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Research Protocol

Imaging in a Cohort of Real-World Patients with Spondyloarthritis from Five European Countries - Protocol for the European Spondyloarthritis Research Collaboration Network (EuroSpA) Imaging Project

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Abstract

Background: Magnetic resonance imaging (MRI) and radiography of the sacroiliac joints and spine play a key role when diagnosing and monitoring patients with spondyloarthritis (SpA) in routine clinical practice and clinical trials. However, much of the knowledge on the use of imaging in clinical practice is based on clinical trials, rather than on the more heterogeneous group of real-world patients.

The EuroSpA Research Collaboration Network, consisting of 17 European registries collecting clinical data on patients with axial SpA (axSpA) and psoriatic arthritis (PsA), has created an imaging sub-group to combine the clinical data in the registries with imaging data. The overarching aim of this initiative is, through the collection and analysis of sacroiliac joints and spine radiographs and MRIs in a very large cohort of patients with SpA followed in routine practice across several European countries, linked to clinical data, to answer a series of research questions on the pattern of disease, and the quality, reliability, and value of imaging for prediction and monitoring in routine care.

Methods: MRI and radiographs of the SIJs and spine from approximately 2800 patients with axSpA and PsA followed in routine care in five different European countries (Czech Republic, Denmark, Iceland, Slovenia, and Switzerland) are collected along with clinical data. The images are pseudonymized locally and transferred to the coordinating center in Copenhagen, where they are quality-checked and sorted. Images are evaluated in an online DICOM viewer and scored using an online platform according to the principles of the established and validated scoring systems. In addition, questionnaires regarding diagnosis, lesions and differential diagnoses are answered. All images are read by at least two readers and adjudicated if there is disagreement about diagnosis/differential diagnosis. Both cross-sectional and longitudinal readings are performed.

Discussion: This EuroSpA Imaging collaboration combines clinical and imaging data on thousands of routine care patients and offers unprecedented opportunities for studying numerous aspects of SpA, which we believe will contribute to a better understanding of how imaging is and should be used in SpA and thereby improving diagnostics and an optimization of management in patients with SpA.

Keywords: Spondyloarthritis; Psoriatic Arthritis; Imaging; Magnetic Resonance Imaging; Radiography

Abbreviations

MRI: Magentic Resonance Imaging; SpA: Spondyloarthritis; axSpA: Axial Spondyloarthritis; PsA: Psoratic Arthritis; DICOM: Digital Imaging and Communication in Medicine; IBD: Inflammatory Bowel Disease; SIJ: Sacroiliac Joint; HLA-B27: Human Leukocyte Antigen B27; PRO: Patient Reported Outcome; r-axSpA: Radiographic Axial Spondyloarthritis; nr-axSpA: Non-Radiographic Axial Spondyloarthritis; AS: Ankylosing Spondylitis; mSASSS: Modified Stoke Ankylosing Spondylitis Spine Score; TNF: Tumor Necrosis Factor; IL: InterLeukin; EuroSpA: European Spondyloarthritis Research Collaboration Network; eCRF: electronic Case Report File; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drug; bDMARD: biologic Disease Modifying Anti-Rheumatic Drug; T1w: T1 Weighted; STIR: Short Tau Inversion Recovery; T2wFS: T2 weighted Fat Saturated; ICC: Interclass Correlation Coefficient; SPARCC: SpondyloArthritis Research Consortium of Canada; mNY: Modified New York; ASAS: Assessment of Spondyloarthritis International Society; SSS: Sacroiliac joints Structural Score; CANDEN: Canada-Denmark; DVU: Disco-Vertebral Unit; PACS: Picture Archiving and Communication System; CASPAR: Classification for Psoriatic Arthritis; HAQ: Health Assessment Questionnaire; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; DAS28: Disease Activity Score in 28 Joints; DAPSA28: Disease Activity Index for Psoriatic Arthritis in 28 Joints; DAPSA: Disease Activity Index for Psoriatic Arthritis; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score;

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TRIPOD: Transparent Reporting of a multivariable prediction model for individual Prognosis or Diagnosis

Introduction

Axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) are part of the spondyloarthritis (SpA) group of disorders, which also include arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated SpA. These diseases share several common features such as association with human leukocyte antigen B27 (HLA-B27), inflammatory involvement of the axial skeleton, peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis, and IBD. A cornerstone is the involvement of axial and/or peripheral joints and entheses [1-4].

