REPORT

Seronegative spondyloarthropathies: to lump or split?

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The advent of novel biological therapies for the treatment of rheumatic disease has renewed interest in the seronegative spondyloarthropathies (SpAs). International efforts are re-defining disease classification and measures of disease activity, outcome, metrology, and imaging. However, opinion is divided between those who propose that the SpA group represents the same disease with variable expression (the ''lumpers'') and those who consider these to be separate diseases with shared clinical features (the ''splitters''). This review presents the evidence for both approaches.

Table 1 Spectrum of spondyloarthropathy (SpA)

Inflammatory arthropathies	Predominant feature
Ankylosing spondylitis	Axial involvement
Psoriatic spondyloarthritis	Psoriasis, nail changes
Inflammatory bowel disease related spondyloarthritis	Colitis
Reactive spondyloarthritis	Conjunctivitis/uveitis, urethritis
Undifferentiated SpA	Characteristic symptoms, no specific features

''A decade ago it was popular to support the school of 'lumpers' which considered rheumatoid arthritis as a non-specific syndrome triggered by many diverse aetiological factors such as psoriasis, urethritis or ulcerative colitis … recently the trend has changed in favour of the school of 'splitters' which regard all so-called variants of classical rheumatoid arthritis as discrete entities''.[1]

The debate over grouping or dividing rheumatological conditions is an age old one, and from a modern perspective it seems incongruous to ''lump'' all diagnoses under rheumatoid arthritis (RA) in the terms described by Moll *et al*.[1] Their seminal work lent strong support for the establishment of the seronegative spondyloarthropathies (SpAs) group. (Either spondyloarthropathies or spondyloarthritides is valid nomenclature; the European League Against Rheumatism (EULAR) has recommended use of the latter,[2] and the success of recent anti-inflammatory treatment strategies supports the use of a term that stresses the inflammatory nature of this group of diseases.) Many would argue that such separation of entities has been instrumental in the breakthroughs, particularly aetiological (for example, in reactive arthritis), that have followed subsequently.

The arrival of biological therapies offering the promise that disease (including radiological progression) can be controlled, has rekindled interest in the seronegative SpAs as we assess the results of these therapies in these diseases.[3 4] This, in turn, has led to reassessment of the diseases that make up this group (table 1) and renewed attempts to classify and validate disease outcomes and measures of disease activity, function, and imaging. An ongoing debate exists, and opinion is divided about this group and the features that they have in common. It has been suggested that either they show varying manifestations of the same disease (''lumpers'') or sufficient differences exist despite the shared features to justify studying this group as individual diseases under the same umbrella (''splitters'').

- Which view has the most credence, and is the distinction a worthwhile one?
- Are there situations in which it is most appropriate to lump the diseases together and others wherein it is advantageous to split them?

The argument depends upon the purpose of the discussion—clinical practice, clinical trials, scientific or practical points of view. In recent trials, all patients with ankylosing spondylitis, whether ''primary'' or ''secondary'', have been included as the spinal inflammation is the more relevant feature. Scientific interest centres upon common pathogenic pathways and genetic, immunological, and histopathological data. For example, practicalities highlight cooperation with dermatologists.

HISTORY

Original descriptions distinguished the SpA group by rheumatoid factor seronegativity, absence of nodules, an inflammatory peripheral arthritis, and radiological sacroiliitis with or without classic ankylosing spondylitis. The original group definition included Whipple's disease and Behçet's syndrome. The distinction was thought to have practical importance as it:

- allowed clinicians ''to give a more optimistic prognosis'' than RA
- allowed earlier diagnosis in atypical presentations
- drew attention to inflammatory spinal inflammation
- highlighted familial associations
- had ''profound aetiological implications'' especially post-infective.[1]

In an attempt to include patients with limited and undifferentiated SpA features, Amor *et al*[5] and the European Spondyloarthropathy Study Group (ESSG)[6] defined criteria which allowed designation of an undifferentiated SpA group (tables 2 and 3). These patients have either early stage disease, abortive or forme fruste forms, or overlap syndromes that with time turn from undefined to fully differentiated SpA. They present a common clinical problem, representing as many as 43% in some studies.[7] In the USA, these patients have sometimes been classified as incomplete Reiter's syndrome.[8]

These criteria have shown varying sensitivity (79–87%) and specificity (87–90%).[9] The gain in sensitivity is obtained at

