of anti-CD74 in the pathogenesis of SpA.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ankara University School of Medicine Ethical Committee (Approval Date: June 24, 2013; Approval Number: 10-404-13).

Informed Consent: Written and verbal informed consent was obtained from the individuals who participated in this study.

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