In patients with axSpA, inflammation in the bone marrow of the sacroiliac joints (SIJs) and spine is characteristic of the disease and is associated with back pain, stiffness, and impaired function; ankylosis may develop over time causing severe loss of function [3,5]. Patients with PsA may solely present with peripheral disease, while others demonstrate involvement of both the peripheral and axial joints and entheses. The prevalence of axial disease in patients with PsA varies with disease duration and the definition used, and has been reported to occur in 5–28% of patients with early disease [6] and 25–70% of patients with longstanding PsA [7].

Evaluation of axial disease in both axSpA and PsA is done by clinical assessment, patient-reported outcomes (PROs) and imaging. The imaging modalities used in clinical practice are radiography and MRI. Radiography only allows evaluation of structural damage of the SIJs and spine [8]. Depending on the presence or absence of characteristic findings on SIJ radiography, axSpA can be divided into radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA). R-axSpA is largely identical to ankylosing spondylitis (AS) [4]. Despite its widespread and ongoing use for many decades, radiography of the SIJs has several limitations; firstly, there is a low to moderate inter-reader agreement, even between expert radiologists [9-11], and secondly, radiography is unable to detect structural changes early in the disease course. Since radiography only visualizes structural changes that become visible later in the disease course (i.e, early changes as inflammation or early structural joint damage remain undetected) the diagnosis is considerably delayed when radiography is the only modality used [12,13]. Furthermore, radiography involves ionizing radiation. MRI on the other hand can demonstrate both inflammatory lesions, i.e., active disease, and structural changes in the SIJs and the spine early in the disease course and MRI has better inter-reader agreement than radiography [14,15]. Therefore, MRI is highly relevant for diagnostic purposes to obtain an earlier diagnosis as well as for sensitive monitoring of disease activity and treatment response. Since other conditions may resemble early SpA, the interpretation of MRI of the SIJs requires careful consideration and training of readers, both when used for diagnostic and scientific purposes [16-18].

Scoring systems for radiography and MRI of the SIJs and spine have been developed and validated and are widely used in research [19-23].

Radiography of the spine has been used to monitor disease progression in axSpA/AS cohorts and trials. The sensitivity to change is, however, very limited, even when using the internationally recommended scoring method (the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [23], as it is generally accepted that it requires at least 2 years of follow-up to detect a change/progression in damage [24,25]. Since a 2-year period of placebo therapy is not ethically justifiable, placebo-controlled randomised controlled trials with radiographs as an outcome have never been undertaken in axSpA/AS. Thus, it has not been possible to formally study a structure-modifying effect of any therapies using radiography, but radiography has been used for long-term follow-up regarding progression in structural lesions in both the SIJs and spine after initiation of treatment [26-29].

In the first-ever head-to-head trial of two biologics in axSpA with radiography as the primary endpoint, the SURPASS trial, the tumor necrosis factor (TNF) inhibitor adalimumab and interleukin (IL) 17A inhibitor secukinumab were recently compared, with radiographic progression over two years using the mSASSS method as the primary endpoint. No difference in radiographic progression after two years was observed between the treatments [30].

In clinical trials and cohorts, MRI can be used for monitoring changes in inflammation in the SIJs and spine, and significant differences between active therapy and placebo have been observed as early as six weeks after treatment initiation [21,31]. Therefore, MRI is nowadays often used as an outcome measure

for monitoring treatment effects in axSpA clinical trials [32-35]. Furthermore, the presence of axial MRI inflammation at baseline is a predictor for clinical treatment response [36]. As mentioned above, structural changes on SIJs are visible earlier on MRI than on radiography and with better inter-reader agreement therefore structural changes on MRI are well-suited as an outcome measure of disease progression [37-40]. In addition, MRI is used as an inclusion criterion in some clinical trials of patients with axSpA or axial PsA to ensure presence of active axial disease before inclusion and initiation of treatment [41].

Patients included in clinical trials differ markedly from patients in routine clinical practice, since they are enrolled with strict inclusion and exclusion criteria. In contrast, patients followed and treated in routine care constitute a heterogenous population with a broad spectrum of various comorbidities, varying disease activity, and concomitant medications. It has been shown that less than half of patients treated with biologics in clinical practice meet the inclusion criteria of randomised controlled trials [42,43]. Images are generally not a part of registry data, thereby making registry-based studies on imaging data difficult and comprehensive. Such studies would be highly relevant since imaging is widely used in routine clinical practice for diagnosing and monitoring patients and much of the evidence for this use is from clinical trials, whereas the full spectrum of real-world patients might have different and more varied imaging findings.

