Management of Seronegative Spondyloarthropathies

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Abstract: Although there is currently no known cure, most patients with seronegative spondyloarthropathies can be well managed. Early diagnosis and awareness of the related extra-articular manifestations is important. Drugs form only one part of the management. Patient education and timely enlistment of the relevant medical and paramedical expertise is important. Nonsteroidal anti-inflammatory drugs form the basis of therapy. Oral steroid has no therapeutic value in the long term management of the musculoskeletal aspects of ankylosing spondylitis. The conventional disease modifying drugs used in the treatment of spondyloarthropathies largely overlap with those used in rheumatoid arthritis. However, they are largely ineffective in the control of axial disease. Recently, the tumor necrosis factor inhibitors have been shown to be exceptionally effective and well tolerated in patients with both axial and peripheral inflammatory arthritis. Their efficacy in placebo controlled trials and long term safety needs further evaluation. Antibiotics may have a role in the treatment of reactive arthritis.

Keywords: Antibiotics, seronegative spondyloarthropathies, TNF inhibitors

Introduction

The spondyloarthropathies are a group of rheumatic disorders that include ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis and enteropathic arthritis. These disorders are unified in their ability to manifest axial and/or peripheral inflammatory disease with the associated features of enthesitis, ocular inflammation, skin and nail changes, and mucosal lesions affecting the gastrointestinal tract or genitourinary tracts. Other common features include negative rheumatoid factor and association with HLA B27, which suggests a common or related aetiology. It may not always be possible to differentiate clearly between the various forms of spondyloarthropathies in early stages because these diseases generally share many common clinical features. The strength of the association with HLA B27 varies markedly not only among the various spondyloarthropathies but also among the various racial and ethnic groups. Their combined prevalence in the general population is estimated to be approximately 1%, which is comparable to that of rheumatoid arthritis.

Salient Principles of Management

Most patients can be well managed, even though there is currently no known method to cure or prevent these disorders. Early diagnosis and awareness of the related extra-articular manifestations is important. Drug therapy forms only one part of the management. Team approach is vital to the success of management. Timely enlistment of the relevant medical (e.g. ophthalmologist, orthopaedic surgeons) and paramedical (e.g. physiotherapists, occupational therapists) expertise is always helpful.

There is no special diet or any specific food that has anything to do with the initiation or exacerbation of these conditions. The patients should be educated about their disease and the mode of action and the side effects of the medications which they are to be put on. This would be helpful to increase compliance. They should also be alerted to the importance of daily exercises to preserve good posture and minimize limitation of chest expansion. Intensive group physiotherapy
programmes are beneficial for these patients. Swimming is very often the best exercise for this group of patients. They should also be advised on the other appropriate sports and recreation. Supportive measures and counseling with regard to social, sexual and vocational aspects should be given. Patient self support groups are equally important and helpful. Locally, there are two such organizations, namely the Hong Kong Ankylosing Spondylitis Association and the B27 Association.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) form the basis of therapy.\textsuperscript{1-3} They provide pain relief and control of inflammation and are useful in mild cases. In order to achieve the maximum anti-inflammatory effect, they should be used regularly in full therapeutic anti-inflammatory dose over an extended period of time. The patient should be advised against using the NSAIDs occasionally or only for their analgesic effect. There is no evidence to support the preference of one drug over the other. The responses by patients differ, as do the side effects, and it is worthwhile to search out the best alternative NSAID for each individual. Phenylbutazone used to be the most effective NSAID for spondyloarthropathies but has been banned because of its potentially serious bone marrow toxicity. One should avoid using combination of NSAIDs. Co-prescription of gastroprotective agents or the use of the COX 2 inhibitors may be considered if there is history of peptic ulcer disease or dyspepsia. It has been suggested that some NSAIDs may aggravate the skin lesions in psoriasis but this is not specific to one agent. It might also be helpful to note that in some patients with enteropathic arthritis, NSAIDs may aggravate their bowel disease.

Corticosteroid

Joint aspiration and intra-articular corticosteroid administration may be needed to obtain prompt and prolonged relief from severe or persistent synovitis, only after septic arthritis has been excluded. CT- or X ray-guided corticosteroid injection of sacroiliac joints has been shown to lead to an improvement in symptoms, often lasting many months, and to reduce bone marrow oedema on MRI.\textsuperscript{4,5} Enthesitis may also respond to local steroid injections although great caution should be exercised injecting in or near the insertion of the Achilles tendon in view of the risks of tendon rupture. Oral steroid has no therapeutic value in the long term management of the musculoskeletal aspects of AS because of their serious side effects, and they do not halt disease progression. However, in a very severe case of acute reactive arthritis where many joints are affected and NSAIDs alone have failed, a short course of oral steroid may be needed; tapering down the dose according to improvement. It is advisable to avoid prolonged oral steroid therapy in chronic cases because it is rarely effective.

