ASAS consensus definition of early axial spondyloarthritis

Navarro-Compán, V.; Benavent, D.; Capelusnik, D.; Heijde, D. van der; Landewé, R.B.M.; Poddubnyy, D.; ... ; Ramiro, S.

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Victoria Navarro-Compán [1,2] Diego Benavent [1,2] Dafne Capelusnik [3,4] Désirée van der Heijde [5] Robert BM Landewé [6,7] Denis Poddubnyy [8,9] Astrid van Tubergen [10,11] Xenofon Baraliakos [12,13] Filip E Van den Bosch [14,15] Floris A van Gaalen [5] Lianne Gensler [16] Clementina López-Medina [17,18] Helena Marzo-Ortega [19,20] Anna Molto [21,22] Rodolfo Pérez-Alamino,[23] Martin Rudwaleit [24] Marleen van de Sande,[25] Raj Sengupta [26] Ulrich Weber [27] Sofia Ramiro [5,7]

Handling editor Josef S Smolen

For numbered affiliations see end of article.

Correspondence to
Dr Victoria Navarro-Compán, Rheumatology, La Paz University Hospital, Madrid 28046, Spain; mvictoria.navarroc@gmail.com

Received 30 March 2023
Accepted 30 May 2023

To cite: Navarro-Compán V, Benavent D, Capelusnik D, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ard-2023-224232

ABSTRACT

Objectives To develop a consensual definition for the term 'early axial spondyloarthritis—axSpA'—and 'early peripheral spondyloarthritis—pSpA'.

Methods The ASAS (Assessment of SpondyloArthritis international Society-Spondyloarthritis EARly definition) steering committee convened an international working group (WG). Five consecutive steps were followed: (1) systematic literature review (SLR); (2) discussion of SLR results within the WG and ASAS community; (3) a three-round Delphi survey inviting all ASAS members to select the items that should be considered for the definition; (4) presentation of Delphi results to the WG and ASAS community and (5) ASAS voting and endorsement (2023 annual meeting).

Results Following the SLR, consensus was to proceed with an expert-based definition for early axSpA (81% in favour) but not for pSpA (54% against). Importantly, early axSpA should be based on symptom duration taking solely axial symptoms into account. 151–164 ASAS members participated in the Delphi surveys. Consensus was achieved for considering the following items within early axSpA definition: duration of symptoms ≤2 years; axial symptoms defined as cervical/thoracic/back/buttock pain or morning stiffness; regardless of the presence/absence of radiographic damage. The WG agreed that in patients with a diagnosis of axSpA 'early axSpA' should be defined as a duration of ≤2 years of axial symptoms. Axial symptoms should include spinal/buttock pain or morning stiffness and should be considered by a rheumatologist as related to axSpA. The ASAS community endorsed this proposal (88% in favour).

Conclusions Early axSpA has newly been defined, based on expert consensus. This ASAS definition should be adopted in research studies addressing early axSpA.

INTRODUCTION

Currently, spondyloarthritis (SpA) is split according to the predominant symptoms, as either axial SpA (axSpA) or peripheral SpA (pSpA).[1 2] One of the main challenges in the management of SpA has always been the identification of the disease at an early stage.[3 4] In this sense, axSpA is more challenging as it involves deep anatomical structures, where inflammation at this level is often only manifested by axial pain, such that both the patient and physician may either not recognise it or relate it to a possible axSpA. Historically, axSpA has been diagnosed at a later stage of disease, when persistent inflammation may have already caused structural damage visible on conventional radiographs. Consequently, the vast majority of patients previously included in research studies to date reflect established and longstanding disease.[5] However, thanks to more recent advances, especially the use of MRI, it is now possible to identify the disease earlier,[6] and this has been reflected in an increased representation of patients with shorter disease duration in clinical trials. However, when including patients in studies, it is important that they represent a homogenous population and, to date, there is no consensus on how to classify early axSpA patients. On the other hand, for pSpA the detection of disease manifestations by the patient and physician is less challenging as peripheral musculoskeletal abnormalities are easier to identify by a simple clinical examination. Nevertheless, classification criteria for pSpA emerged only about a decade ago,[2] and similarly, there is no consensus definition for classifying patients at an early stage of disease.

Recently, researchers started using the terms 'early axSpA' and 'early pSpA' to refer to the initial phase of the disease. Nevertheless, despite the increased use of these terms in research, no consensual definition has been established. For axSpA, the lack of a standardised definition has led to a substantial heterogeneity and arbitrary definitions being used in new studies by different stakeholders, including pharmaceutical industry and experts, which may be confusing.[7–12] In the context of pSpA, sometimes definitions used for rheumatoid arthritis (RA) are extrapolated[13]; however, the evidence to support this approach is unclear.

