Original paper

Reumatologia 2025; 63, 4: 216–221
DOI: https://doi.org/10.5114/reum/203129

Serum levels of tumor necrosis factor-like cytokine 1A and its receptors, death receptor 3 and decoy receptor 3, in patients with spondyloarthropathies: preliminary results from a cross-sectional study

Emilia Anna Frąckiel[1], Adrianna Błahuszewska-Omyła[1], Paweł Bielecki[2], Magdalena Bagrowska[1], Natalia Szymańska[1], Krzysztof Kowal[3], Otylia Kowal-Bielecka[1]

[1]Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Poland
[2]Department of Otolaryngology, Medical University of Bialystok, Poland
[3]Department of Experimental Allergology and Immunology, Medical University of Bialystok, Poland

Abstract

Introduction: Tumor necrosis factor (TNF)-like cytokine 1A (TL1A) is a member of the TNF superfamily of cytokines, involved in regulation of the immune and inflammatory response. Recently, therapies aimed at blockade of the TL1A pathway have shown benefit in the treatment of inflammatory bowel diseases (IBDs). However, very little is known regarding activation of the TL1A axis in spondyloarthropathies (SpA), which are clinically and pathogenetically linked to IBDs. Our study investigated soluble forms of TL1A and its receptors, death receptor 3 (DR3) and decoy receptor 3 (DcR3), in the serum of patients with SpA, and evaluated potential associations between concentrations of the investigated molecules and clinical features of SpA.

Material and methods: Tumor necrosis factor-like cytokine 1A, DR3, and DcR3 concentrations were measured (using enzyme linked immunosorbent assay – ELISA) in the serum of 82 patients with SpA and 36 healthy controls.

Results: We found no significant difference in serum concentrations of TL1A or DR3 between the study and the control groups. However, we observed a significantly higher concentration of DcR3 (median [min.–max.]: 292.31 [93.241–13,862.10] pg/ml) in patients with SpA than in the controls (median [min.–max.]: 126.73 [10.68–1,482.74] pg/ml; $p = 0.003$). The DR/DcR ratio was significantly lower in patients with SpA (median [min.–max.]: 4.05 [0.14–235.39]) than in the controls (17.22 [0.00–750.66]; $p = 0.002$). Moreover, there were weak but significant correlations between serum concentrations of DcR and TL1A (Spearman's rho: 0.28, $p < 0.05$) and between DcR3 and C-reactive protein as well as erythrocyte sedimentation rate values (Spearman's rho: 0.25 and 0.24 respectively, $p < 0.05$ for both) in patients with SpA.

Conclusions: The results of our study indicate that the TL1A/DR3/DcR3 axis is activated in patients with SpA and may represent a new target for therapies in this group of diseases. Further studies are needed to confirm our data.

Key words: TL1A, DR3, spondyloarthropathies, DcR3.

Introduction

Spondyloarthropathies (SpA) are a group of chronic, inflammatory musculoskeletal diseases which includes ankylosing spondylitis, currently referred to as "radiographic form of axial spondyloarthritis" (r-axSpA) psoriatic arthritis (PsA), non-radiographic axial spondyloarthritis (nr-axSpA), and peripheral spondyloarthritis (pSpA), which also covers patients with reactive arthritis, inflam-

Address for correspondence
Emilia Anna Frąckiel, Department of Rheumatology and Internal Medicine, Medical University of Bialystok, 24A M. Sklodowskiej-Curie St., 15-276 Bialystok, Poland, e-mail: emilia.frackiel@sd.umb.edu.pl
Submitted: 15.11.2024; **Accepted:** 19.03.2025

matory bowel disease-associated SpA and the peripheral form of PsA [1–4].

