Available online at www.pharmacie-globale.info ISSN 0976-8157

Review Article

PHARMACIE GLOBALE

INTERNATIONAL JOURNAL OF COMPREHENSIVE PHARMACY

REVIEW ON: ANKYLOSING SPONDYLITIS

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Received: 16 May 2011; Revised: 2 June 2011; Accepted: 25 July 2011; Available online: 7 August 2011

ABSTRACT

Ankylosing spondylitis (AS) is a chronic, progressive, connective tissue disorder that is characterized by inflammation of the joints of the spine (vertebral joints), hipbones, and sacrum (sacroiliac joints). There is no cure for ankylosing spondylitis, but treatments can decrease pain and lessen symptoms. Treatment includes pain relieving drugs, DMARDs and TNFα blockers; herbal and homeopathic medications are also available.

Keywords: Ankylosing spondylitis (AS), autoimmune disease, DMARDs.

INTRODUCTION

Ankylosing Spondylitis is a progressive autoimmune disease, which causes inflammation of and arthritic reactions to the spine and large joints. Chronic inflammation in these areas causes pain and stiffness in and around the spine. Over time, chronic spinal inflammation (spondylitis) can lead to a complete cementing together (fusion) of the vertebrae, a process called ankylosis. (Figure **1**) Ankylosis causes total loss of mobility of the spine. A back disorder in which the vertebrae become squared and connected by fibrous tissue causing the spine to become rigid (known as bamboo spine). Ankylosing spondylitis usually begins in the sacroiliac joints and progresses up the spine. It is a disease that mainly affects people between 20 and 40 years. It is characterized in the early stages by low back pain (especially morning stiffness), which is relieved by exercise and non-steroidal anti-inflammatory drugs, and is aggravated by rest. Physiotherapy combined with good posture constitutes an essential part of the treatment.[1-5] AS is also known as rheumatoid spondylitis or Marie-Strümpell disease (among other names). AS is a systemic disorder that may involve multiple organs, such as the:

- eye (causing an inflammation of the iris, or iritis)
- heart (causing aortic valve disease)
- lungs
- skin (causing a scaly skin condition, or psoriasis)
- gastrointestinal tract (causing inflammation within the small intestine, called ileitis, or inflammation of the large intestine, called colitis)

Less than 1% of the population has AS; however, 20% of AS sufferers have a relative with the disorder.[6,7]

CAUSES AND SYMPTOMS

Genetics play an important role in the disease. More than 90% of patients have a gene called HLA-B27, but only 10-15% of those who inherit the gene develop the disease.[8-10] Symptoms of AS include:

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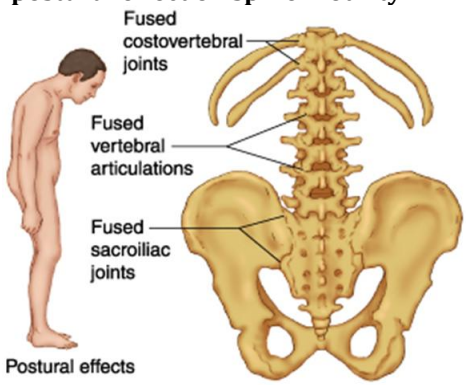
- low back and hip pain and stiffness
- difficulty expanding the chest
- pain in the neck, shoulders, knees, and ankles
- low-grade fever
- fatigue
- weight loss

Figure 1. postural effect on spine motility



AS is seen most commonly in males 30 years old and older. Initial symptoms are uncommon after the age of 30, although the diagnosis may not be established until after that age. The incidence of AS in Afro-Americans is about 25% of the incidence in Caucasians.