The growing interest in understanding the early disease stages of axSpA and pSpA highlights the need for standardised definitions of the terms 'early axSpA' and 'early pSpA'. The Assessment of SpondyloArthritis international Society (ASAS)-Spondyloarthritis EARly definition (SPEAR) project aimed to address this unmet need by developing a consensual definition for the terms 'early axSpA' and 'early pSpA' under the auspices of ASAS, to be used in a research setting.

METHODS

Working group

The two convenors (VN-C and SR) of the project invited an international steering committee, which convened the ASAS-SPEAR working group, formed in total by 20 ASAS members, including two fellows (DB

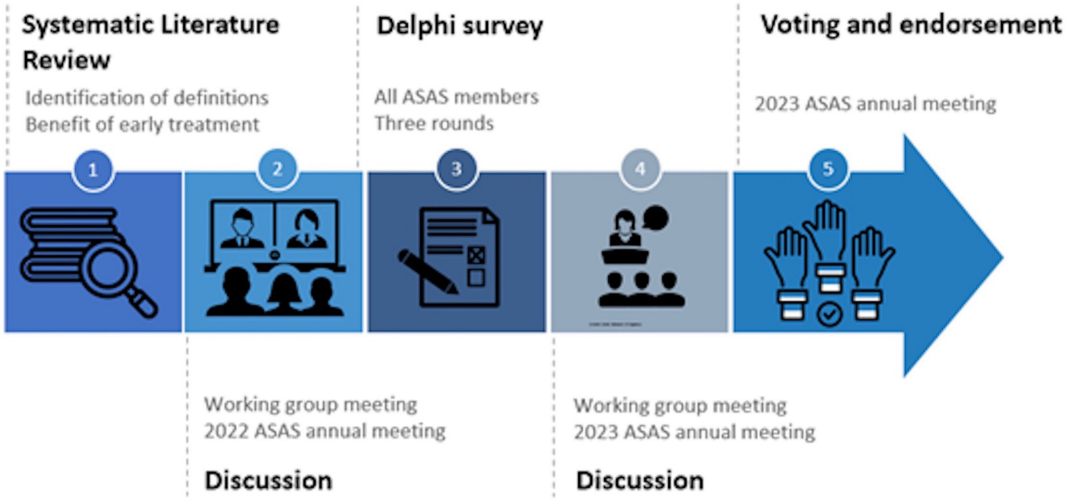

Figure 1 Development process of the ASAS consensus definition of early axial spondyloarthritis. ASAS, Assessment of SpondyloArthritis international Society.

and DC), rheumatologists and methodologists with special interest in SpA, and two representatives from Young ASAS.

The overall process to develop the definition term is shown in figure 1. Five consecutive steps were followed: (1) systematic literature review (SLR); (2) discussion of SLR results within the working group and ASAS community; (3) a three-round Delphi survey inviting all ASAS members to select the items that should be considered for the definition of the term; (4) presentation of the Delphi survey results to the working group and ASAS community and (5) ASAS voting and endorsement.

Systematic literature review

The first step of the project was to perform an SLR to address two different research questions relevant to the process. The first research question aimed to identify all possible definitions used in the published literature to define the terms early axSpA/pSpA. The objective of the second research question was to summarise the evidence on the relationship between early treatment (based on symptom/disease duration or radiographic damage) and clinical response to treatment in patients with SpA. Both SLRs have been reported in detail in two manuscripts.[14 15]

2022 working group and ASAS annual meetings

The results of the SLR were presented and discussed first within the working group (12 December 2021) and later with the entire ASAS community (14 January 2022). According to the ASAS bylaws, only full members participating in the meeting voted on the decisions to proceed with the definition development, requiring a simple majority for this specific purpose.

Delphi survey

Following the decision making, a three-round Delphi survey was conducted to find consensus on which items should be considered for the definition of the term. The survey was launched on 26 April 2022 (first round), 22 September 2022 (second round) and 4 November 2022 (third round), allowing 2 weeks to answer and sending at least one reminder. Each Delphi round was followed by a discussion of the results within the working group, leading to the adaptation of the questionnaire for the next round. The questionnaire was developed by the working group and asked to select or exclude 19 items relevant to the definition of the term, divided into three different aspects: cut-off point for duration of symptoms, axial symptoms (anatomic location and how to define these) and radiographic damage involvement. The final items included in the survey can be seen in table 1.

