Principal Investigator

First Name: Sofia
Last Name: Ramiro
Degree: Medical Doctor
Primary Affiliation: Consultant, Department of Rheumatology, Leiden University Medical Center
E-mail: diegobenavent90@gmail.com
Phone number: 0034685351866
Address:

City: Leiden
State or Province: Leiden
Zip or Postal Code: 2333
Country: the Netherlands

General Information

Key Personnel (in addition to PI):
First Name: Sofia
Last name: Ramiro
Degree: MD
Primary Affiliation: Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands. Department of Rheumatology, Zuyderland Medical Center, Heerlen, the Netherlands
SCOPUS ID: Ramiro, Sofía G.

First Name: Victoria
Last name: Navarro-Compán
Degree: MD
Primary Affiliation: Consultant, Hospital Universitario La Paz
SCOPUS ID: Navarro-Compán, Victoria

First Name: Diego
Last name: Benavent
Degree: MD
Primary Affiliation: Consultant, Hospital Universitario La Paz
SCOPUS ID: Benavent-Núñez, Diego

First Name: Dafne
Last name: Capelusnik
Degree: MD
Primary Affiliation: Department of Rheumatology, Instituto de Rehabilitación Psicofísica (IREP), Ciudad de Buenos Aires, Argentina
SCOPUS ID: Capelusnik, Dafne

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: The Assessment of SpondyloArthritis international Society (ASAS) supports the ASAS-SPEAR project.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_yoda_2.pdf

https://yoda.yale.edu/system/files/coi_yoda_sofia.pdf
https://yoda.yale.edu/system/files/pdf_dc.pdf
https://yoda.yale.edu/system/files/yoda_vnc.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-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis
2. NCT01248793 - C0524T29 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects with Ankylosing Spondylitis
3. 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
4. NCT02186873 - CNTO148AKS3001 - 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

SPondyloarthritis: EARly Definition (ASAS-SPEAR): Analysis of Symptom Duration Thresholds Using Pooled Data from Randomized Controlled Trials

Narrative Summary:

As a result of significant advances in the field of spondyloarthritis (SpA) researchers started using the terms ‘early axial SpA’ (axSpA) to refer to the first phase of the disease. Nevertheless, no consensual definition has been established. The ASAS-SPEAR (SPondyloarthritis EARly definition) project aims at proposing a consensus definition of ‘early axSpA’ to be employed in research, in order to avoid the use of arbitrary or heterogeneous definitions. To inform the final decision on the ‘early axSpA’ definition, we aim to evaluate the relationship between symptom duration and clinical response in patients with axSpA.

Scientific Abstract:

Background: The Assessment of SpondyloArthritis international Society (ASAS) identified the need to establish a standardized definition for the term ‘early axSpA’ in research setting. The ASAS-SPEAR (SPondyloarthritis EARly definition) project aims at proposing a consensus definition of ‘early axSpA’ to be employed in research, in order to avoid the use of arbitrary or heterogeneous definitions.
Objective: To evaluate the relationship between symptom duration and clinical response in patients with axSpA treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs).
Study design: A systematic review with meta-analysis will be performed. The SLRs conducted in the context of the ASAS-EULAR recommendations for the management of axSpA are used to identify eligible studies. This includes the SLR conducted for the ongoing, 2022 update of the recommendations. Inclusion criteria for the studies, following the PICO (Participants, Intervention, Comparator and Outcomes) framework.

Participants: Participants will be adult patients (age ?18 years) with axSpA categorized in early vs established disease based on symptom duration and with definitions using different cut-offs. Interventions will be treatment with bDMARDs, or tsDMARDs; comparator will be placebo. Main Outcome Measure(s): The primary endpoint of this SLR/meta-analysis will be ASAS40 at 6 months in treated patients compared with placebo for patients with early vs established disease.

