EXTENDED REPORT

Staging of patients with ankylosing spondylitis: a preliminary proposal

J Braun, D van der Heijde, M Dougados, P Emery, M A Khan, J Sieper, Sj van der Linden

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See end of article for authors' affiliations

Correspondence to: Professor J Braun, Rheumazentrum Ruhrgebiet, Landgrafenstr. 15, 44652 Herne, and UKBF, Free University, Berlin, Germany; j.braun@rheumazentrum-ruhrgebiet.de

Patients with ankylosing spondylitis (AS) are characterised by a wide range of clinical presentations, radiographic profiles, and outcomes, which are not well differentiated by current diagnostic and classification systems for the disorder. Inadequacies in these systems may limit clinicians' ability to manage their patients with AS appropriately and act as an obstacle to reasonable comparison of therapeutic trial results. A standardised staging system for AS is therefore proposed that would provide a more detailed categorisation of patients based on assessment of structural damage, peripheral joint and organ involvement, presence of concomitant diseases, and the severity and extent of disease activity and functional impairment. The proposed system needs to be evaluated closely and amended as needed to assure its usefulness in clinical and research settings.

Ankylosing spondylitis (AS), the prototype of the spondyloarthropathies (SpAs), is one of the most common inflammatory rheumatic diseases.[1] Like rheumatoid arthritis (RA), AS is associated with significant disability[2] and increased socioeconomic costs.[3 4] However, compared with the treatment available for RA, therapeutic options for AS are limited. Only non-steroidal anti-inflammatory drugs and physiotherapy are currently accepted treatments for reducing the signs and symptoms of AS based on clinical research.[5] No available agents have demonstrated a disease modifying effect in AS, although anti-tumour necrosis factor α therapy holds promise in this regard.

An increasing number of treatment trials in AS are being conducted, heralding the potential availability of more effective treatments in the future. To allow comparison of findings between trials of different agents, a better classification system of patients with AS is needed. Because AS is a chronic disease with a wide variety of clinical presentations and outcomes, the development of a staging system that categorises patients accordingly seems mandatory. This paper will review existing assessment tools used in AS and propose improvements that will help satisfy emerging needs.

DIAGNOSTIC AND CLASSIFICATION CRITERIA

The difference between diagnostic and classification criteria has been the subject of considerable debate in recent years. Basic epidemiological research indicates that diagnostic criteria should be very sensitive, particularly at an early stage of disease, whereas classification criteria need to be very specific. However, given the high prevalence of back pain and much lower relative prevalence of AS in the population, diagnostic criteria with a high specificity would be very desirable. High specificity in clinical practice is increasingly important because the diagnosis of a patient is more critical in light of financial and legal issues such as disability, pensions, insurance, and reimbursement. Thus, with the existence of diagnosis related groups and expensive, but very effective, new biological treatments, the need for specific criteria in clinical practice is particularly great.

Throughout the past decade, in clinical studies and especially daily practice, the diagnosis of AS has often been made based on the 1984 modified New York criteria.[6] These criteria have established radiographic evidence of sacroiliitis as the most important factor for the diagnosis of AS. In practice, the cut off of grade II radiographic assessments of sacroiliitis has proved difficult.[7] However, this criterion has been used successfully because the vast majority of patients with AS do have sacroiliitis,[8] indicating a high sensitivity in established disease. As a result, the modified New York diagnostic criteria, as published in 1984, are currently used as classification criteria and diagnostic criteria. The ESSG criteria have a >80% sensitivity to recognise patients with an established disease belonging to the spectrum of SpA.[16] Thus, it needs to be emphasised that all available criteria lack sensitivity in early disease, making their use unacceptable for such patients. Therefore, many clinicians are attempting to diagnose sacroiliitis with magnetic resonance imaging (MRI) early in the disease course of AS.