According to various estimates, SpA affects approximately 0.5–1.9% of the population and may cause significant disability [1]. A very diverse clinical picture characterizes the group of SpA. In addition to several manifestations of the musculoskeletal system, such as sacroiliac joint and spine inflammation, involvement of peripheral joints, enthesitis, and dactylitis, there may also be numerous extraarticular manifestations, including uveitis, psoriasis, and/or frequent association with inflammatory bowel diseases (IBDs). It has been estimated that extra-articular changes are present in approximately 40% of patients with SpA [1, 3, 4]. High clinical heterogeneity and unclear pathogenesis make management of SpA very challenging. Nonsteroidal anti-inflammatory drugs are considered the first-line treatment in axial SpA and conventional disease-modifying antirheumatic drugs (such as methotrexate and sulfasalazine) in pSpA. The second line treatment involves biological drugs (including tumor necrosis factor [TNF] inhibitors, interleukin-17 [IL-17] inhibitors, IL-23 inhibitors) or Janus kinase inhibitors. Proper management of patients with SpA requires individualization of treatment and combination of pharmacotherapy with non-pharmacological treatment [4, 5]. Despite the progress made in the last several years, there are still significant unmet needs in the treatment of SpA.

Tumor necrosis factor-like cytokine 1A (TL1A) is a cytokine belonging to the TNF super-family of molecules and is also known as TNF superfa-mily member 15 (TNFSF15) or vascular endothelial growth inhibitor 251 (VEGI-251). Tumor necrosis factor-like cytokine 1A is expressed by cells of the immune system, such as monocytes, macrophages, or dendritic cells, but also by non-immune cells, including endothelial cells, chondrocytes, and synovial fibroblasts. Tumor necrosis factor-like cytokine 1A is involved in regulation of the inflammatory response through the regulation of production of pro-inflammatory cytokines and chemokines in various immune cells, including innate lymphoid cells, T cells, and natural killer cells [6].

Tumor necrosis factor-like cytokine 1A interacts with 2 different receptors: death receptor 3 (DR3) and decoy receptor 3 (DcR3). The TL1A-DR3 interactions play an important role in the development of the inflammatory response by regulation of activation, proliferation, and differentiation of different immune cells, such as T cell and B cells, as well as stimulation of production of pro-inflammatory cytokines, such as IL-2, IL-4, interferon γ, IL-17, and IL-23 [7, 8]. Interestingly, some studies indicate that activation of the TL1A-DR3 pathway may also have an anti-inflammatory role through the expansion of regulatory T cells [9].

Decoy receptor 3 binds TL1A, but also other cytokines from the TNF superfamily, such as Fas cell surface death receptor (FAS) ligand (TNFSF6) and LIGHT (TNFSF14). The DcR3 receptor has two functions. The first – "decoy function" – is revealed when DcR3 competitively binds to soluble TL1A, which in turn leads to destruction of the sTL1A-DR3 complex, and prevention of its immunostimulatory effects, and inhibition of apoptosis. The second – "non-decoy function" – is when DcR3 acts as an effector molecule to modulate the activities of many cell types directly, including regulation of dendritic cell differentiation and maturation.

Indeed, elevated levels of TL1A and/or its receptors, DR3 and DcR3, have been reported in the peripheral blood of several inflammatory rheumatic diseases such as rheumatoid arthritis (RA) [10], systemic sclerosis [11], systemic lupus erythematosus [12], and non-rheumatic conditions including atopic dermatitis [13], psoriasis [14], and IBDs [15]. Recently, biological therapies targeting the TL1A-related axis have shown very promising results in the treatment of patients with IBDs, confirming the significant role of the TL1A axis in development of these groups of diseases [16].

Since SpA are closely related, clinically and pathogenetically, to IBDs, we hypothesized that the TL1A axis may also be involved in the pathogenesis of this group of inflammatory joint diseases and may represent a new, promising target for treatment of SpA.

As of now, there is very little evidence regarding the TL1A axis in patients with SpA. Except for one paper reporting evaluated levels of TL1A in a group of patients with AS [17], our search of the literature failed to find studies addressing this question.