Symptoms of ankylosing spondylitis are similar to those of the more common rheumatoid arthritis, including pain, swelling, and stiffness in the affected joints.[11] The difference is that spondylitis primarily affects the spine, forming bony outgrowths (syndesmophytes) between the vertebrae, which may fuse vertebrae and lead to total spinal immobility (ankylosis). Fusion of the vertebrae also can stiffen the rib cage, reducing lung capacity and function. Constitutional symptoms may develop as the condition progresses, including anemia, fatigue, loss of appetite, weight loss, bowel inflammation, and eye inflammation (iritis). The presence and severity of symptoms varies among individuals.[12]

Disease starts with low back pain that comes and goes.[13]

- Pain and stiffness are worse at night, in the morning, or when the person is not active. It may wake a person from your sleep.

- The pain typically gets better with activity or exercise.[14]
- Back pain may begin in the sacroiliac joints (between the pelvis and the spine). Over time, it may involve all or part of the spine.[15]

Person may lose motion or mobility in the lower spine. Person may not be able to fully expand chest because the joints between the ribs are involved. Fatigue is also a common symptom.[16-18]

Other, less common symptoms include:

- Eye inflammation or uveitis
- Heel pain
- Hip pain and stiffness
- Joint pain and joint swelling in the shoulders, knees, and ankles
- Loss of appetite
- Slight fever
- Weight loss
- The typical patient is a young man of 15-30 years old (although women are also affected) with pain and stiffness in the spine. It is also associated with iridocyclitis (anterior uveitis), ulcerative colitis, psoriasis and Reiter's disease, through HLA-B27 (see below).

Organs affected by AS, other than the axial spine, are the hips, heart, heels, and other areas (peripheral). The typical patient is a young male, aged 20–40, when symptoms of the disease first appear, with chronic pain and stiffness in the lower part of the spine or sometimes the entire spine, often with pain referred to one or other buttock or the back of thigh from the sacroiliac joint.[19-22] Men are affected more than women by a ratio about of 3:1, with the disease usually taking a more painful course in men than women. In 40% of cases, ankylosing spondylitis is associated with an inflammation of the eye[23] (iridocyclitis and uveitis), causing redness, eye pain, vision loss, floaters and photophobia. This is thought to be due to the association that these two conditions have with inheritance of HLA-B27. Another common symptom is generalized fatigue[24] and sometimes nausea. Less commonly aortitis, apical lung fibrosis and ectasia of the sacral nerve root sheaths may occur. When the condition presents before the age of 18, it is relatively likely to cause pain and swelling of large limb joints, particularly the knee. In pre-pubescent cases, pain and swelling may also manifest in the ankles and feet, where calcaneal spurs may also develop. Pain is often severe at rest, but improves with physical activity. However, many experience inflammation and pain to varying degrees regardless of rest and movement.[25,26] Ankylosing spondylitis is one of a cluster of conditions known as seronegative spondyloarthropathies, in which the characteristic pathological lesion is an inflammation of the enthesis (the insertion of tensile connective tissue into bone).

The current study will serve to become a ready reference for identification and standardization of *Piper nigrum* and *Piper longum* on the basis of microscopy and chemical analysis. The preliminary phytochemical investigation will further help in isolation of important compounds in future.

PATHOPHYSIOLOGY

The ankylosis process.-Ankylosing spondylitis (AS) is a systemic rheumatic disease meaning it affects the entire body and is one of the seronegative spondyloarthropathies. Approximately 90% of AS patients express the HLA-B27 genotype, meaning that there is a strong genetic association. However, only 5% of individuals with the HLA-B27 genotype contract the disease. Tumor necrosis factor-alpha (TNF α) and IL-1 are also implicated in ankylosing spondylitis. Autoantibodies specific for AS have not been identified. Anti-neutrophil cytoplasmic antibodies ANCA are associated with AS but don't correlate with disease severity. The association of AS with HLA-B27 suggests that the condition involves CD8 T cells, which interact with HLA-B. It is not proven that this interaction involves a self antigen and at least in the related Reiter's syndrome (reactive arthritis), which follows infections, the antigens involved are likely to be derived from intracellular microorganisms. There is, however, a possibility that CD4 T cells are involved in an aberrant way, since HLA-B27 appears to have a number of unusual properties, including possibly an ability to interact with T cell receptors in association with CD4 (usually only cytotoxic T lymphocytes with CD8 react with HLAB antigen as it is a MHC class 1 antigen). There has been a longstanding claim that AS arises from a cross-reaction between HLA-B27 and antigens of the Klebsiella bacterial strain.[27] The problem with this idea is that no such cross reactivity with B27 has been found i.e. although antibody responses to Klebsiella may be increased, there is no antibody response to B27, so there seems to be no cross reactivity.[28-32]

