INTRODUCTION

The spondyloarthropathies are a group of inflammatory rheumatic diseases with predominant involvement of the axial and peripheral joints and enthesis. The various names which have been and are still used for spondyloarthropathies include seronegative spondarthropathies, spondarthritis and spondyloarthritis. There is no substantial difference between them. The prefix seronegative, referring to the general absence of rheumatoid factors in the spondyloarthropathies, is historical. The term spondyloarthropathy (SA) is a preferred one.

The sub-types of SA are as follows-
1. Ankylosing spondylitis
2. Reactive arthritis (e.g., Reiter’s syndrome)
3. Psoriatic arthritis
4. Arthritis associated with inflammatory bowel disease (e.g., Crohn’s disease or ulcerative colitis)
5. Undifferentiated spondyloarthritis.

The clinical features of these may overlap. However, they can sometimes be distinguished on the basis of patients' history and clinical examination. For example, psoriasis skin lesions in psoriatic arthritis, urogenital tract infection in reactive arthritis. Imaging does not differentiate the sub-types as the appearances may be quite similar, especially in the early stages of the disease. All the sub-types, if long standing, can ultimately progress to develop ankylosis. Individuals with HLA-B27 have a 20-fold higher risk of developing SA than those who do not have this antigen.

Axial skeleton involvement is the most common manifestation of SA. The lumbosacral spine, the sacroiliac joints, and the hip joints affected the most. The synovial joints of the vertebral column, the vertebrae, and the intervertebral discs, the tendon and ligament attachments to bone (enthesis) are all involved as a part of the inflammatory process. This inflammation can lead to erosions, joint space widening, sclerosis, ankylosis and syndesmophytes which can be picked up on imaging. Also, inflammation can lead to oedema of the underlying bone marrow which can be detected by CT/MRI scanning. Hence, an appropriate imaging protocol is very much essential in co-relation with history and clinical examination for timely diagnosis and treatment before irreversible damage occurs.

Acute anterior uveitis, the most common extraskeletal manifestation of ankylosing spondylitis, occurs in up to 40% of patients with ankylosing spondylitis, especially those who possess the HLA-B27 gene. Uveitis may lead to visual impairment. Subclinical lung abnormalities are somewhat common in patients with ankylosing spondylitis; however, clinical pulmonary manifestations are uncommon. Other less common extraskeletal manifestations of ankylosing spondylitis may involve the gut, aorta, or heart. Cauda equina syndrome is a rare neurological complication of ankylosing spondylitis.

In the absence of diagnostic criteria for ankylosing spondylitis, the modified New York criteria are the most commonly used classification criteria. These criteria are highly specific rather than sensitive and are used mainly for including patients in clinical studies.

Psoriatic arthritis. This inflammatory arthritis occurs in 10% to 30% of patients with psoriasis, which may not be readily apparent because psoriasis lesions may be limited to the scalp, ears, umbilicus, perineum, and perianal area. Therefore, a thorough skin examination should be performed in every patient with inflammatory arthritis.

The onset of arthritis usually follows or coincides with the onset of psoriasis, although it may antedate psoriasis in up to 15% of patients. Arthritis may present in various overlapping forms, including polyarthritis, asymmetrical oligoarthritis (involving fewer than 5 joints), arthritis that is primarily limited to the distal interphalangeal (DIP) joints, monarthritis, arthritis mutilans, sacroiliitis, and spondylitis. The polyarthritis form resembles RA but has several features characteristic of psoriatic arthritis, including the involvement of the DIP joints; the presence of dactylitis, or “sausage digits,” and enthesitis; and nail involvement (discoloration, onycholysis, ridging and, especially, pitting). Psoriatic spondylitis is clinically similar to ankylosing spondylitis but is more often associated with peripheral arthritis and less often with uveitis.
The modified New York classification criteria for ankylosing spondylitis

**Clinical components:** low back pain and stiffness for more than 3 months that improves with exercise but not with rest; limitation of lumbar spine mobility in both the sagittal and frontal planes; and limitation in chest expansion, compared with normal range for patient's age and sex

**Radiological component:** unilateral grade 3 or grade 4 sacroiliitis or bilateral grade 2 or higher sacroiliitis

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**Grading:** definite ankylosing spondylitis if the radiological component is associated with at least 1 clinical component; probable ankylosing spondylitis if 3 clinical components are present or the radiological component is present without signs or symptoms that satisfy the clinical component


Reactive arthritis. This condition classically occurs within 1 to 4 weeks after a triggering infection of the gut or the genitourinary tract, although many patients may not recall such a history. Patients with reactive arthritis usually present with acute, asymmetrical oligoarthritis of the lower extremities. They also may have constitutional symptoms, urethritis, cervicitis, conjunctivitis, uveitis, genital lesions (circinate balanitis or vulvitis), keratoderma blennorrhagica, dactylitis, enthesitis, nail discoloration and onycholysis without nail pitting, or sacroiliitis/spondylitis. The uncommon classic triad of arthritis, conjunctivitis, and urethritis may be present in a subset of patients with reactive arthritis.