All ASAS members at the time of launching the survey (n=209) were invited. For the second and third rounds, all members were also invited, regardless of whether they had responded to the previous round(s).[16] Each participant was asked to rate each item using a 1–9 Likert scale, where 1 reflected complete disagreement with the inclusion of the item in the definition and

Table 1 Items included in the Delphi survey

I. symptoms cut-off	
a.	Early axSpA should be defined as a duration of symptoms of less than 1 year
b.	Early axSpA should be defined as a duration of symptoms of less than 2 years
c.	Early axSpA should be defined as a duration of symptoms of less than 3 years
d.	Early axSpA should be defined as a duration of symptoms of less than 4 years
e.	Early axSpA should be defined as a duration of symptoms of less than 5 years
f.	Early axSpA should be defined as a duration of symptoms of less than 10 years
g.	The upper boundary cut-off should be formulated as 'less or equal'
II. Axial symptoms	
a.	Axial symptoms should also include buttock pain
b.	Axial symptoms should also include hip pain
c.	Axial symptoms should also include shoulder pain
d.	Axial symptoms should also include morning stiffness
e.	Axial symptoms should also include spinal mobility impairment
f.	Axial symptoms should include inflammatory and non-inflammatory back pain
g.	If pre-existing chronic back pain, but later development of 'inflammatory' symptoms, date of onset would be considered as the onset of chronic back pain
h.	Axial symptoms should include thoracic pain
i.	Axial symptoms should include cervical pain
j.	Axial symptoms should be defined by a rheumatologist
III. Radiographic damage	
a.	A patient with axSpA with axial symptoms <2 years has early axSpA regardless of the presence or absence of radiographic damage of the SIJ
b.	A patient with axSpA with axial symptoms <2 years has early axSpA regardless of the presence or absence of syndesmophytes on radiographs of the spine

axSpA, axial spondyloarthritis; SIJ, sacroiliac joints.

9 complete agreement. Consensus on acceptance was achieved if 70% or more of the responses fell within 7–9 (completely agree). Consensus on rejection was achieved if 70% or more of the responses fell within 1–3 (completely disagree).

2023 working group meeting

After the final round of the Delphi, the results were discussed again, first within the working group, during a virtual meeting on 15 December 2022, and later with the entire ASAS community at the ASAS annual meeting, which was held in Athens on 13 January 2023 and 14 January 2023. During the discussions, a formulation for the definition was proposed, which was edited until a final consensus within the working group was reached.

ASAS voting

The definition proposal from the working group was presented, discussed by the entire ASAS community at the 2023 annual meeting and again edited until a final proposal was reached. Full ASAS members attending the meeting voted on the final proposal.

RESULTS

Systematic literature review

The results of the SLR have been published in detail.[14 15] In summary, in recent years the term 'early SpA' has been increasingly used, but more than one third of the studies did not include a clear definition. Remarkably, only one study using the term 'early pSpA' was found. Within those studies reporting a specific definition for early SpA, mostly early axSpA, there was heterogeneity in the definitions identified, with two out of three based on symptom/disease duration. Furthermore, evidence towards better outcomes in early axSpA is very limited and restricted to non-radiographic axSpA (nr-axSpA) and <5 years symptom duration. When early axSpA was defined by symptom duration (<5 years) in randomised controlled trials, early treatment was associated with better outcomes in patients with nr-axSpA (n=2 studies) but not in axSpA (including radiographic-axSpA and nr-axSpA) (n=1 study). However, when early axSpA was defined based on disease duration (n=7 studies) or radiographic damage (n=4 studies), no differences were found in clinical treatment outcomes between the groups of early and established axSpA.

2022 working group and ASAS annual meetings

The results of the SLRs were first presented and discussed at the working group meeting, and thereafter by the entire ASAS community. The following agreements were reached:

- To proceed with a definition for early axSpA (81% voted in favour) but not for pSpA (54% voted against). Given the increasing use and heterogeneity of the term 'early axSpA' shown in the published literature, members felt it was necessary to have a standardised definition for this term. However, it was decided not to pursue the definition of the term 'early pSpA'. This decision was mainly based on the limited use of the term so far and the lack of guidance to define it.
- To pursue with an expert-based definition for the term 'early axSpA'. The SLR results highlighted the inability to establish an evidence-based definition of early axSpA. Notwithstanding, the substantial heterogeneity of the definitions retrieved by the SLR clearly showed the need to have a consensual definition for this term, even if it could only be based on expert consensus.
- The definition of 'early axSpA' should be based on symptom duration (91% votes in favour). There was broad agreement that the most relevant aspect of defining early axSpA should be the time course of the disease, as reflected by the time since the onset of symptoms.
- Only axial symptoms should be used as the defining symptom of onset (77% votes in favour). The last aspect agreed on was that only axial symptoms of the disease should be taken into account to define early axSpA. This means that other typical symptoms of the disease such as peripheral manifestations (arthritis, dactylitis, enthesitis), extramusculoskeletal manifestations (uveitis, inflammatory bowel disease, psoriasis) or systemic symptoms (fatigue, fever) should not be considered when specifying the onset of the disease to define the term 'early axSpA'.