Brief Project Background and Statement of Project Significance:

As a result of significant advances in the field of spondyloarthritis (SpA) researchers started using the terms ‘early axial SpA’ (axSpA) to refer to the first phase of the disease. Nevertheless, no consensual definition has been established. In this respect, the Assessment of SpondyloArthritis international Society (ASAS) identified the need to establish a standardized definition for the term ‘early axSpA’ in research setting. The ASAS-SPEAR (SPondyloarthritis EARly definition) project aims at proposing a consensus definition of ‘early axSpA’ to be employed in research, in order to avoid the use of arbitrary or heterogeneous definitions.
As a first step of this project, a systematic literature review (SLR) was conducted. This review had as objectives: 1) to identify all possible definitions used in the literature to define ‘early SpA’, including ‘early axSpA’ and ‘early pSpA’; 2) to summarize the evidence on the relationship between symptom/disease duration or the presence of radiographic damage and clinical treatment response in patients with axSpA. Two abstracts summarizing the results of the systematic literature review (SLR) will be presented at EULAR 2022 Congress (1,2). In addition, a full manuscript has been submitted for publication, another is in preparation.
The main conclusions of the SLR were that there is substantial heterogeneity in the definitions of ‘early SpA’ in the current literature, and that evidence on whether the duration of symptoms is related with different treatment outcomes is scarce and mostly inconclusive. Of note, when early was defined by disease duration or radiographic damage, no association with clinical treatment response was found. The results of this SLR were discussed among all ASAS members in the 2022 ASAS annual meeting. A voting took place, in which there was a consensus to pursue a definition of ‘early axSpA’. Additionally, the group voted this definition to be based on symptom duration. Currently, a Delphi survey among ASAS members is being conducted to decide on the details of this definition, as for example the final cut-off of this symptom duration (e.g. < 2 years).
To inform the final decision on the ‘early axSpA’ definition, one of the steps of the ASAS-SPEAR project is to conduct analyses to assess treatment outcomes according to the different thresholds of symptom duration in patients included in randomized controlled trials (RCT). In this sense, it is relevant to know whether patients who are treated earlier or later in the course of their disease (with a definition based on symptom duration) have different outcomes or response to treatment. This information is not readily available for most of the conducted trials as it is not part of the regulatory requirements. Relying on an SLR with published data only is subject to publication bias. We therefore want to systematically obtain data through the sponsors or authors from eligible trials. The latter are identified through the SLRs conducted in the context of the ASAS-EULAR recommendations for the management of axSpA (previously published SLRs and also the recent SLR performed as basis of the ongoing, 2022 update of the recommendations).

Specific Aims of the Project:

To evaluate the relationship between symptom duration and clinical response in patients with axSpA treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs):
a) To investigate whether symptom duration has an effect on treatment outcomes in patients with axSpA
b) To investigate whether there is a different efficacy of different b/tsDMARDs in patients with early vs established axSpA
c) To analyse whether the efficacy of different b/tsDMARDs in patients with early vs established axSpA differs according to different cut-offs of symptom duration

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

Research Methods

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

Data from patients with a diagnosis of axSpA who have duration of (axial) symptoms collected will be used. Patients will be categorized according to symptom duration, defined by the following thresholds: 1, 2, 3, 4 and 5 years of symptom duration. Patients with symptom duration below these thresholds will be considered early disease, whereas patients with symptom duration above these thresholds will be considered established disease, for each of the analysis. Hence, a patient might be included as early disease in one analysis and as established disease in other analysis, depending on the cut-off used.

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

The primary endpoint of this SLR/meta-analysis will be ASAS40 at 6 months in treated patients compared with placebo for patients with early vs established disease. Secondary endpoints, also at 6 months, are: ASAS20, ASAS 5/6, ASAS partial remission, change (from baseline) in Ankylosing Spondylitis Disease Activity Score (ASDAS), ASDAS clinical important improvement, ASDAS major improvement, achievement of ASDAS<2.1, achievement of ASDAS-inactive disease, change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), BASDAI50, change in Bath Ankylosing Spondylitis Functional Index (BASFI), change in C-reactive protein (CRP), change in the Bath Ankylosing Spondylitis Metrology Index (BASMI), change in ASAS Health Index (ASAS-HI), change in Ankylosing Spondylitis Quality of Life (ASQoL), change in European Quality of Life-5 Dimensions (EQ-5D), and change in the 36-Item Short Form Health Survey (SF-36), physical and mental components. Depending on the data from the original studies, different timing of endpoints may be analysed.