**Arthritis of IBD.** Arthritis occurs in about 30% of patients who have IBD; arthritis of IBD manifests with inflammatory back pain, enthesitis, or peripheral arthritis, fulfilling the ESSG criteria for spondyloarthropathy; 10% of patients fulfill the criteria for ankylosing spondylitis. In addition, some patients have asymptomatic sacroiliitis. Peripheral arthritis usually is nonerosive and, unlike axial disease, correlates with the IBD activity.

**Undifferentiated spondyloarthropathy.** This encompasses related disorders such as isolated enthesitis or dactylitis and RF-negative oligoarthritis or polyarthritis; it usually involves the lower extremities and often is HLA-B27-associated. Patients who have undifferentiated spondyloarthropathy may have episodes of acute anterior uveitis with 1 of the above-mentioned features but not psoriasis or GI or genitourinary tract involvement.

**LABORATORY FEATURES**

The C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) often are elevated. Anemia of chronic disease might occur. The results of a fecal occult blood test may be abnormal in patients with IBD. When reactive arthritis is suspected on clinical grounds, bacterial studies might provide helpful information. Testing for HLA-B27 cannot be used for screening or as a routine test for making a diagnosis of ankylosing spondylitis and related spondyloarthropathies because these diseases may occur in the absence of this gene.

Obtaining an anteroposterior x-ray film of the pelvis may be sufficient for detecting sacroiliitis, but the results may be normal or equivocal. MRI may detect sacroiliitis or spondylitis long before these abnormalities become evident on plain x-ray films. The recently described total body MRI scan may very nicely identify the characteristic bone edema that results from osteitis/enthesitis at axial as well as peripheral sites. The scan takes only 30 minutes to perform. Spinal osteopenia, which is common, correlates with disease severity and duration. Measurements of the spine by dual-energy x-ray absorptiometry (DEXA) scan to detect osteoporosis may be less reliable than measurements at the femoral neck because of the presence of spinal syndesmophytes and ligamentous ossification. Peripheral DEXA scanning may be used in patients who have had bilateral hip arthroplasty.

**MANAGEMENT**

The management of spondyloarthropathies should be individualized.

**Patient education**

Patients’ posture problems and difficulties in performance of activities of daily living should be identified, and workplace modifications may be needed. Frequently changing position when sitting at a desk and taking breaks for body stretching are helpful. Activities that cause back muscle strain should be avoided (eg, prolonged stooping or bending and assuming positions that may cause a stooped posture, such as prolonged slouching in chairs or leaning over a desk).

**Exercise and physical therapy.** A lifelong program of regular exercise should be encouraged; such a program should include spinal extension exercises; deep breathing; and range of motion exercises of the back, neck, shoulders, hips, and other joints. Swimming and aquatic exercises and other appropriate recreational exercises are especially useful. Short-term intensive physical therapy followed by lifelong home exercises might be helpful for patients with spondyloarthropathies, including core strengthening of trunk muscles.

**Pharmacological treatment.**

NSAIDs are the first line of treatment. The traditional disease-modifying antirheumatic drugs—eg, methotrexate (MTX), leflunomide, and sulfasalazine—are not recommended for managing axial disease because they lack efficacy. However, they may be considered in patients with peripheral arthritis. Oral corticosteroids should be avoided, but intra-articular or local corticosteroid injection may provide rapid relief in monarticular or oligoarticular peripheral arthritis or enthesitis.

Osteoporosis is common in patients with spondyloarthropathies and should be recognized and managed early: adequate intake of calcium and vitamin D should be ensured.

Tumor necrosis factor (TNF)-alpha inhibitors have transformed the management of ankylosing spondylitis (AS) and some of the
related spondyloarthropathies.

TNF inhibitors are the large unmet clinical need in spondyloarthritis. Whereas these diseases were once considered to be relatively benign, evidence is growing, particularly in psoriatic arthritis and ankylosing spondylitis, that many affected patients manifest significant radiographic joint damage, functional impairment, reduced quality of life, and long-term work disability. Moreover, although they may have a modest effect on peripheral arthritis and certain other aspects of disease, traditional disease-modifying antirheumatic drugs (DMARDs) have been proven ineffective for spinal disease in spondyloarthritis. The three currently available TNF inhibitors, etanercept, infliximab, and adalimumab, have been shown not only to significantly improve the signs and symptoms of spondyloarthritis but also to improve functional status and quality of life and even to attenuate disease progression. The dramatically impressive clinical efficacy of these agents has occurred in parallel with, and to some extent has driven, considerable progress in disease classification and stratification.