Delphi survey

In total, 164 (78%), 158 (76%) and 151 (72%) ASAS members participated in the three rounds of the Delphi survey, respectively. The majority of the participants were male (63%) and rheumatologists (90%), while the rest were researchers (5%), radiologists (4%) or other healthcare professionals (physiotherapists, public health researchers (1%)). This distribution reflects the overall ASAS community.

After the final Delphi round, consensus was achieved for acceptance of nine items covering the three different aspects of the Delphi (two for duration of symptoms, five for axial symptoms and two for radiographic damage involvement) and rejection of four items (three for duration of symptoms and one for axial symptoms) (figure 2).

Furthermore, following the analysis of the results after each round and taking into account the feedback from the participants, the working group made some adjustments to the questionnaire for the subsequent rounds, either to clarify some of the items or to defer the decision for meeting discussion.

The final decision (acceptance or rejection to be considered for the definition of the term), the round of the survey in which the decision was taken, the percentage of participants supporting the decision, as well as the specific adjustments to the questionnaire are listed below, split by the three different aspects of the definition.

Cut-off point for duration of symptoms

Two items on duration of symptoms reached consensus on their acceptance, namely that the upper boundary cut-off is formulated as 'less or equal' (second round, 86%) and a duration of symptoms ≤2 years (second, 76%). There was consensus on the rejection of 3 items, all related to the duration of symptoms: cut-off ≤10 years (first, 89%), ≤4 years (second, 70%) and ≤5 years (second, 73%). Since one of the cut-off points (≤2 years) achieved acceptance criteria already after the second round of the survey, the remaining cut-off points (≤1 and ≤3 years) were removed from the questionnaire for the third round.

Axial symptoms

In relation to how axial symptoms should be defined, five items reached consensus for their acceptance, stating these should be defined by a rheumatologist (first, 77%) and as cervical pain (second, 76%), thoracic pain (second, 77%), buttock pain (first, 88%) or morning stiffness (first, 89%). There was consensus on rejection for one item expressing axial symptoms should be defined as shoulder pain (second, 81%). Following the first round, many participants commented that hip can be a confusing anatomical region to use to define axial symptoms, since in some geographic regions patients often use hip to refer to the lower back region. On the contrary, others associated hip pain in axSpA

