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# Ankylosing spondylitis – The history of medical therapies

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## ABSTRACT

*This is a concise overview of the history of medical therapies for patients suffering from ankylosing spondylitis. Recent therapeutic advances are also summarised.*

## Introduction

Ankylosing spondylitis (AS) is a relatively common chronic inflammatory rheumatic disease of uncertain etiology, usually affecting young adults, often in their late teens or early twenties. The disease has a predilection for the axial skeleton, including the sacroiliac joints. Spinal and peripheral joint involvement may cause physical limitations, and sometimes leads to early retirement due to inability to work. Its prevalence has been underestimated in the past, and recent studies using MRI techniques for detecting early sacroiliitis and spondylitis now suggest 0.86% prevalence for AS among the adult population of Berlin, Germany (1).

## Past history of medical therapies in ankylosing spondylitis

The use of vaccines, including typhoid vaccine, in the treatment of AS, as in other chronic forms of arthritis of undetermined etiology, was purely empirical when the physicians had nothing better to offer (2, 3). And so was the use of arsenic therapy. Success of bismuth sodium tartrate in the treatment of yaws in Africa, with improvement of accompanying rheumatic symptoms led to its use in AS but without much success (2).

The introduction of gold therapy for rheumatoid arthritis (RA) by Forestier in 1930 was a great advance in the management of this severe and potentially crippling disease. The relative success of gold naturally led to its use in patients with AS, which was at one time regarded as a variant of RA and was called rheumatoid spondylitis. The results were disappointing (2).

Forestier in 1936 reported beneficial effect of weekly injections of thorium

X in the treatment of AS (2, 4). Thorium X is a disintegration product of thorium, a radioactive element, and it gives off only *alpha* rays (atoms of helium) that move at a comparatively low speed. These rays have high ionizing effect but their range is limited. Thorium X, like radium emanation (radon), has a short life, being reduced to half value in less than 4 days (2). Therefore, it becomes practically inert in 2 or 3 weeks.

Radon is the first disintegration product of radium. It has a short life, just as thorium X, but it emits 92% *alpha* rays, and the rest 8% are *beta* and *gamma* rays (2). It is soluble to some extent in water, and is used in hydrotherapy in many spas in continental Europe.

X-ray therapy for various diseases had evolved in the beginning of the 20th century, and it was subsequently realized that the effect was both direct and indirect. Its use in the treatment of AS in the United Kingdom was popularized by Gilbert Scott in 1930's (5), and later by his former colleague Hernaman-Johnson (2). They observed that majority of their AS patients responded to x-ray therapy, although some had later relapsed, but a few had not responded. It was generally accepted that x-ray therapy applied locally to the sacroiliac joints and to all the actively involved regions of the spine was beneficial in AS and serves as an important adjunct to treatment (3). The immediate effect was the reduction of back pain and stiffness, as well as local tenderness, and more often there was partial improvement. The more recently involved regions showed a better response than the regions that were involved for many years. In some patients there was resolution of all clinical evidence of the disease and the erythrocyte sedimentation rate returned to or towards normal (3).

Hernaman-Johnson claimed that in his experience of treating well over 1,000 AS patients with x-ray therapy, he had "never heard of any damage to the

blood from the x-rays so used" (3). However, there is now a general consensus that spinal radiotherapy has no role in the modern management of patients with AS because of the high risk of leukemia and aplastic anemia in later years (6). Low dose external beam radiotherapy has occasionally been used to treat recalcitrant enthesitis (7), but such patient can now be managed with anti-TNF-alpha therapy (8).

In Germany, for reasons unknown to me, radium (224Ra) has recently become commercially available for the treatment of AS (9). An uncontrolled short-term study was recently conducted in a nuclear medicine department in Dresden, Germany, in which 20 AS patients were treated with weekly intravenous injections of 1MBq 224Ra for 10 weeks, 12 patients demonstrated clinical improvement (9). This clinical improvement was still present in 10 of these 12 patients at 6-month follow up. Reversible leucopenia and thrombocytopenia were observed in 25% of the patients in this study.

### Recent history of medical therapies in ankylosing spondylitis

Currently, there is no cure for the disease; the objectives of treatment are to relieve pain and stiffness, and to maintain good posture and physical functioning. Since their introduction in the 1950's, chronic regular use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAID) in full therapeutic (anti-inflammatory) doses, especially during the active (inflammatory) phases of the disease, forms the mainstay of management of AS (8,10,11). The proper management also requires a lifelong program of appropriate regular exercises, that should preferably include swimming. The patients' cooperation and compliance with recommended therapy are best achieved by familiarizing them with pertinent facts pertaining to their illness (12). It is not known whether long-term continuous NSAID treatment has advantages over intermittent therapy (8, 10, 11). Formal sessions of group physical therapy and hydrotherapy and passive stretching of the joints are generally underutilized. A few randomized, controlled studies

have demonstrated the benefits of these therapies in increasing range of movement and improving posture or minimizing deformity (13-16).

Up to 20% of AS patients are either intolerant, or show lack of adequate response to NSAIDs (6-8). Although phenylbutazone is undoubtedly very effective, it is now not available in most countries, or can only be used in severe cases under close monitoring of the full blood count to avoid bone marrow suppression. No NSAID has documented superiority in terms of efficacy and safety, but once daily or twice daily prescription regimens improve patient compliance. A controlled study found celecoxib, a cyclooxygenase-2-selective nonsteroidal anti-inflammatory drug, to be as effective as ketoprofen, and it cause less gastric ulcers (17). Aspirin does not provide adequate relief of pain and stiffness as compared to non-aspirin NSAIDs in AS.

The currently used disease-modifying antirheumatic drugs that are available for rheumatoid arthritis (RA), including sulfasalazine and methotrexate, do not inhibit the spinal inflammation in AS. Sulfasalazine has been used in AS since 1984, but it is only effective in reducing synovitis in patients with peripheral joint involvement, and has no beneficial effect on axial disease (18, 19). Methotrexate is not effective in AS patients who are unresponsive to NSAIDs and sulfasalazine (20-25). There is a clear need for effective new drug therapies in the treatment of AS because no drug is currently available that can retard the process of fibrous and bony ankylosis.

However, recent controlled studies have demonstrated dramatic efficacy of drugs that work by blocking the proinflammatory cytokine called tumor necrosis factor-alpha (TNF-alpha) in treating patients with AS, psoriatic arthritis, or enteropathic arthritis that are unresponsive to conventional therapies (26-30). But it needs to be demonstrated by long term prospective controlled studies that retardation of the process of fibrous and bony ankylosis can be achieved if the treatment is begun in early phase of AS.

As in RA, therapy must be continued

because disease activity returns a few weeks after administration of anti-TNF-alpha therapy is stopped. Studies are under way to find the optimum long-term dose to maintain remission. High cost and potentially serious adverse effects, including predisposition to bacterial infections, reactivation of tuberculosis, and demyelination, and as yet unknown other possible side effects of long-term therapy are the major deterrents or disadvantages of this therapy (31).

There are some novel therapies under study; these include pamidronate and thalidomide (32,33). Oral corticosteroids rarely provide general relief, but are effective when injected locally for enthesitis or intra-articularly for persistent synovitis (34). Acute anterior uveitis, that occurs in about 30 percent of the patients, can be well managed with corticosteroid eye drops and mydriatics to prevent synechiae formation.

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