Diagnosing axial spondyloarthropathy. The new Assessment in SpondyloArthritis international Society criteria: MRI entering centre stage

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In this issue of the *Annals of Rheumatic Disease* the Assessment in SpondyloArthritis international Society (ASAS) have published three interrelated papers ***(see pages 770, 777 and 784)***[1–3] that could contribute to a new era in the diagnosis and classification of axial spondyloathritis (SpA). The first paper focuses on a new definition of inflammatory back pain (IBP), the "expert" criteria, followed by two reports on the development of new classification criteria for axial SpA and their validation in a large multicentre study. These criteria for axial SpA will be welcomed by the spondyloarthropathy community, since the currently available criteria[4–6] do not allow for the diagnosis of preradiographic axial SpA. The proposed new set of criteria includes early (preradiographic) and established ankylosing spondylitis (AS), recognising them as a continuum of disease. This is of major importance as it is now clear that the burden of early AS is comparable to that of the later stages.[7] The benefit of MRI in the diagnosis of early axial SpA is recognised by the authors and included in the new classification criteria. Indeed, the inclusion of MRI is the most significant change compared to previous criteria[4–6] and is in line with clinical experience where MRI is of recognised value as a diagnostic and outcome tool.[8 9 14] Furthermore, with the emerging data on the efficacy of tumour necrosis factor (TNF)α blocking therapies in early disease[10 11] a new horizon has opened whereby AS sufferers can be identified and treated in the early stages of their disease process before structural damage has occurred.

In the first report Sieper *et al*[1] propose new clinical criteria for IBP. The study adopted a novel approach in which the "experts" were blinded to patient diagnosis, and the criteria judged for an ability to discriminate for a "diagnosis" of IBP (rather than for a diagnosis of SpA, as previously performed).[12 13] This, along with the robust statistical analysis, performed using logistic regression to identify which criteria/parameters independently contributed specifically to IBP, are the strong points of the study.

However, the need for new criteria to define IBP might be questioned since it is only 3 years after the last set of IBP criteria were published by the same core group.[12] Indeed, the authors point out that the existing criteria performed reasonably well and that there are only small differences between the new criteria and the previous 2006 Berlin criteria.[12] In addition the new IBP criteria surprisingly omit the assessment of early morning stiffness (EMS) of greater than 30 min as well as pain in the second half of the night, which were present in the previous criteria. These were dropped because the duration of EMS and timing of nocturnal pain were not specifically analysed. Given the central role of EMS duration in inflammatory rheumatic diseases this approach seems to lack face validity.

Therefore, while the improved methodology of this study to define new criteria for IBP are most welcome, whether the new criteria represent a significant advance will, as the authors highlight, depend on further assessment, particularly validation in the primary care setting.

The subsequent two papers focus on the development[2] and validation[3] of candidate classification criteria for axial SpA, including patients with and without radiographic sacroiliitis. These patients without radiographic sacroiliitis have up to now been mostly labelled as undifferentiated SpA (uSpA) following The European Spondyloarthropathy Study Group criteria (ESSG).[5] However, uSpA does not differentiate between patients with isolated axial or isolated peripheral disease. The data reported in this issue of the journal show that it is possible to robustly classify cases of axial SpA hence facilitating the conduct of future clinical trials and observational studies. This is particularly critical in the context of therapeutics as the newly proposed criteria might serve as a basis for a judicious use of TNF blockers in the non-radiographic stage of axial SpA. This is all the more likely given the increasing evidence that MRI can predict the future development of AS,[14 15] that early preradiographic axial patients with SpA have just as much disease activity and pain as established AS[7] and that early preradiographic axial SpA responds well to anti-TNF therapies.[10 11]

A strength of the ASAS papers lies within the inclusion of international experts' opinions on 71 real-life paper patients. Their opinion regarding diagnosis, as well as the strength of certainty of their opinion were sought with both being subsequently reviewed and accepted or rejected by a five-strong expert panel. The subsequent validation study[3] is a unique and unprecedented clinical study in terms of international collaboration and the recruitment of nearly 650 cases. Although the mean duration of symptoms of the studied cohort was 6.1 years, the patient population was representative of the clinical spectrum of disease from early preradiographic axial involvement to radiographically confirmed sacroiliitis. Given the emerging power of MRI for predicting the development of AS,[14 15] this imaging modality was importantly included in the assessment of these patients.

