Quality indicators, guidelines and outcome measures in ankylosing spondylitis

J. Zochling, J. Braun

ABSTRACT
The challenge of managing knowledge is a difficult one, and it is no longer enough simply to conduct clinical trials. Quality of care requires the incorporation of research knowledge into clinical practice. As our knowledge of the chronic inflammatory rheumatic disease ankylosing spondylitis (AS) has grown, evidence-based recommendations for the early diagnosis and management of AS and scientifically-derived outcome measures have been developed to aid the clinician at the point of care. Some of these, including the ASAS/EULAR recommendations for the management of AS, are now being validated in national and international studies. This article discusses existing recommendations and the need for specific quality indicators in the field of AS.

Introduction
There have been a number of recent initiatives in the field of ankylosing spondylitis (AS) aimed at rationalizing the rapidly increasing body of evidence in a manageable, efficient and effective way. These include the development and validation of international treatment recommendations, initial strategies to aid early diagnosis, introduction of national AS registries, and the development of evidence-based core sets for use in point of care consultations. This review will examine some of these initiatives as a means of improving the quality of care in AS.

Treatment recommendations
One method of improving information delivery to the end-user involves the development of evidence-based statements that summarize the available research evidence in a given field in a single accessible document. A number of such evidence-based recommendations for AS have been published over the past few years, directed both at general disease management and more specifically at the use of anti-tumor necrosis factor (TNF) alpha agents in AS.

ASAS/EULAR recommendations for the management of AS
With the emergence of biological agents, therapeutic options for AS have increased greatly, which can be confusing when considering the best management strategies for patients. The Assessment in Ankylosing Spondylitis (ASAS) international working group, in collaboration with the European League Against Rheumatism (EULAR), has produced a set of recommendations to guide treatment choices in AS, incorporating research evidence and expert opinion (Table I) (1, 2). A group of 22 rheumatologists and surgeons with internationally recognized expertise in AS were presented with a summary of the available therapeutic options for AS as retrieved from a general systematic search of the research literature. They identified the 10 items that they felt to be the most important for patient care, using a three-round Delphi exercise approach. The literature was then searched in a systematic, directed way to identify all the clinical trials relevant to each of the 10 items. This evidence base was fed back to the group, and the 10 recommendations were refined in the light of the research evidence. The final recommendations address how to approach therapy in AS patients based on a combination of research evidence and expert opinion, and are directed at any health professional involved in the management of AS.

As with any set of clinical recommendations or guidelines, the greater challenge is not the development of a document, but rather its dissemination, implementation and the continuous evaluation of its effectiveness in initiating changes in practice. Preliminary circulation and evaluation of the ASAS/EULAR recommendations has...
The treatment of AS should be tailored according to:
- the current manifestations of the disease (axial, peripheral, enthesal, extra-articular symptoms and signs)
- the level of current symptoms, clinical findings, and prognostic indicators
  - disease activity/inflammation
  - pain
  - function, disability, handicap
  - structural damage, hip involvement, spinal deformities
- the general clinical status (age, gender, co-morbidity, concomitant medications)
- the wishes and expectations of the patient.

There is no evidence for the efficacy of DMARDs, including sulfasalazine and methotrexate, for the treatment of axial disease. Sulfasalazine may be considered in patients with active AS (10-12). Nevertheless, other issues – including patient selection, toxicity and cost – are important in the use of these agents, and therefore a number of published guidelines and consensus statements have emerged for the use of anti-TNF-alpha agents in AS (13-18).

The first updated version of the international ASAS consensus statement for the use of anti-TNF agents in patients with active AS (Table II) (13) was published in 2006 and provides guidance for the introduction, monitoring and cessation of biologic therapy in AS, independent of local regulations. For the initiation of anti-TNF-alpha therapy, a patient must have a diagnosis of AS according to recognized criteria, active disease for at least 4 weeks (indicated by a Bath AS Disease Activity Index (BASDAI) > 4 and clinical findings, disease refractory to two NSAIDs over a 3-
Table II. ASAS consensus statement for the use of anti-TNF therapy in ankylosing spondylitis.

