Editorial

Can we currently and confidently assess the true burden of illness due to non-radiographic axial spondyloarthritis?

S. van der Linden[1], M.A. Khan[2]

[1]*Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, the Netherlands;*
[2]*Case Western Reserve University, Cleveland, OH, USA.*

Sjef van der Linden, MD, PhD
Muhammad A Khan, MD, FRCP, MACP

Please address correspondence to:
Dr Sjef van der Linden,
Department of Internal Medicine,
Division of Rheumatology,
Maastricht University Medical Center,
P.O. Box 5800,
6202 AZ Maastricht, The Netherlands.
E-mail: s.vander.linden@mumc.nl
svdlinden@scarlet.be

Dr Muhammad A. Khan,
MetroHealth Medical Center,
2500 MetroHealth Drive,
Cleveland, OH 44109, USA
E-mail: mkhan@metrohealth.org

Received on September 3, 2016; accepted in revised form on September 19, 2016.

Clin Exp Rheumatol 2016; 34: 963-965.

Competing interests: none declared.

Ankylosing spondylitis (AS) is the prototype of the group of diseases known as the *spondyloarthropathies* or, better, *spondyloarthritides*. Radiographic sacroiliitis is considered a hallmark in AS, but it is not an early manifestation of AS. It takes, on average, 6 to 8 years between the onset of inflammatory back pain and establishing a definite diagnosis of AS. This delay in diagnosis mostly results from the relatively late appearance of definite radiographic sacroiliitis on conventional plain radiographs. Thus many patients at an early stage of AS typically present with characteristic clinical symptoms but may not show definite sacroiliitis on radiographs. Therefore they may not be classified as AS according to the modified New York criteria (1). An as yet unknown proportion of patients will remain at the non-radiographic stage of disease, with inflammation of sacroiliac joints at some point, but without radiographically detectable damage over the subsequent years.

Already in 1985, we had reported occurrence of symptomatic spondylitic disease but with normal looking sacroiliac joints on plain radiography among some of the first degree relatives, quite often women, in our family studies of HLA-B27+ probands with AS (2). More recently, this form of what we had called "spondylitic disease without radiologic evidence of sacroiliitis" (2) has been termed *non-radiographic axial spondyloarthritis* (nr-axSpA) (3) while the term axial spondyloarthritis (axSpA) encompasses this nr-axSpA as well as the classical AS (by modified New York criteria).

An as yet not fully defined proportion of patients with nr-axSpA may never progress to classical AS, or may go on to spontaneous remission due to the natural history of the condition. Further understanding such aspects of axSpA requires valid criteria. One may conclude that the conceptual construct of axSpA is appropriate and fully justified. There is a major unmet need to correctly recognise and treat patients with nr-axSpA as they often have active disease that can be treated if current therapies used for classical AS are utilised. The challenge, therefore, is how to translate the valuable concept of axSpA into definitions that enable proper clinical diagnosis, correct classification and accurate assessment of the true burden of illness.

Establishing clinical diagnosis by health providers and application of classification criteria are associated with errors (false negative or missed cases and false-positive or incorrectly labelled patients). Classification criteria should have high specificity (even at a loss in sensitivity) in order to avoid many incorrectly labelled patients, *i.e.* to limit the false-positive rate. This holds true particularly in settings with a rather low probability or prevalence of the target disease.

The ASAS classification criteria for axSpA comprise both an *imaging* arm (sacroiliitis on conventional radiography or positive MRI of SI joints together with ≥ 1 SpA feature) and a *clinical* arm (HLA-B27+ plus ≥2 SpA features) (4). It has been shown that the complex multi-arm selection design of the ASAS criteria induces considerable heterogeneity among patients so classified, and applying them in settings with a low prevalence of axSpA greatly increases the proportion of subjects falsely classified as suffering from axSpA (5). This is due to a rather low (only 84%) specificity of the ASAS criteria for axSpA. If the prevalence of axSpA among chronic back pain (CBP) patients is about 5% one expects almost 4 false positively

labelled persons for each true axSpA patient. In that case the majority of patients that meet the ASAS criteria do not really have axSpA. Therefore, assessing studies investigating the burden of illness, one should clearly keep in mind that current criteria capture both patients with true axSpA as well as patients incorrectly labelled as having axSpA (Table I).

Table I. Categories within the spectrum of axSpA as defined by criteria that lack specificity.

True radiographic axSpA
- Classical AS (by modified New York criteria) with syndesmophytes
- Classical AS (by modified New York criteria) without syndesmophytes

True non-radiographic axSpA
- "Early" not yet radiographic AS
- "Spondylitic disease" without ever developing radiographic sacroiliitis

False axSpA
- Look-alike conditions (incorrectly labelled as axSpA due to lack of specificity of criteria)

There is now growing evidence that the current ASAS criteria need to be improved (5-7). Misclassification due to low specificity of these criteria was shown in a population based study (8). An unrealistic high proportion (17 of 20 or 85%) of the subset of HLA-B27+ patients with chronic back pain (CBP) and onset before age 45 met the ASAS criteria for axSpA in this study; and the 3 remaining HLA-B27+ patients (15%) had non-specific CBP. Interestingly, prevalence of HLA-B27 among the 278 CBP patients who did *not* have axSpA was only 1.1%, clearly considerably lower than the expected prevalence of HLA-B27 in that group (8.8%) (5, 8). Therefore, this study shows that many of the HLA-B27+ CBP patients get incorrectly labelled as having axSpA; they are "look-alikes" that will also get captured in a cost-of illness study. Thus presentations of some non-specific non-inflammatory conditions may also get classified as axSpA by the ASAS criteria.

