Best Practices—Spondyloarthritis

The spondyloarthritides (SpA) represent a combination of pathogenically related diseases that share many clinical manifestations. As a group, the prevalence of SpA is 0.5% to 1.9%, and the most common subgroups are ankylosing spondylitis (AS) and undifferentiated spondyloarthritis (uSpA). The typical age of onset of AS is between 20 and 30 years of age. Several studies have shown that there may be a delay of 5 to 10 years before diagnosis [Khan MA. *Ann Rheum Dis* 2002; Mau W et al. *J Rheumatol* 1988; Feldtkeller E et al. *Rheumatol Int* 2003].

Martin Rudwaleit, MD, University Hospital Charité Berlin, Berlin, Germany, offered 2 possible reasons for this delay in diagnosis: the relatively late appearance of radiographic sacroiliitis (a definitive diagnosis criterion for AS) in one subgroup of patients with SpA and the low degree of awareness of SpA among non-rheumatologists. Early diagnosis is important, however, because very effective new treatments have become available for this group of disabling diseases.

It is important to realize that the disease does not start when radiographic changes occur. Inflammatory back pain (IBP), the leading symptom of AS and uSpA, precedes the development of radiographic changes in the sacroiliac joints, sometimes by many years [Rudwaleit M et al. *Ann Rheum* Dis 2004]. It is during this stage that MRI is a particularly important diagnostic tool to possibly visualize sacroiliitis.

The lesions that can be seen on MRI mainly are active (acute) inflammatory lesions (eg, bone marrow edema [BME; osteitis], capsulitis, synovitis, enthesitis), but structural damage (sclerosis, erosions, fat deposition, bony bridges/ankylosis) also may be detected. However, conventional X-rays are superior in the detection of structural changes.

Based on interviews with AS patients (n=101) and patients with mechanical back pain (n=112), Dr. Rudwaleit and colleagues identified 4 items that differentiated the 2 groups: morning stiffness >30 minutes, pain that improves with exercise but not with rest, awakening in the early morning hours because of pain, and alternating buttock pain. Based on this study, the investigators determined that IBP is present if at least 2 of the 4 conditions are met (Sensitivity 70%; Specificity 81%) [Rudwaleit M et al. *Arthritis Rheum* 2006].

Dr. Rudwaleit concluded by telling the audience that making an early diagnosis of SpA without definite radiographic changes in the sacroiliac joints is feasible in daily practice. The presence of IBP as such is not sufficient for diagnosis, a combination of several SpA features are necessary, including the presence of IBP, MRI results, and the human leukocyte antigen (HLA)-B27.

Monitoring Patients in Clinical Practice

AS is a multifaceted disease that affects multiple outcome domains. To assist rheumatologists in monitoring their patients, the Assessment in AS (ASAS) working group has established a core set of domains for clinical record keeping as well as specific assessment methods for each domain [van der Heijde et al. *J Rheumatol* 1999; ASAS workshop Ghent, Oct 2002; Bath 2007]. Two types of assessments are provided: patient self-assessments and measurements that are performed by health care providers. Robert B.M. Landewé, MD, University Hospital Maastricht, Maastricht, The Netherlands, reviewed the most recent set of recommendations that were considered appropriate for individual patients (Table 1).

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Table 1. ASAS Core Set for Clinical Record Keeping.

Domain	Instrument
Function	BASFI
Pain	NRS/VAS-last week-spine at night due to AS ***and*** NRS/VAS-last week spine due to AS
Spinal mobility	Chest expansion ***and*** modified Schober ***and*** occiput to wall ***and*** cervical rotation ***and*** lateral spinal flexion or BASMI
Patient global	NRS/VAS-global disease activity last week
Peripheral joints and entheses	Number of swollen joints (44 joint count) Validated enthesitis score (eg, MASES, San Francisco, Berlin)
Stiffness	NRS/VAS duration of morning stiffness-spine-last week
Acute phase reactants	Erythrocyte sedimentation rate (ESR) C-reactive protein (CRP)
Fatigue	Fatigue question on the BASDAI