DIAGNOSIS

Diagnosis of ankylosing spondylitis is based on clinical features such as presence of low back pain and stiffness for more than 3 months, limited motion in the lumbar spine, and limited chest expansion.[33,34] AS is termed primary or idiopathic (of unknown origin) if the disease occurs with radiographic evidence of inflammation of the sacrum (sacroiliitis) and without an associated spondyloarthropathy. It is termed secondary if it occurs in conjunction with psoriasis or chronic inflammatory bowel disease. Doctors usually diagnose the disease simply by the patient's report of pain and stiffness. Doctors also review spinal and pelvic x-rays since involvement of the hip and pelvic joints is common and may be the first abnormality seen on the x-ray. (Figure **2**, **3** & **4**)The doctor may also recommend a blood test to determine the presence of HLA-B27 antigen. When a diagnosis is made, patients may be referred to a rheumatologist, a doctor who specializes in treating arthritis. Patients may also be referred to an orthopedic surgeon, a doctor who can surgically correct joint or bone disorders.[35]

Figure 2. Lateral lumbar spine X-ray demonstrating in ankylosing spondylitis.

Figure 3. Magnetic resonance images of sacroiliac joints. Shown are T1-weighted semi-coronal magnetic resonance images through the sacroiliac joints (a) before and (b) after intravenous contrast injection. Enhancement is seen at the right sacroiliac joint (arrow, left side of image), indicating active

sacroiliitis. This patient had psoriatic arthritis, but similar changes can occur in ankylosing spondylitis.

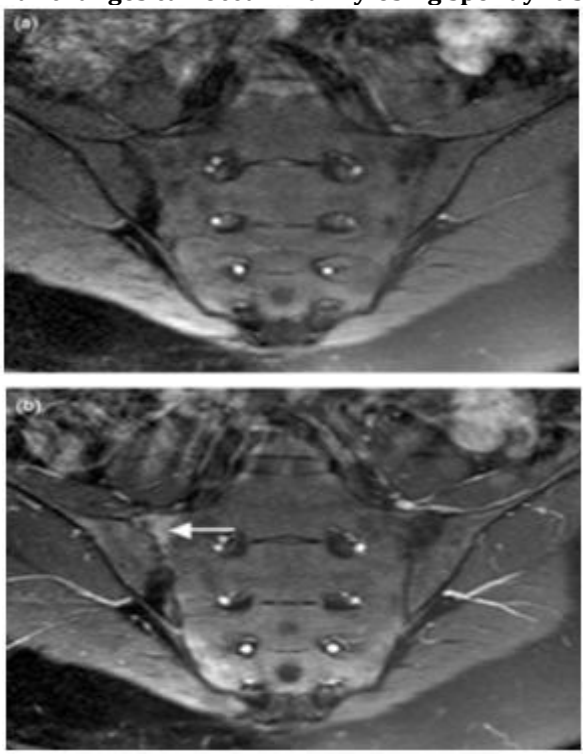


Figure 4. X-ray showing bamboo spine in a patient with ankylosing spondylitis.