<table>
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<th>Specification (definition of the terms)</th>
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**Patient selection**

**Diagnosis**

- Patients normally fulfilling the modified New York Criteria for definitive AS
- Modified New York criteria 1984 (van der Linden et al.)
  - Radiological criterion
  - Sacroiliitis, grade II bilaterally or grade III to IV unilaterally
  - Clinical criteria (2 out of the following 3)
    - Low back pain and stiffness for > 3 months that improves with exercise but is not relieved by rest
    - Limitation of motion of the lumbar spine in both the sagittal and frontal planes
    - Limitation of chest expansion relative to normal values correlated for age and sex

**Active disease**

- Active disease for ≥ 4 weeks
- BASDAI ≥ 4 (0-10) and an expert* opinion**

*The expert is a physician, usually a rheumatologist, with expertise in inflammatory back pain and the use of biologics. Expert should be locally defined.

**An expert opinion is based on both clinical features (history and examination) and serum acute phase reactant levels and/or imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating ongoing inflammation.

**Treatment failure**

- All patients must have had adequate therapeutic trials of at least 2 NSAIDs. An adequate therapeutic trial is defined as:
  - Treatment for at least 3 months at the maximal recommended or tolerated anti-inflammatory dose unless contraindicated
  - Treatment for < 3 months where treatment was withdrawn because of intolerance, toxicity, or contraindications
  - Patients with only with axial manifestations do not have to take DMARDs before anti-TNF therapy can be started
  - Patients with symptomatic enthesitis should have an insufficient response to at least one local corticosteroid injection if appropriate
  - Patients with persistent peripheral arthritis must have had a therapeutic trial of sulfasalazine*
  - Patients with symptomatic enthesitis must have failed appropriate local treatment

*Sulfasalazine: Treatment for at least 4 months at the standard target dose or maximally tolerated dose unless contraindicated or not tolerated. Treatment for less than 4 months, where treatment was withdrawn because of intolerance, or toxicity or contraindications.

**Contraindications**

- Women who are pregnant or breastfeeding; effective contraception must be practised
- Active infection
- Patients at high risk of infection, including:
  - Chronic leg ulcer
  - Previous tuberculosis (note: please follow local recommendations for prevention or treatment)
  - Septic arthritis of a native joint within the last 12 months
  - Septic prosthesis or prosthetic joint within the last 12 months, or indefinitively if the prosthesis remains in situ
  - Endocarditis or recurrent chest infections
  - Indwelling urinary catheter
  - History of lupus or multiple sclerosis
  - Malignancy or pre-malignancy states, excluding:
    - Basal cell carcinoma
    - Malignancies diagnosed and treated more than 10 years previously (where the probability of a total cure is very high)

**Assessment of disease**

**ASAS core set for daily practice**

- Physical function (BASFI or Dougados functional index)
- Pain (VAS, average overall spinal pain due to AS in the last week and VAS, average nocturnal spinal pain due to AS in the last week)
- Spinal mobility (chest expansion and modified Schober and occiput to wall distance and lateral lumbar flexion)
- Patient’s global assessment (VAS, last week)
- Stiffness (duration of morning stiffness, spine, last week)
- Peripheral joints and entheses (number of swollen joints [44 joint count], enthesitis score such as those developed in Maastricht, Berlin or San Francisco)
- Acute phase reactants (ESR or CRP)
- Fatigue (VAS)

**BASDAI**

- VAS, overall level of fatigue/tiredness past week
- VAS, overall level of AS neck, back or hip pain past week
- VAS, overall level of pain/swelling in joints other than neck, back or hips past week
- VAS, overall discomfort from any areas tender to the touch or pressure past week
- VAS, overall level of morning stiffness from time of awakening past week
- Duration and intensity of morning stiffness from time of awakening (up to 120 minutes)

**Assessment of response**

**Responder criteria**

- BASDAI: 50% relative change or absolute change of 20 mm (on a scale between of 0 and to 100) and expert opinion in favor of continuation

**Time of evaluation**

Between 6 and 12 weeks

VAS: visual analogue scale; all VAS scales can be replaced by numerical rating scales (NRS).
Adapted from Braun et al. (13).
month period as well as to sulfasalazine if peripheral disease is present, and no contra-indications to biological therapy. Exclusion criteria include current or recurrent infections, pregnancy or lactation, malignancy, multiple sclerosis, lupus and tuberculosis. Screening for tuberculosis is mandatory, and the guidelines for prevention and treatment should be followed before commencing an anti-TNF-alpha agent. Monitoring of patients receiving these therapies is vital, and should include the ASAS core set domains for clinical practice (patient global assessment, pain, spinal mobility, BASDAI, BASFI, number of swollen joints, and acute phase reactants). Indications for withdrawal of therapy are not clear-cut and should be assessed on an individual basis.

