Axial spondyloarthritis: thoughts about nomenclature and treatment targets

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ABSTRACT

The spondyloarthritides (SpA) are a heterogenous group of rheumatic diseases which are genetically linked. The strongest genetic factors, HLA B27, ERAP-1 and IL-23R, are found at variable rates in subgroups. The new nomenclature differentiates predominantly axial SpA (axSpA) from predominantly peripheral SpA (pSpA). Axial SpA (AxSpA) is further classified as classical ankylosing spondylitis (AS) and a non-radiographic form, nr-axSpA, which may occur in association with psoriasis (Pso) or chronic inflammatory bowel disease (IBD). Peripheral SpA includes patients with psoriatic arthritis (PsA) and IBD, patients who report a triggering infection (reactive arthritis), and other patients who may be classified simply as 'undifferentiated'. The most relevant target of therapy clinically is reduction of disease activity, which is associated with control toward ablation of inflammation, normalisation and/or improvement of function and mobility, prevention of osteoporotic fractures, and inhibition of structural changes (new bone formation) in the spine.

Introduction

Ankylosing spondylitis (AS) is the major subtype and a major outcome of an interrelated group of rheumatic diseases now increasingly named as spondyloarthritides (SpA, 1, 2). The SpA are genetically linked, the strongest known contributing factor is the MHC class I molecule HLA B27, others are ERAP-1 and IL23R, the combination seems to be pathogenetically relevant (3).

The most important clinical features of this group are inflammatory back pain (IBP, 4), asymmetric peripheral oligoarthritis, predominantly of the lower limbs, enthesitis, and specific organ involvement such as anterior uveitis, psoriasis and chronic inflammatory bowel disease. Aortic root involvement and conduction abnormalities are rare complications of AS. Recently classification criteria for axial (axSpA, 5) and peripheral (pSpA, 6) SpA have been proposed which also enable an earlier diagnosis which is related to the predominant involvement of either the axial skeleton or the periphery. Since MRI has become part of the criteria definitions for a positive MRI have been published – based on both, clinical data and expert opinion (7, 8).

In relation to the ESSG criteria (9) subgroups of axSpA have been differentiated on the basis of presence or absence of structural changes in the sacroiliac joints, as defined in the 1984 modified New York criteria for AS (10). Structural changes in the spine such as syndesmophytes have not been part of classification criteria to date (11). Early forms of AS were frequently labelled as undifferentiated SpA (uSpA, 12). Now, based on the new criteria, axSpA is subdivided into a non-radiographic form (nr-axSpA) and AS (13), and peripheral SpA. Other subtypes are differentiated on the basis of presence or absence of psoriasis (14) and/or chronic inflammatory bowel diseases (15, Crohn's disease and ulcerative colitis), and a preceding infection in the urogenital, enteral or respiratory tract (16). The classical nomenclature for these forms of SpA has been psoriatic and reactive arthritis or enteropathic arthritis. Different approaches to the nomenclature are SpA associated with psoriasis, (PsSpA), reactive SpA (ReSpA), SpA associated with inflammatory bowel disease (SpAIBD) and uSpA.

Most frequently and characteristically, AS begins in the sacroiliac joints at a mean age of 26 years affecting men only slightly more frequent than women. In about 80% of the patients, the disease appears spreads to the spine, in which all three segments are affected, most frequently the thoracic spine. Osteodestructive structural changes such

as erosions occur less frequently than osteoproliferative changes which are pathognomonic for AS being clinically impressive by their appearance as syndesmophytes and ankylosis. Osteoporosis and vertebral fractures occur more frequently in patients with AS compared to the general population (17). The cardiovascular morbidity (18) and the mortality, especially in active male patients (19) also are increased.

Since established classification criteria for AS (10) have performed less well in early disease stages, new criteria for axial SpA have been developed by the 'ASessment in AS working group (ASAS) (5,6). There is hope that this will improve the delay of diagnosis of AS which is still in the range of 5–7 years in many countries (20) – mainly due the high frequency of back pain, and even inflammatory back pain (21) in the population. Major factors to improve the rate of AS patients diagnosed early are guidance of general practitioners (GPs) and orthopaedic surgeons to improve the recognition of IBP in primary care (22), HLA B27 and magnetic resonance imaging (MRI) of the sacroiliac joints and the spine (11).

