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Is the new ASDAS nomenclature in agreement with therapeutic decision making in patients with axial spondyloarthritis?

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ABSTRACT

Objectives: To evaluate the association between low disease activity according to the new ASDAS nomenclature and the physician therapeutic decisions in patients with axial spondyloarthritis (axSpA).
Material and Methods: Longitudinal retrospective study including patients diagnosed with axSpA receiving a tumor necrosis factor-inhibitor between January 2014 and June 2019 as a first treatment. For each visit, disease activity was determined afterwards according to the new ASDAS nomenclature (inactive, low, high and very high activity), and the physician's therapeutic decision was recorded. The association between disease activity and the physician's decision was evaluated through descriptive statistics.
Results: A total of 304 visits of 104 patients with axSpA were analyzed. For those visits where a low activity ASDAS score was obtained, the physician's therapeutic decision was no escalation of treatment in 98.2% of cases. However, for those visits with a high or very high disease activity ASDAS score, the physician's therapeutic decision was to escalate treatment in 33.7% and 82.8% of cases respectively.
Conclusions: The state measured by the ASDAS index formerly defined as 'moderated disease activity' is considered in clinical practice as 'low disease activity' because of the physician's choice in these situations to not-escalate the treatment. Our data substantiate the recent updating in ASDAS nomenclature.

Introduction

Axial spondyloarthritis (axSpA) is an inflammatory rheumatic disease whose main symptom is inflammatory axial pain. In clinical practice, the recommendation to obtain an adequate axSpA inflammatory assessment is to use composite indexes reflecting different disease manifestations [1].

There are two primarily composite indexes: The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [2] and the Ankylosing Spondylitis Disease Activity Score (ASDAS) [3] but due to its better instrument properties, the ASDAS is nowadays the recommended index to monitor disease activity in patients with axSpA.

The ASDAS was developed a decade ago. At the beginning, the disease was classified as inactive if the ASDAS score was lower than 1.3, moderate disease activity if $\geq$ 1.3 and $<$ 2.1, high activity if $\geq$ 2.1 and $\leq$ 3.5, and very high activity if $>$3.5 [4]. Nevertheless, there was not a score of ASDAS established to classify low/minimum disease activity, and later it was theorized that what was initially defined as moderate activity could in fact refer to low disease activity.

For this reason, at the beginning of 2018, the Assessment of SpondyloArthritis International Society (ASAS) [5] proposed to update the nomenclature as follows: what had been initially classified as moderate activity (ASDAS $\geq$ 1.3 and $<$ 2.1) would now be defined as low activity. The following hypothesis is underlying this decision: in common clinical practice, rheumatologists consider that patients with a score between these parameters have low disease activity, and consequently do not implement changes in the treatment plan in most of the cases. However, ASAS's decision was made without being based on enough scientific evidence proving this hypothesis.

Objective

To evaluate association between ASDAS's score for low disease activity according to new nomenclature and the clinician's judgement based on their therapeutic decision for patients with axSpA.

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Material and Methods

A longitudinal retrospective observational study analysing data collected from all patients diagnosed with axSpA receiving anti-tumor necrosis factor biologic treatment (TNFi) as a first treatment between January 2014 and June 2019 in the *Hospital San Jorge Huesca*. Inclusion criteria were as follows: axSpA diagnosis according to a rheumatologist's clinical judgement, having at least one follow-up visit after starting TNFi therapy, and available data to calculate ASDAS-C-reactive protein (CRP) being provided during this follow-up visit.

The study was approved by the Research Ethics Committee of *Aragón* according to the principles of the Declaration of Helsinki.

Socio-demographic and disease characteristics of patients when starting treatment with TNFi were recorded. Values of disease activity and physical function were also collected at the baseline visit: BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), patient's global assessment (PGA) on a numeric rating scale (0–10 point), ESR (mm/h), and CRP (mg/L). These variables were again collected 3 months, 6 months, one year and two years after the initiation of treatment.

For each baseline and follow-up visit, calculations with the ASDAS-CRP algorithm formula [6] were carried out. This measure had never been collected before, but was able to be calculated for this study thanks to the CRP values, PGA on a numeric rating scale (NRS) and patient's subjective responses to the BASDAI questionnaire being available. The formula used to calculate ASDAS-CRP index was as follows: 0.12 × low-back pain (BASDAI question 2) + 0.06 × morning stiffness duration (BASDAI question 6) + 0.11 × NRS + 0.07 × peripheral joint pain and swelling (BASDAI question 3) + 0.58 × Ln (CRP + 1).