A number of national recommendations for anti-TNF-alpha therapy in AS have been developed with varying scope and complexity, although the messages given do not differ greatly between documents, with the exception of the role of methotrexate (14). High level evidence for the efficacy of methotrexate in AS is scarce, and therefore the input of different expert opinions based on differing clinical experience has resulted in different guidelines. Finally, in implementing any set of recommendations, consideration must be given to the specific requirements of local health policy and regulations, and to the preferences and wishes of the individual patient.

### Early referral recommendations

If any evidence-based recommendations for the treatment of AS are to be of use, suitable patients must be identified in a timely and effective manner. This has long been a challenge in AS, with a recognized long delay to diagnosis (19). The delay may be explained in part by low awareness of the condition in primary care, the slow progression to the radiologic sacroiliitis required to make a diagnosis based on the modified New York criteria (20), and the absence of well-defined clinical indicators to aid in early case detection.

In order to address the latter issue, early referral recommendations have been developed to assist primary care physicians in identifying those patients who may have early axial spondyloarthritis (SpA) and who are candidates for rheumatologic review (21). The key screening parameters were identified using diagnostic likelihood ratios from a selection of clinical, laboratory and imaging features. It is suggested that in the presence of chronic low back pain of more than 3 months’ duration in patients under the age of 45, the presence of either inflammatory back pain or HLA-B27 positivity suggests an increased likelihood of disease and therefore referral is recommended. Initial validation of these criteria carried out on 350 chronic back pain patients showed that approximately half of all the patients referred could be diagnosed with axial SpA or AS (22). The presence of both inflammatory back pain and HLA-B27 doubled the likelihood of a final diagnosis of AS. This approach is a useful tool to improve referral and early diagnosis; however, it must be appropriately disseminated, with primary care physician education and the presence of adequate, accessible referral centers ensured.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Instruments</th>
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<tr>
<td>Patient global assessment</td>
<td>VAS in the last week</td>
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<tr>
<td>Spinal pain</td>
<td>VAS, average overall spinal pain spine due to AS in the last week, and VAS, average nocturnal spinal pain due to AS in the last week</td>
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<tr>
<td>Spinal stiffness</td>
<td>VAS, morning stiffness</td>
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<tr>
<td>Spinal mobility</td>
<td>Chest expansion, and Modified Schober index, and Occiput-to-wall distance, and Lateral spinal flexion or Bath Ankylosing Spondylitis Metrology Index</td>
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<tr>
<td>Physical function</td>
<td>Bath Ankylosing Spondylitis Functional Index, or Dougados Functional Index</td>
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<tr>
<td>Peripheral joints and entheses</td>
<td>Number of swollen joints (44 swollen joint count) Validated enthesis score</td>
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<tr>
<td>Acute phase reactants</td>
<td>ESR</td>
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CR: clinical record keeping; DC-ART: disease-controlling anti-rheumatic therapy; SMARD: symptom-modifying anti-rheumatic drugs; PT: physical therapy; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; AP: antero-posterior; SI: sacroiliac.

Adapted from (24, 25) and updated ASAS workshop (Gent).

<table>
<thead>
<tr>
<th>Topic</th>
<th>Issues</th>
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<tr>
<td>Patient identification</td>
<td>Time between onset of symptoms and diagnosis</td>
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<td>% of AS patients fulfilling current classification criteria</td>
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<tr>
<td>Treatment</td>
<td>Time between diagnosis and the initiation of appropriate therapy</td>
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<td></td>
<td>% of AS patients treated and monitored according to current recommendations</td>
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<td></td>
<td>% of AS patients treated with biologics</td>
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<td>Hours of exercise and physiotherapy per month/year</td>
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<td>Outcomes</td>
<td>Symptom-free periods per month/year</td>
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<td></td>
<td>% of AS patients with syndesmophytes</td>
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<td>% of AS patients with functional decline and persistent high disease activity</td>
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<td></td>
<td>Frequency and completeness of documentation of relevant outcome measures</td>
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<td></td>
<td>% of AS patients who are well informed about their disease</td>
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The ASAS core sets have been discussed previously in this forum (23); in particular, the core set for clinical record keeping is relevant to improving the quality of information gathering at
the point of care (24, 25). A rigorous literature search and statistical analysis of the value of various outcome measures was undertaken, resulting in the creation of a set of measurement domains and tools advised for use in clinical practice (Table III). The core set is continually being updated as more research evidence regarding outcome measures becomes available.