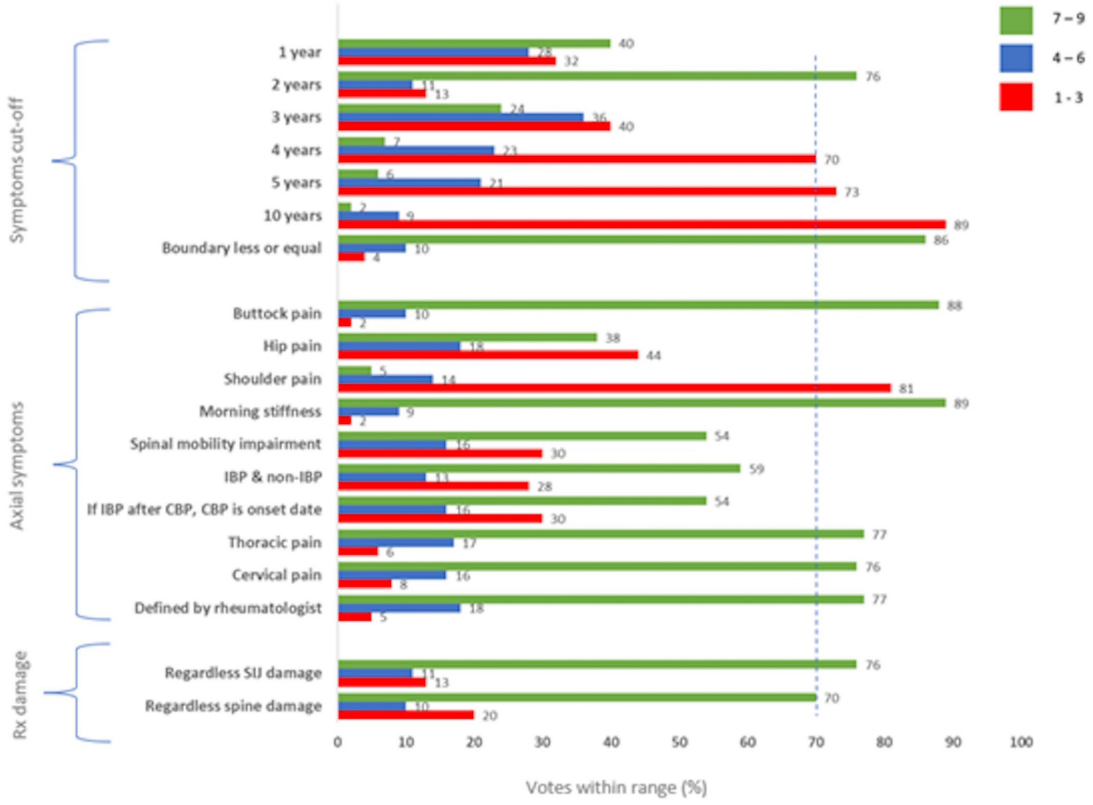

Figure 2 Results of the Delphi Survey from the latest round in which each of the items was included. In total there were three rounds, eventually less for one specific item if consensus on it could be achieved earlier, either to include it (complete agreement, score 7–9) or to exclude it (complete disagreement, score 1–3). Regardless of Rx SIJ damage was defined as 'damage on radiographs of the sacroiliac joint should not be taken into account'. Full description of the items is available on table 1. CBP, chronic back pain; IBP, inflammatory back pain; Rx, radiographic; SIJ, sacroiliac joints.

with coxitis. To avoid confusion, it was decided to omit the item defined as hip pain from the questionnaire for the second and third rounds and to thoroughly discuss it further in the meetings.

Radiographic damage involvement

Consensus on acceptance was achieved for two items related to radiographic damage, namely that radiographic damage of the sacroiliac joints (third, 76%) or syndesmophytes on conventional radiographs of the spine (third, 70%) should not be taken into account.

2023 working group and ASAS annual meetings

After the final Delphi round, there were still some pending items for which a consensus had not been reached for either acceptance or rejection. These items were discussed one by one in the working group meeting.

When developing the survey, it was assumed that back pain would be considered as an axial symptom to define early axSpA. Therefore, the Delphi items focused on asking whether back pain should have inflammatory characteristics or not. The item that required back pain to be inflammatory did not achieve consensus neither on acceptance nor on rejection, resulting in no items regarding back pain being selected through the Delphi survey. Nevertheless, recognising back pain as the cardinal symptom in patients with axSpA, the working group concluded that it should be explicitly included in the definition.

The inclusion of hip pain to define axial symptoms was also discussed. Some members proposed to use coxitis but in some languages, coxitis is not translated as inflammation of the hip but as hip involvement, which could lead to misunderstandings and a large heterogeneity of patients included under the definition of early axSpA. After consideration, the working group deemed it best not to consider hip pain as part of the axial symptoms that define early axSpA.

The last item discussed was spinal mobility impairment. The assessment of this, especially in patients with short symptom duration, may be unfeasible and importantly influenced by inter-assessor variability.[17 18] After discussion, the working group was in favour of leaving spinal mobility impairment out of the definition, also as it would not further add to the axial symptoms on which there was already consensus.

Finally, other aspects for the formulation of the definition were deemed important by the working group. First, the definition should only be applied in patients with an established diagnosis of axSpA. Second, the following axial symptoms: cervical pain, thoracic pain and back pain could be merged as spinal pain, but buttock pain should be specifically mentioned as this may not be comprehended as part of spinal pain. Third, morning stiffness should refer solely to axial morning stiffness, not to peripheral symptoms. In addition, the working group emphasised the importance of specifying that axial symptoms should be assessed by a rheumatologist, in line with the results of the Delphi.

Taking all these points of consensus into account and after discussing some details of wording, the working group agreed to bring a proposed definition for the term early axSpA to the whole ASAS community. At the ASAS 2023 annual meeting, the proposal was presented, preceded by a summary of the process and reasoning followed to reach this point. Here, further

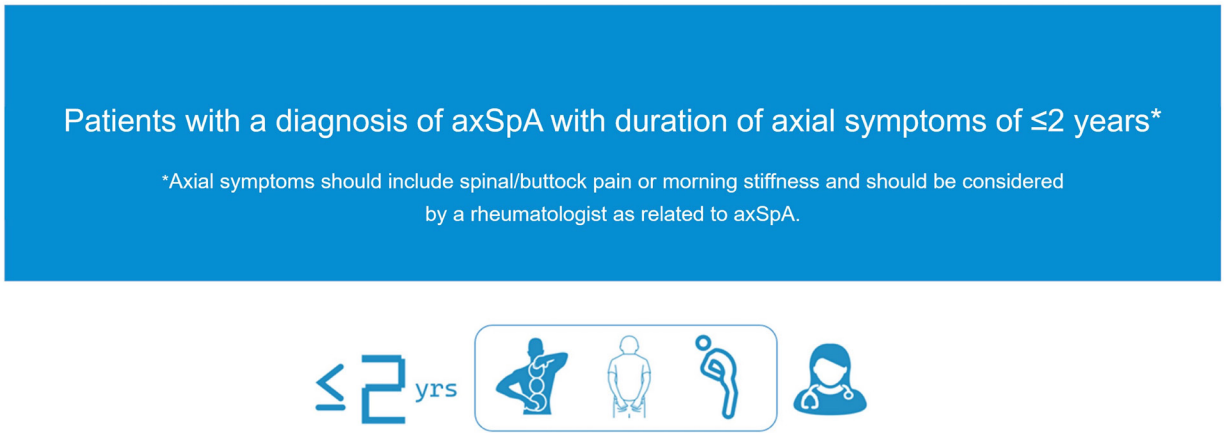

Figure 3 ASAS definition of early axial spondyloarthritis (axSpA). ASAS, Assessment of SpondyloArthritis international Society.