Significant progress has also been made in standardising the measurement of clinical disease activity and functional ability in AS. The Bath AS Disease Activity Index (BASDAI)[9] and the Bath AS Functional Index (BASFI)[10] are easy to use, reliable, sensitive tools that have become frequently used to define disease status.[11] A real step forward was the definition of core sets of end points by the Ankylosing Spondylitis Assessment (ASAS) Working Group for use in different research settings and in clinical practice.[12 13]

DEFINING THE SPECTRUM OF DISEASE

It is important to recognise AS as merely a single disorder, albeit a dominant one, in the broader spectrum of the SpAs.[14] In 1991, milestone classification criteria were proposed by the European Spondylarthropathy Study Group (ESSG) that defined AS and the other disorders categorised as SpA,

Abbreviations: AS, ankylosing spondylitis; ASAS, Ankylosing Spondylitis Assessment (Working Group); BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; CRP, C reactive protein; DC-ART, disease controlling anti rheumatic treatment; DISH, diffuse idiopathic skeletal hyperostosis; ESSG, European Spondylarthropathy Study Group; HAQ, Health Assessment Questionnaire; IBD, inflammatory bowel disease; J, joint; MRI, magnetic resonance imaging; NSAID, non-steroidal antirheumatic drug; O, organ; Ps, psoriasis; RA, rheumatoid arthritis; ReA, reactive arthritis; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis; SpA, spondyloarthropathy; TNF, tumour necrosis factor; uSpA, undifferentiated spondyloarthropathy

including psoriatic arthritis, reactive arthritis (ReA), inflammatory bowel disease-related arthritis (IBD-A), and undifferentiated spondyloarthropathy (uSpA).[15]

The ESSG criteria pose a problem for the clinical rheumatologist, in that patients with only peripheral joint or entheseal inflammation are classified as having SpA (that is, "spondyloarthropathy"), which may suggest both inflammatory and non-inflammatory involvement of spinal structures. A proposed solution to this terminological problem is the use of "spondyloarthritides" to define the entire spectrum of these partially human leucocyte antigen (HLA)-B27 related rheumatic diseases—similar to the use of "connective tissue diseases" for partly antinuclear autoantibody related rheumatic diseases, such as lupus and scleroderma. Although several arguments favour the term "spondyloarthropathy",[17] we suggest that "spondyloarthritis" be used instead to emphasise the inflammatory nature of these disorders, which are defined by their involvement of spinal and peripheral structures of the musculoskeletal system and provide a common solution.

In addition, the clinical rheumatologist may find it difficult to diagnose AS in patients who demonstrate only the distinct radiographic degree of grade II sacroiliac changes bilaterally as defined by the New York criteria. The difficulty may stem, at least in part, from the significant inter- and intraobserver variability associated with the interpretation of radiographs,[18] a major problem in the diagnosis of AS, but not SpA. Differentiation between possible early and abortive cases is often incomplete when only conventional radiography (roentgenography) is used. MRI provides better visualisation of sacroiliitis in the early stages but is not yet widely available or sufficiently standardised to be generally used.[19 20]

Because spondylitis is itself part of the term AS (that is, ankylosing spondylitis), it would seem to define inflammatory involvement of the vertebral column as a condition sine qua non for a diagnosis of AS. As a result, many rheumatologists diagnose AS only in patients with clear cut clinical or radiographic evidence of spinal involvement. This may imply the presence of syndesmophytes, calcification of spinal ligaments, or other radiographic signs of spondylitis, spondylodiscitis or arthritis of the zygapophysial joints.[21] However, as previously mentioned, spondylitis without sacroiliitis is rare and often a late phenomenon, and no data or consensus exist about the quantity or size of syndesmophytes required to establish a diagnosis of AS. Moreover, the differentiation from diffuse idiopathic skeletal hyperostosis (DISH) can sometimes be a serious problem. An HLA-B27 positive patient with a radiological image of DISH can sometimes be a challenge.[22] In such cases, the presence or absence of other signs of SpA (other than diminished spinal mobility and impaired chest expansion) or radiographic signs of sacroiliac and zygapophysial joint involvement can be helpful but may sometimes require computed tomography for conclusive assessment.[23 24] A history of inflammatory back pain is usually absent in young patients with DISH. The diagnostic role of MRI in detecting spinal inflammation at an early stage is not sufficiently well established to recommend its routine use at present.