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Table 2 European Spondyloarthropathy Study Group (ESSG) criteria for spondyloarthropathy[6]

Inflammatory spinal pain or synovitis that is asymmetrical or predominantly lower limb and one or more:
  Sacroiliitis
  Alternating buttock pain
  Enthesopathy
  Positive family history
  Psoriasis
  Inflammatory bowel disease
  Urethritis or cervicitis or acute diarrhoea occurring within one month before arthritis

the cost of specificity. The ESSG variables were developed as classification criteria and not diagnostic criteria and, may, in fact, perform poorly if used diagnostically, with low sensitivity (68%) in patients with disease duration of less than one year.[10] Follow up studies have tested both sets of criteria. In one, 76.5% of those patients with possible SpA who had initially fulfilled the Amor criteria developed SpA, compared with 46.6% of those who had initially fulfilled the ESSG criteria.[11] In another study of 68 patients with undifferentiated SpA according to ESSG criteria over a two year period, 75% remained undifferentiated SpA, in 13% disease went into remission, and 10% developed ankylosing spondylitis and 2% psoriatic arthritis (PsA). Logistic regression analysis showed that buttock pain and positive human leucocyte antigen (HLA)-B27 (trend) were statistically associated with progression to a definite SpA.[12]

Following on from these criteria, unresolved issues include classification of groups such as elderly onset SpA, juvenile SpA, and SAPHO syndrome, the latter bringing in hyperostosis as a typical feature but with only a slightly increased B27 frequency, significant numbers of patients meeting Amor and ESSG criteria for SpA; it has been suggested that psoriasis is ''the missing link between SAPHO and SpA''.[13]

CASE FOR THE ''LUMPERS''
The lumpers argue that the different entities of the SpA group represent variable expression of the major characteristic features of the same disease. The features include:

- axial disease involvement—when predominant with radiographic sacroiliitis the designation ''ankylosing spondylitis'' is used

- peripheral arthritis—especially asymmetrical and large lower limb joints
- enthesitis and dactylitis—common across the subgroups
- skin involvement—when severe and/or with nail changes, ''psoriatic arthritis'' is the label given
- uveitis—common across the subgroups
- inflammatory bowel disease (IBD)—when histologically defined.

Further, it has been proposed that patients be diagnosed as having an SpA, and thereafter the clinical presentation be described to highlight the major manifestation or resistant feature, such as: SpA active, severe, with refractory axial involvement. It is argued that this would be more readily understood than refractory ankylosing spondylitis, which does not define which feature of a multifaceted disease is refractory as far as therapy and prognostication is concerned.[14]

Others think that these diseases should be considered as SpA or ankylosing spondylitis-like, RA-like, and osteoarthritis-like with psoriasis plus arthritis or spondylitis as the main combining feature. A number of aspects support the ''lumping'' approach.

The strength of the disease association with HLA-B27 lent cohesion to the group. The proportion of B27-positive patients decreases from 95% in ankylosing spondylitis, 70–80% in reactive arthropathy, 50% in PsA and IBD with sacroiliitis/spondylitis to anywhere from 0–10% to 60–70% in undifferentiated SpA depending on the study chosen.[15] There is a long recognised familial clustering of these arthropathies and strong heritability of the disease. Disease frequency in relatives of affected individuals compared with the disease frequency in the general population significantly exceeding 1.0 in SpA (if disease frequency is close to 1.0, there is no evidence of familial clustering), ranging from 10 in IBD to 50 in ankylosing spondylitis.[10] Further, B27 transgenic rat models develop disease with axial involvement, with ossification of ligaments, peripheral arthritis, skin abnormalities similar to psoriatic lesions, and gut involvement suggestive of human inflammatory bowel disease, all supporting the notion that this is a single disease with variable disease expression.[16]

Medications shown to have benefit in one disease have similar efficacy in the others; examples include sulfasalazine and antitumour necrosis factor (anti-TNF) therapy.