Conventional Disease Modifying Drugs

When the disease is not being adequately controlled by NSAIDs, or when the patients are intolerant to such drugs, disease modifying anti-rheumatic drugs (DMARDs) have to be used. The DMARDs used in the treatment of spondyloarthropathies largely overlap with those used in rheumatoid arthritis.

Sulphasalazine has been shown to be of benefit in double blind randomized controlled trials for the peripheral arthritis of AS, but has no proven benefit on axial pathology nor on persistent peripheral enthesitis.\textsuperscript{6,7} It has also been shown to be helpful in psoriatic arthritis. In a double blind placebo controlled trial, 3 gm of sulphasalazine daily was found to be effective in controlling inflammation in patients with psoriatic arthritis.\textsuperscript{8} In a further controlled trial of sulphasalazine in spondyloarthropathies, it was most effective in psoriatic arthritis.\textsuperscript{6} In addition to its efficacy in controlling joint disease, it may be effective in controlling skin disease, and may thus provide another option in the management of psoriatic arthritis. It is also effective in treating enteropathic arthritis. Subclinical inflammatory lesions in the gut have been observed on ileocolonoscopic mucosal biopsy in many spondyloarthropathy patients without any gastrointestinal symptoms. These patients seem to respond better to treatment with sulphasalazine than those with normal gut histology, suggesting that sulphasalazine may have a beneficial effect on the patients with spondyloarthropathy by healing their gut inflammation.\textsuperscript{9} Recently, uncontrolled studies have shown comparable improvement in clinical, physical and laboratory measures with mesalazine. It will be important to confirm these findings in randomized controlled trials, because mesalazine offers the advantage over sulphasalazine of not causing oligospermia.\textsuperscript{10,11} G6PD deficiency should be screened before starting patients on sulphasalazine.
A few patients with severe AS with peripheral joint involvement unresponsive to NSAIDs and sulphasalazine have sometimes responded to oral methotrexate therapy. On the other hand, methotrexate has been used regularly in the treatment of psoriatic arthritis, since it controls both skin and joint manifestation. While it seems to control the inflammatory component of the disease, it too has not been shown to prevent disease progression. Although many physicians have avoided using methotrexate because of fear of liver toxicity, methotrexate has been relatively safe in patients with psoriatic arthritis. Nevertheless, methotrexate should be best avoided in patients who are chronic carriers for hepatitis B or C. This is of special relevance to our local patients, since the prevalence of carriers for hepatitis B is relatively high locally.

Although anecdotal reports suggest that antimalarials aggravate psoriasis, this has not been borne out in studies, and these medications remain good choices in patients whose psoriasis is not severe. Obviously, they should be used with caution. Its efficacy has not been well studied in AS.

Gold therapy, particularly through intramuscular route, has been shown to be effective in controlling inflammation in psoriatic arthritis. However, it is not clear that it prevents disease progression. Again, it has not been well studied in AS.

Penicillamine has been shown to be effective in psoriatic arthritis, but its toxicity and slow onset of action has not supported its regular use. It has been shown to be not effective in AS.

Azathioprine has not been extensively studied in psoriatic arthritis, but may act to control both skin and joint disease in psoriatic arthritis. Indeed, there have been recent studies using intravenous loading doses of azathioprine to decrease its initial response time.

Cyclosporin A has worked for psoriatic arthritis as well as for the skin psoriasis. However, it cannot be recommended for regular use because of its toxicity and is reserved for the patient with severe skin and joint disease who has either had adverse effects or has not responded to other medications. This was recently highlighted in a study comparing cyclosporin A and methotrexate in psoriatic arthritis, in which a larger number of patients treated with the former withdrew because of toxicity.

Retinoic acid derivatives, such as etretinate, have been shown to be effective for both skin and joint manifestations of psoriatic arthritis, but have proven more toxic than methotrexate, with skin drying effect and hyperlipidaemia being the most bothersome features of toxicity.

Novel Treatments for Spondyloarthropaties

Anti-TNF Alpha Therapy

Since the conventional disease modifying drugs are only partially effective in some and are often associated with significant toxicities, the need for more effective and tolerable therapies for the spondyloarthropathies has been perceived by many for years.