RATIONALE FOR AS STAGING SYSTEM

AS encompasses a broad spectrum of clinical presentations, disease courses, and outcomes, with differing pain, function, quality of life, and radiographic damage. The disease in some patients does not progress beyond sacroiliitis; other patients have rapidly progressing disease and experience complete ankylosis at a young age. In addition to the varying rates of progression and severity of spinal disease, AS can also affect peripheral joints, entheses, anterior uvea, and other structures, such as the aortic valve, the aorta, and the lung. Because differences in disease severity, extent, or outcome are not captured when using the New York criteria, the diagnosis of AS currently does not distinguish between patients with very different disease manifestations and courses. The classification of AS shows no more than that the patient has at least grade II radiographic sacroiliitis. For a clinical diagnosis of AS, it seems at present best to ask for definite radiographic sacroiliitis as the main differentiation factor towards uSpA and non-SpA rheumatic diseases and syndromes and then use different stages to describe the current status of disease as follows.

In clinical practice, the lack of a standard staging system for AS impedes the precise characterisation of individual patients. In clinical studies, patients in varying stages of AS are not differentiated, and potential differences in their responses therefore cannot be evaluated. Moreover, findings across studies cannot be reasonably compared without sufficient information about patients' disease status. The latter is particularly important in view of the extreme differences in disease duration among patients with AS enrolled in previously conducted therapeutic trials (5–20 years)—for example, trials of sulfasalazine in AS.[25–27]

This paper proposes a standardised staging system for AS that would allow more specific categorisation of patients included in future studies, recognising differences in structural damage, disease severity and extent, and outcome. Different degrees of spinal changes have been shown significantly to affect radiological scoring by using methods published to date.[28–30] Furthermore, a core set of end points for clinical trials in AS has been published by the ASAS expert group,[12] which also recently proposed criteria for short term clinical improvement.[31]

DOMAINS IN RHEUMATIC DISEASE STAGING

In rheumatology, staging is typically used to describe the patient's status in reference to the disease process and damage. To date, staging in rheumatology has relied on the classical Steinbrocker therapeutic criteria established in 1949 for RA[32] and, less directly, the Health Assessment Questionnaire (HAQ)[33] and SpA adjusted HAQ. The latter adds five items to the original HAQ in recognition of the functional importance of neck rotation.[34]

To describe the stage of a rheumatic disease in general, we suggest that four different, although related, domains be delineated to cover different aspects of the disease and its consequences:

- *Disease activity*—The biological inflammatory processes that may transiently or permanently influence structure and function.
- *Damage*—The partly reversible or irreversible structural and/or functional changes caused by the disease in musculoskeletal or organ systems. Although functional changes are usually reversible, structural changes are generally irreversible.
- *Health status*—A person's situation (impairments, limitations, and handicaps) on a variety of health dimensions or domains, independent of disease and diagnosis, which is influenced by changes in structure and function.
- *Appreciation of health status*—An estimation of health status as valued by an individual or by a society, which is usually expressed as utilities or satisfaction.

DEFINING THE STATE OF DISEASE IN ANKYLOSING SPONDYLITIS

To put our proposal in a broad context covering practical and scientific aspects of the disease, we start by describing the different levels of information which are required to define the state of disease.

When describing a patient with SpA in daily practice or for precise inclusion criteria in clinical research studies, the following basic definitions need to be clarified:

1 Definite disease diagnosis, classification

2 Disease activity (signs, symptoms, imaging)

3 Disease severity (stage, burden of disease)

4 Potentially severe prognosis, prognostic factors

5 Refractory to treatment, treatment options, evidence based medicine.

Diagnosis, classification

Available classification criteria are either the modified 1984 New York criteria (which require the presence of radiological sacroiliitis) or the ESSG (European Spondylarthropathy Study Group) set of criteria.

There are no definite criteria for presence or proof of axial disease. These might possibly include:

- Spinal pain
- Reduced spinal mobility
- Imaging (MRI, *x* ray examination)

Disease activity

Mainly clinical and laboratory variables evaluating the inflammatory process of the disease but, possibly, imaging tools may also be used.