Therefore, in the present study we aimed to determine the serum concentrations of soluble forms of TL1A and its receptors, DR3 and DcR3, in patients with SpA in comparison with healthy controls, and to evaluate possible relationships between concentrations of the investigated molecules and the clinical pattern of the diseases.

Material and methods

All consecutive patients diagnosed with SpA who were admitted to the Department of Rheumatology and Internal Medicine of the University Clinical Hospital in Bialystok between October 2021 and December 2023 and gave informed consent were included. All patients recruited into this study had to fulfill classification criteria of one of the following forms of SpA: the 1984 modified New York criteria for ankylosing spondylitis, the Classification criteria for Psoriatic Arthritis (CASPAR), the 2009 Assessment of SpondyloArthritis International Society

(ASAS) classification criteria for nr-axSpA, or the 2011 ASAS classification criteria for pSpA [18–21].

The following exclusion criteria were used: presence of active infectious disease, history of allergy and/or recent neoplasm, overlap with other systemic autoimmune condition.

Clinical assessment of patients with SpA included evaluation of the presence of sacroiliitis (based on X-ray and/or magnetic resonance imaging [MRI]), axial inflammation (based on X-ray and/or MRI of the spine and clinical assessment), peripheral joint inflammation, dactylitis, enthesitis, uveitis, skin psoriasis, presence of inflammatory bowel disease.

Disease activity was measured using scales in common use, depending on the dominant form of the disease: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in cases of axial involvement, or the Disease Activity Score in 28 joints (DAS28) in cases of peripheral joint involvement [22].

In addition, the levels of inflammatory parameters (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) were examined in the study group.

The control group consisted of 36 volunteers without diagnosed inflammatory arthritis or other inflammatory conditions, allergy, or a recent history of cancer.

Measurements of the serum concentrations of TL1A and soluble forms of DR3 and DcR3 were performed using commercially available ELISA kits (R&D Systems) in accordance with the manufacturer's recommendations. All measurements were performed in duplicate.

Statistical analysis

The collected data were statistically analyzed with Statistica Version 14.1.0.4 software using descriptive statistics, the Shapiro-Wilk test (for testing distribution of all parameters), non-parametric tests and Pearson's χ^2 test, as appropriate. Because of the lack of normality of the data distribution, the assessment was made using the Mann-Whitney U test. All data have been reported as median (min.–max.), unless stated otherwise.

Bioethical standards

The study was approved by the Bioethics Committee of the Medical University in Bialystok (ethics approval number: APK.002.321.2021) on June 24th 2021, and all subjects gave written informed consent to participate.

Results

Characteristics of study groups

The study group consisted of 82 patients with SpA, including 29 patients with r-axSpA, 24 with PsA, 14 with nr-axSpA, and 15 patients with pSpA (including 2 with reactive arthritis and 3 with arthritis associated with inflammatory bowel disease).

There were 33 females (mean age 44.5, median age 45 years) and 49 males (mean age 44.7, median age 44 years). The median age of patients with SpA was 44 years, the youngest participant was 18 years old, and the oldest 81 years of age. Information regarding

Table I. Clinical characteristics of the study groups (the results are given as number of patients with the presence of specific diagnosis/symptom if not indicated otherwise)

Clinical characteristics (total number of patients with available information, if data not available for all)	Patients with SpA	Control group
Age [years], median (min.–max.)	44 (18–81)	44 (19–77)
Presence of HLA B27	36	
Sex		
Female	33	28
Male	49	8
Patients with r-axSpA	29	
Patients with PsA	24	
Patients with nr-axSpA	14	
Patients with pSpA*	15	
Presence of HLA B27 (n = 55)	36	
Presence of inflammatory bowel disease	3	
Presence of uveitis	12	

** The group of patients with peripheral spondyloarthritis includes patients with reactive arthritis (n = 2) and patients with arthritis associated with inflammatory bowel disease (n = 3).*
r-axSpA – radiographic axial spondyloarthritis, nr-axSpA – non-radiographic axial spondyloarthritis, PsA – psoriatic arthritis, pSpA – peripheral spondyloarthritis, SpA – spondyloarthropaties.

the presence of HLA B27 was available for 55 patients, 36 (66%) of whom had HLA B27 haplotype.