The TNF-α inhibitors are effective as monotherapy without concomitant MTX, and they have maintained long-term effectiveness. Clinical improvement is accompanied by a significant decrease in inflammation, as evidenced by a dramatic reduction of the CRP level and ESR; the improvement also may be demonstrated on MRI, but it is too early to say that these agents will slow down or prevent progressive bony ankylosis. A few patients with reactive arthritis and with undifferentiated spondyloarthritis that is refractory to traditional therapies who have been treated with TNF-α inhibitors also have shown good response.

Guidelines for the use of TNF-α inhibitors for the spondyloarthropathies have been developed. Treatment must be continued on a long-term basis to maintain disease control. When one TNF-α inhibitor has not succeeded or adverse effects develop that are not related to the TNF-α inhibitors as a class, switching to another agent may be indicated. All 3 TNF-α inhibitors—infliximab, etanercept, and adalimumab—are highly and equally effective in patients with active ankylosing spondylitis and in those with psoriatic arthritis and enthesopathic arthritis that is unresponsive to traditional therapy. These biologic agents also are very effective in managing the cutaneous and nail lesions of psoriasis. Infliximab and adalimumab (monoclonal antibodies) are effective in managing IBD, but etanercept (receptor-fusion protein) lacks such an effect. The monoclonals also are somewhat more effective in preventing recurrences of acute anterior uveitis.

Golimumab

Efficacy and safety of golimumab—a new human monoclonal TNF-alpha antibody—and its impact on work productivity in patients with AS were reported in various abstract and podium presentations, including results from a multicenter, randomized, placebo-controlled, phase 3 trial in patients with AS with subcutaneous injection of golimumab given every 4 weeks (GO-RAISE).

Golimumab was effective and well tolerated in this relatively large cohort of patients with AS during a 24-week study period. They also observed significant improvement in self-reported work productivity (measured on a Visual Analogue Scale; 0 cm = productivity not at all affected, 10 cm = affected very much) in the golimumab 50-mg and 100-mg groups compared with the placebo group at week 16.

Golimumab was significantly better than placebo in improving signs and symptoms of PsA at week 24, and efficacy was maintained through week 52. There was also significant improvement in psoriatic nail changes and enthesitis, but significant improvement was achieved only with the golimumab 100-mg dose. Golimumab 50 mg and 100 mg also significantly improved physical function.

Adalimumab

AS begins at a young age (mean age, approximately 26 years) and takes a chronic course that results in substantial physical impairment, reduced QoL, and socioeconomic burden for the patients and the society at large. This study found that adalimumab reduces absenteeism from work and improves work presenteeism and participation in activities outside of work. Predictors of good WPAI response include younger age, no prior TNF antagonist exposure, and more severe AS. The data suggest that early intervention with adalimumab in AS may enhance work productivity.

The Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT)—a 24-week, double-blind, randomized clinical trial—demonstrated that adalimumab 40 mg every other week significantly improved arthritis, skin disease (as measured by the Psoriasis Area and Severity Index [PASI]), and inhibited radiographic progression in patients with PsA. Results of 144 weeks of treatment with adalimumab demonstrated that patients with PsA whose psoriasis responded well to adalimumab had less radiographic progression because patients who were treated with adalimumab who had PASI 50, PASI 75, and PASI 90 responses also had inhibition of radiographic progression. Patients with less than a PASI 50 response demonstrated more radiographic progression than patients with at least a PASI 50 response.

Etanercept

The efficacy of etanercept in AS and PsA is well recognized on the basis of the data from randomized clinical trials. A study of a prospective cohort of AS patients demonstrated sustained efficacy over 5 years, and another similar study in patients with PsA has reported 3-year safety and sustained efficacy of etanercept in improving arthritis, dactylitis, psoriasis, and QoL.