Table 3 Amor criteria for classifying spondyloarthropathies[5]

Variable	Score
A Clinical symptoms or past history of:	
(1) Night-time lumbar or dorsal pain or morning stiffness of lumbar or dorsal spine	1
(2) Asymmetric oligoarthritis	2
(3) Buttock pain or pain alternately affecting the right or left buttock	1 or 2
(4) Sausage-like toe or finger	2
(5) Heel pain or other well defined enthesopathic pain	2
(6) Iritis	2
(7) Non-gonococcal urethritis or cervicitis within one month before onset of arthritis	1
(8) Acute diarrhoea within one month before onset of arthritis	1
(9) Psoriasis, balanitis, or inflammatory bowel disease (ulcerative colitis or Crohn's disease)	2
B Radiological finding:	
(10) Sacroiliitis (grade 2 if bilateral; grade 3 if unilateral)	3
C Genetic background:	
(11) Presence of human leucocyte antigen (HLA)-B27 and/or family history of ankylosing spondylitis, reactive arthritis, psoriasis, uveitis, or inflammatory bowel disease	2
D Response to treatment:	
(12) Clear improvement within 48 hours after non-steroidal anti-inflammatory drug (NSAID) initiation and/or rapid relapse after discontinuation	2

A patient is considered to have spondyloarthritis if the total score is at least 6.

An infectious aetiology and bowel inflammation are postulated shared pathogenic mechanisms. Enteric infections with *Klebsiella pneumoniae* and *Escherichia coli* have been implicated in the pathogenesis of ankylosing spondylitis in genetically susceptible hosts. Molecular mimicry involving streptococcal antigens has been implicated in the pathogenesis of psoriasis and PsA.[17] Subclinical gut inflammation is found in 40–60% of patients with ankylosing spondylitis—the acute form typical of bacterial enterocolitis and the chronic form a chronic ileocolitis indistinguishable from Crohn's disease. Serial ileocolonoscopy demonstrates that remission of the rheumatic disease occurs with disappearance of the gut lesion. Indeed, the B27 transgenic rat model did not develop joint or gut inflammation in germ free conditions.[18] Human immunodeficiency virus (HIV) is associated with a 10 times increased frequency of development of PsA.[19] Molecular mimicry between epitopes of the infecting organism that cross-reacts with self-peptides is the most persuasive explanation for the pathogenesis of SpA. We do know, however, that 80–90% of the pathogenesis of AS has a genetic basis and that HLA-B27 accounts for a small increment of that genetic load; the rest is unknown.[20]

The association with HLA-B27 has been demonstrated worldwide, and evidence for a role of HLA-B27 in ankylosing spondylitis comes from linkage and association studies in humans and transgenic animal models. However, twin studies indicate that HLA-B27 contributes only 16% of the total genetic risk for the disease. Furthermore, there is compelling evidence that non-B27 genes, both within and outside of the major histocompatibility complex (MHC), are involved in the disease aetiology.

Psoriasis is commoner in patients with Crohn's disease and their first-degree relatives than in controls, suggesting the possibility of a genetic link. Psoriasis could be included among the extraintestinal manifestations of the condition.[21] In addition, considerable overlap exists as common conditions, such as psoriasis, RA, and osteoarthritis, occur randomly in the same individual, and presentations are highly variable as illustrated in the following examples from the PsA literature.

A study in which 40% of the cohort had oligoarticular PsA and 60% polyarticular PsA illustrates this variability, including changes over time and therapy.[22] However, the patients with polyarticular PsA were administered disease modifying antirheumatic drugs (DMARDs) more frequently than patients with oligoarticular PsA. This resulted in a significant number of polyarticular PsA patients being reclassified as oligoarticular PsA at one year (39%) and at two year (49%) follow up. Fewer patients initially classified with oligoarticular PsA were reclassified as polyarticular PsA. More patients with oligoarticular PsA at baseline were in DMARD free remission, and there was less radiological damage at the two year follow up. Distal interphalangeal (DIP) disease was associated with other classic seronegative disease features (enthesopathy and nail dystrophy) but did not influence clinical or radiological outcome, and the separation of DIP disease as a distinct subgroup in classification criteria was not supported.[22]

In another PsA cohort, asymmetrical oligoarthritis (AO) was commonest, occurring in 43% of patients.[23] Symmetrical polyarthritis (SP) was present in 33%, and this subgroup had the highest number of erosions and deformities, as well as a higher proportion of patients with grade III/IV American Rheumatism Association (ARA) functional disability. Whereas the DIP joints were involved in 46%, predominant DIP joint disease occurred in 16%. As the DIP group had the shortest duration of arthritis, it was suggested that this group represented recent onset PsA which evolved into one of the other subgroups. Sacroiliitis was a feature in 14%, with

predominant spondylitis (SPON) in 4%. Arthritis mutilans was rare, occurring in only 2% of this population, perhaps representing patients with end stage SP disease. Finally, 2% of patients had features of the synovitis–acne–pustulosis–hyperostosis–osteomyelitis (SAPHO) syndrome. A classification comprising just three subgroups (AO, SP, SPON) was proposed as being of most use clinically, although a long term prospective study was suggested for verification.[23]