Of note, in the first classification paper,[2] raised C-reactive protein (CRP)

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levels were more frequent in the non-SpA (42.1%) than the SpA population (27.8%), yet elevated CRP was included in set 1 and set 2 candidate classification criteria. However, in the validation paper[3] this observation is reversed with raised CRP being more common in SpA. Likewise in the initial classification[2] of the three studied IBP criteria, the new ''expert'' criteria[1] performed worse, with only 57.1% compared to 84.4% for the Calin criteria[13] and 85.3% for the Rudwaleit/Berlin criteria.[12] Again however this changed considerably in the follow-up validation study. The proposed new classification criteria for axial SpA has an 82.9% sensitivity and 84.4% specificity out of a large data set of 649 patients with a positive likelihood ratio of 5.3 for axial SpA, which increases the post-test probability of a diagnosis of axial SpA from 60.2% to 89.0%. Furthermore when benchmarked against existing long-standing criteria such as the Amor and ESSG criteria,[4 5] they were shown to be superior.

One important observation is the fact that the reported studies further support the diagnostic utility of MRI in axial SpA. Indeed MRI of the sacroiliac joints (SIJs) changed the diagnosis to axial SpA in a fifth of cases.[2] These findings justify the well established use by rheumatologists of MRI for the assessment of suspected AS in the real world clinical setting. However, it also recognises the limitations of MRI given that spinal/SIJ inflammation is variable in the natural history of the disease, and that current MRI technology has some limitations in detecting active inflammation.[16] This is shown by the fact that only 38% and 65% of sample patients in the classification and validation paper, respectively, had a positive MRI. Hence criteria have been established that permit a diagnosis of axial SpA on clinical grounds only without the need for a positive MRI. This is essential, partly for the diagnosis of the subgroup of axial SpA who present with normal MRI scans but more importantly for clinicians who have poor or no access to MRI scanning facilities.

It should be noted that only the SIJs were imaged with MRI in the initial classification paper, and in the validation paper only a proportion of the 650 patients had spinal as well as SIJ MRI. Spinal inflammation is well recognised in SpA and it has been reported that as many as 23% of patients with clinically active AS have normal MRI of the SIJ[17] and that thoracic spinal lesions are as common as SIJ lesions.[18] Therefore classification criteria that include spinal as well as SIJ MRI could have improved the overall sensitivity and specificity of these criteria.

Importantly the definition of active MRI sacroiliitis is needed for research as well as clinical practice. Variable ''degrees'' of active MRI sacroiliitis are recognised depending on the intensity and/or extent of the MRI signal when using fat suppression techniques[8 19] which may lead to different clinical and radiographic outcomes.[14] Indeed, low grade bone marrow oedema lesions as identified by MRI are not specific for SpA and are also evident in degenerative joint disease and occasionally in healthy people,[8 18] and hence a clarifying definition of active MRI sacroiliitis is essential.

In summary, these are exciting times in the field of research in SpA. Only a decade ago there was little recognition of early disease and treatment in early and established AS was woefully inadequate. Now, we have widespread access to the non-ionising radiation of fat suppression MRI that can predict progression to AS as well as showing efficacy of TNF blocking agents in the suppression of inflammation leading to major improvements in early and late disease. Furthermore MRI has a major role in the diagnosis of the early disease stages.

The present studies have utilised a breadth of expert knowledge on SpA and MRI to take us further along the clinical translational road to a better understanding of axial SpA. The formulation of new international classification criteria for axial SpA, which embraces early axial SpA and AS, as described in this journal, is essential for future research and the management of axial SpA. Given the falling costs of MRI and its great potential in SpA the case for using MRI in inception cohorts of patients with IBP, and other non-IBP diagnosis for comparison, is growing. The present studies produce compelling evidence for the use of MRI for the diagnostic evaluation of SpA in routine practice. However, it is vital to remember that a negative MRI scan does not exclude a diagnosis of SpA and that it can still be difficult to discern the basis of some types of back pain even with IBP and MRI criteria.

Competing interests: PE and HM-O are members of Assessment in SpondyloArthritis international Society (ASAS).

Accepted 10 March 2009

Ann Rheum Dis 2009;**68**:765–767.
doi:10.1136/ard.2009.111435

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New tumour necrosis factor inhibitors for rheumatoid arthritis: are there benefits from extending choice?