The European Spondyloarthritis Research Collaboration Network (EuroSpA) comprises registries from 17 European countries. The registries were established between 1999 and 2013 and the start of data capture varies by registry and by clinical diagnosis. Data in all registries are collected prospectively through web-based electronic case report forms (eCRFs) or paper forms. Registries collect information on the clinical diagnosis (AS, nr-axSpA or PsA), demographics, PROs, clinical data, biomarkers (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), HLA-B27), and applied treatments with biological and conventional synthetic disease-modifying anti-rheumatic drugs (bDMARDs and csDMARDs) [44-46]. EuroSpA offers unprecedented opportunities for providing real-world evidence on European patients with axSpA and PsA by combining clinical data with imaging. The EuroSpA imaging initiative has been created to extend these opportunities by including imaging data as well.

Five registries (ATTRA (Czech Republic), Danbio (Denmark), ICEBIO (Iceland), biorx.si (Slovenia), Swiss Clinical Quality Management (SCQM (Switzerland)) are part of the imaging collaboration in EuroSpA. Detailed information on the registries can be found in Supplementary table S1. Enriching the clinical dataset in the well-established EuroSpA Research Collaboration Network with imaging data from patients followed in routine practice in the registries, creates a unique opportunity to study numerous aspects of SpA, including the pattern of disease in routine care patients, and the quality, reliability, and value of imaging for prediction and monitoring in routine management of SpA.

Country	Registry acronym	Registry title	Website
Czech Republic	ATTRA	Anti-TNF Therapy in Rheumatoid Arthritis	https://attra.registry.cz/index-en.php
Denmark	DANBIO	Danish Rheumatology Database	https://sdn.danbio-online.dk/front-page
Iceland	ICEBIO	Icelandic Nationwide Database of Biologic Therapy	
Slovenia	biorx.si	Slovenian registry	
Switzerland	SCQM	Swiss Clinical Quality Management in Rheumatic Diseases	https://www.scqm.ch/en/

Supplementary table S1.

Objective

The overarching aim of this initiative is, through collection and analysis of a very large set of SIJ and spine radiographs and MRIs in a large cohort of patients with SpA followed in routine practice across several European countries, linked to clinical data, to answer a series of research questions.

This overarching aim will be accomplished through sub-studies, addressing the aims described below.

Sub-aims

- To describe the occurrence, anatomical location, and pattern of inflammatory and structural MRI findings in the SIJ and spine in real-life patients with axSpA.
- To describe the occurrence, anatomical location, and pattern of inflammatory and structural MRI findings in the SIJ and spine in real-life patients with PsA and possible axial involvement.
- To compare centrally performed reads with local reads regarding classification and diagnosis as well as detection of individual lesions in patients with a registered diagnosis of axSpA or PsA.
- To compare damage on MRI and radiographs of SIJs and define an MRI SIJ classifier equivalent to the radiographic part of the modified New York criteria.
- To describe damage progression on MRI and radiographs of the SIJs.
- To compare damage and damage progression on MRI and radiographs of the spine and to explore whether an MRI spine structural score has similar performance as the radiographic mSASSS score.
- To develop prediction models for clinical response during treatment with TNF inhibitor and IL-17 inhibitor based on baseline clinical characteristics, CRP and imaging findings.
- To investigate predictors of structural progression based on baseline clinical characteristics, laboratory, and imaging findings.
- To explore the relationship between inflammatory and structural lesions, and structural damage progression, and age, disease duration, function, and patient-reported outcomes.

Methods/Design

Design

The project consists of collection and central reading of MRIs and radiographs from five European countries participating in the EuroSpA collaboration in order to undertake several retrospective, observational sub-studies. These studies are based on images (radiographs and MRIs) and clinical data, that have already been acquired as part of routine clinical practice, from patients with a clinical diagnosis of axSpA (i.e. axSpA cohort) or a clinical diagnosis of PsA with possible axial involvement (i.e. PsA cohort). This study will include approximately 2800 patients. Preliminary calculations estimated the inclusion of approximately 2300-2550 patients with axial spondyloarthritis (some of which may have a history of psoriasis or current psoriasis) and 250-500 patients with PsA with suspected axial involvement, defined as availability of MRIs of the axial skeleton.