National registers
There are a number of nationally-run AS registries for patients who are receiving biologic therapy. These have been established to improve our knowledge of patient characteristics, the natural history of the disease, treatment efficacy and — most importantly — toxicity, whose impact is inadequately reflected in randomized controlled trials. A new initiative to create a core set of measurement domains for data collection in such registries is underway, to allow standardization of data collection across registries, improved data quality, and facilitate collaboration between countries in the future.

Clinical classification systems
The World Health Organization has developed the International Classification of Functioning, Disability and Health (ICF), which allows the concepts of functioning to be described in standardized language (26). Its utility in the clinical setting remains to be determined, and current projects are aimed at defining core sets of ICF categories relevant to specific disease states, including AS, from the differing perspectives of the patient (27), the health professional and the researcher (28). This information will be combined by expert consensus into a short set of ICF concepts specifically relevant to the care and management of AS patients. Potential uses for such a core set include the improvement of communication between the different health professions involved in a patient’s care, improved assessment of patient functioning and disability at baseline and with changes in therapy, and the development of improved measurement instruments for physical functioning in research and clinical practice.

Quality indicators
Formal quality performance indicators, such as are currently available for osteoarthritis (29), rheumatoid arthritis (30) and gout (31), have not yet been published for the management of AS. Quality indicators represent minimal standards of care for disease management, and include areas such as diagnosis, treatment and the monitoring of disease progression, drug efficacy and drug toxicities. Some of the issues dealt with in existing quality indicators are relevant to AS patients, in particular quality indicators for the use of non-steroidal anti-inflammatory drugs (NSAID) (32) and the American College of Rheumatology’s (ACR) starter set of quality of care indicators for rheumatoid arthritis (30), which covers drug safety, the monitoring of disease-modifying anti-rheumatic drugs (DMARD), informing patients about risks, prophylaxis for patients at risk of gastrointestinal bleeding, and laboratory monitoring for drug toxicities. Nevertheless, some issues specific to AS remain to be addressed (Table IV). Improving time to diagnosis is one. Researchers remain unclear regarding the best way to reach an early diagnosis of AS or axial SpA, but it is difficult to define a clear quality indicator regarding patient identification. Should all patients under the age of 45 who suffer from chronic low back pain be screened for HLA-B27 and inflammatory back pain, as was recently recommended (21), or is it more reasonable to suggest that all patients with inflammatory back pain undergo HLA-B27 screening and imaging of the sacroiliac joints? Issues of the sensitivity and specificity of clinical measures and diagnostic tests become important here.

What is the ideal interval for patient review once a diagnosis is made, and what tests should be performed? How should a clinician identify disease progression, or the failure to respond to treatment, and what is the ideal sequence of therapeutic options? Some of these issues are addressed in the ASAS/EULAR recommendations, but are they specific enough to be translated into quality indicators? There is a real need for a collaborative approach to refine these issues before ‘quality’ quality indicators can be developed for AS.

Conclusions
A number of evidence-based recommendations and outcome measures in AS have been developed on the basis of sound scientific principles. There is now the need for regular ongoing revision and updating of these documents to ensure that they reflect the latest in research evidence. More effort must be devoted to the significant problems of dissemination, and the evaluation of the effect of these initiatives in improving clinical practice. Unless we focus sufficient effort in terms of research and practice on better organizing, filtering, and utilizing the research results that we have, the gap between what we know and what we do will continue to grow. The ASAS international working group has accomplished a great deal already in terms of standardizing and improving the measurement of research outcomes and point of care delivery. It is now time to take the next step.

References
6. GOSSEC L, KVLEEN K, PHILLIPS C et al.: Dissemination and evaluation of the ASAS/EULAR recommendations for the management of ankylosing spondylitis: results of