In clinical research studies definitions of a particular value of the BASDAI (for example, at least 30 or 40) or a specific value of nocturnal pain and/or duration of morning stiffness and/or a certain level of C reactive protein (CRP) may be used. In fact, such a definition (which summarises the main inclusion criteria for a specific trial) depends on the objective of the therapeutic trial and on the nature of the treatment (differing when evaluating a non-steroidal anti-inflammatory drug (NSAID) from when evaluating a potential disease controlling antirheumatic treatment). In daily practice, one might consider an important measure to be the level of NSAID intake required in order to maintain the patient's disease at an acceptable level (low disease activity).

Severity of disease

This measure usually refers to the level of functional disability and to structural damage. There is no consensus about this definition. Here the staging parameters proposed in this article (see below) become relevant. Especially important parameters leading to significant functional disability are:

- Widespread ankylosis, bamboo spine
- Intervertebral ossification bridges (zygapophysial joints, entheses, ligaments)
- Hip joint involvement

Bad prognosis of disease

This definition is probably one of the most important to consider because of the interest of potentially costly, aggressive but also effective treatments, such as drug treatment (for example, anti-TNFα) or non-drug treatment (for example, admission to hospital in a department of rehabilitation).

There is no specific recommendation. However, it seems that an early rapid structural progression and constantly raised CRP levels can be considered important to take into account for this definition.

Unresponsiveness to previous treatment

This definition is important when considering the initiation of potentially active disease controlling antirheumatic treatment (DC-ART) such as anti-tumour necrosis factor α (anti-TNFα) therapies in patients already taking NSAIDs.

There is no consensus on this definition yet. However, the following characteristics can be taken into account:

- Use of a conventional DC-ART (sulfasalazine)
- Number of NSAIDs tested
- Use of an "optimal" dose for each NSAID
- Duration of NSAID intake.

Other points of interest in this regard are relevant comorbidity factors which possibly affect NSAID intake—for example, in cases of renal insufficiency.

AS STAGING SYSTEM

Radiographic grading

Staging should be basically unidirectional, such that a patient in a more advanced stage of disease cannot improve and be classified into a lower stage over time. Therefore, we propose to use radiographic bony changes of the sacroiliac joints and spine as the main parameter to differentiate between the stages of AS, as has been previously suggested by the German rheumatologists Ott[35] and Schilling.[36] Expanding on their work, which has not been published in English, we recommend the following radiographic grading system for AS diagnosed on the basis of the 1984 Modified New York criteria:

- *Stage I* Grade II or higher bilateral radiographic sacroiliitis
- *Stage II* Minor radiographic evidence of spinal involvement in ⩽1 spinal segment (⩽3 vertebrae which equals <15% of the spine)
- *Stage III* Moderate radiographic evidence of spinal involvement in ⩽2 spinal segments (4–12 vertebrae which equals 15–<50% of the spine)
- *Stage IV* Radiographic evidence of spinal involvement in >2 spinal segments (13–19 vertebrae which equals 50–<80% of the spine)
- *Stage V* Widespread (⩾80%) fusion of the spine (⩾20 vertebrae)

Radiographic spinal involvement suggests evidence of spondylitis, spondylodiscitis, square vertebrae, syndesmophytes, ligament ossification, ankylosis, or arthritis of zygapophysial joints. Because zygapophysial joints are known to be difficult to assess and are often affected in patients with degenerative spinal disease, the involvement of these joints needs to be evaluated carefully.

The basis for grading stages II to IV is involvement of one or more spinal segments, with stage V indicating widespread ankylosis (bamboo spine). One spinal segment indicates involvement of the cervical, thoracic, or lumbar spine. Vertebral counts and percentages of vertebrae are included in brackets with the stage definitions to allow an individual approach to be taken with patients. This approach would allow a patient with minor involvement in two or three spinal segments to be graded at a lower stage. For example, a patient with involvement of the lumbar and thoracic spine affecting eight vertebrae would be graded at stage III, whereas a patient with involvement of the lumbar and thoracic spine affecting 20 vertebrae would be graded at stage V.