Patients

All patients are required to be ≥18 years old at initial diagnosis to be included (Table 1).

Diagnosis	Registered diagnosis of axSpA or PsA in the clinical registries
Images	For axSpA patients: MRI of the SIJs with STIR or T2-weighted fat saturated and T1-weighted images. For PsA patients: At least one of the following two imaging examinations: MRI of the SIJs MRI of the entire spine (i.e. both cervical, thoracic and lumbar parts) For both, STIR or T2-weighted fat saturated and T1-weighted images are required
Treatment	No requirements for specific treatments, however if bDMARD treatment, this should be initiated in 2009 or later
Clinical data	Age, gender

Table 1: Inclusion criteria/requirements for patients in the EuroSpA Imaging project.

Abbreviations: axSpA: Axial Spondyloarthritis; PsA: Psoriatic Arthritis; MRI: Magnetic Resonance Imaging; SIJ: Sacroiliac Joint; STIR: Short Tau Inversion Recovery; bDMARD: Biological Disease Modifying Anti-Rheumatic Drug

Patients eligible for inclusion are identified based on their clinical diagnosis (axSpA or PsA) in the registries, and availability of appropriate images (see Table 1).

Collection and preparation of images

Procedures in the individual countries

Patients with a registered diagnosis of axSpA or PsA are identified, and their available images obtained from 2005 or later were reviewed. Inclusion of patients with axSpA require the availability of at least one MRI of the SIJs, including T1-weighted (T1w) and STIR/T2-weighted fat-saturated (T2wFS) images, whereas patients with PsA require the same or at least one MRI of the entire spine (i.e. cervical, thoracic, and lumbar), including T1w and STIR/T2wFS images to be included. The inclusion criteria are shown in table 1. All available MRIs and radiographs of the SIJs and the spine of the patients, who fulfill the inclusion criteria are collected and pseudonymized in each registry before transfer to the EuroSpA Coordinating Centre in Copenhagen via a secure server. In addition to the images, the local radiology reports are extracted, pseudonymized, and transferred, as are clinical data.

Procedures in the EuroSpA Coordinating Centre

Based on the image metadata and clinical data regarding diagnosis and treatment, reading lists for the sub-studies mentioned in the aims section are created by an image selection algorithm. The images on the reading lists are then quality checked. This entails control of image quality, scan plane and available sequences. If semi-coronal images of the SIJs are available, the following slices are selected for evaluation: from 1 cm visible joint anteriorly to 1 cm visible joint. This ensures that the readers score the same slices. In addition, all scans are split into SIJ and spine images, respectively, to ensure that the reader only has access to either the SIJs or the spine.

The images are divided into databases which are then sent to the readers, thereby ensuring that the reader can only access the relevant cases in the viewer and the scoring interface. Gender and age are provided to the reader in the scoring interface. The readers access the images in an online DICOM viewer dedicated to this project. An online scoring interface created for this purpose is used for answering a questionnaire (explained in detail below in figure 1) and b) entering detailed scores of the various pathologies (Figure 2).

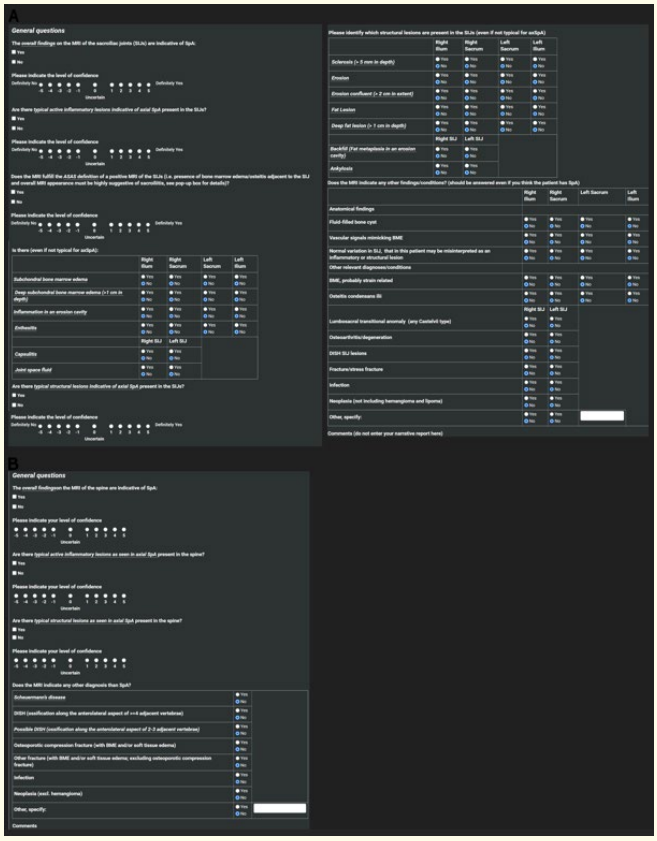

Figure 1: online scoring interface for the questionnaires.