NRS/VAS=numerical rating scale/visual analogue scale; selected forms available at www.asif.rheumanet.org/index.htm and www.asas-group.org. (Table derived from van der Heijde et al. *J Rheumatol* 1999)

Prof. Landewé reminded the audience that improvement criteria such as the ASAS20 and 40, while validated for use in clinical trials, are not considered appropriate for use in individual patients. Although the BASDAI contains only patient-reported outcomes, it frequently is used in clinical practice because of its feasibility. However, the rheumatologist always needs to consider that there are many potential reasons for back pain, also in SpA patients. The ASAS working group has initiated a new project to develop a disease activity score for AS (the ASDAS) that includes both patient-reported outcomes as well as acute phase reactants. It is expected to be published later this year. In the meantime, Prof. Landewé urged the members of the audience to monitor their patients with AS using the existing guidelines.

How to Use Biologics

Several anti-TNF-α agents (infliximab, etanercept, adalimumab) are now approved for the treatment of rheumatoid arthritis, AS, and psoriatic arthritis (PsA) in the United States and in Europe. In patients with active AS and PsA whose condition is not sufficiently controlled with NSAIDs (for axial disease) or sulfasalazine or methotrexate (for peripheral arthritis), anti-TNF-α agents may be considered as first-line treatment.

Jürgen Braun, MD, Ruhr-Universität Bochum, Bochum, Germany, discussed the use of TNF inhibitors in the treatment of SpA.

For infliximab, a dose between 3 to 5 mg/kg is required at intervals of 6 to 8 weeks to provide constant suppression of disease activity. The efficacy of infliximab can persist for over 3 years [Baraliakos X et al. *Arthritis Res Ther* 2005; *J Rheumatol* 2007]. Now, data for up to 7 years are available [Baraliakos X et al. EULAR 2008], and although almost all patients relapse after withdrawal, readministration is safe and efficacious [Baraliakos X et al. *Arthritis Res Ther* 2005]. The standard dosage of etanercept is 2 x 25 mg subcutaneously per week. For adalimumab, the standard dose is 40 mg subcutaneously every 2 weeks. Although most controlled studies of the anti-TNF therapies have permitted concomitant therapy with methotrexate, there is no evidence that concomitant therapy provides significant additional effect on either axial symptoms [Breban M et al. *Arthritis Rheum* 2007] or MRI lesions for patients with AS [Li et al. *Rheumatology* 2008, in press].

All SpA-related symptoms seem to respond to anti-TNF therapy; swollen joints [van den Bosch et al. *Arthritis Rheum* 2002], enthesitis [D'Agostino MA et al. *Arthritis Rheum* 2002 and 2003], flares of anterior uveitis [Braun J et al. *Arthritis Rheum* 2005], and acute inflammatory bowel disease [Braun J et al. 2007 *Arthritis Rheum*] do not occur or occur less frequently. Adalimumab has been shown to work in subgroups of SpA patients, such as those with total spinal ankylosis [van der Heijde et al. *Arthritis Rheum* 2006], and in patients with early axial uSpA [Haibel et al. *Arthritis Rheum* 2008].

Additional studies are needed to document the long-term efficacy of anti-TNF treatment. Limited evidence suggests that the efficacy may last for 7 years in about 50% of the initially treated patients. Importantly, function and spinal mobility are preserved and even improve over time.

There is evidence that anti-TNF therapy has an effect on structural damage in PsA that relates to osteodestructive changes, but the osteoproliferative changes of AS, such as syndesmophytes and ankylosis, do not seem to be prevented. More studies are needed to clarify this issue.

Severe adverse events are rare, although complicated infections including tuberculosis have been reported. These can largely be prevented by appropriate screening. Autoantibodies have been reported to occur, especially with infliximab therapy, but associated clinical symptoms are rare. No increase in malignancies has been observed so far.

In Prof. Braun's view, "As it stands now, the benefits of anti-TNF therapy in AS seem to clearly outweigh the few shortcomings." Given the lack of efficacy of conventional DMARDs to treat axial symptoms of SpA, anti-TNF therapy becomes more and more a standard of care.