For each visit, the attitude adopted by the physician about the patient's situation recorded in the medical file was collected according to these two options: a) to keep therapy unchanged or optimize it (treatment strategy of no escalation) since it was considered that the patient was stable or has improved, b) to withdraw or change biologic therapy (treatment strategy of escalation) since it was considered that the patient had worsen or had not improved. Those patients whose medical file reflected changes in dose or type of treatment due to side effects or other reasons (such as extra-articular/peripheral manifestations worsening), and were not axial disease worsening/improvement according to medical judgement were excluded of the analysis.

Statistical analysis

A descriptive analysis was performed. Results are expressed as absolute and relative frequencies for categorical variables, and as mean and standard deviation (SD) for continuous variables. Chi-squared test or Fisher's exact test were applied to compare frequencies among different disease activity groups in accordance with ASDAS-CRP.

The physician's attitude at each visit was considered as categorical variable (choosing escalation and no escalation strategy) and it was compared with different ASDAS disease activity states according to new nomenclature: inactive disease (ASDAS-CRP <1.3), low activity (ASDAS-CRP ≥ 1.3 and < 2.1), high activity (ASDAS-CRP ≥ 2.1 and ≤ 3.5) and very high activity (ASDAS-CRP >3.5).

All statistical analyses were performed with SPSS V.23.0 software (SPSS, Chicago, Illinois, USA) and $p < 0.05$ was considered for statistical signification.

Results

A total of 304 visits for 104 patients with axSpA were analyzed. Out of these patients, 57% were women, 47% had non-radiographic axSpA and 42% were positive for human leucocyte antigen (HLA)-B27. The mean age at diagnosis (± SD) was 46.9 ± 12.5 years. Mean ± SD values of activity indexes and physical function at the start of treatment with TNFi were: 5.5 ± 1.8 (BASDAI), 3.1 ± 0.4 (ASDAS-CRP) and 5.1 ± 2.2 (BASFI). Only 3 patients starting a TNFi had an ASDAS-CRP value within 1.3 ≤ and < 2.1. Further information on demographic characteristics is shown in Table 1. Out of 304 visits, 90 visits were carried out after a 3-month treatment, 82 visits after a month treatment, 61 visits after 1-year treatment, 44 visits after 2-year treatment and 27 visits after 3-year treatment.

Table 1
Characteristics of recruited patients at baseline visit.

Characteristics	*N* = 104
Women	57 (54.8)
Age at diagnosis (years)	46.9 ± 12.5*
Non-radiographic axSpA	47 (45.2)
HLA-B27 positive (*n* = 95)	42 (40.4)
BMI (Kg/m^2)	
<25	32 (30.8)
25–30	39 (37.5)
>30	33 (31.7)
Extra-articular Manifestations	
IBD	4 (3.8)
Anterior uveitis	7 (6.7)
Psoriasis	29 (27.9)
Time until anti-TNF (Years)	3.5 ± 4.8*
ESR (mm/h)	15.8 ± 15.3*
CRP (mg/L)	5.2 ± 5.14*
Patient global NRS (0–10)	5.9 ± 1.8*
BASDAI (0–10)	5.5 ± 1.8*
BASFI (0–10)	5.1 ± 2.2*
ASDAS	3.1 ± 0.4*
ASDAS <1.3	0 (0)
1.3 ≤ ASDAS < 2.1	3 (2.9)
2.1 ≤ ASDAS ≤ 3.5	81 (77.9)
ASDAS >3.5	20 (19.2)

Values with *: mean ±SD and the rest: n (percentage); SD: Standard Deviation; axSpA: axial spondyloarthritis; BMI: body mass index; IBD: inflammatory bowel disease, anti-TNF: anti-tumor necrosis factor biologic treatment; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NRS: numerical rating scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity. Score, measured by CRP.

Fig. 1 shows the main analysis results. As for low activity, physician attitude of no escalation of treatment was observed in 98.2% of visits. Likewise, for inactive disease state (ASDAS-CRP <1.3), no escalation was applied at all visits. Nevertheless, for high activity (ASDAS-CRP ≥ 2.1 and ≤ 3.5) treatment was escalated in 33.7% of visits, and this percentage was increased up to 82.8% for very high activity (ASDAS-CRP >3.5).

In addition, table 2 shows the results stratified for the timepoint of each visit, which are consistent with the global results. For low disease activity, escalation attitude was taken only in 1 patient after 6 month of initiating TNFi.

For further details, supplementary file (Table S1) shows mean values of disease activity indexes and physical function, as well as mean CRP value and PGA for each ASDAS activity score at each visit.

Discussion

The current recommendations to manage patients with axSpA [7] stated that the treatment objective is to reach remission (inactive disease), and if not possible, that achieving a low/minimum activity state could be an acceptable objective.