One might ask whether the situation would be very different if the diagnosis axSpA would have been based upon clinical assessment by individual health providers as is the case in the study by Sieper *et al*. in this issue of the journal (9). However, this does not seem very likely. Clinicians are also liable to diagnostic mistakes due to lack of sensitivity and specificity. Furthermore, it appears likely that nowadays clinicians in establishing a clinical diagnosis use a *Gestalt* of axSpA that closely resembles the "image" provided by the ASAS classification criteria for axSpA. In this context it is important to note that the FDA has expressed concerns that a considerable proportion of patients with frequently occurring non-specific back symptoms may fulfill the ASAS criteria for nr-axSpA, and they get treated inappropriately with TNF inhibitors. This fear has led to the FDA's refusal to approve the use of TNF inhibitors for the treatment of nr-axSpA (10).

The study by Sieper *et al*. in this issue of the journal (9) aimed at assessing (i) clinical and demographic characteristics of patients with nr-axSpA, (ii) how these patients are diagnosed and classified by health providers in 5 European countries, and (iii) to quantify the burden in terms of quality of life (EQ-5D-3L) and loss of productivity and activity impairment (WPAI). Furthermore an attempt was made to assess *avoidable* burden defined as the extent to which burden of disease could be alleviated through treatment with a *biological* agent in biologically-naïve but biologically-eligible patients. These patients were compared with controls currently receiving a biological agent. But please, note that there is no randomisation of patients in this study, and the controls constitute a different group. Improvement in the biologically-naïve but biologically-eligible patient group might be due to treatment effect, but could also be a result of spontaneous improvement by the natural history of the underlying condition (nr-axSpA or any "look-alike" condition), and regression to the mean.

Therefore, the conclusion of the authors that more widespread use of biologic agents may reduce the burden of nr-axSpA may at least seem somewhat biased and imprecise. Note that 231 of 631 (36%) patients were currently receiving a TNF inhibitor, although – as the authors report – these agents are not yet widely approved for use in patients with nr-axSpA. Their study also shows quite a lot of variation among the 5 European countries. The diagnosis nr-axSpA was based upon each physician's clinical judgment. Inter-observer variation was not assessed. Fulfillment of the ASAS classification criteria for axSpA ranged from 24% to 75%.The use of biologics varied from 25% to 49%; severity of disease at diagnosis varied from 10% to 24%, and the proportion of HLA-B27+ ("most recent HLA-B27 result") patients ranged from 58% to 84%. These variations in the characteristics of patients considered to have nr-axSpA are somewhat surprising as the prevalences and characteristics of radiographic axSpA (classical AS) do not vary so much among the 5 European countries. Differences in health care systems, treatment practices, and awareness of the concept nr-axSpA might contribute to the observed variation. Moreover differences in application of the imaging or the clinical arm of the ASAS criteria might have also contributed to the observed heterogeneity, as has been shown earlier (5).

It is important to note that the reported burden of illness is in fact a composite of the burden due to true axSpA and the burden associated with the axSpA "look-alike" conditions. The relative contribution of each of these components is currently unknown. There is a need to develop better definitions and criteria that enable discrimination between true axSpA and "look-alike" conditions. The needed improved criteria for axSpA should also address construct and criterion validity, and those for nr-axSpA should demonstrate a strong (biologic) relationship with radiographic axSpA, *i.e*. AS by the modified New York criteria.

References

1. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.

2. KHAN MA, VAN DER LINDEN SM, KUSHNER I *et al*.: Spondylitic disease without radiologic evidence of sacroiliitis in relatives of HLA-B27 positive ankylosing spondylitis patients. *Arthritis Rheum* 1985; 28: 40-3.
3. SIEPER J, VAN DER HEIJDE D: Nonradiographic axial spondyloarthritis: new definition of an old disease? *Arthritis Rheum* 2013; 65: 543-51.
4. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
5. VAN DER LINDEN S, AKKOC N, BROWN MA *et al*.: The ASAS criteria for axial spondyloarthritis: strengths, weaknesses, and proposals for a way forward. *Curr Rheumatol Rep* 2015; 17: 62.
6. ROBINSON PC, WORDSWORTH BP, REVEILLE JD *et al*.: Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis. *Ann Rheum Dis* 2013; 72: 162-4.
7. TAYLOR WJ, ST CLAIR EW: Shifting the goal posts: treatment recommendations for ankylosing spondylitis and the newly defined condition of nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2016; 68: 265-9.
8. VAN HOEVEN L, LUIME J, HAN H *et al*.: Identifying axial spondyloarthritis in Dutch primary care patients, ages 20-45 years, with chronic low back pain. *Arthritis Care Res* (Hoboken) 2014; 66: 446-53.
9. SIEPER J, HOLBROOK T, BLACK C *et al*.: Burden of illness associated with nonradiographic axial spondyloarthritis: a multiperspective European cross-sectional observational study. *Clin Exp Rheumatol* 2016; 34: 975-983.
10. DEODHAR A, REVEILLE JD, VAN DEN BOSCH F *et al*.: The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis international Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol* 2014; 66: 2649-56.