modifications were proposed by ASAS members regarding the specific wording or the order of some items in the formulation of the definition. The use of should be 'assessed' by a rheumatologist was considered inappropriate as assessment also includes interpretation and it may be that the rheumatologist is not present at the symptom onset. After discussing various alternatives, should be 'considered' by a rheumatologist seemed more appropriate to refer to this item. In this sense, it was also deemed important to stress in the definition that axial symptoms should be related to axSpA according to the judgement of a rheumatologist. Lastly, the conjunction used to list the different axial symptoms in the definition was discussed, concluding that 'or' was the most appropriate term, as it allows having one or multiple axial symptoms (spinal pain, buttock pain or morning stiffness) to define the onset of the disease.

Voting and endorsement

Finally, taking all these suggestions into account, the wording of the proposal was reformulated as follows (figure 3): In patients with a diagnosis of axSpA 'early axSpA' should be defined as a duration of ≤2 years of axial symptoms. Axial symptoms should include spinal/buttock pain or morning stiffness and should be considered by a rheumatologist as related to axSpA. This proposal was voted and endorsed by the ASAS community, with 88% of full members voting in favour.

DISCUSSION

As a result of the ASAS-SPEAR project, the term 'early axSpA' has for the first time been defined. This covers one of the unmet needs in the field of axSpA.[19] The aim of this definition is to standardise the use of the term early axSpA in the research setting, enabling the inclusion of homogeneous study populations in studies evaluating research questions in patients with axSpA at an early stage of the disease. Hence, ASAS recommends that from now on, studies referring to early axSpA use this definition.

It is important to note that the ASAS-SPEAR initiative also aimed to develop a consensual definition for the term 'early pSpA' in addition to developing a consensual definition for the term 'early axSpA'. Yet, after discussing the results of the SLR, the decision by the working group was not to pursue a definition of early pSpA at this stage, since this term appears to be rarely used with almost no data available in the current medical literature. In the future, the need for a definition of early pSpA may be reconsidered.

This ASAS definition of early axSpA is based on expert consensus, following an SLR and Delphi survey. One limitation is the lack of scientific evidence to support it, especially with regard to the specific duration of symptoms from the time of disease onset. To date, most of the patients included in studies have longstanding disease, and only a very small proportion of them are in the early stages of the disease.[15] Therefore, there is very limited evidence on whether there is any benefit of early treatment on disease outcomes, and if this benefit is more pronounced at a certain cut-off point such as 1, 2 or 5 years. But at the same time, this lack of evidence precisely reflects the need for a standardised definition of the term 'early axSpA', so that studies can now be conducted in patients at a presumed early stage of the disease. Within the ASAS community, there was a broad consensus in choosing the 2 years cut-off point for symptom duration. Compared with other rheumatic and musculoskeletal diseases such as RA, this cut-off point might seem too long at the present time but intriguingly, it aligns with the first-developed definitions for early disease in RA[20 21]; in this sense, the opinion of ASAS members is that for axSpA this definition is aspirational, as we know that in clinical practice there is unfortunately still a long diagnostic delay and therefore it may initially not be feasible to include patients with ≤2 years of symptom duration in research studies.[22] On the other hand, a relatively recent study showed a median diagnostic delay of 2.3 years, which is not far away from the proposed cut-off.[23] This was possibly the reason behind most members not selecting a shorter time of disease evolution for the definition of early axSpA.

It is important to emphasise that the aim of this definition is to allow the inclusion of a homogeneous sample of patients in research studies, that is, to classify patients who are already diagnosed with axSpA and are at an early stage of the disease and to distinguish them from those with a longer disease duration. For clinical practice, it is important to make a timely diagnosis. In this context, the ASAS quality standards to improve the quality of health and care services for patients with axSpA must be taken into account as a reference guide, which are stricter and more aspirational than the proposed definition for early axSpA.[24] This definition of early axSpA is to be used in patients in whom a diagnosis has already been made, considering the entire clinical presentation and usual reasoning process recommended for this.[12] The early axSpA definition only aims to define when to establish the onset of the disease for research purposes, that is, to include a specific patient in a clinical trial.