There is no direct test to diagnose AS. A clinical examination and X-ray studies of the spine, which show characteristic spinal changes and sacroiliitis, are the major diagnostic tools. A drawback of X-ray diagnosis is that signs and symptoms of AS have usually been established as long as 8–10 years prior to X-ray-evident changes occurring on a plain film X-ray, which means a delay of as long as 10 years before adequate therapies can be introduced. Options for earlier diagnosis are tomography and magnetic resonance imaging of the sacroiliac joints, but the reliability of these tests is still unclear. The Schober's test is a useful clinical measure of flexion of the lumbar spine performed during examination.[36] During acute inflammatory periods, AS patients will sometimes show an increase in the blood concentration of C-reactive protein (CRP) and an increase in the erythrocyte sedimentation rate (ESR), but there are many with AS whose CRP and ESR rates do not increase so normal CRP and ESR results do not always correspond with the amount of inflammation a person actually has. Sometimes people with AS have normal level results, yet are experiencing a significant amount of inflammation in their bodies.[37] Variations of the HLA-B gene increase the risk of developing ankylosing spondylitis, although it is not a diagnostic test. Those with the HLA-B27 variant are at a higher risk than the general population of developing the disorder. HLA-B27, demonstrated in a blood test, can occasionally help with diagnosis but in itself is not diagnostic of AS in a person with back pain. Over 95% of people that have been diagnosed with AS are HLA-B27 positive, although this ratio varies from population to population (only 50% of African American patients with AS possess HLA-B27, and it is close to 80% among AS patients from Mediterranean countries). In early onset disease HLA-B7/B*2705 heterozygotes exhibited the highest risk for disease.

TREATMENT

Herbal

Herbal based supplements such as the herbal essence of evening primrose oil contains a potent anti-inflammatory chemical and can be used for topical application as well as a dietary supplement. Essential fatty acids such as gamma-linolenic acid (GLA), which is one of the many essential fatty acids and is not manufactured naturally in the human body can be used for the treatment of acute pain in the joints and to alleviate the worst symptoms of inflammation. The fat-soluble vitamin vitamin E or tocopherol can also be effectively used in the alleviation of the worst symptoms of this disease. The metallic element selenium in ionic form has potent antioxidant properties and is an important co-factor in the activation and internal usage of vitamins in the body. Among the water based vitamins ascorbic acid or vitamin C used by the body in great volumes to fight inflammation and is an important component of the body's self-repair system, for example in collagen structure. Along with vitamin C all flavonoids such as the important bioflavonoids act together in a coupled action with vitamin C and the inclusion of one should always followed by the inclusion of the other. Calcium and Magnesium are structural components of the bones, the very building materials needed if the body were to carry out a successful self repair, other ions like silica taken as a supplement in water-soluble and preferably in vegetal form or more easily as a silica gel is known to be an effective defense against the loss of bone mass. In the cases where acute ankylosing spondylitis has set in the water-based pyridoxine vitamin B6 is almost always lacking in sufficient quantities to be useful in the body. These deficiency of this particular vitamin gets especially more pronounced in individuals whose body's lack the enzymes necessary to convert vitamin B6 to an active form or into the co-factor pyridoxal-5-phosphate (P-5-P), therefore in those cases where, the body lacks such conversion enzymes a similar substitute of this active co-factor called P-5-P has to substituted instead of the vitamin B6, this is an essential substance and is an important supplement. In all cases of acute pain cause due to the chronic and persistent symptoms of ankylosing spondylitis and especially in cases where the pain is dreadful and inflammation has set in to a grave degree a naturally occurring anti-inflammatory relieving substance called bromelain (it is found in pineapple) can be taken in the the diet as a dietary supplement. This substance called bromelain is a naturally occurring enzyme and has remarkable anti-inflammatory properties and which must be one of the most effective natural substances against inflammation caused due to acute cases of ankylosing spondylitis. Bromelain is the most efficient and acts in the speediest way only when it is taken by itself and not along with food. The enzyme cannot take effective action if it does not act on an empty stomach. Asides from such substances a variety of herbal-based substances reduce the effects of inflammation on the body and greatly aid in