Numerous reports have demonstrated the efficacy and safety of the recently released tumor necrosis factor (TNF) inhibitors – etanercept and infliximab – in spondyloarthropathy patients. The TNF inhibitors appear to be exceptionally effective and well tolerated in patients with both axial and peripheral inflammatory arthritis. The rationale for the use of these agents stems from the research of Emery and colleagues, who have shown that the primary pathology underlying the spondyloarthropathies is enthesitis and that enthesopathy can explain many of the articular and axial manifestations of these disorders. Synovitis in spondyloarthropathies is secondary to enthesal inflammation, in contrast to the primary synovitis in rheumatoid arthritis. Enthesitis in spondyloarthropathies most frequently involves the lower limbs, perhaps related to the greater bulk or physical stress on entheses at these sites. Studies of genetically manipulated animals that overexpress and overproduce TNF-α have shown a propensity for the development of enthesitis. Thus, it appears that TNF may play an important role in the initiation or perpetuation of enthesitis. Indeed, preliminary observations of TNF-α blockade in both psoriatic arthritis and AS have been highly encouraging. For example, etanercept has been shown to improve both the skin and joints of patients with psoriatic arthritis in a 12-week randomized double-blind placebo-controlled trial. Open-label phase 1 clinical trials of infliximab have found rapid improvement, not only of peripheral arthritis but also of axial symptoms and function in AS. It is currently not known whether such therapies will be able to change the natural course of disease or if they will have differential clinical efficacy on axial disease, peripheral disease, and extra-articular disease (e.g. uveitis).
**Thalidomide**

Preliminary reports suggest that thalidomide, a drug which is known to have TNF activity, may also be efficacious in AS.\(^3\)

**Biphosphonates**

There has been a recent upsurge of interest in the use of biphosphonates in the treatment of spondyloarthritis.\(^3\) The benefits may relate more to their anti-inflammatory effects rather than effects on bone resorption. Randomized clinical trials are now underway. In parallel with this work there is increasing interest in the incidence of osteoporosis in spondyloarthritides. In one AS study, 86% of patients had osteoporosis or osteopenia in the proximal femur.\(^3\) Osteoporosis is more likely in those with active disease.\(^3\) In patients with long standing disease, bone mass loss is best evaluated in the femur because of the presence of paravertebral calcification and ossification in the lumbar spine. In view of these findings it is logical to use steroid with caution in AS.

**Antibiotic Treatment in Reactive Arthritis**

The clear association of bacterial infection with reactive arthritis suggests a pathogenic link between spondyloarthritis and infection. Both bacterial products and T-cells responding to arthritis-associated bacteria can be detected in inflamed joints. The recent dramatic increase in the African frequency of spondyloarthopathy in association with HIV infection suggests that either loss of CD4 T-cells or a relative increase in CD8 T-cell might be important in spondyloarthritis. An alternative but less probable explanation is that coinfection with a separate urogenital trigger (or even HIV itself) might have a direct aetiological role in spondyloarthopathy.

In view of the long standing hypothesis that infection plays a role in the pathogenesis of many forms of inflammatory arthritis, it is not surprising that there have been a number of trials of antibiotic therapy in this group of patients. The rationale of antibiotic treatment has been more evident in reactive arthritis.\(^3\) Antibiotic treatment of the triggering infection is recommended if the presence of infection can still be identified after the onset of arthritis. The use of short courses of antibiotic treatment (up to three weeks) to eradicate genital tract infection remains logical. However, short courses of antibiotic treatment have not been shown to be of benefit to the arthritis. Use of ciprofloxacin for periods of three months to one year have not been shown to be beneficial in reactive arthritis following gastrointestinal infection.\(^3\) Indeed, a cautious approach should be exercised since antibiotic treatment may prolong the carrier state in some forms of enteritis. It is obvious that once the trigger has been pulled, the chain of events takes its path anyway. It is of interest that early treatment of patients with urogenital Chlamydial infection in endemic areas has resulted in decreasing subsequent development of reactive arthritis, and vigorous antibiotic treatment of Chlamydia reinfections significantly reduced relapses of Chlamydia-induced reactive arthritis.\(^4\) Recently, an uncontrolled study by Bardin and colleagues also suggested that treatment of genital tract infection with tetracycline or erythromycin might reduce the likelihood of the occurrence of reactive arthritis.\(^5\) Potentially viable chlamydiae may be present in the affected joints when conventional laboratory methods indicate no infection; reactivation of such infection may account in large part for the disease recurrence and persistence. The value of chronic antibiotic treatment in persistent severe reactive arthritis is not yet known. Preliminary findings suggest that some benefit is obtained.\(^4\) Lymecycline appeared to be beneficial in established sexually acquired Chlamydia-induced reactive arthritis.\(^4\)

Further collaborative studies are in progress, though it is of interest that no studies have yet addressed the issue of whether antibiotic treatment eradicates microorganisms from the joint.

**Conclusion**

There have been significant recent advances in our understanding of the pathogenesis of the spondyloarthropathies. Effort is continuously made to refine how spondyloarthropathies should be treated. There is renewed interest in enthesitis as an important diagnostic and pathogenic process. Advances in the pathogenesis of these disorders have already shown that TNF inhibition may be effective in the control of axial and peripheral inflammatory disease. Based on these reports, the use of TNF inhibitors in spondyloarthropathies is becoming more widespread and thus offers more options to those patients not adequately managed with conventional therapies. These definitely hold great promise but their efficacy in placebo-controlled trials and long term safety needs further evaluation.
MANAGEMENT OF SERONEGATIVE SPONDYLOARTHRITIS