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

- ASAS response criteria (ASAS40) achievement (yes/no) at 6 months.

Separate analyses will be conducted for different thresholds of disease duration , when possible, i.e. when the data allows such a comparison

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

- Socio-Demographic and clinical characteristics:
-- Symptom duration (with different thresholds)
- Age
- Gender
- Presence of any syndesmophyte
- bDMARD-IR

- Disease subtype: r-axSpA, nr-axSpA
- Disease activity:
- ASAS response criteria (ASAS20, ASAS40, ASAS5/6 and ASAS partial remission)
- Change in Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP)
- ASDAS response criteria (clinical important improvement - ASDAS-CII [ASDAS ? ?1.1] and major improvement - ASDAS-MI [ASDAS ? ?2.0])
- ASDAS <2.1 and ASDAS inactive disease (ID) (ASDAS < 1.3)
- Change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (0-10)
- BASDAI 50 (? 50% improvement on the initial BASDAI).
- Change in C-reactive protein (CRP)
- Function: Change in Bath Ankylosing Spondylitis Functional Index (BASFI)
- Spinal mobility: Change in Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Overall functioning and health: Change in ASAS Health Index (ASAS-HI) (0-17), change in Ankylosing Spondylitis Quality of Life (ASQoL) (0–18), change in EQ-5D (?0.224-1), change in SF-36 PCS and MCS (0-100) (0-10)

Statistical Analysis Plan:

The analysis will have 2 steps: 1) analysis at the individual study level; 2) meta-analysis of all included studies. From the individual included RCTs, aggregated data will be computed based on the above-mentioned outcomes at the timing of the primary endpoint as well as baseline characteristics of the included patients (age, gender, symptom duration) in each treatment arm. Missing data will be imputed using the non-responder imputation (NRI) method for categorical outcomes.

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Concerning outcomes, for categorical variables relative risk (RR) (ratio of the incidence in the early group and the incidence in the established group) will be calculated for the groups of active treatment and placebo (3). Additionally, relative risk ratios (RRR) will be calculated, representing the treatment effect [active vs placebo] between the two groups [early vs established]), together with the 95% confidence interval (95% CI) (4,5). Number needed to treat (NNT) (number of patients we need to treat in order to achieve one additional patient reaching the outcome) will be assessed (6). For the continuous variables, differences in differences (DID), which represent the difference between treatment effect in early and established disease, will be calculated (7).

Making use of the aggregated data from each trial, pooled analyses will be performed (8). Pooled RR and RRR, as well as DiD will be estimated using fixed (I2 <50%) or random (I2 ?50%) effects depending on the heterogeneity of the studies.

Sensitivity analyses: we plan to assess the primary and secondary endpoints in defined subgroups, if the obtained data allows it:
i) Stratified by SpA phenotype, i.e. separately for r-axSpA and nr-axSpA
ii) Stratified by the presence of any syndesmophyte
iii) Stratified by drug class, i.e. separately for patients treated with TNF inhibitors, IL-17 and JAK inhibitors
iv) Stratified by bDMARD experience, i.e. separately for patients with inadequate response to non-steroidal anti-inflammatory drugs (NSAID-IR) and patients with inadequate response to bDMARDs (bDMARD-IR)

R-Cran V.3.5.1 software and the package ‘meta’ will be used for the statistical analysis.
Software Used:
R

Project Timeline:

The present study will be carried out over a period of 10 months after we obtain the data from all eligible RCTs. The schedule will be as follows:
- 5 months: to prepare the database and perform the statistical analysis.
- 5 months: to discuss the main findings and their interpretation and to prepare the manuscript to be submitted.

Dissemination Plan:

A manuscript including a meta-analysis of the eligible studies will be published. Suitable journals: Annals of the Rheumatic Diseases, Rheumatology.

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