Eligibility criteria for TNFi therapy in axSpA: BASDAI vs ASDAS

Abstract

Background The Ankylosing Spondylitis Disease Activity Score (ASDAS) has been developed as a composite disease activity measure for axial spondyloarthritis (axSpA), as it incorporates inflammatory markers (preferably C-reactive protein - CRP) in addition to patient-reported outcomes. ASDAS high disease activity (≥2.1) has been suggested as a suitable disease activity cut-off for eligibility for tumour necrosis factor inhibitor's (TNFi) therapy in axSpA patients, but whether this is a better cut-off than the current standard (Bath Ankylosing Spondylitis Disease Activity Index - BASDAI ≥4) remains to be determined.

Aims The main aim of this project is to compare different disease activity cut-offs according to ASDAS and BASDAI in selecting patients for treatment with TNFi. Specifically, we will describe the demographic and clinical characteristics of the patients captured by each cut-off, as well as their response to TNFi.

Patients and methods Patients included in the longitudinal cohort of Reuma.pt (Portuguese Register of Rheumatic Diseases) with a clinical diagnosis of axSpA, according to their rheumatologist, who are starting the first TNFi, will be included. They will be grouped according to the ASDAS categories of disease activity and cross-tabulated with BASDAI (<4 and ≥4). The response rate at 3 and 6 months will be compared across the different subgroups as assessed by: ASDAS clinically important (Δ ASDAS≥1.1) and major improvement (Δ ASDAS≥2.0), ASAS 20 and ASAS 40 responses, ASDAS inactive disease (<1.3), ASAS Partial Remission and BASDAI 50 response (2-point and/or 50% improvement).

Expected results We expect that the results may contribute to improve the selection of patients for TNFi therapy as ASDAS high disease activity definition (≥ 2.1) seems to be promising in capturing patients with potential to respond to this treatment, otherwise missed by using only BASDAI (≥4).

1. Rationale

The ability of TNF inhibitors (TNFi) to reduce disease activity in patients with axial spondyloarthritis (axSpA), including both radiographic axial SpA (r-axSpA, also known as ankylosing spondylitis) and non-radiographic axial SpA (nr-axSpA), has been demonstrated in several randomized trials and meta-analyses [1-4]. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a patient-reported outcome (PRO) measure and has been commonly used to assess disease activity in axSpA. In the latest update Assessment of Spondyloarthritis International Society (ASAS) recommendations for the use of TNFi in axSpA, BASDAI ≥4 has been chosen as an eligibility criterion in addition to the clinician's expert opinion, failure of conventional therapy and absence of contraindications[5]. However, this cut-off is largely arbitrary and the BASDAI has been criticized for being solely patient reported. Previous studies suggest that demographic and disease characteristics such as C-reactive protein (CRP) may influence response to TNFi and could, therefore, help to select the best candidates for treatment with these drugs[6-11]. The Ankylosing Spondylitis Disease Activity Score (ASDAS) has been more 'recently' developed and incorporates inflammatory markers (preferably CRP) in addition to PRO (back pain, duration of morning stiffness, patient global assessment and peripheral joint pain). An ASDAS high disease activity (≥2.1) has been suggested as a suitable

cut-off for eligibility for TNFi therapy, but whether this is a better cut-off than BASDAI ≥4 is still a matter of intense debate in the scientific community. A previous large cross-sectional study on patients with r-axSpA has shown that ASDAS high disease activity (≥ 2.1) captures more patients otherwise missed by BASDAI (≥4) with only few being 'lost' (210/37% patients had ASDAS ≥2.1 with BASDAI<4 and only 32/5,4% had BASDAI ≥4 with ASDAS <2.1)[11]. These results suggest that ASDAS ≥2.1 is more sensitive as compared to BASDAI, but the authors failed to address the next relevant question: will the additional patients captured by ASDAS benefit from treatment, at least as much as the ones captured only by BASDAI, to justify using it as an (additional) eligibility criterion? A smaller cohort study attempted to address this issue in patients with axSpA according to the treating rheumatologist[12]. In this study, it was shown that patients who only fulfill the ASDAS criterion responded well to TNFi, but better results were seen in patients fulfilling both criteria. Moreover, the latter were younger, had lower BASFI and higher CRP levels, features that have been associated with a better response to TNFi[7,10]. These preliminary data suggest that using only BASDAI≥4 as the eligibility criterion (as done so far) excludes patients with a potential to benefit from TNFi therapy. Whether using ASDAS can give resolution to this issue needs further ascertainment and this concept embodies the overarching goal of this proposal.

2. Aims

2.1 Main aim

- To compare the TNFi eligibility criteria based on the ASDAS and BASDAI in patients with axSpA.