Detailed characteristics of the study groups are presented in Table I.

At the time of the study, 36 patients were receiving conventional disease-modifying drugs, 13 patients were receiving biological therapy (12 patients anti-TNF-α antibodies and one patient anti-IL-17 antibody), and 12 were receiving glucocorticosteroids. Detailed data regarding treatment are presented in Table II.

The control group included 28 women and 8 men.

Serum concentrations of soluble forms of tumor necrosis factor-like cytokine 1A, death receptor 3, and decoy receptor 3

We found no significant differences between the study and the control groups in the serum concentration of TL1A (median [min.–max.]: 18.82 pg/ml [0.00–24,556.00 pg/ml] vs. 16.18 pg/ml [0.00–17,606.00 pg/ml], respectively, $p > 0.05$) or DR3 (median [min.–max.]: 1,766.77 [52.00–26,958.8 pg/ml] vs. 2,517.76 pg/ml [234.32–25,791.80 pg/ml], respectively, $p > 0.05$). However, we observed a significantly higher concentration of DcR3 in patients with SpA (median [min.–max.]: 292.31 pg/ml [93.241–13,862.10 pg/ml]) as compared with the controls (126.73 pg/ml [10.68–1482.74 pg/ml], $p = 0.003$). The DR/DcR ratio was significantly lower in patients with SpA (median [min.–max.]: 4.05 [0.14–235.39]) as compared with the controls (17.22 [0.00–750.66] ($p = 0.002$).

We found a weak correlation between serum levels of Tl1A and DcR (Spearman's *rho*: 0.28, $p < 0.05$) and between serum concentration of DcR3 receptor and CRP concentration as well as ESR values (Spearman's *rho*: 0.25 and 0.24, respectively, $p < 0.05$ for both) in patients with SpA. There were no significant differences in the concentrations of investigated molecules between patients with different forms of SpA or between patients with or without specific manifestations of the diseases (e.g. with and without uveitis). We did not find any significant correlations between serum concentrations of TL1A, DR3, or DcR3 and clinical activity of the disease measured with BASDAI (in axial forms of SpA) or DAS28 (in peripheral forms of SpA).

Discussion

To the best of our knowledge, this is the first study evaluating soluble forms of all 3 molecules of the TL1A/DR3/DcR3 axis in the serum of patients with SpA. We did not find significant differences in the concentration of TL1A between patients with SpA and healthy controls. This is in contrast with the study by Konsta et al. [17], who reported significantly higher levels of TL1A in the blood of patients with r-axSpA in comparison with healthy controls [15]. The difference between our results and the findings of Konsta et al. [17] may be due to the fact that we investigated TL1A levels in a more heterogenous population, including patients with different forms of SpA, of whom only 29 (35%) had r-axSpA. Moreover, 7 (24%) of those 29 patients with AS were on biological therapy at the time of enrollment. Although we did not find a significant difference in the concentration of TL1A between patients with or without biological therapy in the total group of patients with SpA, it cannot be excluded that the treatment with biologics influenced the results. Indeed, Konsta et al. [17] noted significantly higher levels of TL1A in patients with r-axSpA naïve to anti-TNF agents as compared with patients receiving anti-TNF agents, in whom the serum concentration of TL1A was comparable to healthy controls. Also, there was no significant difference in the serum concentration of soluble DR3 receptor between patients with SpA and the controls. However, we found a significantly higher concentration of soluble forms of the DcR3 receptor in patients with SpA as compared with the control group.

There were no significant differences in the serum concentrations of TL1A, DR3, DcR3 receptor, or DR3/DcR3 ratio between patients with different forms of SpA. Also, we did not find any significant differences in the serum concentrations of the investigated molecules or the DR3/DcR3 ratio between patients with or without biological therapy.

