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General Information

Key Personnel (in addition to PI):

First Name: Dafne

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Degree: MD

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_yoda_4.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00265083 - C0524T09 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF \$\alpha\$ Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis](#)
2. [NCT00207701 - C0168T51 - A Randomized, Double-blind Trial of the Efficacy of REMICADE \(Infliximab\) Compared With Placebo in Subjects With Ankylosing Spondylitis Receiving Standard Anti-inflammatory Drug Therapy](#)
3. [NCT02186873 - CNT0148AKS3001 - A Study of Golimumab in Participants With Active Ankylosing Spondylitis](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Validating a Personalised Ankylosing Spondylitis Metrology Index.

Narrative Summary:

The aim of this study is to assess the psychometric properties of the newly developed Personalised Ankylosing Spondylitis Metrology Index (PASMI) and to compare them with the psychometric properties from BASMI and the individual spinal mobility measurements in RCTs of patients with axSpA treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs).

- a) To compare the construct validity of the PASMI, BASMI and individual spinal mobility measures in patients with axSpA
- b) To compare the discriminatory capacity of the PASMI, BASMI and individual spinal mobility measures in patients with axSpA

Scientific Abstract:

Background: Furthermore, in previous versions of the BASMI, the lower end of the reference range (0) for each measurement was supposed to represent the predicted 'normal' score, but it is now clear that these predicted values vary widely between individuals based on factors such as age, height, and gender. We therefore hypothesized that an adjusted version of the BASMI, taking age, height and eventually gender into account, would have better psychometric properties than the ones from the original BASMI.

Objectives: The aim of this study is to assess the psychometric properties of the newly developed PASMI and to compare them with the psychometric properties from BASMI and the individual spinal mobility measurements in RCTs of patients with axSpA treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs).

- a) To compare the construct validity of the PASMI, BASMI and individual spinal mobility measures in patients with axSpA
- b) To compare the discriminatory capacity of the PASMI, BASMI and individual spinal mobility measures in patients with axSpA

Study design: Data from RCTs fulfilling the eligibility criteria and available by the sponsors through public data repository (Vivli, YODA, ClinicalStudyDataRequest) will be analysed.

Participants: RCTs in patients with axSpA fulfilling the ASAS classification 2009 criteria or the modified New York criteria with available data of spinal mobility.

Different RCTs with diverse subpopulations of axSpA (early axSpA, established axSpA, non-radiographic axSpA (nr-axSpA), radiographic axSpA (r-axSpA), axSpA (complete spectrum) will be assessed.

Patients with available data of spinal mobility assessments at baseline and at the timing of the primary endpoint will be included.

Outcomes: The following mobility measurements will be assessed at baseline and at timing of the primary endpoint: BASMI and the following individual mobility measures: tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lateral spinal flexion, intermalleolar distance and the occiput to wall distance.

Statistical analysis: The psychometric properties will be assessed according to the OMERACT filter.

For the construct validity analysis, hypotheses of correlation strength will be formulated between BASMI/PASMI components and disease activity, functional ability, spine radiographic damage, as well as age, symptom duration and height (weak, moderate, strong). Then, Spearman correlation (or Pearson) will be calculated and the compliance of the hypothesis will be checked. Correlation will be considered low if ≤ 0.30 , moderate if > 0.30 and < 0.69 , strong if ≥ 0.70 .(7)

To assess the construct validity of the indices and spinal mobility measures patients groups will be compare (low and high disease activity, low or high functional impairment, high or low structural damage) the standardised mean difference (SMD) will be calculated (difference of the group means divided by the pooled SD of the group means). For the longitudinal construct validity, the Guyatt's effect size (ES) will be calculated as a measure of sensitivity to change. Guyatt's ES is the mean change in the active treatment group divided by the SD of the change in the placebo group. Lastly, subgroups analyses, similar to the described main analyses, will be performed by stratifying

the population in different subgroups.

Brief Project Background and Statement of Project Significance:

The Bath Ankylosing Spondylitis Metrology Index (BASMI) has been widely used in research into axial spondyloarthritis (axSpA) since it was first published in 1994.(1) It is a composite index of four spinal measures (cervical rotation, tragus to wall distance, modified Schober's test and lateral lumbar flexion) and one hip mobility test (intermalleolar distance). Although these tests have been validated as repeatable and clinically relevant, doubts remain about the responsiveness of BASMI particularly in trials studying patients with early axSpA and non radiographic axSpA (nr-axSpA). Several recent trials have failed to report any mobility tests and they have now been 'demoted' from the mandatory ASAS 'core domains' recommended for inclusion in all axSpA therapeutic studies, and included as important but optional for all trials.(2) Some of the reasons for this change are the floor effect, particularly in patients with short disease duration, the lack of standardisation and poor reliability and sensitivity to change.(3) Furthermore, in previous versions of the BASMI, the lower end of the reference range (0) for each measurement was supposed to represent the predicted 'normal' score (except for tragus to wall distance, that corresponds to the lower end), but it is now clear that these predicted values vary widely between individuals based on factors such as age, height, and gender. This has been shown even in a population of normal individuals, in the MOBILITY study, in which spinal mobility measures were shown to be influenced by age, and several also by gender and height. Consequently, no normal individual had a fully normal BASMI, i.e., BASMI linear score of zero.(4)

We therefore hypothesized that an adjusted version of the BASMI, taking age, height and eventually gender into account, would have better psychometric properties than the ones from the original BASMI. As a first step of this project, the Personalised Ankylosing Spondylitis Metrology Index (PASMI) was developed. The PASMI allows, by adjusting each individual spinal mobility measure for age, height and gender, as appropriate, to deliver a more 'truthful' representation of spinal mobility for each individual. The aim is now to validate the PASMI and assess its psychometric properties, particularly in comparison to the ones from the BASMI and the individual spinal mobility measures.