The figure shows screenshots of the online scoring interface for the questionnaires concerning the sacroiliac joints (A) and the spine (B). Both questionnaires start with questions regarding readability and available sequences (not shown here).

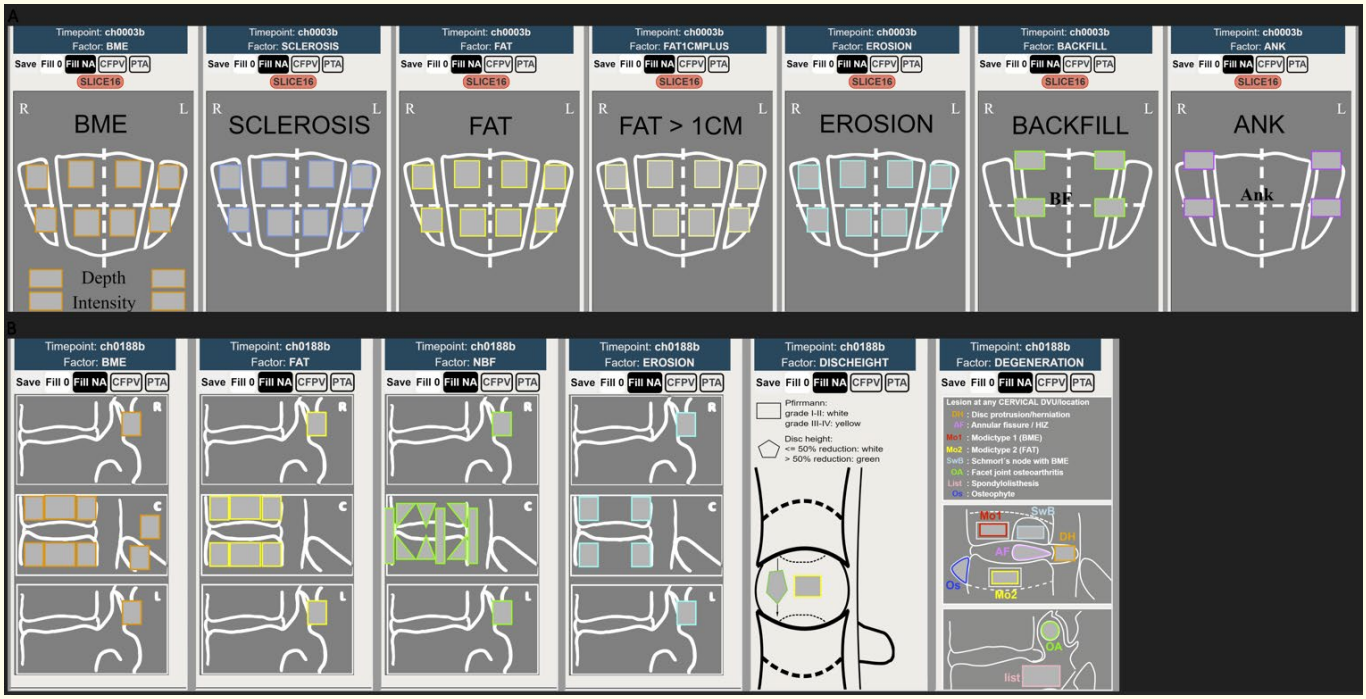

Figure 2: Online scoring interface for the detailed scoring.

The figure shows screenshots of the online scoring interface for the detailed scoring of the sacroiliac joint (SIJs) (A) and the spine (B). For the SIJs this is done for all slices from 1 cm visible joint anteriorly to 1 cm joint posteriorly. For the spine this is done for all disco vertebral units.

Readers

Readers are experienced musculoskeletal radiologists, expert readers with more than 5 years' experience or centrally trained less experienced readers. Centrally trained readers are defined as readers who are trained by experts with more than 10 years of experience in reading MRIs of the SIJs and spine, and who after centrally provided training (explained below) and calibration obtain a sufficient inter-reader agreement (assessed with intraclass correlation coefficient (ICC)) with an expert musculoskeletal radiologist.