As mentioned above, to the best of our knowledge, in the available literature there are no reports evaluating soluble receptors of TL1A in patients with SpA. Our finding of an elevated DcR3 receptor concentration is in line with

Table II. Therapies of patients during the study

Treatment	Number of patients
Nonsteroidal anti-inflammatory drugs	39
Glucocorticosteroids*	12
Methotrexate**	18
Sulfasalazine***	18
Biological treatment	
Adalimumab	6
Golimumab	2
Infliximab	2
Etanercept	2
Secukinumab	1
Patient without treatment	11

** Methylprednisolone at a dose of 2 to 24 mg per day.*
*** Methotrexate at a dose of 5 to 30 mg per week.*
**** Sulfasalazine at a dose of 1 to 3 g per day.*

findings in other inflammatory conditions such as IBD [15] or RA [23, 24].

We also found weak but statistically significant correlations between the level of the soluble DcR3 receptor and laboratory markers of inflammation, such as ESR and CRP. This observation indicates that an increase in DcR3 concentration is associated with inflammatory activity in patients with SpA. This is again in line with reported TL1A and DcR3 receptor concentrations in other inflammatory conditions such as RA [24], which might point to activation of the TL1A-DcR3 axis.

Conclusions

The TL1A/DR3/DcR3 axis is activated in patients with SpA, and the serum level of DcR3 is elevated. It suggests that the TL1A axis may be considered a therapeutic target in SpA patients, as it remains a promising target for biological therapy in patients with inflammatory bowel disease, a condition clinically linked to SpA. Further investigations of the phenomena are needed.

Disclosures

Conflict of interest: The authors declare no conflict of interest.

Funding: This study was supported by a research grant from the Medical University of Bialystok (grant number: B.SUB.23.176, B.SUB.24.132).

Ethics approval: The study was approved by the Bioethics Committee of the Medical University in Bialystok (ethics approval number: APK.002.321.2021) on June 24 2021.

Data availability: The data that support the findings of this study are available on request from the corresponding author (E.A.F.).