In addition, axial symptoms are the only disease manifestations to consider in the definition. Therefore, if patients had previously either peripheral, extra-musculoskeletal or other manifestations of the disease than axial symptoms these should not be

considered to define the onset of the axial disease when applying the definition of early axSpA. Furthermore, the same is true for imaging findings in the absence of axial symptoms. According to the consensual definition, the presence of radiographic sacroiliitis would not prevent from classifying a patient as early axSpA if the axial symptoms started less than 2 years ago. Moreover, it was agreed that spinal pain, buttock pain or morning stiffness are the axial symptoms that should be considered to define the onset of the disease. Spinal or buttock pain is the most common manifestation of axSpA, being the first symptom in approximately 75% of patients. After this, the most common manifestation is spinal stiffness.[25] Nevertheless, the diagnosis of axSpA is usually made considering other disease manifestations, especially if morning stiffness is the starting symptom, which can make it more difficult for the patient to accurately establish the onset of this symptom. Finally, it was decided that the axial symptoms should be considered by a rheumatologist as related to axSpA. In other words, it is the rheumatologist who, with all the information, must judge whether the axial symptoms reported by the patient, are due to axSpA, but admittedly, this does not overcome the known problem of recall bias. The potential recall bias is a limitation of this definition approach, as well as the difficulty to differentiate axSpA-related from axSpA-nonrelated back pain/stiffness. This is a common challenge in most, if not all, definitions of early disease as there is no more reliable approach, and that is why the opinion of the rheumatologist on the axSpA-related symptoms was incorporated as the best solution.

In summary, the ASAS-SPEAR project has successfully developed, for the first time, a consensus definition of 'early axSpA', fulfilling an unmet need in research in this field. It is now proposed that going forward, this definition should be used for research studies addressing early axSpA. However, future steps should not be overlooked. First, it is important to work on the dissemination and implementation of this definition. In this regard, ASAS is following the same strategy as for other ASAS projects, by maximising their dissemination through all platforms (website, social media, courses, congresses, publications). In addition, it is also essential to promote research studies, at high methodological standards, to provide evidence on whether treatment at a particular early stage of the disease leads to better outcomes. In this sense, when more scientific evidence becomes available, this ASAS definition of early axSpA may need to be revised.

Author affiliations
[1]Rheumatology, La Paz University Hospital, Madrid, Spain
[2]IdiPAZ, Madrid, Spain
[3]Universiteit Maastricht Care and Public Health Research Institute, Maastricht, The Netherlands
[4]Rheumatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[5]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[6]Department of Rheumatology & Clinical Immunology, Amsterdam University Medical Centres, Duivendrecht, The Netherlands
[7]Rheumatology, Zuyderland Medical Centre Heerlen, Heerlen, The Netherlands
[8]Department of Gastroenterology, Infectious Diseases and Rheumatology, Charite Universitatsmedizin Berlin, Berlin, Germany
[9]German Rheumatism Research Center, Berlin, Germany
[10]Maastricht University Care and Public Health Research Institute, Maastricht, The Netherlands
[11]Rheumatology, Maastricht University Medical Centre+, Maastricht, The Netherlands
[12]Rheumatology, Rheumazentrum Ruhrgebiet, Herne, Germany
[13]Ruhr-Universitat Bochum, Bochum, Germany
[14]Internal Medicine and Pediatrics, VIB-UGent Center for Inflammation Research, Zwijnaarde, Belgium
[15]Ghent University, Gent, Belgium
[16]Medicine, Division of Rheumatology, University of California, San Francisco, California, USA
[17]Rheumatology, Reina Sofia University Hospital, Cordoba, Spain
[18]Maimonides Biomedical Research Institute of Cordoba, Cordoba, Spain
[19]Rheumatology, Leeds Biomedical Research Centre, Leeds, UK
[20]University of Leeds Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, UK
[21]APHP, INSERM U-1158, Rheumatology, Hospital Cochin, Paris, France
[22]Center of Research in Epidemiology and Statistics Sorbonne Paris Cité, Paris, France
[23]Rheumatology, Avellaneda Hospital, Tucuman, Argentina
[24]Internal Medicine and Rheumatology, Klinikum Bielefeld Rosenhohe, Bielefeld, Germany
[25]Department of Rheumatology and Clinical Immunology, University of Amsterdam, Amsterdam, The Netherlands
[26]Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, UK
[27]Practice Buchsbaum, Rheumatology, Schaffhausen Hospitals, Schaffhausen, Switzerland

Twitter Anna Molto @annamolto and Sofia Ramiro @sofiaramiro82

Acknowledgements We would like to thank all ASAS members for their participation in the project.

Contributors VN-C and SR designed the study and developed the study protocol. DB and DC performed the survey and summarised the data. All authors participated actively in the project. VN-C and SR wrote the first draft of the manuscript. All authors critically reviewed the manuscript for important intellectual contribution and approved the final version.