the improvement of general circulation. They even have anti-pyretic and pain relieving functions and can greatly aid in lessening pain in the affected region, a good example is eucalyptus oil, which when used as topical ointment on the affected region and its use as a rubbing lotion can actually increase the blood flow to such areas. Bringing on profound and soothing warmth that greatly makes the pain in the area bearable, eucalyptus oil is also a great help against the general stiffness felt in the body due to ankylosing spondylitis. For the general treatment of injured and strained muscles and in general muscle injuries it is advisable to take a tbsp the herbal horsetail juice, horsetail juice can also be used as a tincture by mixing about 15-20 drops of the essence to a glass of water, this can alleviate pain when applied topically. These herbal extract of horsetail juice can also easily aid in the reduction of an inflamed bowel and will readily help out in remedying some of the aches bought on by chronic pain in the lower back, which comes on in most cases with the onset of ankylosing spondylitis. The roots of another herb are an effective protection against aching joints; a good example is devil's claw root, which is quite efficient against pain in the lower regions of the spine. Some of the qualities that devil's claw root has are proven antirheumatic, antiarthritic and anti-inflammatory abilities. In order to make sufficient use of devil's root extract 30 drops in a glass of water applied locally as a tincture will rid most pains in the affected area, the regimen being to apply it topically about twice in a day directly onto the affected parts. The tincture can also be used as a dietary supplement and it has the unique ability of cleansing the blood of impurities, consumption in the diet should be about 1 tbsp a day along with food. The juice of the dandelion flower mixed in a tincture that contains about 20 drops in a glass with water can also be used as a topical ointment when applied about thrice per day for a period of three weeks. Another anti-inflammatory and pain relieving herb is white willow, which should be consumed, in a tinctured solution containing about 20 drops in water thrice a day.[38]

S. No.	Herb Used	English Name	Latin Name	Parts Used	Quantity
1.	Ashwagandha	Winter Cherry	Withania somnifera	Roots	60 gm
2.	Methi	Fenugreek	Trigonella foenum graecum	Seeds	20 gm
3.	Suranjaan	Autumn crocus	Colchicum automnale	Roots	40 gm
4.	Gorakhmundi	Rice field weed	Sphaeranthus indicus	Whole	30 gm
5.	Giloy	Tinospora	Tinospora cordifolia	Stem	30 gm
6.	Sonth	Dry ginger	Zingiber officinale	Rhizome	20 gm

Allopathy

There is no perfect cure for AS is known, although treatments and medications are available to reduce symptoms and pain. Physical therapy and exercise, along with medication, are at the heart of therapy for ankylosing spondylitis.[39] Physiotherapy and physical exercises are preceded by medical treatment in order to reduce the inflammation and pain (Figure **5**); are commonly followed by a physician. This way the movements will help in diminishing pain and stiffness, while exercise in an active inflammatory state would just make the pain worse.[40-43]

Drugs used to treat ankylosing spondylitis:

Pain-relieving drugs:

- Anti-inflammatory drugs: NSAIDs such as ibuprofen, phenylbutazone, indomethacin, naproxen and COX-2 inhibitors.
- Opioid analgesics

DMARDs: Cyclosporin, Methotrexate, Sulfasalazine, And Corticosteroids (To Reduce The Immune System Response Through Immunosuppression)

TNFα blockers (antagonists) such as etanercept, infliximab and adalimumab (biologics), are indicated for the treatment of and are effective immunosuppressants in AS as in other autoimmune diseases.

Mechanism of action

S No	Category of Drugs	Mechanism
1	Pain-relieving drugs: Antiinflammatory drugs (NSAIDS)	NSAIDS act by inhibition of PG (prostaglandin) synthesis at the site of injury and inhibit COX.
2	DMARDs (Disease modifying antirheumatic drug) Cyclosporin	Selectively inhibit T lymphocyte proliferation
3	TNFα blockers (Tumour necrosis factor α) Infliximab	TNF inhibitor mainly suppress macrophage and T cell function