All images (both cross-sectional and longitudinal) are assessed by two readers for both the questionnaire and the detailed scoring. For educational reasons, one reader with less experience do one of the two Spondyloarthritis Research Consortium of Canada (SPARCC) scorings of the SIJs, while all remaining reads are done by expert readers or musculoskeletal radiologists.

Before scoring, all readers are calibrated as explained below.

To train and calibrate multiple readers at one time in a systemized way, two studies are carried out: one for training SPARCC scoring of SIJ MRIs and one for the modified New York (mNY) grading of SIJ radiographs [47].

Readers of the spine, both MRI and radiographs, are all experienced prior to scoring in EuroSpA, and therefore no systemized training is done before scoring, only calibration.

Reading of MRIs

All MRIs (both SIJs and spine separately) are assessed by filling-in a questionnaire in addition to performing a detailed scoring of both inflammatory and structural lesions.

The SIJ and spine questionnaires contain questions on whether 1) the changes seen on the MRI are indicative of axSpA, and 2)

whether there are typical inflammatory lesions indicative of axSpA and 3) whether there are typical structural changes indicative of SpA. In relation to each of these, the reader should indicate the level of confidence on a scale from -5 (definitely no) to +5 (definitely yes). In addition, alternate diagnoses are registered with a fixed vocabulary for the most common differential diagnoses. For MRIs of the SIJs, fulfillment of the Assessment of SpondyloArthritis international Society (ASAS) imaging criteria, including level of confidence, and features defined by the ASAS working group [48-50] are also assessed in the questionnaire.

In the detailed scoring of the SIJs, the inflammatory lesions are assessed using the SPARCC MRI SIJ Inflammation Index [20] and the structural lesions (i.e. erosions, fat lesion, backfill, and ankylosis) by the SPARCC MRI SI Joint Structural Score (SSS) [19]. In addition, sclerosis is scored. The detailed scoring of the spine is done in accordance with the Canada-Denmark (CANDEN) [22] spine scoring system for both inflammatory and structural lesions (i.e. fat metaplasia, erosion, bone spurs, and ankylosis). In addition to this, disc height and Pfirrmann grade are assessed for each disco-vertebral unit (DVU) and different degenerative changes are assessed for each spinal segment (i.e. cervical, thoracic, and lumbar). See figure 2.

Reading of radiographs

Radiographs of the SIJs are assessed with the radiographic part of the mNY criteria (grade 0-4 for each SIJ) (4), moreover, the specific features in the criteria (erosion, sclerosis, joint space widening, joint space narrowing and ankylosis) are assessed. The readers judge whether the changes on the radiograph are indicative of axSpA or not, and the level of confidence will be registered in the same way as for MRIs, described above.

Radiographs of the spine are assessed according to the mSASSS method. Furthermore, differential diagnoses and whether the overall findings are indicative of SpA are registered in a questionnaire.