Funding The Assessment of SpondyloArthritis international Society (ASAS) funded Diego Benavent to work on this project.

Competing interests VN-C: Speaker fees—AbbVie, Eli Lilly, Janssen, MSD, Novartis, Pfizer, UCB Pharma; Consultancy fees- AbbVie, Eli Lilly, Galapagos, MoonLake, MSD, Novartis, Pfizer, UCB Pharma; Grants: AbbVie, Novartis. DB: Grant/research support from Novartis, and speaker fees from Janssen, Abbvie, and Galapagos. DvdH: Consulting AbbVie, Bayer, BMS, Cyxone, Eisai, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Lilly, Novartis, Pfizer, UCB Pharma. Director of Imaging Rheumatology bv. RBML: Consulting AbbVie, Eli-Lilly, Janssen, Galapagos, Gilead, Novartis, Pfizer, UCB. Director of Rheumatology Consultancy BVD. DP: Research grant from AbbVie, Eli Lilly, MSD, Novartis, Pfizer, Consultation AbbVie, Biocad, BMS, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Samsung Bioepis, UCB, Speaker AbbVie, BMS, Lilly, MSD, Novartis, Pfizer, UCB. AvT: Speaker fees: Pfizer; Consulting fees: Novartis, Galapagos, UCB; Grants: Pfizer, UCB, Novartis XB: Abbvie, Amgen, Chugai, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer, Roche, Sandoz, UCB. FEVdB: received speaker and/or consultancy fees from AbbVie, Amgen, Eli Lilly, Galapagos, Janssen, Moonlake, Novartis, Pfizer and UCB FAvG: Research Grants—Novartis; consultancy -MSD, AbbVie, Novartis and BMS LG: Research grants UCB, Novartis, Consulting fees AbbVie, Acelyrin, Eli Lilly, Fresenius Kabi, Janssen, Novartis, Pfizer, UCB Pharma CL-M: Speaker fees AbbVie, Eli Lilly, Novartis, Janssen, UCB Pharma. Consulting fees Eli Lilly, Novartis, UCB Pharma. HM-O: Speaker fees/consultancy: ABvie, Eli-Lilly, Janssen, Moonlake, Novartis, Pfizer and UCB. Research grants from Janssen, Novartis and UCB. AM: Consulting fees AbbVie, Biogen, BMS, Cyxone, Eisai, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, UCB Pharma. Grants: UCB RP-A: Speaker fees Abbvie, Eli Lilly, Novartis, Janssen, Pfizer. Consulting fees Abbvie, Eli Lilly, Janssen, Novartis. MR: Speaker- AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Novartis, UCB Pharma; Consultancy AbbVie, Eli Lilly, Novartis, Pfizer, UCB Pharma MvdS: Speaker -Janssen, Novartis, UCB; Consultancy Abbvie, Eli Lilly, Novartis, UCB; Research Grants: Eli Lily, Novartis, UCB RS: Speaker - AbbVie, Biogen, Eli Lilly, MSD, Novartis, UCB; Consultancy—AbbVie, Eli Lilly, Novartis, Pfizer, UCB. Grants: AbbVie, Novartis, UCB UW: Speaker fees NovartisS. SR: Research Grants—AbbVie, Galapagos, MSD, Novartis, Pfizer, UCB; consultancy—AbbVie, Eli Lilly, MSD, Novartis, Pfizer, Sanofi, UCB.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Victoria Navarro-Compán http://orcid.org/0000-0002-4527-852X
Diego Benavent http://orcid.org/0000-0001-9119-5330
Dafne Capelusnik http://orcid.org/0000-0001-9336-0416
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
Robert BM Landewé http://orcid.org/0000-0002-0577-6620
Denis Poddubnyy http://orcid.org/0000-0002-4537-6015
Astrid van Tubergen http://orcid.org/0000-0001-8477-0683
Xenofon Baraliakos http://orcid.org/0000-0002-9475-9362
Filip E Van den Bosch http://orcid.org/0000-0002-3561-5932
Floris A van Gaalen http://orcid.org/0000-0001-8448-7407
Lianne Gensler http://orcid.org/0000-0001-6314-5336
Clementina López-Medina http://orcid.org/0000-0002-2309-5837
Helena Marzo-Ortega http://orcid.org/0000-0002-9683-3407
Anna Molto http://orcid.org/0000-0003-2246-1986
Martin Rudwaleit http://orcid.org/0000-0001-5445-548X
Raj Sengupta http://orcid.org/0000-0002-9720-0396

Ulrich Weber http://orcid.org/0000-0001-6701-670X
Sofia Ramiro http://orcid.org/0000-0002-8899-9087

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