The ASessment in Ankylosing Spondylitis international working group (ASAS) has defined and validated outcome measures for the various domains of AS,[24] but there has not yet been an adequate effort to assess their validity and utility in the other SpA subgroups and to test their utility.

CASE FOR THE ''SPLITTERS''
In contrast, many have argued that the diseases that make up the SpA group should be considered separately but under the same umbrella. Implementing the ESSG criteria leaves 20–30% of patients who do not fit into the SpA framework. An argument can be made that a clinical manifestation such as psoriasis could be considered a common denominator in the presence of an inflammatory arthropathy that presents in a rheumatoid-like or spondylitis-like manner. Moreover, a study comparing patients with ankylosing spondylitis with patients with PsA with spondylitis demonstrated that there are both clinical and genetic differences between the two groups. Patients with ankylosing spondylitis have more severe spondylitis, as evidenced by a higher number with grade 4 sacroiliitis and higher number of syndesmophytes, whereas PsA patients have an increased frequency of peripheral arthritis. Patients with ankylosing spondylitis have a higher frequency of HLA-B27, whereas those with PsA have a higher frequency of HLA-B17, HLA-B39, and HLA-Cw6.

Aetiological differences justify research targeting individual diseases; for example, there is supporting evidence that, in some cases, psoriasis represents a sterile antibacterial tissue reaction, which is mediated by streptococcal specific T cells that cross-react against epidermal autoantigens,[17] in contrast with the enteric triggering postulated in ankylosing spondylitis.

It is estimated that genes within the major histocompatibility complex account for less than 50% (probably only 36%) of the heritable aspects, studies with twins have found that the concordance in monozygotic twins is 67%, whereas in dizygotic twins the concordance is only 12%. The low incidence of B27 positivity in the non-ankylosing spondylitis members of the group argues that B27 does not define disease diagnosis but is a disease manifestation, such as axial inflammation when present. Many class I MHC candidate genes are involved in SpA diseases. HLA-B27 in ankylosing spondylitis and Reiter's syndrome,[25] HLA-B51, and MICA-A6 in Behcet's disease,[26 27] HLA-Cw6, and tumor necrosis factor α (TNFα) in psoriasis vulgaris,[28 29] and HLA-Cw6, MICA-A9, and TNFα in PsA. Either different combinations of several independent predisposing factors lead to a variety of phenotypic expressions of disease or, alternatively, there is a predominant predisposing component common to most forms of SpA, but different manifestations occur because of the additional influence of minor factors.[29–31]

Outcome measures validated in one disease subset when tested in another have been disappointing. Taylor and Harrison[32] have tested the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), validated in ankylosing spondylitis, in PsA; they have shown that BASDAI is ambiguous as a measure of disease activity in patients with PsA. It correlated highly with patients' own perception of arthritis activity, and this was independent of whether disease was axial or not. It demonstrated better correlation

with patient perception than metrology measures or Health Assessment Questionnaire (HAQ), and better correlation with Medical Outcome Survey Short Form 36 (SF-36) scores than HAQ for all dimensions other than physical function. However, the factor analysis suggested that BASDAI is mainly related to other self-report indices rather than active inflammatory disease in PsA, and that it may be the method of measurement rather than the underlying construct that caused these self-report indices to co-vary. It can be argued that this strong correlation between BASDAI and other patient reported outcomes with weak correlation with physician or laboratory assessments also occurs in ankylosing spondylitis.[33] Furthermore, when an attempt was made to measure disease activity independently by means of treatment decisions in rheumatology clinics in a different consecutive group of patients, BASDAI (and patients' perception of disease activity) failed to significantly discriminate between patients with high and low disease activity in their studies.[32] Only physicians' perception of disease activity was related to treatment decisions. Compared with patients with ankylosing spondylitis, BASDAI scores in this cohort of patients with PsA were significantly lower overall, although the patients with axial disease had values approaching those of patients with ankylosing spondylitis (median 4.26). It was considered likely that disease severity was significantly greater in the ankylosing spondylitis patients than in this cohort of PsA patients.[32] However, others suggest that this might be influenced by a real difference in severity. Researchers have tested BASDAI in patients with ankylosing spondylitis and without peripheral arthritis and the index performed well in both and showed more disease activity in patients with peripheral arthritis.[34] Nonetheless, Taylor and Harrison showed that in PsA BASDAI was independent as to peripheral involvement or not.[32]