Ten main recommendations for the management of AS have been proposed very recently by a combined ASAS/European League Against Rheumatism (EULAR) task force (23). Physiotherapy is of major importance in the general approach to patients with AS. The conventional medical treatment is mainly based on NSAIDs, patients with peripheral arthritis may be treated with sulfasalazine, and patients with persistently active disease benefit from therapy with anti-TNF agents according to the ASAS recommendations (24).

The treat-to-target (T2T) initiative that was initiated some years ago has changed the approach to rheumatic diseases, especially rheumatoid arthritis, considerably over recent years. The process to develop recommendations for treat-to-target has been standardised using established tools such as the systematic literature search and expert committee meetings, first publications have recently been released (25, 26). The nature of the basic thought behind T2T is strategic. It follows the rationale that inflammation should be systematically reduced to the lowest possible level to prevent structural damage, according to quantitative targets, and the most important feature of treatment is the strategy, rather than any specific agent (27).

AxSpA including AS is a common inflammatory rheumatic disease that usually requires specialist care and cooperation among specialists because of the extraarticular manifestations of the disease. The T2T approach creates an opportunity to discuss the definitions of the different subtypes and their nomenclature. In parallel an expert committee has started work on an evidence-based approach.

Nomenclature of SpA and its subtypes

This proposal presenting the opinion of only one expert follows discussions within ASAS and elsewhere, and is regarded as a starting point for further discussions.

The main change that has occurred in the field of SpA in the last years is the central differentiation between axial and peripheral disease. There are two main unmet needs for this change: 1. the need for an early diagnosis of axSpA, and 2. the need for a classification of patients with axSpA without definite structural changes. Furthermore there is some evidence that therapies differ in efficacies in axial and peripheral disease – one example is sulfasalazine (28).

Based on the recently published classification criteria for axial and peripheral SpA (5, 6) the terminology and disposition of the main groups and the subgroups could be as follows:

- **a.** <u>(predominant) axial spondyloarthritis (axSpA)</u>
  - i. non-radiographic axSpA (nr-axSpA)
  - ii. ankylosing spondylitis (AS) = radiographic axSpA (both) associated with:
    - a. psoriasis
    - b. inflammatory bowel disease (IBD)
- **b.** <u>(predominant) peripheral spondyloarthritis</u>
  - i. psoriatic arthritis (PsA) and/or peripheral SpA associated with psoriasis
  - ii. peripheral SpA associated with IBD
    - a. type I
    - b. type II
  - iii reactive arthritis (ReA)
  - iv undifferentiated peripheral SpA
- **c.** <u>(in case of no real predominance) spondyloarthritis associated with:</u>
  - a. psoriasis
  - b. inflammatory bowel disease
  - c. preceding infection
  - d. undifferentiated SpA

This proposal is further defined by the following statements and definitions:

1. The term axial SpA covers both AS as defined by the 1984 New York criteria (10) and nraxSpA as defined by the ASAS criteria (5).
2. Axial SpA can be further subdivided in three stages: the non-radiographic stage I, stage II as defined by structural changes in the sacroiliac joints ('radiographic sacroiliitis') but no structural changes in the spine, and stage III as defined by structural changes in the spine. The role of inflammatory changes in the spine requires further study.
3. The term 'undifferentiated' is no longer used for SpA patients with predominant axial involvement who have no structural changes in the axial skeleton as detected by conventional radiographs.
   This subgroup is now termed non-radiographic axial SpA (nr-axSpA). In my view, this should also mean that there are no definite structural changes in the spine (syndesmophytes). However, there is currently no consensus on this suggestion, and patients with syndesmophytes may be included in trials with nr-axSpA patients, if they have no definite changes in the sacroiliac joints.
4. No further differentiation is made between primary and secondary axial SpA, including AS. In the case of axSpA with concomitant psoriasis and/or chronic inflammatory bowel disease (IBD) this is mentioned as 'in association with'.
5. All patients with peripheral arthritis who have present or past psoriasis are termed 'psoriatic arthritis' according to the CASPAR criteria

(14) – unless their clinical presentation is very typical for SpA (29). This would potentially be the case if arthritis of the lower limbs and/or enthesitis are the predominant features. However, a precise definition of a cut-off may prove difficult.