As a general rule, spinal involvement should be obvious. Clear cut disease at one site (Anderson or Romanus lesion) or minor changes at two or more sites should be present in any stage of spinal involvement. For example, one very small syndesmophyte seems insufficient to clearly indicate spinal disease in AS. The clinician currently is responsible for the final judgment in individual cases, but digitalised programs may be available in the future to make such assessments. Nevertheless, using this staging system as a framework, for the first time clinicians will be able to clearly differentiate patients by degree of spinal involvement.

Peripheral joint and organ involvement

To classify patients with AS further, additional information about the involvement of other joints or organs may be provided. Past or present clinical evidence of the following may be included in the staging system:

- Joints (J+)
- Peripheral joints (pJ+)
- Root joints (rJ+)
- Enthesitis, dactylitis (e+d+)
- Anterior uveitis (aU+)
- Other organs (oO+)

Root joints are defined as sternoclavicular joints, acromioclavicular joints, shoulders, and hips. Peripheral arthritis has been shown to influence outcome significantly.[27 35 37 38] As many as 10–20% of patients with AS have hip involvement, with many requiring joint replacement surgery[36]; clinical status after surgical intervention may also become relevant. Anterior uveitis is relatively common[38] and may be a severe problem,[39] and other organ involvement, albeit rare, may also be a concern, as in the case of aortic valve disease and renal amyloidosis.[38]

The involvement of non-axial joints and other organ systems has variable onset among patients with AS, and the timing of onset can be difficult to classify. Therefore, we prefer not to distinguish between previous, recent, or current onset of involvement, but rather to record the involvement regardless of the time of onset.

Concomitant disease

In about 85% of patients, AS develops without other preceding or accompanying diseases (that is, primary AS).[40] However, in the remainder, AS may be triggered by, or occur concomitantly with, other disorders, such as psoriasis (Ps), ReA (including Reiter's syndrome), IBD, and the synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome. The proposed staging system would also include information about the presence of such disorders—for example, AS + Ps, ReA, IBD, SAPHO.

Clinical activity/function

We also propose to indicate the current clinical activity and the functional status of patients with inflammatory spinal pain in their staging index by adding their respective BASDAI and BASFI scores. To specify whether spinal or peripheral symptoms predominate, an "s" or "p" may be included with the BASDAI score.

The proposed staging system allows the possible differentiation of 20 stages based only on the radiographic grading from I to V and the specification of joint/organ involvement (that is, J+,O+; J+,O–; J–,O+; J–,O–). Inclusion of additional components exponentially increases the number of possible stages. For example, the staging notation for a patient with active AS, including a full complement of indices, might be: stage III; J+, Ps; BASDI 4.7s; BASFI 3.5. Only positive involvement is noted. When used in combination with the AS core set of end points, such a detailed staging system would provide a thorough description of structural damage, disease activity, and function.

SUMMARY

Currently available diagnostic and classification criteria are inadequate in differentiating patients with AS, who demonstrate a wide spectrum of clinical presentations, radiographic profiles, and outcomes. To improve care for individual patients in clinical practice and interpretation of clinical study results, we propose an AS staging system based on grading of radiographic data and assessment of peripheral joint and organ involvement, concomitant diseases, and the severity and extent of clinical activity and functional deficits. Clearly, the proposal should be evaluated to determine its feasibility and potential benefits in different settings. Discussion and refinement of the proposed system will hopefully lead to much needed improvements in the classification and treatment of patients with AS.

Authors' affiliations

J Braun, Rheumazentrum Ruhrgebiet, Herne, Germany and Department of Gastroenterology and Rheumatology, Free University, Berlin, Germany
J Sieper, Department of Gastroenterology and Rheumatology, Free University, Berlin, Germany
D van der Heijde, Sj van der Linden, Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht, Maastricht, The Netherlands
M Dougados, Department of Rheumatology, René Descartes University, Hôpital Cochin, Paris, France
P Emery, University of Cleveland, Cleveland, Ohio, USA
M Khan, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

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