2.2 Specific aims

- To describe the demographic and clinical characteristics of patients grouped according to different cut-offs of disease activity by BASDAI and ASDAS.
- To assess the response to therapy with TNFi in each group

3. Global work plan for the entire project

The present study will be performed using data from the Rheumatic Diseases Portuguese Register (Reuma.pt) whose main goal is to register all rheumatic patients (treated with biological agents) in Portugal, ensuring effective monitoring of treatment indication, efficacy and safety. Reuma.pt has been described in detail elsewhere[13]. This register was launched in 2008 and continuously includes patients from almost all rheumatology departments in Portugal. Data from the previous years, from the introduction of the biologicals in rheumatoid arthritis in 2000 until 2008, have been collected on paper and later entered into the electronic register. These data have been collected according to a standardized, published protocol, which contained the same items as the ones included in the electronic register[14]. Reuma.pt is also used as an electronic patient chart or electronic medical record and, therefore, the frequency of observations of patients is not pre-determined. Assessments are made by rheumatologists, in general every 3-4 months, and include clinical information, such as monitoring of disease activity and function, medication, adverse events and comorbidities.

Additional clinical information is collected at baseline. Data refer to usual clinical practice without any intervention on the decision of the rheumatologists.

3.1 Study design

Prospective, multicentre, open cohort study.

3.2 Study population

The study will include all patients with axSpA according to their rheumatologist, registered in the Reuma.pt, starting their first TNFi. We will only take into account the patients who have the minimum data in order to assess treatment response (at least 3 months of follow-up).

3.2.1 Sample size

The 2015 Reuma.pt annual report had 2,326 patients registered with axSpA diagnosis, 957 of them using bDMARDs. This is the largest sample yet used to answer the proposed research question.

3.3.1 Analysis plan (summary)

Patients will be grouped according to the ASDAS categories of disease activity and cross-tabulated with BASDAI (<4 and ≥4) to compare subgroups with respect to: i) demographic (such as gender, age, education, smoking-status, alcohol consumption, BMI, comorbidities, date of diagnosis of axSpA, co-treatment at beginning of biologic) and clinical baseline characteristics (BASDAI, ASDAS, CRP, ESR, BASFI, SF-36, ASQoL, biological agent); and ii) TNFi response rate at 3 and 6 months (+/-90 days) as assessed by the ASDAS clinically important and major improvement (≥1.1 and ≥2.0 improvement respectively in ASDAS-CRP), ASAS 20 (≥20% and ≥1 unit improvement in ≥3 of the 4 domains physical function, pain, patient's global disease activity and inflammation, with no worsening ≥20% in the remaining domain), ASAS 40 responses (≥40% and ≥2 units improvement in ≥3 of 4 domains, with no worsening in remaining domain), ASDAS inactive disease (ASDAS<1.3), ASAS Partial Remission (<2 units in each of the 4 domains described above) and BASDAI 50 response (50% improvement in BASDAI).

3.3.2 Statistical analysis

Cross-tabulation reflecting baseline-characteristics and response to TNFi, according to BASDAI (≥4 e <4) and ASDAS (<1.3; ≥1.3 and <2.1; ≥2.1 and ≤3.5; >3.5), will be performed. This will enable the comparison of the above-mentioned characteristics for patients fulfilling the eligibility criterion according to the BASDAI with those that would be selected if the ASDAS was used.

Percentage response rates as well as mean change for continuous measures will be presented. Groups will be compared using chi-square test (for categorical variables) and independent sample t-test (for continuous measures) with correction for multiple-testing.

Stata software package will be used to analyse the data collected from this study. Continuous covariates will be reported as mean +/- standard deviation (or in case of non-normal distribution as median and quartiles). Nominal covariates will be displayed as proportions. p-values less than 0.05 will be considered significant.

3.3.3 Variables

Table I. Variables to be collected

Variables to be collected	
Baseline patient characteristics	• Demographic (gender, age, race, education, smoking-status, alcohol consumption, familiar antecedents, BMI, comorbidities, date of diagnosis of axSpA, date of beginning of symptoms, co-treatment and previous medication at beginning of biologic) • Clinical (BASDAI, ASDAS, CRP; ESR, BASFI, SF-36, ASQoL
Biological therapy	• Biological agent • Starting date of treatment • Stop date and reasons for discontinuation • Doses used • Frequency of administration • ASDAS improvement (clinically important and major improvement) • ASDAS inactive disease • BASDAI 50 response. • ASAS 20 and ASAS 40 responses and ASAS Partial Remission

3.3.4 Approximate duration of the study

Timelines for the several steps of this project are presented in Table II. Globally, this study will take 6 - 8 months to be concluded.

Table II. Timeline

	September-October	November-December	January-February
Data extraction			
Data analysis			
Final report/publication			

4. Expected results

We expect that the results may contribute to improve the selection of patients for TNFi therapy as ASDAS high disease activity definition (≥ 2.1) seems to be promising in capturing patients with potential to respond to this treatment, otherwise missed by using only BASDAI (≥4). Hopefully, our conclusions may be a step further to the inclusion of validated measures

(as CRP/ESR in ASDAS), in addition to the clinical expert opinion, when selecting patients for TNFi therapy.
Results will be submitted for presentation at the National Congress in Portugal and at main international congresses (EULAR and ACR). We expect to submit the manuscript to a moderate to high impact factor journal in the area of rheumatology.

5. Study limitations

The main limitation to the study is the possibility of missing data (information bias). The database has been previously optimized for other projects.

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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.

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