Performance of the Ankylosing Spondylitis Disease Activity Score (ASDAS)

in patients under biological therapies

1. Introduction

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a new instrument to measure disease activity in Ankylosing Spondylitis (AS)[1, 2]. The Assessment of SpondyloArthritis international Society (ASAS) recently proposed this new composite index, as the currently used single-item measures (e.g. pain, stiffness, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], patient/physician global assessment) and composite indices (e.g. Bath Ankylosing Spondylitis Disease Activity Score - BASDAI[3]) have limitations because they measure only part of disease activity, are fully patient or physician oriented, or lack face and/or construct validity [1, 4, 5].

The ASDAS was statistically derived in analogy with the methodology adopted for the development of the disease activity score (DAS) in rheumatoid arthritis [1, 6] and it is the first validated disease activity index in AS which combines patient-reported assessments and acute phase reactants. It includes the following items: back pain, duration of morning stiffness, patient global assessment of disease activity, peripheral pain or swelling, and an acute phase reactant, preferably CRP, alternatively ESR[2].

Cut-off values for disease activity states and levels of improvement have also been developed and endorsed by the ASAS membership [7]. It has been shown that the ASDAS performs at least equally well as the BASDAI, but frequently outweighing it [1, 2, 7]. The ASDAS fulfills important aspects of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) filter, as it reflects disease activity from both the patient and

the physician perspective, which are known to be inherently different [1, 5, 8], it is highly discriminatory in differentiating patients with different levels of disease activity and in differentiating those with different levels of change [2], and it is a feasible and practical tool. Therefore, the ASDAS has also been endorsed by the OMERACT community [9].

Our aim is to address validity and discriminatory aspects of the ASDAS, as well as to analyze the performance of the ASDAS disease activity states and response criteria in the setting of an observational cohort of patients with AS under biological therapy. A preliminary analysis with data from BioRePortEA (Portuguese Biologics Register of patients with Ankylosing Spondilytis) from three centres has been performed and the results are encouraging: ASDAS had good correlations with other measures of disease activity and the longitudinal evolution of the different ASDAS disease activity states corresponded to the expectations (Table 1) and was similar to the findings of other analyses, namely from observational studies and clinical trials [7].

Table 1: Preliminary data from BioRePortEA

Timepoint	N	ASDAS <1.3 N (%)	1.3≤ ASDAS <2.1 N (%)	2.1≤ ASDAS <3.5 N (%)	ASDAS >3.5 N (%)
Baseline	83	0 (0%)	1 (1.2%)	33 (39.8%)	49 (59.0%)
12 weeks	53	17 (32.1%)	14 (26.4%)	16 (30.2%)	6 (11.3%)
24 weeks	57	16 (28.1%)	15 (26.3%)	22 (38.6%)	4 (7.0%)

2. Objectives

a) To investigate the validity and discriminatory aspects of the ASDAS, through a comparison between the ASDAS and the BASDAI, their individual components and the patient global assessment.

b) To analyze the performance of the ASDAS on the long term, by assessing the longitudinal distribution of ASDAS disease activity states after treatment, and by comparing it with the BASDAI.

c) To analyze the performance of ASDAS response criteria, by comparing it with classical response criteria.

3. Methods

3.1. Study design and population

The current study will be a longitudinal observational study conducted within the framework of the Rheumatic Diseases Portuguese Register, Reuma.pt[10], which also includes BioRePortEA, a register of patients with AS, diagnosed by the treating rheumatologist, who have started biological therapy. This registry is also used as an electronic patient chart and, therefore, the frequency of the observations is not pre-determined. Assessments are made by rheumatologists, in generally every 3 months, and include monitoring of disease activity (BASDAI, ASDAS, patient global assessment), function (Bath Ankylosing Spondylitis Functional Index[11]), medication, adverse events, hospitalizations and comorbidities. Demographic and clinical characteristics are collected at the onset of biological therapy and include age, gender, education,

working status, disease duration, extra-articular manifestations, comorbidities, and previous therapy.

All patients with baseline data will be used for cross-sectional analysis. For the longitudinal analyses all patients with at least one follow-up visit at either 12 weeks or 24weeks will be included. For this purpose, the closest observation to the desired follow-up time-point will be identified and selected. For the 12-week time point the maximum accepted deviation will be 8-18 weeks, and for the 24-week time point the maximum accepted deviation will be 20-30 weeks.

3.2. Assessments

The following disease activity assessments will be used: patient global assessment of disease activity and the six individual questions of the BASDAI: BASDAI 1, fatigue; BASDAI 2, total back pain; BASDAI 3, pain and swelling of joints; BASDAI 4, pain at enthesis locations; BASDAI 5, severity of morning stiffness; BASDAI 6, duration of morning stiffness (with the maximum score of 10 representing a duration of 2h or longer). All scores have been collected on a 0-10 cm visual analogue scale (VAS), with 0 representing the normal situation and 10 cm the most extreme situation. In addition, ESR (mm/h) and CRP (mg/l) levels have also been obtained. With these assessments, the ASDAS (ASDAS-CRP and ASDAS-ESR) and BASDAI can be calculated.