The ASDAS index is the recommended measurement to assess inflammatory disease activity [4]. Nevertheless, in the ASDAS former nomenclature, none of the disease activity states was defined as low. For this reason, it was proposed that there needed to be an ASDAS score interval reflecting a state of low/minimum inflammatory activity in order to improve disease management and make achievement

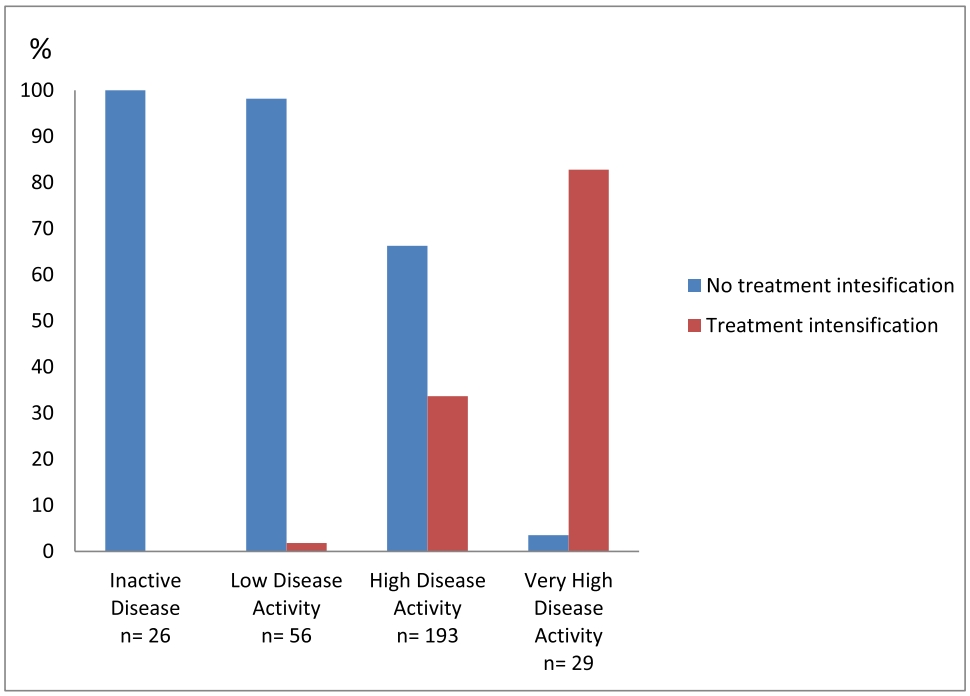

Fig. 1. Physician attitude to treatment (no escalation vs. escalation) for all activity states measured by ASDAS-CRP, shown as percentage of visits.

of objectives in clinical trials and observational studies feasible. This study substantiates that the recent update carried out in ASDAS nomenclature is appropriate since, in the majority (over 98%) of situations of clinical practice, the range formerly defined as moderate activity is interpreted by physicians as low activity, not considering necessary to escalate treatment.

Certainly, the most important strength of our work is that ASDAS was calculated ex post for the study, so the physician did not know these data when considering the patient's clinical situation and making therapeutic decisions. The physician's decision could then be correlated with ASDAS score obtained ex post, therefore ensuring that it was not influenced by the ASDAS score obtained. Furthermore, this study's cohort is representative of patients evaluated in habitual clinical practice representing the whole spectrum of axSpA. The low percentage of patients with HLA-B27 positive could be explained by the large number of patients with associated psoriasis.

Nevertheless, this study also presents certain limitations. In the first place, those limitations associated with a retrospective design including loss of follow-up visits and missing monitoring values. Secondly, patients were recruited from just one center, although there were various physicians involved. Thirdly, only patients receiving TNFi treatment were recruited, therefore it is unknown if the results can be extrapolated to patients having axSpA and receiving different treatments such as nonsteroidal anti-inflammatory drugs or interleukin-17 inhibitors. Another limitation is that this study lacks the physician's global assessment, and their opinion regarding the patient situation is obtained from the comments on medical histories and therapeutic decisions. In addition, it would have been desirable to obtain external constructs based on other subjective assessments by the patient, such as the Patient Acceptable Symptom State [8]. However, in this study, both physician and the patient views concur regarding low activity ASDAS scores, as shown by the mean PGA score of 2.8 (measured from 0 to 10) and the main findings of the study. Lastly, another possible limitation could be that there is a certain degree of correlation between BASDAI and ASDAS, with an average ASDAS of 2.1 grossly corresponding to an average BASDAI of 3.5. Since the BASDAI cut-off of 4 is commonly used to start biologic therapy, this could have influenced the results of the study. However, 97.1% patients who started TNFi had an ASDAS-CRP $\geq$ 2.1; therefore, most patients fulfilled BASDAI and ASDAS eligibility criterion for initiation of TNFi.