6. In patients with peripheral symptoms who have a history of psoriasis the term peripheral SpA associated with a history of psoriasis is preferred. In case of definite erosive or osteoproliferative changes the old term PsA 'sine psoriase' may also be satisfactory. I also would not change the terminology for the SAPHO syndrome (synovitis, acne, pustolosis, hyperostosis, osteitis, 30).
7. Osteodestructive changes in peripheral joints occur mainly in PsA and AS but also may occur rarely in other subtypes.
8. In the case of joint and/or entheseal pain in patients with a suspicion of SpA based on clinical symptoms, laboratory assessments including CRP and HLA B27 should be performed, as well as imaging studies of magnetic resonance imaging, ultrasound or, in special cases, scintigraphy to make a diagnosis.
9. Peripheral arthritis associated with IBD may be subdivided further into types I and II as proposed some years ago (31,32). In the first study (31), 976 patients with ulcerative colitis (UC) and 483 with Crohn's disease (CD) were assessed for the presence of arthritis. Type I arthropathy occurred in 3.6% of patients with UC (83% acute and self-limiting) and in 6.0% of those with CD (79% self-limiting). Relapsing IBD was reported in 83% and 76% of the patients with arthritis, respectively. Type II arthropathy occurred in 2.5% of patients with UC and 4.0% of those with CD. Persistent symptoms of arthritis were seen in 87% and 89%, respectively, whereas only 29% and 42% of those with arthritis, respectively, were associated with relapsing IBD. In the second study a weak association with HLA B27 was found only for Type I arthropathy (31).
10. Reactive arthritis is diagnosed primarily in patients with a clinically convincing preceding infection in the urogenital-, enteral- or respiratory tract (15). Alternatively, a significant change in antibody titers or a positive polymerase chain reaction (PCR) result for Chlamydia either from synovial fluid or urine or by smear from the urogenital tract has been widely accepted as indicative of ReA (15).

A recent 9-month, prospective, double-blind, triple-placebo trial was conducted to assess a 6-month course of combination antibiotics in Chlamydia-induced ReA. Patient eligibilty required a positive result for either Chlamydia trachomatis or Chlamydia pneumoniae by PCR as detected in samples obtained from peripheral blood and/or from the synovial fluid (33). The data suggested that a 6-month course of combination antibiotics is effective for chronic Chlamydia-induced ReA. The inclusion criteria for that study have changed the paradigm of ReA, because the presence of DNA of a microbe was mandatory for the diagnosis. Although this certainly is an interesting approach, it is far from being agreed on in the scientific community and it is also pretty far from daily clinical practice.

The following table lists the most prominent targets for treatment of SpA, based on the experience of the author:

Targets for treatment of SpA

a. axial symptoms: chronic (inflammatory) back pain
- i. sacroiliitis
- ii. spondylitis
- iii. vertebral fractures

b. peripheral symptoms
- i. arthritis
- ii. enthesitis
- iii. dactylitis

c. extraarticular manifestations
- i. uveitis
- ii. psoriasis
- iii. colitis (IBD)
- iv. cardiac pathologies (cardiovascular disease, aortitis)
- v. lung (apical fibrosis)
- vi. kidney (interstitial nephritis, IgA nephropathy, amyloidosis)
- vii. bone (osteopenia, osteoporosis)

d. structural changes (as detected by conventional radiographs)
- i. osteodestruction (hips)
- ii. osteoproliferation (spine)

This list is likely to be incomplete and may be regarded as a starting point for further discussions.

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