The ASDAS will be calculated according to the following formulas[1]:

- ASDAS-CRP (the preferred version):

  0.12 X Back pain + 0.06 X Duration of morning stiffness + 0.11 X Patient global + 0.07 X Peripheral pain / swelling + 0.58 X Ln (CRP + 1)

- ASDAS-ESR (the alternative version):

  0.08 X Back pain + 0.07 X Duration of morning stiffness + 0.11 X Patient global + 0.09 X Peripheral pain / swelling + 0.29 X $\sqrt{ESR)}$

Values below the CRP threshold will be computed as half of the value of the threshold, as previously reported[7].

For disease activity states the following defined cut-offs will be used: ASDAS <1.3 to define “inactive disease”, 1.3≤ ASDAS <2.1 to define “moderate disease activity”, 2.1≤ ASDAS ≤3.5 to define “high disease activity”, and ASDAS >3.5 to define “very high disease activity”. Regarding improvement scores, a change of ≥1.1 units represents “clinically important improvement” (CII), and a change of ≥2.0 units represents “major improvement” (MI) [7].

3.3. Validation constructs

As there is no gold standard to assess disease activity in AS, several constructs that are compatible with an external standard representing high and low disease activity will be used. First, validation of the ASDAS will be investigated through means of estimating correlations between the ASDAS (ASDAS-CRP and ASDAS-ESR) and other assessments of disease activity (BASDAI, patient’s global assessment of disease activity, CRP, and ESR) and physical function (Bath Ankylosing Spondylitis Functional Index – BASFI[11]) at baseline. The correlation between the patient’s global assessment and all the above mentioned measurements will also be investigated. Furthermore, the discriminatory ability of the indices (ASDAS and BASDAI, as well as their individual components, and

the BASFI) will be compared at baseline and after 12 and 24 weeks of treatment using an external construct of high disease activity (e.g. the patient's global assessment of disease activity divided at adequate cut-offs - the following cut-offs will be tested: <4 *vs* ≥4, <4 *vs* >6, <6 *vs* ≥6; the final choice will depend on the number of available patients within each cut-off). The performance of the different disease activity assessments will be investigated in subgroups of patients with normal and raised CRP at baseline.

3.4. Validation of the ASDAS cut-offs for disease activity states and response criteria

The validation of the ASDAS cut-offs for disease activity states and response criteria will be performed in different ways:

- Assessment of the longitudinal distribution of patients over the ASDAS disease activity states before and after start of treatment – the percentage of patients within each ASDAS disease activity state at baseline, 12 and 24 weeks after start of treatment will be calculated.
- Mean BASDAI and ASDAS values across the four ASDAS disease activity states – mean values of both instruments within each ASDAS disease activity state will be compared.
- Percentage of patients achieving ASDAS improvement criteria ("CII" and "major improvement") at 12 weeks and 24 weeks, in comparison to other widely used improvement criteria, such as the ASAS response criteria - ASAS20, ASAS40 and ASAS partial remission [12, 13], and classical BASDAI response measures used for the evaluation of the efficacy of anti-tumour necrosis factor (TNF)

treatment - the proportion of patients achieving at least 2 units improvement (ΔBASDAI≥2) or at least 50% improvement (BASDAI50) [14].

All the validations will be performed both with ASDAS-CRP and ASDAS-ESR.

3.5. Statistical analyses

Continuous variables will be presented as means ± standard deviations, if normally distributed, or median plus interquartile range, if not normally distributed. Categorical variables will be presented as frequencies.

Correlations between the patient global assessment and all the individual and combined scores for disease activity assessment will be calculated and expressed as Pearson's correlation coefficient (if normally distributed) or as Spearman's correlation coefficient (if non-normally distributed). Correlation coefficients between the ASDAS and all the individual and combined scores will also be calculated.

The discriminatory capacity of the indices and measures used to assess disease activity will be evaluated through the approach of standardized mean difference (SMD) between subgroups of patients with high versus low disease activity[15]. The SMD is calculated through the difference of the groups means divided by the pooled SD of the group means, it is unitless and can be used to compare the discriminatory ability across the various measures: the higher the value, the greater the discriminatory capacity. Confidence intervals around SMDs will be calculated and the SMDs will be statistically tested using standard errors around the SMDs[16].

Statistical analysis will be performed assuming a 5% significance level and using Stata SE 10 and SPSS v17.

4. Expected results and possible limitations

We expect to confirm the validity and discriminatory ability of the ASDAS. We also anticipate that the ASDAS will perform at least as well as the BASDAI and potentially even outweighing it.

Possible limitations of this study are a potential selection bias in the inclusion of the patients in the registry as consecutive inclusion may not always be the case, and the analysis may not be entirely representative of the whole population. Furthermore, the possible absence of laboratory values at every evaluation might impair the calculation of the ASDAS. In order to circumvent this and to minimize the potential selection bias, laboratory values will be actively searched for in each hospital record.

5. Timeline for the project

- Period to which the data analysis refers to: since the onset of BioRePortEA until the moment that the dataset can be obtained
- Start of the project: as soon as the dataset can be obtained
- Expected analysis of the data:
    - April/May 2011: data cleaning + statistical analysis
    - June 2011: abstract submission to the ACR meeting

- July – November: preparation of a manuscript to be submitted by the end of the year

6. Research team

- Proponents: Sofia Ramiro and Pedro Machado
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- Senior supervisor: Dra Maria José Santos
- Institutions involved: participation is open to all Portuguese centers interested in collaborating in this project. Co-authorship will be granted to a maximum of 4 co-authors per center, actively collaborating in the project
- External consultants: Prof. Robert Landewé, Prof. Désirée van der Heijde, Dr. Astrid van Tubergen (The Netherlands)

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