CHAPTER

62

Management of Ankylosing Spondylitis

G. Narsimulu, K. Suresh

Introduction

Ankylosing spondylitis (AS) is a human leukocyte antigen (HLA)-B27-associated chronic, inflammatory rheumatic disease characterised by sacroiliitis and spondylitis with formation of syndesmophytes leading to ankylosis. The disease can be accompanied by extraskeletal manifestations, such as acute anterior uveitis, aortic incompetence, cardiac conduction defects, fibrosis of the upper lobes of the lungs, cauda equina syndrome or renal amyloidosis.

Table 1 : Extraskeletal Manifestation of Ankylosing Spondilitis

Inflammatory spinal pain
- Onset before age 40
- Insidious onset
- Persistence for at least 3 months
- Morning stiffness > 30 min
- Improvement with exercise
Alternate buttock pain
Acute anterior uveitis
Synovitis (predominantly of lower limbs, asymmetric)
Enthesitis (heel, plantar)
Positive family history for
Ankylosing spondylitis
Chronic inflammatory bowel disease
Psoriasis

Diagnosis

AS usually manifests in late adolescence or early adulthood and only rarely starts after age 40.[1] The diagnosis of AS at an early stage of disease is difficult and depends primarily on a careful history and physical examination. The presence of inflammatory low back pain is important for the diagnosis. Clinical features of ankylosing spondylitis include modified NewYork criteria,[2] which helps in the diagnosis of Ankylosing spondylitis. It should be stressed that classification criteria are usually not well suited for early diagnosis of disease because radiological proof of sacroiliitis is a late feature of the disease.[3]

It usually takes many years before definite radiographic sacroiliac abnormalities first appear.

Table 2 : Clinical Features of Ankylosing Spondilitis (Modified New York Criteria, 1984[2])

1. Low back pain of at least 3 months' duration improved by exercise and not relieved by rest
2. Limitation of lumbar spine in sagittal and frontal planes
3. Chest expansion decreased relative to normal values for age and sex
4. Bilateral sacroiliitis grade 2 to 4
5. Unilateral sacroiliitis grade 3 or 4
Definite ankylosing spondylitis: unilateral grade 3 or 4, or bilateral grade 2 to 4 sacroiliitis and atleast one clinical criterion

Table 3 : Principles of Management of Ankylosing Spondylitis[8]

- No cure, but most patients can be well managed
- Patient education to increase compliance
- Appropriate use of antirheumatic drugs, primarily nonsteroidal, anti-inflammatory drugs (NSAIDs)
- Daily exercises very important (e.g., swimming)
- Sleep on firm mattress
- Sports and recreation
- Supportive measures and counseling
- Avoid smoking
- Avoid trauma
- Patient support groups
- Family counseling

The New York grading system for sacroiliac joint status is as follows: grade I=suspicious; grade II=evidence of erosion and sclerosis; grade III=erosions, sclerosis, and early ankylosis; and grade IV=total ankylosis.

CT and MRI can detect AS lesions earlier and with greater consistency than plain radiography.[4]

Assessment of Clinical Outcomes in Patients with AS in Practice

The most widely used measure of the inflammatory activity of AS is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[5] This simple instrument is patient-completed, sensitive to change over 3 weeks, and has been validated.[6] BASDAI was developed as a composite index, consisting of an evaluation on a visual analogue scale (0–10) of fatigue, axial pain, peripheral pain, stiffness and enthesopathy. Scores of 4 or greater suggest suboptimal control of disease, and patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrolment in clinical trials evaluating new drug therapies directed at Ankylosing Spondylitis.

Management

For most patients, AS is a relatively mild disease with a good functional prognosis. The objectives for treatment of AS are to relieve pain, stiffness, and fatigue and to maintain good posture and good physical and psychosocial functioning.

Treatment of AS should be tailored according to:

- Current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs)
- Level of current symptoms, clinical findings, and prognostic indicators
  - Disease activity/inflammation
  - Pain
  - Function, disability, handicap
  - Structural damage, hip involvement, spinal deformities
- Wishes and expectations of the patient.
- General clinical status (age, sex, comorbidity, concomitant drugs).[7]

The principles of management are summarized in Table 3.

A complete explanation of the disease is essential to achieve good patient compliance. The Current evidence suggests that none of the conventional disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine and methotrexate (MTX) alter or inhibit the inflammation seen in the spine and entheses in AS.

Physical therapy

Physiotherapy remains the mainstay of management of AS. There is evidence that exercise alone can produce adequate symptom relief in patients with AS. Group exercises are better than home exercises and improve pain, stiffness, movement in the spine.(9) Preferably, they should be started after a hot shower or a hot bath. Swimming and extension-promoting exercises are appropriate. These activities counteract the kyphotic effects of pain and fatigue on posture and reduce stiffness.

NSAIDs and coxibs

NSAIDs and coxibs are useful for spinal pain and physical function. NSAIDs are the first line drug treatment for patients with AS with pain and stiffness. NSAIDs improve spinal pain, peripheral joint pain, and function over a short period of time (6 weeks).[10] The studies of different NSAIDs have not shown one drug to be better than the others. A recent randomised controlled trial comparing the efficacy of continuous celecoxib treatment for AS with intermittent "on demand" use suggests that continuous treatment retards radiographic disease progression at 2 years.[11] This is the first study to show a possible disease modifying effect of continuous treatment.

Coxibs or the addition of GI protectors (misoprostol, double doses of H_2 blockers, or PPIs) to conventional NSAIDs can significantly reduce GI bleeding.