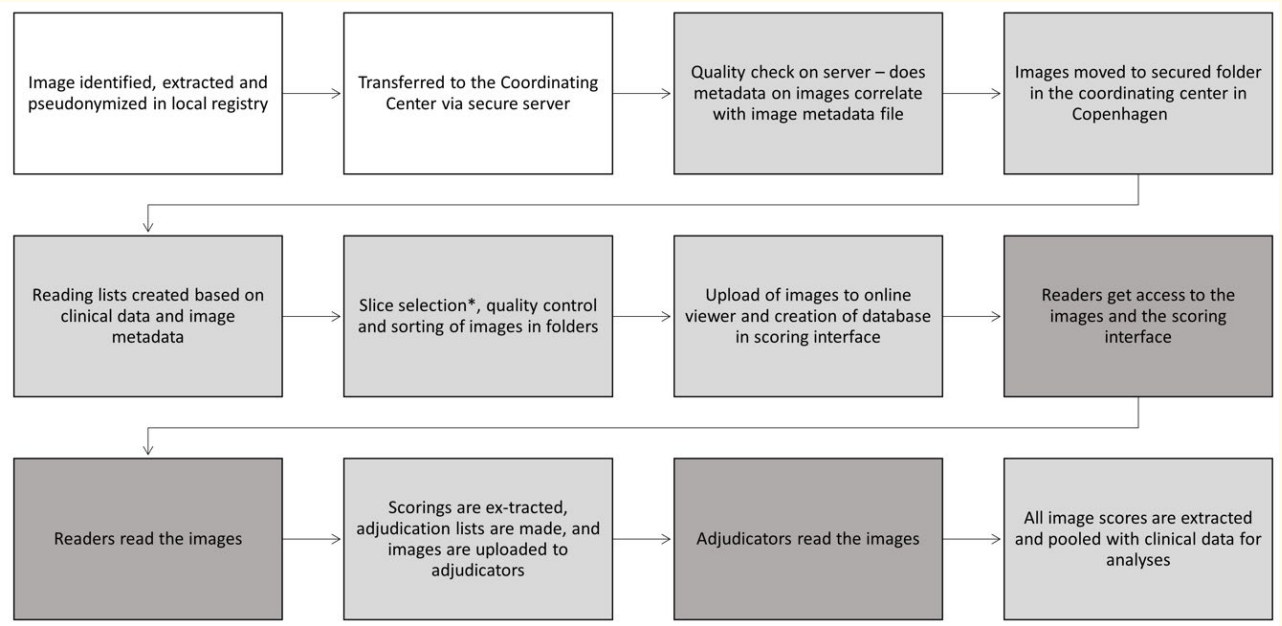

Figure 3: The path of an image from local PACS to central reading and data analysis.

White boxes are the procedures done in the local registries, grey boxes are done at the Coordinating Centre in Copenhagen, and the dark grey boxes are done by the readers. *If semi-coronal images of the sacroiliac joints are available, the following slices are selected for evaluation: from 1 cm visible joint anteriorly to 1 cm visible joint posteriorly.

Abbreviations: PACS: Picture Archiving and Communication System

Adjudication

MRIs are reviewed by an adjudicator if the readers disagree on whether the MRI is indicative of SpA or not and/or on fulfillment of the ASAS MRI criteria (only SIJ). Moreover, if at least one reader has registered either fracture, neoplasia, or infection in the differential diagnoses the MRIs will be adjudicated. Only the questionnaire will be adjudicated and not the complete SPARCC scoring. SIJ radiographs are adjudicated if readers disagree on whether the radiographs are positive/negative for the mNY criteria. Spine radiographs are adjudicated if readers disagree on whether the radiographic changes are indicative of SpA for the spine. For radiographs, the entire scoring will be done by the adjudicator.

The adjudicator is an experienced musculoskeletal radiologist (member of the ASAS/EULAR MRI group) who is blinded to assessments by previous readers.

The path of an image from identification to final scoring and merging with clinical data is shown in figure 3.

Clinical data

Clinical data are extracted locally in the registries, pseudonymized according to the IDs on the images, and transferred to the coordinating center. The following clinical data are included, if available:

- **Patient characteristics:** Age, gender, height, weight, smoking status, diagnosis, year of diagnosis, year of symptom onset, HLA-B27, extraarticular SpA features (psoriasis, uveitis, IBD), month and year of pregnancies, month and year of births.
- **Classification criteria:** Classification for Psoriatic Arthritis (CASPAR) criteria, ASAS criteria for axSpA, mNY criteria.
- **Disease activity measures:** CRP, ESR, patient pain, patient fatigue, patient global, physician global, Health Assessment Questionnaire (HAQ), number of swollen and tender joints (28 and 66/68), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), individual items of BASDAI, Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Disease Activity Score in 28 joints-CRP (DAS28-CRP), Disease Activity Score in 28 joints-ESR (DAS28-ESR), Disease Activity Index for Psoriatic Arthritis in 28 joints (DAPSA28), Disease Activity Index for Psoriatic Arthritis (DAPSA), Leeds Enthesitis Index (LEI), SPARCC enthesitis score and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).
- **Medication:** csDMARDs and bDMARDs (drug name, start and stop dates, reason for discontinuation). Switches between biosimilars of the same drugs are disregarded.

Each registry is urged to send the individual components of the composite measures rather than the composite measure. The composite measures are calculated centrally, to ensure similar calculation across registries.