Surgery

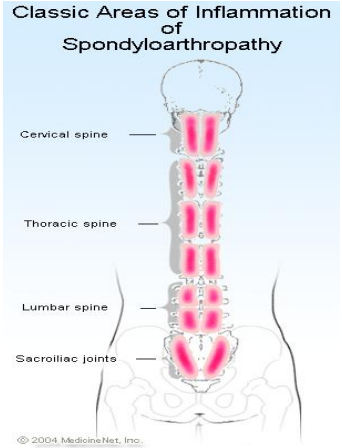
In severe cases of AS, surgery[44] can be an option in the form of joint replacements, particularly in the knees and hips. Surgical correction is also possible for those with severe flexion deformities (severe downward curvature) of the spine, particularly in the neck, although this procedure is considered very risky. In addition, AS can have some manifestations which make anaesthesia more complex. Changes in the upper airway can lead to difficulties in intubating the airway, spinal and epidural anaesthesia may be difficult owing to calcification of ligaments, and a small number have aortic regurgitation. The stiffness of the thoracic ribs results in ventilation being mainly diaphragm-driven, so there may be a decrease in pulmonary function.

Physical therapy

Some of the therapies that have been shown to benefit AS patients include:

- Physical therapy/physiotherapy, shown to be of great benefit to AS patients.

Figure 5. Areas of inflammation in AS



- Swimming, one of the preferred exercises since it involves all muscles and joints in a low-impact, buoyant environment.

- Slow movement muscle extending exercises like stretching, yoga, climbing, tai chi, Pilates method, etc.

Moderate-to-high impact exercises like jogging are generally not recommended or recommended with restrictions due to the jarring of affected vertebrae that can worsen pain and stiffness in some patients.

Homeopathy

Homoeopathic treatment[45] can be a great boon to the patients if the intervention is started well in time. In this disorder too, the homoeopathic medicines work by optimising the body's overactive immune (defense) system. The stage of the disease at which the homeopathic treatment is started, is a major factor in determining the outcome of the treatment. For example if the treatment is started in the initial stages when not too much of the elastic tissue is lost, the prognosis are very good and the condition can be reversed in most of the cases. In stages where extensive bone formation has replaced elastic tissue, homeopathic medicines may not be able to reverse the situation but can still help in easing many symptoms.

RECENT ADVANCES

Exercise is an integral component of treatment for patients with ankylosing spondylitis to maintain flexibility and posture.[46] A recent Dutch study demonstrated that a 3-week course of combined spa therapy and exercise therapy in addition to anti-inflammatory drugs showed favorable cost-effectiveness and cost-utility ratios compared with standard treatment alone for patients with ankylosing spondylitis.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs remain the first therapeutic line of treatment for patients with ankylosing spondylitis. The most exciting study to emerge in recent years relating to NSAID use in ankylosing spondylitis was presented at the ACR meeting in Orlando in 2003. The results of this study suggested that a treatment strategy characterized by continuous use of a fixed dose of NSAIDs was more efficacious in slowing radiographic progression in patients with ankylosing spondylitis than a treatment strategy characterized by on-demand use of NSAIDS. This was the first trial in ankylosing spondylitis suggesting that a slowing of radiographic progression might be possible with NSAID treatment.

Thalidomide

Thalidomide exerts its effect by the inhibition of TNF-α. It selectively suppresses TNF-α production by normal monocytes in vitro and lower plasma levels of TNF-α *in-vivo*.

Tumor Necrosis Factor Blockers

Tumor necrosis factor α messenger RNA and protein have both been identified in the sacroiliac joint biopsy specimens of patients with ankylosing spondylitis with active disease. This suggests that TNF-α may play a role in the pathogenesis of ankylosing spondylitis and that treatment with a TNF blocker may be helpful in controlling inflammation in patients with ankylosing spondylitis. Infliximab and etanercept (both TNF blockers) have been evaluated in the short term for safety and efficacy in ankylosing spondylitis.

CONCLUSION

The review suggests that Ankylosing Spondylitis is spreading widely but can be controlled and detected in earlier stage of disease with available herbal and allopathic treatment.

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