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Certolizumab pegol (UCB, Brussels, Belgium) and golimumab (Centocor, Horsham, Pennsylvania, USA) are the latest tumour necrosis factor (TNF) inhibitors evaluated in double-blind, multicentre randomised controlled trials (RCT). Certolizimab is the pegylated (polyethylene glycolated) Fab′ fragment derived from a high affinity humanised anti-TNFα monocolonal antibody (mAb). Fab′ fragments lack the Fc portion of immunoglobulin, and so the repertoire of Fc-mediated effector responses, such as complement or antibody-dependent cell-mediated cytotoxicity, is distinct from those of other anti-TNF mAb. Nonetheless, it still neutralises membrane TNFα. Derivatisation of the Fab′ fragment prolongs the plasma half-life to 2 weeks. Certolizumab pegol is administered by subcutaneous injection (200 or 400 mg) every 2 weeks. Golimumab is a human anti-TNF mAb administered by subcutaneous injections (50 or 100 mg) every 4 weeks. Three RCT in this issue of *Annals of the Rheumatic Diseases*,[1–3] ***(see pages 789, 797 and 805)*** which report their use in active rheumatoid arthritis (RA), raise two questions. First, do we need more TNF inhibitors? Second, how effective and safe are these new TNF inhibitors?

Successful drugs are invariably replicated. ''Breakthrough'' treatments sound more impressive than subsequent ''me too'' replications, although the latter products might perform better. Lee[4] has elegantly summarised the arguments for ''me too'' products, indicating that their presence ''does not mean that imitation has replaced innovation''. Successful ''me too'' treatments improve efficacy, reduce toxicity and increase ''cost effectiveness''. With biological agents such as TNF inhibitors their added benefits may include more favourable routes or frequencies of administration.

There are cogent reasons to anticipate that ''me too'' biological agents will be commonplace as experience with these agents solidifies and their use increases. There may be special factors with biologicals, particularly around their mechanism of action, which may complicate the comparison of different ''me too'' products. Nevertheless, it is generally appropriate to assume that what holds for conventional drugs also holds for large molecules with regard to the benefits of ''me too'' products. Indeed, regulatory developments have paved the way for future biosimilars or follow-on biologicals to be developed as the patent life of established molecules draws to a close.[5]

There are many critics of ''me too'' conventional drugs.[6] Clinicians often use only one or two drugs in each class and may not need wide choices. Furthermore, much expenditure on drugs is attributable to high-cost ''me too'' products. However, this issue is complex because it could represent either high expenditure on unneeded replication or a realistic preference for refined ''me too'' products over less effective or more toxic ''breakthrough'' products. Overall, the proliferation of agents in a successful treatment class reflects the competitive nature of drug development, the length of the regulatory process and the risks of first agents in a class not achieving registration. It seems unlikely that ''me too'' products stifle the development of novel agents; recent history suggests ''me too'' agents are an inevitable part of the process of finding new products.[7]

Two RCT reported in this issue evaluated the new TNF inhibitors combined with methotrexate in disease-modifying antirheumatic drug (DMARD) non-responders. American College of Rheumatology 50% improvement (ACR50) responder rates at 6 months can be used to place the results in context. With golimumab–methotrexate ACR50 responder rates were 35% compared with 14% with controls;[2] in a previous dose-ranging trial ACR50 responder rates were 31% with active treatment and 6% in controls.[8] Certolizumab pegol/methotrexate gave ACR50 responder rates of 33% compared with 3% with controls;[1] in a previous phase III trial ACR50 responder rates were 37–40% compared with 8% with controls.[9] We extended this analysis of ACR50 responder rates at 6 months across TNF inhibitor–methotrexate combinations, using key RCT in established RA identified in a previous systematic review.[10–13] Although this analytical approach has its limitations as the trials were undertaken at different times and in different populations, it is possible to gain some understanding of the overall efficacy of different TNF inhibitors from this type of comparative analysis. The number needed to treat (NNT) to achieve an ACR50 response compared with methotrexate monotherapy ranges from 3 to 5 (table 1). These results show that both established and new TNF inhibitors have similar efficacy when combined with methotrexate.

Established TNF inhibitors prevent erosive progression over 12 months and beyond. Comparative 6-month data for certolizumab pegol suggest it reduces erosive damage and its efficacy is similar to etanercept and adalimumab[1 12 13] (fig 1). Whereas conventional assessments of erosive damage use 12-month changes, 6-month changes are equally impressive with all these agents. Although comparable 6-month data on erosive progression are not available for infliximab and golimumab, their absence is most likely

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Corrections

The department of one of the authors who co-authored all of the below papers has found that the affiliations were not correct. The correct affiliations for Professor P Emery, for all of the below articles, are: [1]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds; [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK.

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Ann Rheum Dis 2011;**70**:1519. doi:10.1136/annrheumdis-2011-70-08