Construct validity of PASMI is being assessed in cohorts of patients with established axSpA, early axSpA and also of normal individuals. As part of the measurement properties assessment according to the OMERACT filter previously mentioned(6), we need to proceed by conducting analyses to assess the discriminatory effect of the PASMI in patients included in RCTs. With this data request, we aim to obtain access to RCT data (including data on the individual BASMI components, demographic data – age, gender and height, and treatment allocation) in order to analyse the psychometric properties of PASMI.

Specific Aims of the Project:

The aim of this study is to assess the psychometric properties of the newly developed PASMI and to compare them with the psychometric properties from BASMI and the individual spinal mobility measurements in RCTs of patients with axSpA treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs).

- a) To compare the construct validity of the PASMI, BASMI and individual spinal mobility measures in patients with axSpA
- b) To compare the discriminatory capacity of the PASMI, BASMI and individual spinal mobility measures in patients with axSpA

What is your Study Design?:

Individual trial analysis

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Develop or refine statistical methods

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

RCTs in patients with axSpA fulfilling the ASAS classification 2009 criteria or the modified New York criteria with available data of spinal mobility.

Different RCTs with diverse subpopulations of axSpA (early axSpA, established axSpA, non-radiographic axSpA (nr-axSpA), radiographic axSpA (r-axSpA), axSpA (complete spectrum) will be assessed.

Patients with available data of spinal mobility assessments at baseline and at the timing of the primary endpoint will be included.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcomes:

- Tragus-to-wall (TTW)
- Occiput to wall (OTW)
- Lumbar side flexion (LSF)
- Lumbar flexion (Schober test)
- Cervical rotation (seating) (CR)
- Intermalleolar distance (IMD)

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

- Sociodemographic and clinical characteristics
 - Age
 - Gender
 - Height
- Symptom and disease duration

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

- Disease subtype
 - nr-axSpA
 - r-axSpA
- Disease activity
 - BASDAI
 - ASDAS
- Functional ability
 - BASFI
- Structural damage
 - mSASSS
 - number of syndesmophytes
- Treatment
 - Previous treatment (TNFi, IL17i, JAKi)
 - Current treatment (TNFi, IL17i, JAKi)

Statistical Analysis Plan:

The psychometric properties will be assessed according to the OMERACT filter.

For the construct validity analysis, hypotheses of correlation strength will be formulated between BASMI/PASMI components and disease activity, functional ability, spine radiographic damage, as well as age, symptom duration and height (weak, moderate, strong). Then, Spearman correlation (or Pearson) will be calculated and the compliance of the hypothesis will be checked. Correlation will be considered low if ≤ 0.30 , moderate if > 0.30 and < 0.69 , strong if ≥ 0.70 .(7)

To assess the construct validity of the indices and spinal mobility measures patients groups will be compare (low and high disease activity -ASDAS <1.3 vs ASDAS >3.5 -, low or high functional impairment -BASFI <3 vs >6) , high or low structural damage -syndesmophytes ≤ 1 vs >5 -) the standardised mean difference (SMD) will be calculated (difference of the group means divided by the pooled SD of the group means). The SMD is unitless and can be

used to compare the construct validity across the various measures: the higher the value, the greater the construct validity.

For the longitudinal construct validity, the Guyatt's effect size (ES) will be calculated as a measure of sensitivity to change. Guyatt's ES is the mean change in the active treatment group divided by the SD of the change in the placebo group. Higher values indicate a better effect/noise ratio.

Lastly, subgroups analyses, similar to the described main analyses, will be performed by stratifying the population in different subgroups:

- 1) early vs established disease (where early disease is defined as symptom duration less than 3 years, and as a different cut-off, less than 5 years);
- 2) younger vs older patients (cut-off according to the median age of the population);
- 3) male vs female
- 4) bDMARDs naïve vs non bDMARDs naïve.
- 5) nr-axSpa vs r-axSpA
- 6) Current treatment (TNFi vs IL17i vs JAKi)

Software Used:

STATA

Project Timeline:

The present study will be carried out over a period of 12 months after we obtain the data from all eligible RCTs. The schedule will be as follows:

- 6 months: to prepare the databases and perform the statistical analysis.
- 6 months: to discuss the main findings and their interpretation and to prepare the manuscript to be submitted.

Dissemination Plan:

The objective of this project is the presentation of a manuscript to be submitted in high impact factor journals in the field of Rheumatology, as well as presented in Annual International Congress (ACR, EULAR, Ghent). Some potential journal for submission are: Annals of Rheumatic Diseases, Rheumatology Oxford, Journal of Rheumatology, Seminars of Rheumatic Diseases.

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4. Ramiro S, van Tubergen A, Stolwijk C, van der Heijde D, Royston P, Landewé R. Reference intervals of spinal mobility measures in normal individuals: the MOBILITY study. *Ann Rheum Dis.* 2015;74(6):1218-24.
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Supplementary Material:

https://yoda.yale.edu/sites/default/files/data_request-pasmi_score.pdf