Ustekinumab

A phase 2, multicenter, double-blind, placebo-controlled study of ustekinumab—a human interleukin (IL)-12/23 monoclonal antibody—has demonstrated statistically significant improvements in tender joint count, patient assessment of pain, patient global assessment of disease, physician’s global assessment, and Health Assessment Questionnaire in patients with PsA treated with ustekinumab compared with placebo at week 12, with maximal
improvements observed beyond week 12. Treatment with TNF inhibitors does not induce immunologic tolerance or long-term treatment-free remission in ankylosing spondylitis. Thus, virtually all patients with ankylosing spondylitis have a disease flare upon discontinuation of therapy, with a mean time to flare reported to range from about 6 weeks with etanercept to 17.5 weeks with infliximab. This suggests that continuous therapy with TNF inhibitors will likely be necessary to maintain clinical benefit in patients with ankylosing spondylitis. Encouragingly, restarting therapy successfully reinduced significant clinical improvement in most patients. Interestingly, it has been observed that patients with ankylosing spondylitis with elevated C-reactive protein or erythrocyte sedimentation rate tend to respond better to TNF inhibitor therapy. This is all the more striking given that changes in acute-phase reactants are not part of the response criteria in ankylosing spondylitis as they are in rheumatoid arthritis. It has also been noted that patients with ankylosing spondylitis who have greater amounts of spinal inflammation on magnetic resonance imaging (MRI) studies may also have greater levels of response to TNF inhibitors. Importantly, these observed correlations do not imply that patients without elevated acute-phase reactants or spinal inflammation on MRI cannot respond to treatment. Data also suggest that therapy may improve extra-articular inflammatory involvement in ankylosing spondylitis. In a systematic review that included data from double-blind, placebo-controlled, randomized clinical trials and open-label experience, it was observed that flares of anterior uveitis occurred less frequently under TNF inhibitor therapy (6.8/100 patient-years) compared with placebo (15.6/100 patient-years). Perhaps the defining characteristic of ankylosing spondylitis is ankylosis of the spine. The progression of ankylosing spondylitis can be reliably quantified and tracked by plain radiography. The relatively slow rate of change, however, largely obviates the utility of this method for assessing structural effects of TNF inhibitors. There has been great interest in alternative imaging methods, particularly MRI. Not only is this technique able to detect changes in the spine and sacroiliac joints much earlier than conventional radiography, it can also be used to assess and quantify inflammation. Using MRI, treatment with TNF inhibitors has been shown to attenuate spinal inflammation. Although the suppression of inflammation is maintained through treatment, it is not completely eliminated in most patients. The extent to which suppression of inflammation on MRI correlates with attenuation of structural damage as measured by plain radiography remains to be elucidated.

Warnings and precautions in use of biological agents

1. Infections- With anti TNF alpha therapy there is increased propensity for bacterial, mycobacterial and fungal infections. Reactivation of latent TB is a possibility. Primary infection within 12 weeks of therapy is advisable to screen for TB – MT, CT chest, Quantiferon-Gold, r-RNA for ongoing infection (High sensitivity and specificity). Minimize TB by instituting prophylaxis by Isoniazid and Rifampicin.

Hepatitis- The long-term safety of TNF blockers in patients with chronic viral hepatitis is not known. Etanercept did not have an effect on viral load in Hepatitis C but in Hepatitis B, there may be a worsening of viral load with all three agents. Elevations have been observed in liver function tests. TNF blockers should not be used in patients with known hepatitis B infection; in the event that hepatitis B infection is discovered during use of TNF blockers, antiviral therapy can be employed.

2. General- Injection site reactions, headache, nausea, dizziness, abdominal pain, edema, dyspepsia, vomiting, oral ulceration, alopecia.

3. Pancytopenia

4. Heart failure (Worsening)

5. Development of autoantibodies (ANA, anti-dsDNA)

6. Demyelinating illnesses

7. Malignancies- Lung, breast, NHL.

Our experience with biologicals

- 5 pts- Early axial disease, enthesitis, peripheral arthritis, systemic symptoms, high ESR (avg 80 mm), high CRP (40-60), MRI showing marrow edema and erosions at SI joints in all
- Extra axial disease- 2 pts with anterior uveitis,
- AS with IBD- 1
- Agent used- Infliximab- Dose 5 mg/kg infusions ~ 5
- One patient showed complete regression of disease at spinal and SI joints
- None of them had developed syndesmophytes and erosions
- Platform DMARDs reduced
- No major adverse effects

Local treatment

Local treatment of the SI joints by intra-articular corticosteroid injection provides considerable clinical improvement. Several reports have investigated the indications, therapeutic effectiveness, and clinical outcomes of intra-articular injection. Fluoroscopy- and computed tomography (CT)-guided techniques have advantages related to more precise localization of the joint during these procedures. Recently, some studies pointed out that magnetic resonance imaging (MRI) guidance has also been used for SI joint injections. These techniques, however, have some limitations and disadvantages; therefore, sonographically guided injections could be a valuable option.

The accuracy primarily depends on the radiologist’s training and familiarity with this specific technique. When the radiologist gains enough experience, the sonographically guided technique can be safe, rapid, and reproducible.
REFERENCES