In summary, the study's results indicate that ASDAS activity state scores that were initially defined as moderate disease activity are in fact considered in clinical practice as low disease activity based on physician being no escalation of treatment when this situation happens. These data provide for the first time scientific evidence to support the recent ASDAS nomenclature update regarding disease activity states. Nevertheless, multicenter studies including patients with different therapies need to be performed in the future in order to confirm these results.

Table 2
Disease activity score based on ASDAS-CRP according to physician attitude (no escalation vs. escalation of treatment) through all visits.

Visits	n	No Escalation n (%)	Escalation n (%)
1st visit (3 months)	90		
ASDAS <1.3		8 (100)	0 (0)
1.3 ≤ ASDAS <2.1		17 (100)	0 (0)
2.1 ≤ ASDAS ≤ 3.5		41 (71.9)	16 (28.1)
ASDAS >3.5		2 (25)	6 (75)
2nd visit (6 months)	82		
ASDAS <1.3		8 (100)	0 (0)
1.3 ≤ ASDAS <2.1		15 (100)	0 (0)
2.1 ≤ ASDAS ≤ 3.5		29 (59.2)	20 (40.8)
ASDAS >3.5		1 (10)	9 (90)
3rd visit (1 year)	61		
ASDAS <1.3		7 (100)	0 (0)
1.3 ≤ ASDAS <2.1		8 (88.9)	1 (11)
2.1 ≤ ASDAS ≤ 3.5		23 (56.1)	18 (43.9)
ASDAS >3.5		1 (25)	3 (75)
4th visit (2 years)	44		
ASDAS <1.3		1 (100)	0 (0)
1.3 ≤ ASDAS <2.1		10 (100)	0 (0)
2.1 ≤ ASDAS ≤ 3.5		22 (75.9)	7 (24.1)
ASDAS >3.5		0 (0)	4 (100)
5th visit (3 years)	27		
ASDAS <1.3		2 (100)	0 (0)
1.3 ≤ ASDAS <2.1		5 (100)	0 (0)
2.1 ≤ ASDAS ≤ 3.5		13 (76.5)	4 (23.5)
ASDAS >3.5		1 (33.3)	2 (66.7)

ASDAS: Ankylosing Spondylitis Disease Activity Score.

Key messages

The Ankylosing spondylitis disease activity score (ASDAS) was developed a decade ago, but a new nomenclature for this was published in 2018 indicating that what had been initially defined as moderate activity (cut-off point ≥1.3 and <2.1) should be now defined as low activity. This decision was mainly supported by expert opinion.

According to these data ASDAS scores initially defined as moderate disease activity are in fact considered in clinical practice as low disease activity by physicians based on no escalation treatment decision.

The results of study provide for the first time scientific evidence to support the use of new ASDAS nomenclature to manage patients with axial spondyloarthritis in clinical practice.

Contributorship

All authors were involved in the drafting and critical review of the manuscript and approved the final version for submission. BGM and RS were involved in the acquisition of clinical data. BGM, CCV and VNC were involved with the conception or design of the work. BGM and JSO were involved with the analysis of the data in the manuscript. BGM wrote the first draft of the manuscript. CCV and VNC coordinated and supervised the study. All authors were involved with the interpretation of data in the manuscript and have given approval for the publication of this version of the manuscript.

Ethics approval

The study was approved by the Research Ethics Committee of Aragón according to the principles of the Declaration of Helsinki.

Data availability

All data relevant to the study are included in the article. The complete dataset analysed in this study is available from the corresponding author upon reasonable request.

Patient and public partnership

Patients and/or the public were not involved in the design or conduct or reporting or dissemination plans of this research.

Declaration of Competing Interest

The authors have declared no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2020.07.010.

References

[1] Machado PM, Raychaudhuri SP. Disease activity measurements and monitoring in psoriatic arthritis and axial spondyloarthritis. Best Pract Res Clin Rheumatol 2014;28:711–28. doi: 10.1016/j.berh.2014.10.004.

[2] Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21(12):2286–91.

[3] Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24. doi: 10.1136/ard.2008.094870.

[4] Machado P, Landewé R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47–53. doi: 10.1136/ard.2010.138594.

[5] Machado PM, Landewé R, van der Heijde D. Assessment of Spondyloarthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis 2018;77:1539–40. doi: 10.1136/annrheumdis-2018-213184.

[6] Van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68(12):1811–8. doi: 10.1136/ard.2008.100826.

[7] Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77(1):3–17. doi: 10.1136/annrheumdis-2017-211734.

[8] Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis and hip and knee osteoarthritis: results from a prospective multinational study. Arthritis Care Res 2012;64(11) 1699-70. doi: 10.1002/acr.21747.