All outcome measures, metrology, functional measures, and imaging studies validated, for example in ankylosing spondylitis, should be re-tested across the SpA subgroups. (Although this conclusion is not being disputed here, it could be argued that the examples given do not prove this and only support it weakly, as there are also other explanations and the same findings in patients with ankylosing spondylitis.) Minimal clinically significant differences need definition in the subgroups. Given lesser involvement, such as axial inflammation, it would need to be shown that the ASAS outcome measures would be sensitive to change when lesser involvement is present.

These diseases have a sufficient number of unique features, from osteoproliferative lesions, DIP and nail involvement in PsA, and aortitis and apical pulmonary disease in ankylosing spondylitis to liver disease and pyoderma gangrenosum in IBD, to justify separate consideration. Significant radiological differences have been demonstrated within subgroups including severity of involvement, symmetry of sacroiliitis, and morphology of syndesmophytes that would challenge the use of uniform imaging measures across disease subgroups.[35]

The concern arises that if multiple SpA subtypes are lumped together in the same clinical trial, the outcome measures chosen, perhaps validated in one subset but not in others, may inaccurately represent the treatment response. For example, use of the newly developed Psoriatic Arthritis Specific Measure of Quality of Life (PsAQoL)[36] would not accurately reflect changes quality of life of ankylosing spondylitis patients, where the ASQoL would.[37] Concern also arises that in domains that have common denominators, such as peripheral arthritis, subtle differences in the cellular and cytokine pathophysiology between disease subtypes may yield differences in therapeutic response to various targeted therapies that would not be teased out adequately if all subtypes were lumped together in studies.

A MIDDLE GROUND

There are some areas where a middle ground of consensus may occur. For instance, there are many examples where ''lumping'' makes best sense. If a rheumatology department is organised around centres of care—that is, it has a lupus clinic or an RA clinic, then it is more sensible to have a spondyloarthropathy clinic rather than clinics devoted to each of the subsets. This also allows clinical providers to develop bridging expertise in all subsets of SpA and to recognise common patterns, especially in patients with undifferentiated SpA. One caveat is that in those centres developing a working relationship between rheumatologists and dermatologists, specific psoriasis–PsA clinics may be present. It is important to recognise the common threads across subtypes, be it eye, skin, or gut inflammation, as well as unique features other than purely articular manifestations, such as enthesitis.

Until outcome measures can be validated across all SpA subsets, it may be preferable to conduct clinical trials with patients diagnosed within a single subset, or use stratification according to underlying SpA subsets. In some research projects, it may be illuminating to do the same assessments, such as tissue biopsy, in patients with different subset diagnoses in order to demonstrate the similarities and differences between subsets.

CONCLUSION

Clearly, the two camps have their own advocates and more research needs to be done to clarify the issue further, but the experience from the Moll et al[1] era distinguishing the SpA group from RA variants is persuasive. Moll et al initially included Whipple's disease in their classification—a disease, which when studied as its own entity rather than ''lumped'' in a group, has had its aetiological agent defined allowing appropriate therapy and cure. We would like to agree and conclude with the following statement from a recent article on SpA:

> There is a fundamental need to establish universal standards for nomenclature, disease classification, and assessment of treatment outcome, if the precise role of these agents [that is, anti-TNFs] in disease management is to be defined. Uniformity in these areas will facilitate global communication of scientific, clinical, and epidemiological information that can further the understanding of the pathogenesis and treatment of the disease. Disease classification is particularly important in clinical practice because it guides treatment strategy and helps to predict response to treatment and prognosis. Additionally, standardisation of scientific terminology and treatment assessments will enable investigators to design clinical trials with the intention of producing conclusive and reproducible end points that have clinical application in well defined patient populations. Furthermore, such trials will allow valid comparisons of therapeutic outcomes.[38]

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