References

1. Sen R, Goyal A, Hurley JA. Seronegative Spondyloarthropathy. StatPearls. Available at: https://www.ncbi.nlm.nih.gov/books/NBK459356/ (Access: 02.02.2025).
2. van der Heijde D, Molto A, Ramiro S, et al. Goodbye to the term 'ankylosing spondylitis', hello 'axial spondyloarthritis': time to embrace the ASAS-defined nomenclature. Ann Rheum Dis 2024; 83: 547–549, DOI: 10.1136/ard-2023-225185.
3. Puche-Larrubia MÁ, López-Medina C, Ziadé N. Peripheral spondyloarthritis: What have we learned? Best Pract Res Clin Rheumatol 2023; 37: 101862, DOI: 10.1016/j.berh.2023.101862.
4. Navarro-Compán V, Sepriano A, Capelusnik D, Baraliakos X. Axial spondyloarthritis. Lancet 2025; 405: 159–172, DOI: 10.1016/S0140-6736(24)02263-3.
5. Zimba O, Kocyigit BF, Kadam E, et al. Knowledge, perceptions, and practices of axial spondyloarthritis diagnosis and management among healthcare professionals: an online cross-sectional survey. Rheumatol Int 2024; 44: 1501–1508, DOI: 10.1007/s00296-024-05638-w.
6. Xu WD, Li R, Huang AF. Role of TL1A in Inflammatory Autoimmune Diseases: A Comprehensive Review. Front Immunol 2022; 13: 891328, DOI: 10.3389/fimmu.2022.891328.
7. Croft M, Siegel RM. Beyond TNF: TNF superfamily cytokines as targets for the treatment of rheumatic diseases. Nat Rev Rheumatol 2017; 13: 217–233, DOI: 10.1038/nrrheum.2017.22.
8. Migone TS, Zhang J, Luo X, et al. TL1A is a TNF-like ligand for DR3 and TR6/DcR3 and functions as a T cell costimulator. Immunity 2002; 16: 479–492, DOI: 10.1016/s1074-7613(02)00283-2.
9. Yu Y, Jiang P, Sun P, et al. Analysis of therapeutic potential of preclinical models based on DR3/TL1A pathway modulation (Review). Exp Ther Med 2021; 22: 693, DOI: 10.3892/etm.2021.10125.
10. Song YJ, Choi IA, Meylan F, et al. Circulating TNF-like protein 1A (TL1A) is elevated early in rheumatoid arthritis and depends on TNF. Arthritis Res Ther 2020; 22: 106, DOI: 10.1186/s13075-020-02198-9.
11. Xu W, Su L, Qing P, et al. Elevated levels of TL1A are associated with disease activity in patients with systemic sclerosis. Clin Rheumatol 2017; 36: 1317–1324, DOI: 10.1007/s10067-017-3612-y.
12. Xu WD, Chen DJ, Li R, et al. Elevated plasma levels of TL1A in newly diagnosed systemic lupus erythematosus patients. Rheumatol Int 2015; 35: 1435–1437, DOI: 10.1007/s00296-015-3277-2.
13. Hisamoto T, Suga H, Yoshizaki-Ogawa A, et al. Increased Serum Levels of Tumor Necrosis Factor-like Ligand 1A in Atopic Dermatitis. Int J Mol Sci 2023; 24: 1813, DOI: 10.3390/ijms24031813.
14. Li L, Fu L, Lu Y, et al. TNF-like ligand 1A is associated with the pathogenesis of psoriasis vulgaris and contributes to IL-17 production in PBMCs. Arch Dermatol Res 2014; 306: 927–932, DOI: 10.1007/s00403-014-1497-z.
15. Bamias G, Kaltsa G, Siakavellas SI, et al. High intestinal and systemic levels of decoy receptor 3 (DcR3) and its ligand TL1A in active ulcerative colitis. Clin Immunol 2010; 137: 242–249, DOI: 10.1016/j.clim.2010.07.001.
16. Schweckendiek D, Rogler G. Antibodies Targeting the Tumor Necrosis Factor-Like Ligand 1A in Inflammatory Bowel Disease: A New Kid on the (Biologics) Block? Digestion 2024; 105: 411–418, DOI: 10.1159/000540421.
17. Konsta M, Bamias G, Tektonidou MG, et al. Increased levels of soluble TNF-like cytokine 1A in ankylosing spondylitis. Rheumatology (Oxford) 2013; 52: 448–451, DOI: 10.1093/rheumatology/kes316.
18. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006; 54: 2665–2673, DOI: 10.1002/art.21972.
19. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68: 777–783, DOI: 10.1136/ard.2009.108233. Erratum in: Ann Rheum Dis 2019; 78: e59. DOI: 10.1136/ard.2009.108233corr1.

20. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984; 27: 361–368, DOI: 10.1002/art.1780270401.
21. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011; 70: 25–31, DOI: 10.1136/ard.2010.133645.
22. Alonso S, Braña I, Loredo M, et al. Performance of Disease Activity Indices Used in Axial Spondyloarthritis in Real-World Clinical Settings. J Rheumatol 2025; 52: 444–449, DOI: 10.3899/jrheum.2024-0916.
23. Xiu Z, Shen H, Tian Y, et al. Serum and synovial fluid levels of tumor necrosis factor-like ligand 1A and decoy receptor 3 in rheumatoid arthritis. Cytokine 2015; 72: 185–189, DOI: 10.1016/j.cyto.2014.12.026.
24. Soliman MH, Ebaid AM. Association of Tumor Necrosis Like factor 1 A (TL1A) and its Decoy Receptor (DcR3) with The Disease Activity and Autoantibody Production in Rheumatoid Arthritis Patients. Egypt J Immunol 2019; 26: 43–54.