Discussion

This study including real-world clinical and imaging data from approximately 2800 patients with SpA is to our knowledge the first of its kind. We believe that this study will bring unique knowledge on how imaging is and should be used in clinical practice in patients with SpA. Patients treated in routine care may differ from patients enrolled in randomized controlled trials in several aspects, e.g., by having less severe disease activity (less inflammation), by having longer disease duration (potentially more structural damage), by more patients more frequently having other non-inflammatory conditions, and by receiving less intensive monitoring and treatment (potentially having more inflammation and structural damage progression over time). Collecting and integrating a very large set of radiographs and MRIs assessed by semiquantitative methods and qualitatively by questionnaires in combination with clinical data will allow us to explore the intersections of patient characteristics, clinical features, imaging findings, treatment response, and patient outcomes in an unprecedented way.

Reading of such a high number of images by two to three readers per case is very time-consuming and requires the participation of multiple readers to complete the readings without an excessive delay. Therefore, many different readers are involved, which could be seen as a weakness since the readers have varying prior experience in scoring, potentially resulting in some variation between the reader pairs. However, it also reflects the real world, where not only the most experienced readers are assessing MRI and radiographic examinations. This potential weakness is partly

countered by systematic training and calibration exercises and by not allowing readers to score before a sufficient inter-reader reliability is achieved. In addition, adjudication by an experienced musculoskeletal radiologist ensures that the diagnosis, as judged from the images alone, is as accurate as possible. In this project, we have decided, for feasibility reasons, that only the most important differential diagnoses will be adjudicated in addition to disagreement on whether the images are indicative of SpA or not.

Since the clinical data in this project are collected prospectively in the different registries as part of routine clinical practice, the inherent challenge of missing clinical data in registry studies will also affect this study. Patients are included in the project in case of available pre-defined images, and there will be no missing imaging data, however, not all patients will have images that make them eligible for being a part of the analyses for all the sub-aims.

This collaboration across five European countries creates a unique opportunity to study numerous aspects of SpA, including the pattern of disease in routine care patients, and the quality, reliability, and value of imaging for prediction and monitoring in routine management of SpA.

Declarations

Ethics approval and consent to participate

All data from the participating registries that are sent to the coordinating center will be pseudonymized according to current guidelines. All participating registries will obtain the necessary approvals from data protection agencies, research ethics boards and/or other entities as required by national or local regulations prior to data transfer. In Denmark, the Danish Patient Safety Authority approved the project, ethics approval was waived. In Iceland, The National Bioethics Committee approved the project (18-009-V17). In Switzerland, imaging data in SCQM and EuroSpA was included in the ethics approval: Kantonale Ethikkommission, Kanton Zürich, BASEC-Nr: 2022-00272.

This study was designed and will be implemented and reported in accordance with the Good Pharmacoepidemiology Practices, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, the Transparent Reporting of a multivariable prediction model for individual Prognosis or Diagnosis (TRIPOD) Statement and with the ethical principles laid down in the Declaration of Helsinki.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

- AH: received grants from Novartis
- NV: received grants from Novartis
- MØ: received research grants from Abbvie, BMS, Merck, Novartis and UCB, and speaker and/or consultancy fees from Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Gilead, Hospira, Janssen, MEDAC, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB.
- RM: received honoraria for lectures or presentations from Abbvie, Janssen and Eli Lilly.
- BM: received travel expenditures, honoraria for lectures or presentations from Abbvie, Janssen, Novartis and Pfizer.
- MN: received honoraria for travel expenditures, lectures or presentations from Abbvie, Eli Lilly, Janssen, Novartis, Pfizer and UCB.
- SJP: received grants and contracts from Innovation Fund Denmark and Nordic Bioscience A/S, consulting fees, speaking fees, and/or research support from AbbVie, Novartis, MSD, Pfizer, and UCB.
- KB: received honoraria for lectures or presentations from Novartis, AbbVie, Eli Lilly, Pfizer, and Jansen.
- ZS: received honoraria for presentations from BioGen.
- LØ: received grants from Novartis and UCB paid to employer
- SR: received grants from Novartis paid to employer
- ZR: received consulting or speaker fees from Abbvie, Amgen, AstraZeneca, Boehringer, Biogen, Eli Lilly, Janssen, Medis, Novartis, Pfizer, Sandoz Lek, SOBI.

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Conceptualization: AH, SK, NV, AC, AS, KB, MG, SR, MN, RM, JZ, and MØ. Software: AH, MØ, SJP, SK, and NV. Data curation: AH, SK, NV, AC, AS, CT, KB, MG, SR, CT, MN, BM, ZS, KP, BG, ZR, and LØ. Writing – original draft: AH and MØ. Writing – review and editing: all authors. Funding: MØ and MH. Project administration: AH, SK, LØ and MØ

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