Apart from nephrotoxicity, there is increased cardiovascular toxicity with NSAIDs and more so with coxibs.[12]

In general, the choice of NSAID or coxibs should be based on risk factors for cardiovascular disease, renal and GI symptoms. Analgesics, such as paracetamol and opioids, may be used for pain control in patients in whom NSAIDs are contraindicated or poorly tolerated.

Corticosteroids

Local Corticosteroid injections of the involved joints are effective, especially for sacroiliac joints.[13] The long term use of systemic corticosteroids for axial disease has a little role to play. However, intravenous methylprednisolone has been found useful in resistant cases of active AS.[14]

Disease Modifying Antirheumatic Drugs (DMARDs)

There is no evidence for the efficacy of disease modifying antirheumatic drugs (DMARDs) for the treatment of axial disease. However sulfasalazine may be considered in patients with peripheral arthritis. Sulfasalazine (SSZ) has demonstrated some benefit in reducing ESR, severity and duration of morning stiffness. But it has shown no benefit in spinal pain and mobility, enthesitis, patient and physician global assessment. However patients at early and active disease stage with higher level of ESR and those with peripheral arthritis benefit from SSZ.[15] Toxicity with sulfasalazine is common but usually mild which includes GI symptoms, hepatic enzyme abnormalities, mucocutaneous manifestations and hematological abnormalities.

There is no significant effect of methotrexate on spinal pain or function. Methotrexate might benefit patients with peripheral joint involvement. There is not enough evidence to support the use of other DMARDs in AS.

Pamidronate

There is some evidence for a beneficial effect of intravenous pamidronate (60 mg IV monthly for 6 months) on both axial pain and function.[16] There is no study to assess its effect on peripheral joint disease. Side effects include transient post-infusional arthralgias and myalgias and an acute phase response with lymphopenia and raised C reactive protein.

Thalidomide[17]

Open trials suggest a beneficial effect for thalidomide on spinal disease, but toxicity is substantial which includes drowsiness, severe birth defects and irreversible peripheral neuropathies.

Anti-TNF treatment

Anti-TNF treatment should be given to patients with persistently high disease activity despite conventional treatments (NSAIDs and DMARDs) according to the Assessment in Ankylosing spondylitis group (ASAS) recommendations.(18) There is no evidence to support the obligatory use of DMARDs before, or concomitant with, anti-TNF treatment in patients with axial disease.[7] The present evidence supports the use of the TNF inhibitors etanercept, infliximab and adalimumab for spinal pain, function, and peripheral joint disease.

The onset of clinical effect with TNF blockers is rapid, and therapeutic effect persists for up to 3 years with continuing treatment.[7] Stopping treatment results in a high rate of clinical relapse. Adding methotrexate to infliximab treatment reduces side effects without any additional benefit in AS.

Toxicity with anti-TNF treatment includes injection site reactions with subcutaneous injections (etanercept and adalimumab), increased risk of infections in particular, tuberculosis. Screening for *Mycobacterium tuberculosis* is now a standard prerequisite for anti-TNF treatment. Demyelinating disease, lupus-like syndromes, and worsening of pre-existing congestive heart failure have also been reported.

There is insufficient evidence available at present on the role of interleukin 1 antagonists in AS.

Surgery

Total hip arthroplasty is indicated in patients with refractory pain or disability and radiographic evidence of structural damage, irrespective of age.[19] Spinal surgeries like corrective osteotomy and stabilization procedures are useful in selected patients.[20]

Assessment in Ankylosing spondylitis (ASAS) consensus for anti-TNF therapy.[18] (Modified)

Specification (Definition of the terms)

Patient selection

Diagnosis

- Patients normally fulfilling modified New York Criteria for definitive AS

Active disease

- BASDAI ≥ 4 (0–10) and an expert opinion that anti-TNF treatment should be started ≥ 4 weeks

Treatment failure

- All patients must have had adequate therapeutic trials of at least 2 NSAIDs. An adequate therapeutic trial is defined as:
  - Treatment for ≥ 3 months at 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 symptomatic peripheral arthritis (normally having a lack of response to a local steroid injection for those with oligoarticular involvement) must have had adequate therapeutic trial of both NSAIDs and sulfasalazine.
- Patients with symptomatic enthesitis must have had an adequate therapeutic trial of at least two local steroid injections unless contraindicated

Contraindication for anti TNF therapy

- Women who are pregnant or breastfeeding;
- Active infection
- Patients at high risk of infection including:
  - Chronic leg ulcer
  - Previous tuberculosis
  - Septic arthritis of a native joint within the past 12 months
  - Sepsis of a prosthetic joint within the past 12 months, or indefinitely if the prosthesis remains in situ
  - Persistent or recurrent chest infections
  - Indwelling urinary catheter
- History of lupus or multiple sclerosis
- Malignancy or premalignancy states excluding:
  - Basal cell carcinoma
  - Malignancies diagnosed and treated more than 10 years previously (where the probability of total cure is very high)

Assessment in Ankylosing Spondylitis International Working Group (ASAS) Improvement Criteria (ASAS-20) and ASAS Partial Remission Criteria

ASAS-20 Improvement Criteria

At least 20-per cent improvement AND 10 units improvement in three out of the four following domains, without worsening of 20 per cent or more AND 10 units in the remaining domain:

- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Morning stiffness
- Patient global assessment
- Pain

ASAS Partial Remission Criteria

A value below 20 units in all four domains

Assessment of response

- Responder criteria:BASDAI: 50% relative change or absolute change of 2 (scale 0–10) and expert opinion.
- Time of evaluation: Between 6 and 12 weeks.

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